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Traversing the cascade: urgent research priorities for implementing the 'treat all' strategy for children and adolescents living with HIV in sub-Saharan Africa

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Abstract

Children and adolescents living with HIV (CALHIV) in sub-Saharan Africa experience significant morbidity and alarmingly high mortality rates due to critical gaps in the HIV care cascade, including late diagnosis and initiation of treatment, as well as poor retention in care and adherence to treatment. Interventions to strengthen the adult HIV care cascade may not be as effective in improving the cascade for CALHIV, for whom specific strategies are needed. Particular attention needs to be paid to the contexts of sub-Saharan Africa, where more than 85% of the world's CALHIV live. Implementing the 'treat all' strategy in sub-Saharan Africa requires dedicated efforts to address the unique diagnosis and care needs of CALHIV, in order to improve paediatric and adolescent outcomes, prevent viral resistance and reduce the number of new HIV infections. We consider the UNAIDS 90-90-90 targets from the perspective of infants, children and adolescents, and discuss the key challenges, knowledge gaps and urgent research priorities for CALHIV in implementation of the 'treat all' strategy in sub-Saharan Africa.

Keywords: children, adolescents, HIV/AIDS, sub-Saharan Africa, HIV care cascade, HIV care continuum, antiretroviral therapy

Introduction

The ambitious UNAIDS 90-90-90 targets intend that, by 2020, 90% of people living with HIV are diagnosed, 90% of those who are diagnosed are on antiretroviral therapy (ART), and 90% of those on ART are virally suppressed [1]. Central to these targets is achieving them for all people living with HIV, which requires particular attention to vulnerable groups who remain furthest from reaching them [2]. Children and adolescents living with HIV (CALHIV) continue to experience alarmingly high mortality and poorer outcomes in the HIV care cascade compared to adults [2]. CALHIV have much to gain from the 'treat all' strategy, and they also have specific needs that must be addressed to ensure its successful implementation [3–6]. Here, we consider the 90-90-90 targets from a paediatric perspective, and discuss the key challenges, knowledge gaps and urgent research priorities in implementing the 'treat all' strategy in sub-Saharan Africa. This review is informed by systematic activities to set global HIV research priorities undertaken by both the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), and the International Epidemiology Databases to Evaluate AIDS (IeDEA), with adaptation to incorporate current paediatric evidence and the input of stakeholders from sub-Saharan Africa [7].

Challenges throughout the HIV care cascade for infants, children and adolescents

UNAIDS estimates that there were approximately 1.8 million children living with HIV (CLHIV, ages 0–14), and 1.8 million adolescents living with HIV (ALHIV, ages 10–19) globally in 2017, of whom more than 85% lived in sub-Saharan Africa (Table 1) [8]. CALHIV experience complex challenges accessing HIV testing and care and adhering to ART, resulting in late diagnoses, poor viral suppression and high mortality [2]. While deaths have declined substantially among CLHIV, there were 110,000 deaths in this group in 2017 [8]. Meanwhile, ALHIV have been the only age group with increasing deaths in recent years, despite a massive scale-up in the availability of ART [8].

The epidemic among infants and children

Although vertical transmission of HIV has significantly decreased in recent years, global ART coverage for prevention of vertical transmission is currently at 80%, and in 2017 there were 180,000 new paediatric infections [8]. Infants under 12 months and later 24 months of age were the first to have a recommendation for universal treatment in 2008 and 2010, respectively, and they have the most dramatic benefit from immediate treatment [9]. In this context, current gaps in infant diagnosis and treatment are particularly concerning, and contribute to high early HIV-related mortality before the age of 2 years [10]. Paediatric diagnosis is frequently delayed, with the majority of CLHIV in low- and middle-income countries initiating ART at a stage of advanced immunodeficiency [11–13]. Late perinatal diagnosis sets the stage for advanced illness and medical vulnerability, inadequate immune recovery once ART is initiated, development of opportunistic infections, and neurological and inflammatory consequences of uncontrolled HIV [14]. Beyond diagnosis, significant proportions of CLHIV are not accessing ART or achieving viral suppression [2].

The epidemic among adolescents

HIV is a leading cause of death among adolescents in sub-Saharan Africa [15]. The number of ALHIV has been steadily increasing, composed of both adolescents who acquired HIV vertically with long-standing infections and those with recently acquired HIV [16–19]. It is estimated that ALHIV with vertically acquired

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Table 1. UNAIDS estimates of children (ages 0–14) and adolescents (ages 10–19) living with HIV in sub-Saharan Africa and globally, in 2017*

a. Children living with HIV

	Number	Percentage of global total (%)	Number of new infections (%)	Percentage of global total (%)	Number of AIDS deaths (%)	Percentage of global total (%)	Percentage of children with HIV on ART (%)	Percentage coverage of pregnant women receiving ART for PMTCT (%)
Sub-Saharan Africa	**1,700,000**	**94.4**	**159,000**	**88.3**	**97,000**	**88.2**	**49.3**	**81.2**
East and Southern Africa	1,200,000	66.7	92,000	51.1	52,000	47.3	59.0	93.0
West and Central Africa	500,000	27.8	67,000	37.2	45,000	40.9	26.0	48.0
Global	**1,800,000**		**180,000**		**110,000**		**52.0**	**80.0**

b. Adolescents living with HIV

	Number	Percentage of global total (%)	Number of new infections	Percentage of global total (%)	Percentage of new infections among females (%)	Number of AIDS deaths	Percentage of global total (%)
Sub-Saharan Africa	**1,540,000**	**85.6**	**189,000**	**75.6**	**75.1**	**35,000**	**92.1**
East and Southern Africa	1,100,000	61.1	120,000	48.0	80.0	22,000	57.9
West and Central Africa	440,000	24.4	69,000	27.6	66.7	13,000	34.2
Global	**1,800,000**		**250,000**		**68.0**	**38,000**	

*Source: UNAIDS estimates – 2018. Available at: aidsinfo.unaids.org (accessed 24 July 2018).

infection make up a majority of this age group; however, there are limited available data disaggregated by mode of infection [19–21]. Among adolescents who recently acquired HIV, two-thirds are girls, as a result of factors including gender-based inequity and violence, lower HIV education, age-disparate relationships and poverty [22,23]. Adolescence encompasses rapid physiological, developmental, familial and social changes, such that adolescents have specific, evolving needs and capacities (such as the ability to manage one's own appointments, or to adhere to medications, or to make independent decisions about one's own care) over these years that extend into young adulthood (ages 20–24)[24]. Adolescents have unique challenges in their HIV care, including those related to access to testing and care, parental consent policies, adolescent disclosure, a shift from dependence on caregivers to independence in care, and transition to adult HIV services [25–27]. Adolescent HIV care is complicated by stigma, fear of HIV status disclosure, mental health needs, and challenges experienced in family, school and clinic environments [27–30]. These factors are exacerbated by the settings of poverty and marginalisation in which many ALHIV live [31]. Improvements to the ALHIV care cascade are urgently needed, not only to improve adolescent outcomes, but also to end the AIDS epidemic, via reduction of vertical and horizontal HIV transmission and prevention of viral resistance.

Target: 90% of people living with HIV diagnosed

Missed opportunities to diagnose infants and children

While perinatal HIV infection is associated with high mortality in infancy [10], there is a cohort of survivors of untreated perinatal HIV infection who are not diagnosed until reaching advanced illness, even into their second decade of life [16–18]. Current models estimate that two-thirds of infants acquire HIV *in utero* or at delivery, and experience rapid progression of illness, with a median survival of 1 year; the remaining infants acquire HIV during breastfeeding and are projected to experience slower disease progression, with a median survival to age 14 without treatment [32–34]. Many perinatally infected children are not identified, due to missed maternal HIV diagnoses, gaps in coverage of early infant diagnosis, and failures to diagnose children outside prevention of vertical transmission programmes [11,35]. WHO recommends testing all HIV-exposed infants at 4–6 weeks of age, but early infant diagnosis coverage remains a challenge, with huge geographical heterogeneity in sub-Saharan Africa [36]. In 2015, only 49% of HIV-exposed infants globally had a virological HIV diagnosis within the first 2 months of life [2]. An analysis of HIV programmes in six African countries and Haiti found that the proportion of HIV-exposed infants tested for HIV within 6 weeks of birth surpassed 50% only in South Africa and Zambia, and mean result turnaround times ranged from 22 to 38 days [37]. Moreover, there are missed opportunities to diagnose children seen in other healthcare settings, and a high potential yield for identifying children with previously undiagnosed HIV, particularly in inpatient and nutrition centres [16,35,38]. A study of primary school students found a significant burden of undiagnosed HIV, and important barriers to testing, including parental fears of 'unmasking' their own status and of the child experiencing stigma [39]. There is an urgent need to scale up and optimise provider-initiated HIV testing adapted to age, integrated with prevention programmes, HIV, and maternal and child health programmes, and paired with timely treatment initiation.

Most ALHIV have not been diagnosed

Inadequate testing currently presents a significant gap in the adolescent care cascade, and it precludes the subsequent steps of engagement in care and successful treatment. Demographic and health survey data from Congo (Brazzaville), Mozambique, Nigeria and Uganda, including 23,367 respondents aged 15–24 years, showed that 36.5% overall – and only 26.5% of 15–19-year-olds – had ever tested for HIV [22]. As a result of low testing uptake, it is estimated that a majority of ALHIV have not been diagnosed [2]. Population-based HIV Impact Assessments (PHIA) conducted in Malawi, Zambia and Zimbabwe found that only 46% of youths living with HIV (YLHIV, ages 15–24) were aware of their HIV status, compared to 65% of 25–34-year-olds, and 78% of 35–59-year-olds [2,40–42]. Among participants in the SEARCH study in Kenya and Uganda, only 50% of YLHIV were aware of their status at baseline, compared to 67% of older adults [43]. While there are few data on testing in the younger, 10–14-year-old adolescents, a study from Zimbabwe found that

they were less likely to be offered testing than children aged <7 years, despite the burden of undiagnosed perinatal infection in this group [18,44]. In a study from Botswana, in comparison to older age groups, 10–14-year-olds diagnosed with TB were least likely to have an HIV test; however, of those tested, 52% were HIV-infected [45].

Important barriers to adolescent HIV testing include low perceived risk of infection, fear of stigma, financial costs and gender inequality [46]. These may be particularly significant for younger adolescents. In a mixed-methods study from Zimbabwe, a major reason for providers not offering HIV tests to children aged 6–15 was concern about the suitability of the accompanying caregiver to provide consent [44]. This is a significant challenge in countries of sub-Saharan Africa with generalised HIV epidemics, where a high proportion of children are AIDS orphans, adult migration for work is common, children are cared for by multiple relatives, legal documentation of guardianship is unusual, and policies around consent for HIV testing are varied, without clear guidance on who may give consent [44].

Target: 90% of diagnosed people living with HIV on sustained ART

The treatment gap for infants and children

ART is lifesaving for CALHIV. Highlighting the urgency of early infant diagnosis, linkage to care and prompt treatment, initiation of ART before 3 months of age potentially reduces child HIV-associated mortality by 75% [9,47]. Current estimates are that only 52% of CLHIV globally are receiving ART; 59% in eastern and southern Africa, and 26% in western and central Africa [8]. In an analysis of IeDEA global cohort data, including 135,479 CALHIV aged 0–19 (over 95% from sub-Saharan Africa), during 2004–2015, 20% were lost to follow-up (LTFU) prior to ART initiation, possibly representing undocumented mortality [48]. Infants had 66% cumulative incidence of ART initiation at 24 months (95% confidence interval [CI] 66–67%); and infants and ALHIV ages 15–19 had the lowest ART initiation of all age groups [48]. ART initiation was lowest in sub-Saharan Africa [48]. Barriers to high ART coverage among CLHIV include delayed diagnosis, limited health worker capacity and poor supply chain for paediatric HIV commodities [3].

The challenge of retention among adolescents

Data from across sub-Saharan Africa have demonstrated poor ART initiation and retention among ALHIV [43,48–51]. In the SEARCH study, only 64% of previously diagnosed YLHIV were on ART at baseline, compared to 81% of older adults [43]. In the analysis of IeDEA paediatric cohorts, the cumulative incidence of ART initiation was lowest among ALHIV ages 15–19 years, with 62% initiating ART by 24 months (95% CI 62–63%) [48]. Older adolescents were most likely to be LTFU, as has also been reported in studies across sub-Saharan Africa [48,49,52–54]. This finding might reflect that the 15–19-year-old group included those with more recent infection, as ART eligibility at enrolment was correlated with cumulative ART initiation [48]. Adopting the 'treat all' strategy could improve retention among ALHIV who were previously not ART-eligible; however, age- and context-specific strategies for improving retention are urgently needed to reach 90-90-90 targets [43,48,55].

Complex barriers to retention for CALHIV

CALHIV experience significant barriers to retention. A cohort study from South Africa found that only 66% of CLHIV were retained in care, with greater attrition in recent years and in infants [56]. A case–control study of paediatric patients in Botswana found that factors associated with LTFU included: age <5 years, advanced HIV disease, greater immunosuppression and not receiving ART [57]. Nearly half of the LTFU patients had dropped out of care after just one clinic visit [57]. Early attrition from care has been reported in other studies of CALHIV, highlighting the need to engage patients on their initial presentation to HIV care [48,50,57,58]. Barriers cited by parents of LTFU CLHIV included beliefs that the child was well, fear of stigma and disclosure issues [57]. Barriers to retention for ALHIV include stigma, illness or death of family members, mental health challenges, substance abuse, poverty, and factors of clinic and school environments [27,30,38,59–61]. Facilitators to retention for CALHIV include social and family support, as well as future orientation and self-sufficiency of adolescents [27,29,60–62].

Target: 90% of people receiving ART with suppressed viral load

Gaps in viral suppression among infants and children

CALHIV have lower viral suppression compared to adults[52,63–66]. Viral suppression is critical to achieving optimal treatment outcomes, including neurocognitive and growth outcomes [63]. Meanwhile, there is a need for expanded access to routine viral load testing. At present, population-based estimates for paediatric viral suppression are lacking, as are data to identify factors associated with virological failure. A South African study found that only half of retained children achieved viral suppression [56].

Emerging data highlight reduced efficacy of specific ART regimens in CALHIV. A South African study demonstrated lower viral suppression for CLHIV when abacavir was used as part of a first-line ART regimen, compared to older, stavudine-based regimens [67]. With shifts in ART regimens, potential impacts on efficacy and adherence should be considered [67]. A lack of appropriate paediatric formulations remains a critical barrier [68]. There are also significant challenges identifying virological failure and HIV resistance in CLHIV, and providing second- or third-line regimens for lifelong ART [7].

Challenges for viral suppression among adolescents

Among YLHIV on ART, the PHIA surveys found that only 79% were virally suppressed, compared to 90% of adults. Given gaps earlier in the cascade, this translated to only 30% of all YLHIV with viral suppression; far below the target of 73% [2]. Similarly, in the SEARCH study, only 26% of all YLHIV had viral suppression at baseline [43]. In a study of adolescents who acquired HIV perinatally in global cohorts, 65% of African ALHIV experienced viral suppression at last visit, where viral load was available [20].

Adolescents have significant, complex challenges adhering to ART. A meta-analysis estimated that 62% of ALHIV and YLHIV globally are >95% adherent to ART, with higher adherence in Africa and Asia, although there was variability in measures of adherence used [69]. A study of Tanzanian ALHIV found an association between mental health difficulties with both stigma and decreased adherence [70]. Among ALHIV in Malawi, barriers independently associated with missed doses in the past week included alcohol use, missed clinic appointments, violence in the home and poor treatment self-efficacy [71].

Research gaps and priorities for CALHIV

Achieving the 90-90-90 targets for CALHIV will require significant improvements along the HIV care cascade, tailored to the

specific needs of CALHIV. CALHIV may be the furthest behind in reaching the 90-90-90 targets, yet the successful implementation of the 'treat all' strategy will have immense potential benefits for this population [63]. Earlier diagnosis, initiation of ART and improved quality of care to achieve viral suppression will be life-saving for CALHIV. Improvements to the adolescent care cascade will not only reduce their mortality, but also: reduce transmission to partners, reduce vertical transmission, and foster a healthy productive adulthood, as well as improving maternal and child health outcomes. Linkage of testing to prevention services could have the additional benefit of promoting uptake of prevention measures, including pre-exposure prophylaxis (PrEP) [4]. Improved estimates of the CALHIV epidemic are needed to guide the global response and tailor services to this group. Research is urgently needed to identify cost-effective interventions at each stage of the care cascade and to learn how to implement these at scale. Interesting and informative examples of work in these areas are highlighted.

The need for improved estimates for the paediatric and adolescent epidemics

Despite the burden of HIV among children and adolescents globally, there are significant gaps in the empirical data that guide the response to the epidemic. There is a critical need for accurate estimates for CALHIV, regarding: the number and proportion undiagnosed; timeliness in achieving care cascade stages; treatment outcomes, including HIV drug resistance and outcomes after LTFU and transfer-out; and definitive data on mortality. There is a need for disaggregation of data by 5-year age groups, sex and mode of infection. There is also a need for behavioural surveys to be designed for use among adolescents and disaggregated by age, particularly to address ALHIV from key populations [72].

Importantly, it is not currently known what proportion of ALHIV experienced vertical or horizontal routes of infection, and these groups may have different needs and require different responses for successful diagnosis and treatment [20,21,72]. To describe outcomes among likely perinatally infected adolescents, a recent analysis of 12 global paediatric cohorts evaluated ALHIV who enrolled in care before age 10 years and were not known to have horizontally acquired HIV [20]. Rates of LTFU and transfer-out were significantly higher among African ALHIV compared to other regions, and were likely to include unascertained mortality [20]. Given increasing HIV-associated mortality among adolescents, understanding the causes of ALHIV mortality is critically important.

Adapting HIV diagnosis and linkages to care for paediatric populations

Addressing gaps in paediatric and adolescent diagnosis and linkage to care will require an evaluation of appropriate context-specific interventions, their effectiveness, and their implementation within healthcare systems and service delivery models, including integration of HIV care with prevention of vertical transmisson, maternal child health programmes, and paediatric and adolescent healthcare services. Testing innovations, including rapid point-of-care HIV testing for infant diagnosis and expansion of paediatric testing at other entry points to the health system, may enhance timely diagnosis of HIV in CALHIV and decrease the time to ART initiation [73]. Modelling studies evaluating routine HIV testing at birth (to diagnose *in utero* infection requiring urgent ART), in addition to currently recommended testing at 6 weeks, demonstrate improved outcomes, including ART initiation before 3 months and decreased infant mortality, and cost-effectiveness [74,75]. A study in Botswana showed promise for targeted neonatal testing to diagnose *in utero* transmission in high-risk infants [76]. There is potential for community-based interventions to enhance uptake of testing and linkage to care. A nested cohort study in Nigeria evaluated a church congregation-based intervention designed to increase uptake of HIV testing among pregnant women, and found that early infant diagnosis was higher and HIV vertical transmission was lower among participants compared to baseline [77]. The SEARCH trial of a community-based testing and treatment programme achieved an increase from 50.3% to 86.5% of YLHIV being aware of their status; although viral suppression remained suboptimal due to reported difficulties with stigma and care logistics while at boarding school [43].

The WHO has developed guidelines for adolescent HIV testing and care directed at policymakers and programme managers, including recommendations to revisit policies around age of consent for HIV testing and facilitating access to care for ALHIV, particularly those from key populations [78]. There is a need to study service delivery interventions and care models to improve access to testing (and repeat testing), linkage to care, and ART initiation with attention to the needs of ALHIV [7]. In South Africa, implementation of an integrated Youth Centre incentivising utilisation of services resulted in greater numbers of young adolescents (ages 12–15 years), particularly males, testing for HIV; among older adolescents, more individuals tested at the community clinic [79]. A systematic review found that provider-initiated inpatient HIV testing and home-based HIV testing of children and adolescents appear to have high acceptability [80]. Home-based testing in the PopART trial was accepted by 80% of adolescents aged 15–19, and the number of adolescents who knew their status increased from 28% to 89% [81]. Self-testing strategies for adolescents have demonstrated high uptake [82], acceptability [83] and cost-effectiveness [84]. Targeted strategies are urgently needed for adolescents from key populations for increased and repeated testing, enhanced linkage to HIV care for all testing positive, and prevention services for those testing negative, including PrEP [85,86].

Integrating tailored support into service delivery

More research around interventions and service delivery models to improve CALHIV outcomes in the care cascade, including linkage to care and retention on ART, would guide service delivery [3,5,7,27,87]. This should specifically include models to integrate HIV care into other health systems, including maternal child health clinics and general paediatric and adolescent health services. Psychosocial support strategies, such as family support and interventions, disclosure support, and stigma reduction in clinical, school and community settings, should be pursued[7]. Integrating interventions for mental health issues and substance use disorders into HIV care would mitigate the significant mental health barriers CALHIV face in accessing and continuing in care [28,70].

Though a recent systematic review found that few interventions have been studied to improve retention of ALHIV, promising potential strategies include education and counselling, peer interventions, financial interventions, clinic accessibility and specific adolescent-friendly services [87]. There is a need for rigorous, larger studies to evaluate these potential areas of intervention [87]. A few observational studies have evaluated the impact of adolescent-friendly services on retention in care, with mixed results [27,50,58,88,89]. Potential reasons for this are that adolescent-friendly services may be insufficient to mitigate the complex challenges to retention for many ALHIV, or that ALHIV become LTFU before engaging effectively with these interventions [27]. Differentiated care models have shown promise in improving adult engagement with HIV services, but it is less clear how effective this approach will be for ALHIV [87]. In Zimbabwe, CALHIV managed

within a decentralised HIV care model experienced encouraging retention in care, though only 64% achieved viral suppression [64]. Importantly, strategies are needed to specifically address sexual and reproductive health outcomes of ALHIV, pregnant ALHIV and ALHIV from key populations, and there are few studies in these areas [85,86,90,91]. More data on strategies to support ALHIV to successfully transition to adult HIV services are critically needed to reduce attrition from care at this stage [92,93].

Improving viral suppression and treatment outcomes for CALHIV

There is a very small evidence base for interventions to improve paediatric and adolescent adherence to ART, and consequently, viral suppression [85,86,91,94]. A systematic review of ART adherence interventions for ALHIV ages 13–24 found that, out of a few studies meeting inclusion criteria, most were small, unreplicated pilot studies conducted in the USA [94]. Evidence was found for a phone-based adherence monitor intervention, and for individual and family counselling, to improve viral suppression [94]. The BREATHER trial demonstrated that a 'weekends-off' efavirenz-based ART regimen in participants aged 8–24 on first-line ART was non-inferior to a continuous regimen, and had a better safety profile, presenting a treatment option aiming to lessen treatment fatigue, meet lifestyle needs and facilitate adherence [95]. While the introduction of dolutegravir offers promise for ALHIV, given its once-daily dosing, a high genetic barrier for resistance, and lack of cross-resistance to first-generation integrase inhibitors, recent data indicating possible elevated risk of neural tube defects in infants following exposure during conception may impact how it is used in adolescents [96]. Investigational long-acting injectable formulations of ART may have potential future use to facilitate adherence to treatment [97].

Other priority research areas include evaluating the impacts of HIV infection and of ART on paediatric and adolescent clinical outcomes, including virological outcomes, the potential for functional cure with very early ART in infancy, and development of opportunistic infections and non-communicable diseases [7]. Efforts to improve prevention, diagnosis and clinical management of TB and other co-infections will also be critical to improving outcomes.

Conclusions

Dedicated efforts are needed to meet the context- and age-specific needs of CALHIV, including a focus on critical research priorities. Targeted research to strengthen the child and adolescent HIV care cascades in the implementation of 'treat all' will translate to improved outcomes for these children and adolescents, followed by transitions to healthy adulthoods.

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Declaration of interests

The authors declare no conflicts of interest.

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