Adolescents and young adults with HIV and unsuppressed viral load: where do we go from here?

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Purpose of review
Adolescents and youth living with HIV (AYLHIV) have worse outcomes at all stages of the care cascade when compared with adults, yet adolescents and youth with unsuppressed viral load are typically excluded from phase 3 studies of novel HIV therapeutic agents and emerging strategies. Long-acting agents have the potential to radically change outcomes for young people struggling with adherence to daily oral HIV medications.

Recent findings
1.5 million children aged less than 15 years live with HIV and more than 100 000 acquire HIV perinatally every year. Adolescents and youth aged 10–24 years comprise ~40% of global incident HIV infections. Rates of viral suppression among AYLHIV vary markedly from 44 to 88%, resulting in morbidity and risks of transmission to partners and infants. Virological failure is mostly due to poor adherence, and AYLHIV express high levels of interest and acceptability of alternatives to oral daily medications, such as long-acting antiretroviral formulations. Emerging data regarding their use in populations with unsuppressed viral load are encouraging.

Summary
AYLHIV, including populations without virologic suppression, must be prioritized for the programmatic implementation and research of long-acting HIV drugs and other therapeutic strategies to prevent morbidity and mortality and to ultimately end the HIV epidemic.

Keywords
adolescent, antiretroviral therapy, HIV, virological failure, young people

INTRODUCTION

Adolescents and youth aged 10–24 years comprise significant number of people affected by the HIV epidemic, accounting for an estimated three million people living with HIV globally [1]. Almost half a million new infections were estimated to occur among young people aged 10–24 years in 2022, approaching 40% of annual new infections globally [2]. Significant gender-based differences exist among newly diagnosed young people with adolescent girls and young women disproportionately affected in resource-limited settings, conversely young MSM in resource-rich Western countries [3].

One of the biggest challenges in tackling the HIV epidemic among young people is the diversity of definitions due to the age-based overlap within pediatric and adult populations. Global stakeholders typically define adolescents as aged 10–19 years; young people as aged 10–24 years with youth represented by those aged 15–24 years. An alternative approach to differentiate by developmental periods of preadolescence, early, middle, and late adolescence and young adulthood, though age definitions for developmental stages vary greatly globally [4▪]. Furthermore, for decades, an arbitrary age cut-off at 15 years has been used to define pediatric (0–14 years) and adult (>15 years) in HIV programming and data collection. The lack of disaggregated data beyond this cut-off proved a significant obstacle in evaluating the epidemiology and

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KEY POINTS

- Adolescents and young people have worse outcomes at all stages of the HIV care cascade.
- Virological failure is common among adolescents and young people with HIV and leads to transmissions and to HIV-associated morbidity and mortality.
- Adolescents aged 10–17 years with weighing at least 35 kg should be included as standard within adult phase 3 trials of novel therapeutic approaches to treat HIV that facilitate adherence.
- Adolescents and young people with unsuppressed viral load should be prioritized for long-acting ART studies and implementation strategies.

outcomes among adolescents and young people. Encouragingly, in selected recent global programmatic reports, more differentiated analysis by age group (<10, 10 to <19 and ≥20 years) has been included, which allows for better identification of adolescents [5▪▪]. Nevertheless, the ongoing congregation of data on young people with older adults represents an unmet knowledge gap and limits our capacity to serve their specific needs.

Overlapping with this age-based conundrum is the mode of HIV acquisition that poses another challenge in differentiating two epidemiologically and clinically diverse categories of young people with perinatally (PaHIV) and nonperinatally acquired (nPHIV) infection. Within global programmatic data, the transmission mode is frequently assigned based on the age with presumed PaHIV in those aged less than 15 years and is largely lost in adult data except for targeted research studies and data analyses [1]. Given the current 1.5 million children less than 15 years living with HIV, and estimated survival of pediatric populations, the adult population of people with PaHIV is set to reach several millions during the coming decades [1,6]. Moreover, the impact of PaHIV infection on long-term health in adult life is gaining increased attention as we learn more about the long-term effects of *in utero*, childhood and adolescent HIV and antiretroviral therapy (ART) exposure. The ability to identify and differentiate young people by their mode of HIV acquisition is needed to better engage them in the prospective research studies on long-term health outcomes and to better tailor their care, treatment, and support services.

Viral suppression is often suboptimal for YHIV specifically. Despite significant advances in ART formulations, availability and coverage, children aged less than 10 years, who represent future adolescents with PaHIV, and adolescents aged 10–19 years have lower viral suppression rates (84 and 88%, respectively) compared with adults (96%) [5▪▪]. In six high-burden African countries with more than one Population-based HIV Impact Assessment (PHIA) survey during 2015–2022, youth aged 15–24 years had the lowest viral suppression rates compared with adults, ranging from 54.7% in Uganda to 77.1% in eSwatini [5▪▪]. Unfortunately, virological failure and immune suppression, comorbidities and hospitalizations among young people living with HIV are endemic to all regions of the world, including resource-rich countries [7,8▪,9,10,11▪]. These persistent outcome disparities pose significant threats to the global targets for HIV elimination and fuel ongoing transmissions and high morbidity and mortality among this vulnerable population.

RETENTION IN CARE

The period of transition from pediatric to adult healthcare services has been associated with increased rates of loss to follow-up and virological failure with potential for immune deterioration and increased transmission to partners and offspring [12]. Retention following unplanned transition falls rapidly, with those who exit pediatric care with immunosuppression and/or viremia mostly at risk, resulting in HIV-associated morbidity and mortality [13▪,14▪]. Despite high rates of engagement in care, European PaHIV cohorts report posttransition mortality up to 10 times the aged matched population, a picture not dissimilar in sub-Saharan Africa and Thailand [14▪,15▪▪,16]. Mortality in the International Epidemiologic Databases to Evaluate AIDS (LeDEA) PaHIV cohort was the highest in infancy, decreased during childhood but rose again in early adulthood [17]. In stark contrast to adults acquiring HIV in later life, the causes of death in young people with HIV in all settings are almost all due to end-stage AIDS events, primarily opportunistic infections, with HIV-associated malignancies and a small number of suicides reported [14▪,18▪]. Health utilization, including hospital admissions increases with age and is higher in YPPaHIV when compared with younger children and adults [11▪,19]. The consequences of life-long exposure to HIV and ART are emerging with rates of dyslipidemia, obesity, metabolic syndrome and nonalcoholic fatty liver disease higher than aged and ethnically matched controls without HIV [20▪,21▪▪,22,23▪]. Whilst yet to reach the age where cardiovascular events emerge, warning signs include increased carotid intima–media thickness, a biomarker of subclinical atherosclerosis, increased coronary artery thickening, raised inflammatory markers and hypertension [14▪,20▪,21▪▪,22,24]. Although recent data highlight

the benefits of statins for adults greater than 40 years, for young people, any additional pill burden and long-term statin use have to be balanced with the primary goal of maintaining virological suppression [25▪▪]. Suicide is a leading cause of death in young people globally and young people with HIV have an increased risk of mental health diagnoses, most frequently not only anxiety and depression, but also psychosis and substance use, highlighting the importance of integrated mental health and social care services for YPHIV in all settings [26▪,27▪,28,29▪] (Fig. 1).

TREATMENT OUTCOMES: PERINATALLY ACQUIRED HIV

When compared with adults, adolescents have poorer access to ART, lower rates of viral suppression and higher rates of disengagement from care; however, outcomes vary widely by setting even in well resourced regions [5▪▪,14▪]. In a United States, adult perinatal cohort ($n = 444$, median age 21.3 years), 44% were on suppressive ART compared with 81% in a Dutch cohort aged 18–24 years, mirroring previous data from small European cohorts [30▪,31,32▪]. Rates of triple class resistance are higher in young people with PaHIV when compared with nPHIV, a reflection of the years of ART exposure, limited pediatric drugs and formulations, inadequate dosing during growth, drug stock outs and for those born in earlier calendar years, regimens with a lower genetic barrier to resistance. An Italian PaHIV cohort (18–30+ years) reported rates of dual (41%), triple (20%) and four class resistance (6%) with 7% having at least one mutation conferring integrase resistance by 2019, comparable to Spanish PaHIV cohort (15% triple class resistance) although twice that of a UK cohort (6%) [31,33,34]. Extensive prior exposure to nonnucleoside reverse transcriptase inhibitors (NNRTI), the mainstay of pediatric ART in many settings prior to the roll out of dolutegravir (DTG), has resulted in extensive NNRTI resistance rendering currently approved long-acting injectable (LAI) options of cabotegravir (CAB) and rilpivirine (RPV) unsuitable [35]. In Cameroon, 34% of PaHIV adolescents ($n = 270$) were failing NNRTI-based ART, 90% with NNRTI drug resistance mutations (DRM) increasing the risk of transmitted drug resistance (TDR) to partners and offspring [36,37▪,38▪,39▪▪].

Whilst overall rates remain low, integrase resistance is beginning to emerge [40▪,41]. In children and adolescents (median age 10 years) with virological failure on DTG-ART in Malawi, although most resuppressed with adherence counselling, of those with persistent virological failure, 13.5% had integrase DRMS [42]. Sequencing beyond first-line/second-line ART based around dolutegravir requires global access to resistance testing and third-line agents, including boosted protease inhibitors and novel classes [43]. For the majority, virological failure is driven by suboptimal adherence to daily oral therapy and not drug resistance and being highly treatment-experienced does not necessarily equate to harboring multiclass drug resistance

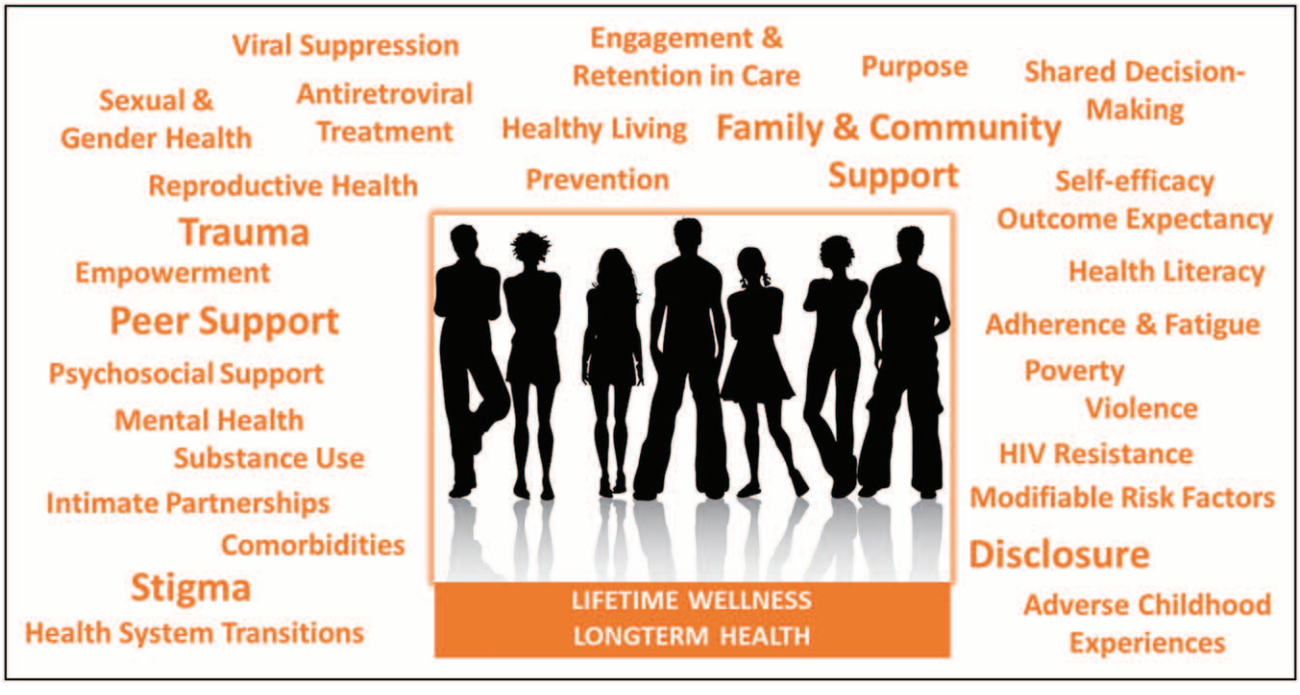

FIGURE 1. Integrated longitudinal approach to care of youth with unsuppressed viral load.

(MDR). For the small number of young people with MDR, the importance of early inclusion in phase 3 clinical trials of novel agents in parallel with adults cannot be over stated [44▪] (Table 1). Similarly, for many young people, poor adherence to oral therapy does not equate to poor attendance and the desire for, and potential benefits of, long-acting ART delivery systems cannot be underestimated for young people, some of whom have struggled with daily oral medication for their entire lives [45▪,46▪▪].

TREATMENT OUTCOMES: NONPERINATALLY ACQUIRED HIV

Young people with nonperinatally acquired HIV (YPnPHIV) are a diverse group acquiring HIV via sexual exposure (consensual and nonconsensual), injection drug use, and a smaller proportion through blood transfusion, female genital mutilation and other modalities [47]. Although there have been declines in overall rates of acquisition of HIV among youth, transmission continues particularly within key populations (e.g. transgender youth, people who inject drugs or those who engage in sex work or transactional sex). For example, in Eastern Europe and Central Asia, injection drug use accounts for 40% of new infections among young people who are less likely to engage in or negotiate well tolerated injection practices, and well tolerated injection programs [48,49]. Adverse childhood experiences (ACES) directly correlate with negative health outcomes; and YPnPHIV are more likely to report negative life experiences than their PaHIV counterparts (39 vs. 16%), which may affect their

Table 1. Research priorities to be addressed for adolescents and youth with unsuppressed viral load stratified by cascade of HIV care and WHO age bands

	10–14	15–19	20–24
Early diagnosis and linkage to care[a]			
Implementation of routine BBV screening within community and secondary care	✓	✓	✓
Optimization of social media strategies to increase screening uptake	✓	✓	✓
Addressing age-determined consent policies	✓	✓	
Removing structural barriers to linkage to care, including for vulnerable groups[b]	✓	✓	✓
Retention in care[a]			
Multimodal interventions optimizing youth friendly services, including peers	✓	✓	✓
Impact of economic strengthening and removing financial barriers to care		✓	✓
Optimization of transition strategies, including peers and third sector		✓	✓
Optimized use of technology to support adherence and retention in care	✓	✓	✓
Consideration of community-based strategies for care delivery	✓	✓	✓
ART treatment strategies[a]			
Inclusion of adolescents aged 10-17 years weighing ≥35 kg within adult phase 3 trials, including ARTs and bNAbs	✓	✓	
Efficacy and safety of LA-CAB/RPV direct to inject for adolescents	✓	✓	
Efficacy and safety of LA-CAB/RPV in regions with high past pediatric NNRTI use	✓	✓	✓
Efficacy and safety of CAB/LEN for NNRTI resistance/exposure	✓	✓	✓
Efficacy and safety of emerging agents such as bNAbs and vaccines as part of LA strategies for adolescents	✓	✓	✓
Feasibility and implementation of Youth Friendly injection services for prevention and treatment	✓	✓	✓
Efficacy and safety of LA-ART combined with long-acting contraception		✓	✓
Management of transition to adult care on LA-ART		✓	✓
Epidemiology of emerging integrase drug resistance in adolescents failing ART or PrEP	✓	✓	✓
Epidemiology of transmitted drug resistance to partners and offspring		✓	✓
Access to and efficacy of PIs and novel agents following INSTI resistance	✓	✓	✓

ART, antiretroviral therapy; BBV, blood born virus; bNAbs, broadly neutralizing antibodies; INSTI, integrase strand transfer inhibitor; LA-ART, long-acting antiretroviral therapy; LA-CAB/RPV, long-acting cabotegravir rilpivirine; LEN, lenacapavir; NNRTI, nonnucleoside reverse transcriptase inhibitors.
[a]Meaningful inclusion of adolescents and young people in developing the research agenda and within clinical trial design.
[b]Including but not limited to; incarcerated young people, orphans, street youth, adolescents in social care, adolescents who inject drugs, adolescent MSM and transgender youth, adolescents undertaking transactional sex and sex workers.

risk of HIV acquisition and their outcomes once diagnosed [50]. Further, if their acquisition risk is accompanied by stigma, discrimination and criminalization (e.g. nonheteronormative sex, substance use), the likelihood of engagement in care may be further reduced. YPnPHIV have the lowest rates of testing, engagement and retention in care, ART initiation, and viral suppression compared with other populations, including PaHIV [1–3,32▪]. Significant comorbidities including mental health (e.g. depression and anxiety) compounded by their HIV, further impact on engagement in healthcare and adherence to ART resulting in HIV-associated morbidity and mortality.

Despite more recent HIV acquisition, YPnPHIV can have both TDR and /or acquired drug resistance. The prevalence of TDR (9–18.4%) reported in YPnPHIV was of greater concern when NNRTIs were the mainstay of first-line therapy. With INSTI regimens being first line across guidelines globally, YPnPHIV are less likely to have been exposed to or have resistance to NNRTIs or protease inhibitors. A recent Dutch study reported rates of viral failure of 19% among YPnPHIV compared with 9% among PaHIV [32▪]. Reports of INSTI resistance have ranged from 3.9 to 8.6%, and as high as 19.6% among treatment-experienced individuals who have transitioned to INSTI-based regimens in the setting of high viral loads [51]. INSTI resistance can be transmitted and has real-world implications for current and future ART options, including long-acting ART.

LONG-ACTING THERAPY FOR ADOLESCENTS AND YOUNG PEOPLE

With the many intersecting challenges that can impact adherence to oral ART, young people are a priority group for considering how to best employ long-acting and extended delivery (LAED) treatment strategies from currently available long-acting injectables to future modalities inclusive of LA-ART delivered by different routes (injectable, implantable and oral) and nonantiretroviral strategies [e.g. broadly neutralizing antibodies (bNAbs), vaccines and cure interventions] [52] (Table 1) Further, the ability to combine strategies [e.g. LAI-ART with long-acting reversible contraceptives (LARC) for women] should be of high priority. young people demonstrate high interest in injectable ART. In a US survey of 303 YHIV (26% PaHIV and 74% nPHIV), 88% reported probable/definite willingness to use LAI-ART with significantly higher interest among nonsuppressed young people [53]. Interest/willingness increased with decreased frequency of administration and among adolescent female individuals with prior LARC use. However, only one in eight South African young people expressed a preference for LAI-ART over single tablet regimens with a preference for LAI-ART associated with stock-outs, side effects, stigma, pill burden and recent ART initiation [54]. LAI-ART CAB/RPV is approved from 12 years and at least 35 kg for those who have attained viral suppression [55]. The More Options for Children and Adolescents (MOCHA) Study [IMPAACT 2017 (NCT03497676)] enrolled virally suppressed 12–17 year-olds from Botswana, South Africa, Thailand and United States and demonstrated comparable pharmacokinetic parameters to adults, with high acceptability and tolerability [56▪▪,57▪].

Although these findings are game-changing for adolescents, current licensing excludes young people with unsuppressed viral load at risk for further sequelae. As nonadherence plagues other vulnerable populations, there are increasing reports of efficacy of LAI-ART in nonsuppressed adults [58–60]. Given the desperate need for options for adolescents, there are emerging reports of off-label CAB/RPV and other combinations, such as cabotegravir and lenacapravir (LEN) use for young people and adults with viremia [59,61▪]. Rousseau *et al.* reported their single center's use of CAB/RPV (without oral lead-in) among 19 young people (21% PaHIV; 79% nPHIV) aged 13–25 years with baseline viremia (76–390 621 copies/ml) and no prior genotypic resistance. All achieved viral suppression by 3 months, maintained for a median of 7 months at the time of publication. Only two missed their injection visit windows with the team able to address and continue them on LAI-ART, countering the narrative that young people will not be able to adhere to LAI-ART schedules.

Uptake and rollout of LAI-ART is not without its challenges, which include but are not limited to manufacturing cost, delivery, payment structure and distribution and the development of resistance, which can compromise downstream treatment options as well as TDR. However, although these challenges require consideration in implementation planning, they are not a rationale to exclude the high-priority population of young people with viremia from the studies and ultimately clinical practice rollout. Instead, there should be intentional forethought, including expertise from adolescent-focused clinicians and researchers and young people themselves into what would be needed to effectively provide long-acting options for youth with viremia. Toward that aim, the Young People's Lusaka Declaration, stated that 'offering alternative options beyond daily oral medications, injectable treatments and preventions provide young people the opportunity to choose a treatment or prevention modality that best suits their lifestyle and preferences, fostering autonomy and self-care

and decreasing exposure to stigma', declare their support for 'the development, accessibility, affordability, and integration of HIV injectable treatments and preventions as an essential component of HIV treatment and care', and call on all stakeholders to mobilize to make this a reality [62▪▪]. The recently updated International AIDS society-US guidelines issues a recommendation for considering CAB/RPV LAI-ART for those without virologic suppression in certain settings, including consistent inability to take oral ART despite optimal support, high risk for HIV progression and intensive clinical follow-up and case management [63▪▪]. Many young people meet these criteria and should be considered for these modalities. The best implementation strategies for LAI-ART among young people without virologic suppression are yet to be defined within clinical trials and clinical practice settings. It is critically important to closely monitor efficacy and safety and ensure real-world data collection as we aim to optimize implementation of LAI-ART for this population.

Long-acting medication has felt like a huge weight off my shoulders by no longer having to feel guilty about missing my tablets because I couldn't bring myself to take them while simultaneously worrying about the effects on my health.

Young person aged 23 when started on LAI-ART

MODELS OF CARE FOR YOUNG PEOPLE WITH UNSUPPRESSED VIRAL LOAD

Adolescents and young people with unsuppressed viral load face multiple complex challenges but these are surmountable with dedicated efforts to facilitate their access to care, assure psychosocial support and enable social protection targeting poverty, stigma and violence [64▪▪] (Fig. 1). Health services, including LA-ART, must be provided in a confidential, nonstigmatizing, respectful, motivating, adolescent-friendly or youth-friendly way that integrates community and peers support, violence prevention, mental health and sexual and reproductive health screening and services [64▪▪,65–67,68▪▪,69,70▪,71▪,72,73]. Key elements include tailored case management, trained community adolescent treatment supporters and peer-led support groups, as well as innovative technology-based interventions, for example, remote coaching sessions informed by real-time adherence data, a comprehensive mobile application for a community forum, topical blogs, medication reminders, and private chat, interactive and tailored SMS reminders and two-way/interactive SMS with peer navigation [70▪,74].

Support groups and individual counselling are the two most used interventions across the globe, followed by the technology-based interventions, family support and peer support, and most interventions were packages with multiple components [70▪]. Gender-sensitive approach for implementing the treatment and support services has been highlighted in several studies from sub-Saharan Africa [68▪▪,75]. Growing evidence from randomized clinical trials suggests that multilevel service delivery model, which include interventions at patient, provider and clinic levels, can improve outcomes [71▪,76–80].

Design of the programs, services and research projects, targeting the most vulnerable young people, requires multidisciplinary collaboration of diverse stakeholders, including funders. Equitable partnership with young people is critically important to assure their engagement in the design, delivery and evaluation of the research agenda and the programs that affect them. Some excellent examples of youth engagement in the research include ATN (https://www.atnconnect.org/community-advisory-board/), PENTA (https://penta-id.org/youth-engagement-at-penta/) and the Africa CDC Youth Advisory Team for Health (YAT4H) [73,81–84]. Although these developments are encouraging, moving forward, it is crucially important to assure sustainable youth engagement in the HIV research and programming with inclusive representation of adolescents and youth with unsuppressed viral load to better understand and address their needs.

CONCLUSION

Adolescents and young people living with HIV have poorer outcomes at all stages of the care cascade when compared with adults, irrespective of their route of HIV acquisition. Whilst many young people manage their health well, a significant proportion struggle with daily adherence to oral medication, resulting in sustained viremia, HIV-associated mortality and onward transmission to partners and children. Adolescents without viral suppression must have equitable access to the clinical trials of LA-ART and new treatment modalities alongside adults and other challenging populations such as pregnant individuals. Ultimately, ending the HIV epidemic will not be an attainable goal if young people with unsuppressed viremia are left behind. They must be prioritized for programmatic implementation and research on long-acting HIV therapeutic strategies.

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Conflicts of interest

There are no conflicts of interest.

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