

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

Leslie A. Enane^{a,b}, Rachel C. Vreeman^{a,b,c}, and Caroline Foster^d

^a The Ryan White Center for Pediatric Infectious Disease and Global Health, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA

^b Academic Model Providing Access to Healthcare (AMPATH), Eldoret, Kenya

^c Department of Child Health and Paediatrics, School of Medicine, College of Health Sciences, Moi University, Eldoret, Kenya

^d 900 and Family Clinics, Departments of GUM/HIV and Paediatrics, Imperial College Healthcare NHS Trust, London, UK

Correspondence to Leslie A. Enane at 1044 W. Walnut St, Rm 402A, Indianapolis, IN, USA. Email: lenane@iu.edu. Tel: +1 (317) 274-8940.

Financial support and sponsorship: The authors received no financial support to write this article.

Conflicts of interest: None.

This is the author's manuscript of the article published in final edited form as:

Enane, L. A., Vreeman, R. C., & Foster, C. (2018). Retention and adherence: global challenges for the long-term care of adolescents and young adults living with HIV. *Current Opinion in HIV and AIDS*, 13(3), 212. <https://doi.org/10.1097/COH.0000000000000459>

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 world wide, 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 leDEA 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 leDEA 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 AYALHIV ages 15-21 [77]. A large multi-country study evaluated factors associated with LTFU of AYALHIV 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 AYALHIV. 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 impactful and relevant to youth, this research should evaluate adolescent needs in local contexts, undertaken through collaborative partnerships with AYALHIV 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.

Acknowledgments

Financial support and sponsorship: The authors received no financial support to write this article.

Conflicts of interest: None.

REFERENCES

1. UNAIDS. UNAIDS Estimates 2017. Available at: <http://aidsinfo.unaids.org>. Accessed 30 November 2017.
 2. UNICEF. For Every Child, End AIDS: Seventh Stocktaking Report, 2016. New York, NY: UNICEF, 2016: 1–92.
 - 3.** Slogrove AL, Mahy M, Armstrong A, Davies M-A. Living and dying to be counted: What we know about the epidemiology of the global adolescent HIV epidemic. *Journal of the International AIDS Society* **2017**; 20:474–12.
- Excellent analysis of the global adolescent epidemic and the further improvements required in national surveillance programs to include adolescent data.
4. Wood SM, Dowshen N, Lowenthal E. Time to Improve the Global Human Immunodeficiency Virus/AIDS Care Continuum for Adolescents: A Generation at Stake. *JAMA Pediatr* **2015**; 169:619–620.
 5. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand RA. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *The Lancet Infectious Diseases* **2014**; 14:627–639.
 6. Fox MP, Rosen S. Systematic review of retention of pediatric patients on HIV treatment in low and middle-income countries 2008–2013. *AIDS* **2015**; 29:493–502.
 7. Zandoni BC, Mayer KH. The Adolescent and Young Adult HIV Cascade of Care in the United States: Exaggerated Health Disparities. *AIDS Patient Care and STDs* **2014**; 28:128–135.
 8. Lamb MR, Fayorsey R, Nuwagaba-Biribonwoha H, et al. High attrition before and after ART initiation among youth (15–24 years of age) enrolled in HIV care. *AIDS* **2014**; 28:559–568.
 9. Reif LK, Bertrand R, Benedict C, et al. Impact of a youth-friendly HIV clinic: 10 years of adolescent outcomes in Port-au-Prince, Haiti. *Journal of the International AIDS Society* **2016**; 19:1–10.
 10. Yehia BR, Rebeiro P, Althoff KN, et al. Impact of Age on Retention in Care and Viral Suppression. *JAIDS Journal of Acquired Immune Deficiency Syndromes* **2015**; 68:413–419.
 11. Colasanti J, Kelly J, Pennisi E, et al. Continuous Retention and Viral Suppression Provide Further Insights Into the HIV Care Continuum Compared to the Cross-sectional HIV Care Cascade. *Clin. Infect. Dis.* **2016**; 62:648–654.
 12. Koech E, Teasdale CA, Wang C, et al. Characteristics and outcomes of HIV-infected youth and young adolescents enrolled in HIV care in Kenya. *AIDS* **2014**; 28:2729–2738.
 13. Auld AF, Agolory SG, Shiraishi RW, et al. Antiretroviral therapy enrollment characteristics and outcomes among HIV-infected adolescents and young adults compared with older adults--seven African countries, 2004-2013. *MMWR Morb. Mortal. Wkly. Rep.* **2014**; 63:1097–1103.
 14. Brinkhof MWG, Pujades-Rodríguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. *PLoS ONE* **2009**; 4:e5790.

15. Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. *JAIDS Journal of Acquired Immune Deficiency Syndromes* **2009**; 51:65–71.
16. WHO. Health for the World's Adolescents: A second chance in the second decade. Geneva, Switzerland: World Health Organization, 2014. Available at: http://www.who.int/maternal_child_adolescent/documents/second-decade/en/. Accessed 29 November 2017.
17. Sawyer SM, Drew S, Yeo MS, Britto MT. Adolescents with a chronic condition: challenges living, challenges treating. *Lancet* **2007**; 369:1481–1489.
18. Sawyer SM, Afifi RA, Bearinger LH, et al. Adolescence: a foundation for future health. *The Lancet* **2012**; 379:1630–1640.
19. Fwemba I, Musonda P. Modelling adverse treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics in Lusaka. *Public Health* **2017**; 147:8–14.
20. Matyanga CMJ, Takarinda KC, Owiti P, et al. Outcomes of antiretroviral therapy among younger versus older adolescents and adults in an urban clinic, Zimbabwe. *public health action* **2016**; 6:97–104.
21. Nachega JB, Uthman OA, del Rio C, Mugavero MJ, Rees H, Mills EJ. Addressing the Achilles' Heel in the HIV Care Continuum for the Success of a Test-and-Treat Strategy to Achieve an AIDS-Free Generation. *Clin. Infect. Dis.* **2014**; 59:S21–S27.
22. Billong SC, Fokam J, Penda CI, et al. Predictors of poor retention on antiretroviral therapy as a major HIV drug resistance early warning indicator in Cameroon: results from a nationwide systematic random sampling. *BMC Infectious Diseases* **2016**; 16:1–9.
23. World Health Organization. Global report on early warning indicators of HIV drug resistance. 2016: 1–64.
24. Olney JJ, Braitstein P, Eaton JW, et al. Evaluating strategies to improve HIV care outcomes in Kenya: a modelling study. *The Lancet HIV* **2016**; 3:e592–e600.
25. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. **2014**; :1–40.
26. Davies M-A, Pinto J. Targeting 90–90–90 – don't leave children and adolescents behind. *Journal of the International AIDS Society* **2015**; 18:1–6.
27. UNAIDS. Ending AIDS: progress towards the 90-90-90 targets. UNAIDS, 2017: 1–198. Available at: http://www.unaids.org/en/resources/documents/2017/20170720_Global_AIDS_update_2017. Accessed 21 November 2017.
- 28.* Davies M-A, Tsondai P, Tiffin N, et al. Where do HIV-infected adolescents go after transfer? – Tracking transition/transfer of HIV-infected adolescents using linkage of cohort data to a health information system platform. *Journal of the International AIDS Society* **2017**; 20:1–9.

Demonstrates how cohort data linkage can facilitate assessment of clinical outcomes post transfer.

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

transmission, AIDS and HIV-related deaths in the UK. London: Public Health England, 2017: 1–51. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/659618/Towards_elimination_of_HIV_transmission_AIDS_and_HIV_related_deaths_in_the_UK.pdf. Accessed 21 November 2017.

HIV surveillance data in the UK by demographic characteristics and geographical region. 90:90:90 targets first achieved in London, England.

30. Centers for Disease Control and Prevention (CDC). CDC HIV Surveillance reports: HIV among youth. Available at: <https://www.cdc.gov/hiv/group/age/youth/index.html>. Accessed 21 November 2017.

31.** Lally MA, van den Berg JJ, Westfall AO, et al. HIV Continuum of Care for Youth in the United States. *JAIDS Journal of Acquired Immune Deficiency Syndromes* **2017**; :1–25.

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

32.** Hussen SA, Chakraborty R, Knezevic A, et al. Transitioning young adults from paediatric to adult care and the HIV care continuum in Atlanta, Georgia, USA: a retrospective cohort study. *Journal of the International AIDS Society* **2017**; 20:21848–9.

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.

33. Foster C, Fidler S. Optimising HIV transition services for young adults. *Current Opinion in Infectious Diseases* **2018**; In Press.

34.* Judd A, Collins IJ, Parrott F, et al. Growing up with perinatal HIV: changes in clinical outcomes before and after transfer to adult care in the UK. *Journal of the International AIDS Society* **2017**; 20:1–10.

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.

35. Lam PK, Fidler S, Foster C. A review of transition experiences in perinatally and behaviourally acquired HIV-1 infection; same, same but different? *Journal of the International AIDS Society* **2017**; 20:16–9.

36. Judd A, Lodwick R, Noguera-Julian A, et al. Higher rates of triple-class virological failure in perinatally HIV-infected teenagers compared with heterosexually infected young adults in Europe. *HIV Med* **2016**; 18:171–180.

37. Collins IJ, Foster C, Tostevin A, et al. Clinical Status of Adolescents with Perinatal HIV at Transfer to Adult Care in the UK/Ireland. *Clin. Infect. Dis.* **2017**; 64:1105–1112.

38. Weijssenfeld AM, Smit C, Cohen S, et al. Virological and Social Outcomes of HIV-Infected Adolescents and Young Adults in The Netherlands Before and After Transition to Adult Care. *Clin. Infect. Dis.* **2016**; 63:1105–1112.

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.

40. Fish R, Judd A, Jungmann E, O'Leary C, Foster C, HIV Young Persons Network (HYPNet). Mortality in perinatally HIV-infected young people in England following transition to adult care: an HIV Young Persons Network (HYPNet) audit. *HIV Med* **2013**; 15:239–244.
 - 41.** Fortenberry JD, Koenig LJ, Kapogiannis BG, Jeffries CL, Ellen JM, Wilson CM. Implementation of an Integrated Approach to the National HIV/AIDS Strategy for Improving Human Immunodeficiency Virus Care for Youths. *JAMA Pediatr* **2017**; 171:687–7.
- 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.
42. Camacho-Gonzalez AF, Gillespie SE, Thomas-Seaton L, et al. The Metropolitan Atlanta community adolescent rapid testing initiative study. *AIDS* **2017**; 31:S267–S275.
 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.
 44. Keller J, Heine A, LeViere AF, et al. HIV patient retention: the implementation of a North Carolina clinic-based protocol. *AIDS Care* **2016**; 29:627–631.
 45. Badawy SM, Kuhns LM. Texting and Mobile Phone App Interventions for Improving Adherence to Preventive Behavior in Adolescents: A Systematic Review. *JMIR Mhealth Uhealth* **2017**; 5:e50–17.
 46. Navarra A-MD, Gwadz MV, Whittemore R, et al. Health Technology-Enabled Interventions for Adherence Support and Retention in Care Among US HIV-Infected Adolescents and Young Adults: An Integrative Review. *AIDS and Behavior* **2017**; 21:3154–3171.
 47. Tanner AE, Mann L, Song E, et al. weCARE: A Social Media–Based Intervention Designed to Increase HIV Care Linkage, Retention, and Health Outcomes for Racially and Ethnically Diverse Young MSM. *AIDS Education and Prevention* **2016**; 28:216–230.
 48. UNAIDS. ALL IN to end the adolescent AIDS epidemic. Geneva: 2016: 1–202.
 49. Mark D, Armstrong A, Andrade C, et al. HIV treatment and care services for adolescents: a situational analysis of 218 facilities in 23 sub-Saharan African countries. *Journal of the International AIDS Society* **2017**; 20:1015–9.
 50. Kim MH, Mazenga AC, Yu X, et al. High self-reported non-adherence to antiretroviral therapy amongst adolescents living with HIV in Malawi: barriers and associated factors. *Journal of the International AIDS Society* **2017**; 20:1–12.
 51. Shisana O, Rehle T, Simbayi LC, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. **2015**; :1–198.
 - 52.* Zanoni BC, Archary M, Buchan S, Katz IT, Haberer JE. Systematic review and meta-analysis of the adolescent HIV continuum of care in South Africa: the Cresting Wave. *BMJ Glob Health* **2016**; 1:e000004–9.

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.

53. Leroy V, Tanser F, Vreeman R, et al. Access to antiretroviral initiation among HIV-infected children aged 0-19 years in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Global Network, 2004-2014. Presented at: International AIDS Society. Durban: 2016.
54. Nuwagaba-Biribonwoha H, Kiragga A, Yiannoutsos CT, et al. Teenage pregnancy: a critical barrier to retention on antiretroviral therapy. Presented at: Conference on Retroviruses and Opportunistic Infections. Seattle: 2017: 1–1.
- 55.** McHugh G, Simms V, Dauya E, et al. Clinical outcomes in children and adolescents initiating antiretroviral therapy in decentralized healthcare settings in Zimbabwe. *Journal of the International AIDS Society* **2017**; 20:21843–9.

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.

56. Sohn AH, Vreeman RC, Judd A. Tracking the transition of adolescents into adult HIV care: a global assessment. *Journal of the International AIDS Society* **2017**; 20:1–3.
57. Dahourou DL, Gautier-Lafaye C, Teasdale CA, et al. Transition from paediatric to adult care of adolescents living with HIV in sub-Saharan Africa: challenges, youth-friendly models, and outcomes. *Journal of the International AIDS Society* **2017**; 20:1–16.
- 58.** Williams S, Renju J, Ghilardi L, Wringe A. Scaling a waterfall: a meta-ethnography of adolescent progression through the stages of HIV care in sub-Saharan Africa. *Journal of the International AIDS Society* **2017**; 20:1–17.

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.
60. Petersen I, Bhana A, Myeza N, et al. Psychosocial challenges and protective influences for socio-emotional coping of HIV+ adolescents in South Africa: a qualitative investigation. *AIDS Care* **2010**; 22:970–978.
61. Busza J, Dauya E, Bandason T, Mujuru H, Ferrand RA. "I don't want financial support but verbal support." How do caregivers manage children's access to and retention in HIV care in urban Zimbabwe? *Journal of the International AIDS Society* **2014**; 17:1–9.
62. Mburu G, Ram M, Oxenham D, Haamujompa C, Iorpenda K, Ferguson L. Responding to adolescents living with HIV in Zambia: A social–ecological approach. *Children and Youth Services Review* **2014**; 45:9–17.
63. Luseno WK, Iritani B, Zietz S, et al. Experiences along the HIV care continuum: perspectives of Kenyan adolescents and caregivers. *Afr J AIDS Res* **2017**; 16:241–250.
64. Midtbø V, Shirima V, Skovdal M, Daniel M. How disclosure and antiretroviral therapy help HIV-infected adolescents in sub-Saharan Africa cope with stigma. *African Journal of AIDS*

Research **2012**; 11:261–271.

- 65.** Dow DE, Turner EL, Shayo AM, Mmbaga B, Cunningham CK, O'Donnell K. Evaluating mental health difficulties and associated outcomes among HIV-positive adolescents in Tanzania. *AIDS Care* **2016**; 28:825–833.

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

- 66.* Vreeman RC, McCoy BM, Lee S. Mental health challenges among adolescents living with HIV. *Journal of the International AIDS Society* **2017**; 20:1–10.

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.

67. Vreeman RC, Scanlon ML, McHenry MS, Nyandiko WM. The physical and psychological effects of HIV infection and its treatment on perinatally HIV-infected children. *Journal of the International AIDS Society* **2015**; 18:1–15.
68. Mburu G, Hodgson I, Kalibala S, et al. Adolescent HIV disclosure in Zambia: barriers, facilitators and outcomes. *Journal of the International AIDS Society* **2014**; 17:1–9.
69. McHugh G, Rylance J, Mujuru H, et al. Chronic Morbidity Among Older Children and Adolescents at Diagnosis of HIV Infection. *J. Acquir. Immune Defic. Syndr.* **2016**; 73:275–281.
70. Ferrand RA, Luethy R, Bwakura F, Mujuru H, Miller RF, Corbett EL. HIV Infection Presenting in Older Children and Adolescents: A Case Series from Harare, Zimbabwe. *Clinical Infectious Diseases* **2007**; 44:874–878.
71. Busza J, Strode A, Dauya E, Ferrand RA. Falling through the gaps: how should HIV programmes respond to families that persistently deny treatment to children? *Journal of the International AIDS Society* **2016**; 19:1–3.
72. MacPherson P, Munthali C, Ferguson J, et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. *Trop Med Int Health* **2015**; 20:1015–1032.
- 73.** Murray KR, Dulli LS, Ridgeway K, et al. Improving retention in HIV care among adolescents and adults in low- and middle-income countries: A systematic review of the literature. *PLoS ONE* **2017**; 12:e0184879–22.

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.

74. Govindasamy D, Meghij J, Negussi EK, Baggaley RC, Ford N. Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings – a systematic review. *Journal of the International AIDS Society* **2014**; 17:1–24.
75. Teasdale CA, Alwar T, Chege D, Fayorsey R, Hawken MP, Abrams EJ. Impact of Youth and Adolescent Friendly Services on Retention of 10–24-Year-Olds in HIV Care and Treatment Programs in Nyanza, Kenya. *JAIDS Journal of Acquired Immune Deficiency Syndromes* **2016**; 71:e56–e59.

76. Ojwang VO, Penner J, Blat C, Agot K, Bukusi EA, Cohen CR. Loss to follow-up among youth accessing outpatient HIV care and treatment services in Kisumu, Kenya. *AIDS Care* **2015**; 28:500–507.
77. Ruria EC, Masaba R, Kose J, et al. Optimizing linkage to care and initiation and retention on treatment of adolescents with newly diagnosed HIV infection. *AIDS* **2017**; 31 Suppl 3:S253–S260.
78. Judd A, Sohn AH, Collins IJ. Interventions to improve treatment, retention and survival outcomes for adolescents with perinatal HIV-1 transitioning to adult care. *Current Opinion in HIV and AIDS* **2016**; 11:477–486.
79. Lee L, Yehia BR, Gaur AH, et al. The Impact of Youth-Friendly Structures of Care on Retention Among HIV-Infected Youth. *AIDS Patient Care and STDs* **2016**; 30:170–177.
80. Arnesen R, Moll AP, Shenoi SV. Predictors of loss to follow-up among patients on ART at a rural hospital in KwaZulu-Natal, South Africa. *PLoS ONE* **2017**; 12:e0177168–12.
81. Machine EM, Gillespie SL, Homedes N, et al. Lost to follow-up: failure to engage children in care in the first three months of diagnosis. *AIDS Care* **2016**; :1–9.
82. Keane J, Pharr JR, Buttner MP, Ezeanolue EE. Interventions to Reduce Loss to Follow-up During All Stages of the HIV Care Continuum in Sub-Saharan Africa: A Systematic Review. *AIDS and Behavior* **2016**; 21:1745–1754.
83. Mavhu W, Willis N, Mufuka J, et al. Evaluating a multi-component, community-based program to improve adherence and retention in care among adolescents living with HIV in Zimbabwe: study protocol for a cluster randomized controlled trial. *Trials* **2017**; 18:1–11.
- 84.** Ronen K, McGrath CJ, Langat AC, et al. Gaps in Adolescent Engagement in Antenatal Care and Prevention of Mother-to-Child HIV Transmission Services in Kenya. *J. Acquir. Immune Defic. Syndr.* **2017**; 74:30–37.

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.

85. Lall P, Lim SH, Khairuddin N, Kamarulzaman A. Review: An urgent need for research on factors impacting adherence to and retention in care among HIV-positive youth and adolescents from key populations. *Journal of the International AIDS Society* **2015**; 18:1–13.
86. Busza J, Mtetwa S, Mapfumo R, Hanisch D, Wong-Gruenwald R, Cowan F. Underage and underserved: reaching young women who sell sex in Zimbabwe. *AIDS Care* **2016**; 28:14–20.
87. Delany-Moretwe S, Cowan FM, Busza J, Bolton-Moore C, Kelley K, Fairlie L. Providing comprehensive health services for young key populations: needs, barriers and gaps. *Journal of the International AIDS Society* **2015**; 18:538–12.
88. Oliveras Rodriguez CA. Engaging adolescents with HIV to ensure better health and more informed research. *Journal of the International AIDS Society* **2017**; 20:1–2.
89. Idele P, Gillespie A, Porth T, et al. Epidemiology of HIV and AIDS among adolescents: current status, inequities, and data gaps. *J. Acquir. Immune Defic. Syndr.* **2014**; 66 Suppl 2:S144–53.

90. Mills EJ, Nachega JB, Buchan I, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA* **2006**; 296:679–690.
91. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to Antiretroviral Therapy for Pediatric HIV Infection: A Qualitative Systematic Review With Recommendations for Research and Clinical Management. *Pediatrics* **2007**; 119:e1371–e1383.
92. Vreeman RC, Wiehe SE, Pearce EC, Nyandiko WM. A Systematic Review of Pediatric Adherence to Antiretroviral Therapy in Low- and Middle-Income Countries. *The Pediatric Infectious Disease Journal* **2008**; 27:686–691.
93. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-Report Measures of Antiretroviral Therapy Adherence: A Review with Recommendations for HIV Research and Clinical Management. *AIDS and Behavior* **2006**; 10:227–245.
94. Tu W, Nyandiko WM, Liu H, et al. Pharmacokinetics-based adherence measures for antiretroviral therapy in HIV-infected Kenyan children. *Journal of the International AIDS Society* **2017**; 20:1–6.
95. Vreeman RC, Nyandiko WM, Liu H, et al. Comprehensive Evaluation of Caregiver-Reported Antiretroviral Therapy Adherence for HIV-Infected Children. *AIDS and Behavior* **2015**; 19:626–634.
96. Chawana TD, Gandhi M, Nathoo K, et al. Defining a Cutoff for Atazanavir in Hair Samples Associated With Virological Failure Among Adolescents Failing Second-Line Antiretroviral Treatment. *J. Acquir. Immune Defic. Syndr.* **2017**; 76:55–59.
97. Pintye J, Bacchetti P, Teeraananchai S, et al. Brief Report: Lopinavir Hair Concentrations Are the Strongest Predictor of Viremia in HIV-Infected Asian Children and Adolescents on Second-Line Antiretroviral Therapy. *J. Acquir. Immune Defic. Syndr.* **2017**; 76:367–371.
98. Okatch H, Beiter K, Eby J, et al. Brief Report: Apparent Antiretroviral Overadherence by Pill Count is Associated With HIV Treatment Failure in Adolescents. *J. Acquir. Immune Defic. Syndr.* **2016**; 72:542–545.
99. Shaw S, Amico KR. Antiretroviral Therapy Adherence Enhancing Interventions for Adolescents and Young Adults 13-24 Years of Age: A Review of the Evidence Base. *J. Acquir. Immune Defic. Syndr.* **2016**; 72:387–399.
100. Rongkavilit C, Naar-King S, Wang B, et al. Motivational Interviewing Targeting Risk Behaviors for Youth Living with HIV in Thailand. *AIDS and Behavior* **2013**; 17:2063–2074.
101. Haberer JE, Sabin L, Amico KR, et al. Improving antiretroviral therapy adherence in resource-limited settings at scale: a discussion of interventions and recommendations. *Journal of the International AIDS Society* **2017**; 20:1–15.
102. Kanters S, Vitoria M, Doherty M, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. *The Lancet HIV* **2016**; 3:e510–e520.
- 103.** World Health Organization. HIV Drug Resistance Report 2017. Geneva: 2017: 1–82. Available at: <http://apps.who.int/iris/bitstream/10665/255896/1/9789241512831-eng.pdf?ua=1>. Accessed 21 November 2017.

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

Study	Country	Populations	Area of study	Barriers	Facilitators
Wolf [59]	Kenya	LTFU AYALHIV 15-21 years; Community health workers who work with LTFU AYALHIV; Educators from schools attended by LTFU AYALHIV	Reasons for LTFU among AYALHIV	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.	Not specifically studied.
Petersen [60]	South Africa	ALHIV 14-16 years; Caregivers of ALHIV	Psychosocial challenges and protective influences for coping in ALHIV	Death of biological parents; coming to terms with HIV infection; external stigma and discrimination; disclosure challenges; lack of financial, family, or social support.	ART; HIV education; future orientation; social support; financial support.
Busza [61]	Zimbabwe	Caregivers of children ages 6-15 engaged in care; Key informants from community organizations providing adherence support	Factors influencing linkage and retention to inform design of a community-based intervention to increase retention of children living with HIV	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.	Family openness; availability of practical assistance and psychosocial support from community members
Mburu [62]	Zambia	ALHIV 10-19 years; Healthcare providers of ALHIV; Caregivers of ALHIV	ALHIV experiences within a socioecological model	Internalized stigma; external stigma and discrimination in schools; inflexible clinic hours, staff shortages; lack of policies addressing ALHIV.	Resilience; family and peer support; livelihood, nutritional support; psychological support
Luseno [63]	Kenya	ALHIV 15-19 years, in care, out of care, or never enrolled; Caregivers of ALHIV	ALHIV experiences with HIV services along the care cascade	ART side effects; pill burden; limited access to clean water and nutrition	Supportive environments in family, school, health facility
Midtbø	Botswana	ALHIV;	Relationship between	External stigma	HIV status disclosure

[64]	and Tanzania	Healthcare workers	disclosure, ART, and ALHIV psychosocial wellbeing		to ALHIV; peer support groups
------	-----------------	--------------------	--	--	----------------------------------

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.

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

Abbreviations: HIV, human immunodeficiency virus.