Retention and adherence: Global challenges for the long-term care of adolescents and young adults living with HIV

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Structured abstract

Purpose of review:
Adolescents living with HIV (ALHIV) are the only age group with increasing HIV mortality at a time of global scale-up of access to antiretroviral therapy (ART). As a “treat all” strategy is implemented worldwide, it is critically important to optimize retention and adherence for this vulnerable group.

Recent findings:
Adolescents and young adults living with HIV (AYALHIV) have poorer outcomes when compared to adults at each stage of the HIV care cascade, irrespective of income setting. Rates of viral suppression are lowest for ALHIV, and adherence to ART remains an enormous challenge. High quality studies of interventions to improve linkage to, and retention in, care on suppressive ART are starkly lacking for AYALHIV across the globe. However, examples of good practice are beginning to emerge but require large scale implementation studies with outcome data disaggregated by age, route of infection, and income setting, and include young pregnant women and key populations groups.

Summary:
There is an urgent need for evidence-based interventions addressing gaps in the adolescent HIV care cascade, including supporting retention in care and adherence to ART.

Keywords: adolescents; young adults; retention; adherence; HIV; antiretroviral therapy
INTRODUCTION

There are an estimated 1.8 million ALHIV globally, 80% living in sub-Saharan Africa [1]. In recent years, older adolescents (15-19 years) are the only age group with increasing HIV mortality, at a time of massive scale-up of treatment programs, and when mortality is declining in all other age groups [2,3**]. High adolescent HIV mortality reflects critical gaps in the HIV care cascade, including low rates of retention in care, and complex challenges with adherence to ART [4-15]. The adolescent years (10-19 years) encompass significant physiological and psychosocial changes that confer particular vulnerability for adolescents living with either perinatally (PHIV) or behaviorally acquired HIV infection (BHIV) [4,5,16-18]. These changes continue to impact outcomes into young adulthood (20-24 years) [7,10,18-20].

Failure to optimally diagnose, retain and treat adolescents and young adults living with HIV (AYALHIV) has broad implications for the global epidemic. Viral suppression is critical to preventing onward transmission and reducing morbidity and mortality [21-24]. The UNAIDS “90-90-90” goal that 90% of persons living with HIV are diagnosed, 90% on treatment, and 90% virally suppressed in order to end the AIDS epidemic, cannot be achieved without a sustained and targeted effort to improve AYA outcomes [25,26]. We review recent research in AYALHIV retention in care and adherence to ART, from high and low or middle income countries (HIC and LMIC).

AYA HIV CARE IN HIGH INCOME COUNTRIES

90-90-90 targets are yet to be met for adults in many HIC and remain an enormous challenge for AYALHIV [27]. The rise in HIV-associated mortality in adolescence is driven by the emerging cohort of long-term survivors of the PHIV epidemic who join the ever-increasing numbers of BHIV AYA, although robust data interpretation is frequently hampered by lack of disaggregation by both age and route of infection [3**]. Further complexity for data collection occurs during transition, with tracking of ALHIV into adult care by accurate linkage of national pediatric and adult surveillance systems proving challenging [28*].
Reported adult retention and suppression rates vary widely for the HIV care continuum in HIC. Encouragingly, in 2016 all 90-90-90 targets were met for the first time in London, where 97% of those diagnosed received ART, with 97% suppressed <200c/ml [29**]. However, when disaggregated by age, disparities persist, with 89% of 15-24 year olds receiving treatment compared to 98% over 50 years. Disaggregation by route of infection reveals lowest rates of suppression in PHIV (88%) [29**]. In the US, an estimated 51% of the 60,900 AYALHIV in 2013 remained undiagnosed, the highest rate in any age group [30]. Of those diagnosed in 2014, 68% were linked to care within one month, the lowest of any age group, 55% were retained in care, and 44% were suppressed [30]. Recent improvements are reported, at least for youth attending specialist services with adherence counselling, case management and integrated mental health and substance use services [31**]. Of 467 BHIV youth, median age 23 years, linked to care for at least 1 year, 86% remained engaged, 98% were prescribed ART, 89% achieved viral suppression, sustained in 59% [31**]. Taking the initial 467 linked to care, 45% remained in care on sustained suppressive ART; leaving considerable scope for improvement.

Looking at factors associated with retention, Hussen et al examined the care continuum for 72 AYALHIV referred to adult services between 2004-2014 [32**]. Almost all attended once, but only 56% were retained in care by year two. Viral suppression in pediatric care and shorter time between last pediatric and first adult appointment were associated with retention on suppressive ART in adult services [32**]. While transfer between pediatric and adult services has been highlighted as a particular barrier to retention, half of this cohort had disengaged from pediatric care prior to re-enrolling in adult care, highlighting the complexity of disentangling the impact of service change from the multiple physical, psychosocial and economic challenges during adolescence [33]. Linked data for 271 PHIV British youth tracked from pediatric to adult care showed a decline in CD4 counts prior to transfer; after transfer, counts continued to decline in black males, remained constant in white males and black females, and increased in white females [34*]. Age at transfer and moving hospital had no apparent impact, however more recent calendar year was associated with better outcomes,
potentially reflecting improvements in ART and/or transition over time. Transition typically occurs during late adolescence in Europe, often extending into young adulthood in the US [33]. Populations vary by route of transmission; with predominantly PHIV in Europe and a larger proportion of BHIV in US cohorts. Comparison of transition outcomes by route of infection reviewed by Lam et al highlights the barriers faced, including the higher rates of accumulation of HIV-1 associated drug resistance mutations in PHIV compared to BHIV, resulting in more complex ART, impacting on adherence [35,36]. The paucity of data on acquired drug resistance in ALHIV is highlighted. In the UK, 291 of 644 adolescents transferring to adult care had resistance data available; 82% with resistance to ≥1 drug class, 56% to ≥2 classes and 12% triple-class resistance, reflecting the long-term consequence of poor paediatric viral suppression rates due to more limited ART options, unpalatable formulations, and dependency on parents/carers [37]. Small European cohorts have recently published post-transition data for predominantly PHIV youth. In Holland, virological failure increased post-transition [38]. In contrast, a very small Swedish cohort (n=23) reported post-transition viral suppression rates above 90%, comparable to adults [39]. However, HIC mortality data is emerging; 117 HIV-related deaths were reported in 60,900 American 15-24 year-olds [3,30]. An mortality audit of young UK adults with PHIV highlights the interplay of mental health diagnoses with poor adherence, leading to advanced disease [40].

How do we improve retention in care and adherence to ART? Fortenberry et al show how addressing the need for structural change in fragmented US services improves outcomes for AYALHIV [41**]. Through a coordinated program of cross-agency collaboration, youth-friendly linkage to care and community mobilization, more than 75% of almost 4000 youth linked to care, with nearly 90% retained [41**]. A US single center pilot intervention comparing a program of non-traditional HIV testing, motivational interviewing, and case management with standard of care for newly diagnosed youth (18-24 years) showed significantly higher rates of linkage to care (96% vs. 57%, P<0.001) within a shorter time frame and improved adherence for the intervention group [42]. Strategies to improve re-engagement after loss to follow-up (LTFU) from adult care through outreach coordinators,
peer facilitators, and LTFU protocols have encouraging results but lack age-disaggregated data for AYA [43,44]. The use of mobile phone technology to improve adherence in adolescents has shown promise in terms of feasibility and acceptability, although more modest efficacy, and is being evaluated further in the US “weCare” program [45-47]. This US-based program targets MSM, ages 13-34 years, who are consumers of social media using Facebook, text messaging, and established GPS-based mobile applications as a platform for improving linkage and retention to care [47]. Outcome data is awaited for this group with typically very low retention rates. The unmet needs and lack of outcome data for young people in key population groups, including pregnant adolescents, those who inject drugs, transgender youth, sex workers, and AYA within the criminal justice system, requires urgent attention.

AYA HIV CARE IN LOW AND MIDDLE INCOME COUNTRIES

HIV poses a significant threat to adolescents in sub-Saharan Africa (SSA) today and an important cause of adolescent mortality in this region, with an estimated 36,000 deaths per year [2,16]. From 2000 to 2015, adolescent AIDS-related deaths more than doubled in the 25 countries with 86% of the world’s ALHIV [48]. Compared to their pediatric and adult counterparts in LMIC – as in HIC – AYALHIV have poorer retention in care, lower rates of virological suppression, and higher mortality [3**,49,50].

Adolescent disengagement from care presents a major challenge for global HIV programs. Only 20% of the world’s ALHIV are on ART [48]. In South Africa, youth (15-24 years) have the lowest proportion on ART of any age group, with only an estimated 10% virally suppressed [51,52*]. In pooled data from global IeDEA cohorts including 115,549 children (0-19 years) enrolled in HIV care, 20.8% were LTFU before ART initiation, and adolescents had the lowest initiation rate (54.3%) [53]. In an analysis of East Africa IeDEA sites, older adolescents (15-19 years) experienced the highest rate of LTFU within 2 years (51%) and the lowest ART initiation rate (20%) [54]. Risk for LTFU was increased for adolescents not eligible for ART prior to implementation of the treat-all strategy [55**].
There is additional concern for LTFU during the transition from pediatric to adult services [28*,35,56,57].

While there is limited qualitative data focused on adolescent retention, available studies from sub-Saharan Africa illustrate emerging challenges faced by adolescents accessing HIV care in this setting (Table 1) [58**-64]. Predominant barriers include perceived and enacted stigma, fear of disclosure of HIV status to the adolescent or others [58**-62], and mental health issues [5,60,65**,66*]. These are particularly complex for PHIV adolescents, who may experience uniquely challenging circumstances, including illness or death of family members; severe, life-threatening illness with delayed diagnosis; the difficult experience of learning their HIV status; and social isolation [5,60,66*-70]. Poverty, food insecurity, and family factors are also dominant [60,61,63,71], in addition to elements of the clinic [59,61] and school environments [59,61]. Emerging facilitators include strong social support networks, supported disclosure of HIV status to the child or close family members, family stability and support, and future orientation and self-sufficiency of adolescents [58**,60-62,64]. Efforts to improve retention of AYALHIV will need to mitigate the significant challenges that pervade adolescent engagement in care, for example by supporting disclosure of HIV status to the adolescent, reducing stigma in the community, school and clinic settings, and facilitating access to mental health support [59,60,62,64,66*,68].

Few studies have evaluated interventions to improve AYALHIV retention in LMIC, including the impact of adolescent-friendly services (AFS) [72-74]. In Kenya, AFS were implemented at six clinics; training providers in adolescent care, monthly dedicated adolescent HIV clinics, integrating sexual and reproductive health, and establishing peer support programs [75]. Pre-ART LTFU decreased at AFS clinics, although not statistically significant, with no difference in LTFU or mortality between AFS and non-AFS clinics, and no impact on post-ART LTFU [75]. Another study in Kenya evaluated factors associated with LTFU in a cohort of 15-21 year-olds enrolled at a youth-dedicated clinic and a family oriented clinic. While there was a high proportion LTFU (57%), with 26% LTFU immediately, enrollment in a youth-specific clinic was not associated with reduced LTFU [76].
By contrast, implementation of an adolescent-friendly clinic in Haiti was associated with improvements in the proportion of adolescents ages 13-19 enrolling in care, being assessed for ART eligibility, initiating ART, and a reduction in pre-ART attrition from 61% to 50% [9]. There was no impact, however, on long-term retention. In Kenya, implementation of AFS providing peer navigators, peer counselling, and psychosocial support at clinics and schools demonstrated substantial improvement in retention of AYA-LHIV ages 15-21 [77]. A large multi-country study evaluated factors associated with LTFU of AYA-LHIV ages 15-24, including availability of specific AFS [8]. Pre-ART LTFU was not associated with any of the evaluated AFS. Post-ART LTFU was lower at clinics providing condoms, or offering adolescent support groups. In Rwanda, where there was heterogeneity in the availability of adolescent peer educators, there was lower post-ART LTFU, though this was not significant due to small clinic size.

While there are considerable limitations to the current literature, evidence from observational studies of the impact of AFS on retention is mixed [8,9,54,72,73**,75,76,78,79]. It is possible that provision of AFS may be insufficient to mitigate the causes of LTFU for many AYA-LHIV. In some contexts, there may be high initial attrition from HIV care prior to engagement with AFS [8,53,54,76,80,81]. Furthermore, stigma, psychosocial issues, family and community factors may be central to disengagement, and must be mitigated to realize optimal adolescent HIV outcomes [9,58,59,75]. In adult studies, community-support models have shown promise in addressing stigma and other social factors while facilitating care [73**,82]. An ongoing cluster randomized controlled trial in Zimbabwe will evaluate the impact of a multifaceted community-based program to improve ALHIV retention and adherence [83].

Studies of interventions to improve adolescent retention in care are needed from multiple approaches [72], particularly for pregnant adolescents and adolescents from key populations (Table 2) [84**,87]. To be most be impactful and relevant to youth, this research should evaluate adolescent needs in local contexts, undertaken through collaborative partnerships with AYA-LHIV themselves [61,88].
Sustaining ART adherence is critical to achieve virological suppression, prevent drug resistance, halt disease progression, and prevent transmission [48,49,89]. Evidence suggests that AYALHIV fail to achieve and maintain adequate adherence. In a study from South Africa, only 27% of 9-19 year-olds achieved viral suppression, compared to 63% of 20-29 year-olds [89]. In addition, adolescents had an increased risk of virological failure (AHR=2.06, p=.002) [89]. While systematic reviews have suggested that children, adolescents and adults in LMIC have higher rates of ART adherence than those in HIC [90-92], adherence is typically measured in LMIC by self- or caregiver-reports, which likely do not capture the full extent of non-adherence [92,93]. Implementing other adherence measures for AYALHIV, including viral load, electronic dose and therapeutic drug monitoring, hair drug concentrations, and novel approaches to pill counts such as looking for “overadherence”, all reveal the non-adherence and challenges such as treatment interruptions that compromise viral suppression [94-98].

The evidence for interventions to improve AYA adherence in LMIC remains extremely sparse [99]. A recent systematic review found only two effective interventions among high-quality studies: a phone-based counseling approach with adherence monitors and weekly individual and family counseling [99]. Only one of these studies was done in a LMIC (Thailand) [100]. Patient-oriented adaptations of healthcare delivery systems are considered a key requirement to improve ART adherence and retention in care for adults, as they can overcome structural barriers; allow more time and resources for adherence, disclosure, or mental health support; and lessen treatment fatigue and LTFU [101]. Evaluations of how such adaptations might improve AYALHIV outcomes are lacking. Another potential strategy for improving AYA adherence may come in the form of ART options with a higher genetic barrier to resistance and in once daily fixed dose combinations. Integrase inhibitors such as dolutegravir [102] have been effective in achieving high rates of viral suppression in other populations and long-acting injectable ART remains an attractive future goal. Access to newer ART classes is particularly pertinent given the extremely worryingly levels of transmitted drug resistance to
both NNRTIs and NRTIs emerging in infants from sub Saharan Africa for whom treatment options currently are extremely limited [103**].

CONCLUSION

AYALHIV are an acutely vulnerable group, with worse outcomes than adults at each stage of the care cascade, in all global settings. There is an urgent need to develop an evidence base for interventions to improve adolescent retention and adherence to ART. As a “treat all” strategy is implemented globally, there is a need to identify interventions that are cost-effective, scalable, and sustainable, to ensure adolescent retention in care and adherence to ART, to halt the rise in adolescent HIV associated mortality, and ultimately to bring an end to the HIV/AIDS epidemic.

KEY POINTS

• Adolescence is the only age group where HIV associated mortality continues to rise
• AYALHIV experience poorer rates of retention in care and adherence to ART compared to adults, due to multiple psychosocial challenges that complicate HIV care at this developmental stage.
• There are remarkably few studies of targeted interventions to improve retention in care and adherence to ART or AYALHIV.
• There is a need for data, disaggregated by age and route of infection on outcomes and targeted interventions for retention in HIV care of for AYALHIV that includes pregnant adolescents, and those from key populations groups, both in HIC and LMIC.
• Interventions are needed which mitigate stigma and strengthen social support for AYALHIV to improve retention in care.

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Excellent analysis of the global adolescent epidemic and the further improvements required in national surveillance programs to include adolescent data.


29.** Brown AE, Kirwan PD, Chau C, Khawam J, Gill ON, Delpech VC. Towards elimination of HIV


Specialist youth services with integrated mental health and substance use provision can achieve viral suppression although sustaining suppression remains a challenge.


Retrospective study of linkage, retention, and viral suppression in youth during transition from pediatric to adult HIV services, demonstrating a significant drop-off in retention by the second year in adult care.


CD4 counts start to fall prior to transition to adult care, and actually improve post transfer in some groups, highlighting the need to consider the broader issues of adherence in adolescence, transition of care being one factor in a complex developmental period.


39. Westling K, Navér L, Vesterbacka J, Belfrage E. Transition of HIV-infected youths from
paediatric to adult care, a Swedish single-centre experience. … Infectious Diseases 2016; 48:449–452.


Description of a multilevel youth- and community-focused approach to reduce fragmentation of HIV care, improve the care continuum, and address health disparities for AYALHIV in the US.


43. Bean MC, Scott L, Kilby JM, Richey LE. Use of an Outreach Coordinator to Reengage and Retain Patients with HIV in Care. AIDS Patient Care and STDs 2017; 31:222–226.


Systematic review and meta-analysis of South African cohorts reporting data for AYALHIV, finding that only 14% of all AYALHIV in 2013 accessed care, and that approximately 10% of all
AYALHIV were virally suppressed.


Prospective cohort study of children ages 6-15 enrolled in HIV care at primary healthcare clinics in a decentralized care model in Harare, Zimbabwe, demonstrating excellent retention for those initiated on ART, but only 64% viral suppression.


Meta-ethnography synthesizing evidence from qualitative studies on factors that influence adolescent engagement along the HIV care cascade in sub-Saharan Africa.

59. Wolf HT, Halpern-Felsher BL, Bukusi EA, Agot KE, Cohen CR, Auerswald CL. ‘It is all about the fear of being discriminated [against]…the person suffering from HIV will not be accepted’: a qualitative study exploring the reasons for loss to follow-up among HIV-positive youth in Kisumu, Kenya. BMC Public Health 2014; 14:1565–11.


Prospective study evaluating the relationship between mental health difficulties, internal and external stigma, adherence, and CD4 counts in ALHIV in Tanzania.


Narrative review of mental health challenges affecting ALHIV, emphasizing the need for proactive mental health support to be integrated into HIV care for adolescents, and highlighting the need for research in this area.


Systematic review of strategies to improve retention of AYALHIV in LMIC, highlighting the sparse literature in this area and need for rigorous studies of interventions addressing adolescents.


Cross-sectional study assessing engagement of adult and adolescent mothers in the PMTCT cascade in Kenya. In comparison to adults, adolescents had poorer attendance to antenatal care visits, and those with HIV were less likely to be on ART or to have infants on ART.


Extremely worrying levels of emerging HIV drug resistance.
Enclosed tables.

Table 1. Qualitative studies which include evaluation of factors underlying adolescent retention in LMIC.

Table 2. Areas of intervention for adolescent retention, for which research is needed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Populations</th>
<th>Area of study</th>
<th>Barriers</th>
<th>Facilitators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolf</td>
<td>Kenya</td>
<td>LTFU AYALHIV 15-21 years; Community health workers who work with LTFU AYALHIV; Educators from schools attended by LTFU AYALHIV</td>
<td>Reasons for LTFU among AYALHIV</td>
<td>Stigma and fear of disclosure within the home/family, school, and clinic, and resulting impact on dependent relationships between AYALHIV and adults in these settings.</td>
<td>Not specifically studied.</td>
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<td>Petersen</td>
<td>South Africa</td>
<td>ALHIV 14-16 years; Caregivers of ALHIV</td>
<td>Psychosocial challenges and protective influences for coping in ALHIV</td>
<td>Death of biological parents; coming to terms with HIV infection; external stigma and discrimination; disclosure challenges; lack of financial, family, or social support.</td>
<td>ART; HIV education; future orientation; social support; financial support.</td>
</tr>
<tr>
<td>Busza</td>
<td>Zimbabwe</td>
<td>Caregivers of children ages 6-15 engaged in care; Key informants from community organizations providing adherence support</td>
<td>Factors influencing linkage and retention to inform design of a community-based intervention to increase retention of children living with HIV</td>
<td>Distance to clinic; transportation cost; fear of HIV status disclosure to the child or others; unstable family structure; drug stock-outs; HCW absenteeism; unsympathetic school environments.</td>
<td>Family openness; availability of practical assistance and psychosocial support from community members</td>
</tr>
<tr>
<td>Mburu</td>
<td>Zambia</td>
<td>ALHIV 10-19 years; Healthcare providers of ALHIV; Caregivers of ALHIV</td>
<td>ALHIV experiences within a socioecological model</td>
<td>Internalized stigma; external stigma and discrimination in schools; inflexible clinic hours, staff shortages; lack of policies addressing ALHIV.</td>
<td>Resilience; family and peer support; livelihood, nutritional support; psychological support</td>
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<tr>
<td>Luseno</td>
<td>Kenya</td>
<td>ALHIV 15-19 years, in care, out of care, or never enrolled; Caregivers of ALHIV</td>
<td>ALHIV experiences with HIV services along the care cascade</td>
<td>ART side effects; pill burden; limited access to clean water and nutrition</td>
<td>Supportive environments in family, school, health facility</td>
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<tr>
<td>Midtbø</td>
<td>Botswana</td>
<td>ALHIV;</td>
<td>Relationship between</td>
<td>External stigma</td>
<td>HIV status disclosure</td>
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<td>[64]</td>
<td>and Tanzania</td>
<td>Healthcare workers disclosure, ART, and ALHIV psychosocial wellbeing</td>
<td>to ALHIV; peer support groups</td>
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</tbody>
</table>

Abbreviations: ALHIV, adolescents living with HIV; ART, antiretroviral therapy; AYALHIV, adolescents and young adults living with HIV; HCW, healthcare worker; HIV, human immunodeficiency virus; LTFU, lost to follow-up.
Table 2. Areas of intervention for adolescent retention, for which research is needed.

<table>
<thead>
<tr>
<th>Area of Intervention to be Studied</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Evaluation or adaptation of evidence-based interventions from adult HIV literature</td>
<td>Home-based care</td>
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<td>Task shifting</td>
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<td>Broad interventions to make HIV care more responsive to the needs of adolescents</td>
<td>Adolescent-friendly services</td>
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<td>Peer counseling</td>
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<td>Peer support groups</td>
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<td>Disclosure support</td>
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<tr>
<td>Targeted interventions to improve retention for adolescents at high risk of disengagement</td>
<td>Adolescent and family counselling</td>
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<td>Financial interventions</td>
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<td>Intensified follow-up from community health workers</td>
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<td>Interventions for pregnant adolescents</td>
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<td>Interventions for adolescents from key populations</td>
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</table>

Abbreviations: HIV, human immunodeficiency virus.