HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2018 May ; 13(3): 179–186. doi:10.1097/COH.0000000000000450.

Growth and Pubertal Development in HIV-Infected Adolescents

Paige L. Williams, PhD[1] and **Julie Jesson, PhD**[2]

[1]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

[2]Inserm U1027, Université Toulouse 3 Paul Sabatier, Toulouse, France

Abstract

Purpose of Review—We present an overview of recent research in the inter-related areas of growth and pubertal development among adolescents with HIV. Growth deficits early in childhood can lead to delayed puberty, with subsequent effects on pubertal growth spurts and bone health.

Recent Findings—Impaired growth remains a critical concern, particularly in low resource settings, where stunting, wasting and underweight remain pervasive. Antiretroviral treatment (ART) initiation results in improved growth, with greatest growth recovery in the first years and more improvement in weight than in height. However, even years after ART initiation, growth deficits persist in low resource settings (LRS), and adolescents appear at particularly increased risk. The high prevalence of stunting translates to delays in pubertal onset and sexual maturity. In contrast, HIV-infected adolescents in developed countries do not demonstrate persistent wasting, yet still have delayed pubertal development. Impaired growth increases the risk for mortality, virologic failure, and abnormal bone health, as well as increased depression and stigma.

Summary—Early initiation of ART across all age groups regardless of immunological status is essential for restoring growth. Coordination of ART initiation, nutritional supplementation programs, and concurrent prophylaxis is required to ameliorate growth deficits and pubertal delays, particularly in LRS.

Keywords

HIV; adolescents; growth; puberty; malnutrition

INTRODUCTION

Approximately 2.1 million adolescents aged 10–19 years were living with HIV in 2016, with 90% of these residing in low resource settings (LRS) [1]. Adolescents with HIV infection often have impaired growth, with frequent stunting (low height for their age), underweight (low weight for age), and wasting (low weight for height), as compared to World Health Organization (WHO) or Centers for Disease Control and Prevention (CDC) growth standards [2,3]. Children with perinatally-acquired HIV infection (PHIV) are at particularly high risk of growth deficits given lifelong HIV and chronic inflammation. As early infant

Corresponding Author: Paige L. Williams, Department of Biostatistics, Harvard T.H. Chan School of Public Health, 655 Huntington Avenue, Boston, MA 02115; +1-617-432-3872, paige@hsph.harvard.edu.

Conflicts of Interest: None

diagnosis and linkage to HIV care improves, the population of PHIV adolescents is likely to increase, and the physical, social, and economic implications of poor growth will continue to expand.

The specific pathways which result in impaired growth are multifactorial, including undernutrition, chronic inflammation, opportunistic infections, gastrointestinal illnesses, and endocrine abnormalities [4]. Previous clinical trials and observational studies have demonstrated improvements in growth after initiation of antiretroviral treatment (ART), although gains have often not been as strong in adolescents as among younger children. HIV infection contributes as a risk factor to the high overall global prevalence of stunting, second in some regions only to preterm birth and fetal growth restriction [5], which are also common among children born to mothers with HIV infection. Without specific treatment for malnutrition, growth deficits are persistent and increase risk for mortality. Decreased growth early in childhood can lead to delayed puberty, with subsequent effects on pubertal growth spurts, final attained height, bone maturation, and increased risk for depression and lower self-esteem. Recently updated WHO recommendations for when to start treatment in children now recommend universal ART for all age groups regardless of CD4 count, but over the previous decade ART initiation was not recommended among children and adolescents until CD4 counts fell below certain thresholds, due to concerns regarding toxicities, drug resistance, and costs [6]. This has resulted in a current cohort of HIV-infected adolescents with delayed initiation of ART, generally at more severe disease stages than for younger children.

EARLY GROWTH MEASURES FOR HIV-INFECTED CHILDREN

Growth deficits in children born with HIV become apparent as early as 6 weeks of age and persist throughout infancy and early childhood [7]. Birth weight and length are significantly below that of uninfected children [8]. In Zimbabwe, 20% of PHIV infants exhibited wasting (WHO weight for height z-score, (WHZ) <−2) and 59% were stunted (WHO height for age z-score (HAZ) <−2) as compared to 3.3% wasted and 18.9% stunted among uninfected children. Head circumference is also decreased among HIV-infected infants, with 11.1% of HIV-infected infants exhibiting microcephaly at birth as compared to 5.4% of uninfected infants [8]. These early growth deficits persist throughout childhood, with average z-scores ranging from −2.9 to −2.3 for HAZ and −2.2 to −1.2 for weight for age z-score (WAZ) in children <5 years old at ART initiation [9.10].

ADOLESCENT GROWTH MEASURES PRIOR TO ART INITIATION

High Resource Settings

Adolescents with HIV have demonstrated impaired growth in both high resource settings (HRS) and LRS. In North America and Western Europe, HIV-infected children exhibit moderate stunting and underweight prior to ART initiation. McGrath et al [11] conducted a comprehensive global systematic review of growth measures before and after ART initiation, including 67 studies (13 in HRS, 54 in LRS). Prior to ART initiation, the weighted average of z-scores across the 13 HRS studies was −0.90 for height and −0.50 for weight. More recently, Schomaker [12] reported mean z-scores at ART initiation of −0.65 for height and

−0.07 for weight among children aged 1–16 years in Europe. The PENPACT study also observed deficits in both height and weight in children prior to ART initiation [13] (Table 1). These evaluations all reported higher means for body mass index z-score (BMIZ) of −0.1 to 0.3, suggesting that despite height deficits, children in HRS less often suffer from wasting (see Table 1) [11–13]. Few additional studies of growth have been recently conducted in HRS among adolescents prior to ART initiation, given the relatively small numbers in this sub-population.

Low Resource Settings

In contrast to developed settings, children in LRS demonstrate severe growth deficits prior to ART initiation. These HIV-related deficits are notable even against a current backdrop of 30% stunting in developing countries [5]. In their global review, McGrath noted HAZ and WAZ means significantly below those in HRS, reflecting high prevalence of stunting and underweight (Table 2) [11]. Recent studies have confirmed these general findings in Asia and many African countries (Table 2). Studies in Asia (primarily Thailand and China) have reported mean z-scores of −2.4 to −1.7 for HAZ and −2.6 to −1.1 for WAZ, with corresponding high prevalences of stunting and underweight [16–18].

Severely impaired growth among HIV-infected children in Africa may be partially attributable to the generally later age at ART initiation, often at more advanced disease stages [19]. Studies conducted in Senegal, West Africa, Uganda, Ethiopia, and Zimbabwe reported high levels of stunting, wasting, and underweight, often exceeding half of children (see Table 2) [19–23]. In a pooled analysis of IeDEA cohorts, means at ART initiation were −2.24 for HAZ, −1.46 for WAZ, and −0.56 for BMIZ in South African children and similar means of −1.98 for HAZ and −1.94 for WAZ in West African children [12]. High levels of stunting (23%) and underweight (27%) were also reported among youth first testing HIV positive at ages 6–13 in Zimbabwe; in addition, 35% had head circumference z-score<−2 [23].

Although the growth deficits observed in developing countries are clearly severe, some improvement has been noted as children are diagnosed at earlier ages and with less severe HIV disease status [22]. Substantial increases in WAZ at ART initiation over time were observed among children in Central Africa, with mean z-scores increasing from −2.2 in 2004–2005 to −1.4 in 2012–2013 [24]; the percent underweight decreased from 56% to 36% over this period. However, it should be noted that younger children (<10 years) comprise the majority of the populations in the studies described above, and several studies which report growth measures specifically for adolescents (age 10–19) have identified more severe growth deficits than among younger children [17,19].

GROWTH IN HIV-INFECTED ADOLESCENTS AFTER ART INITIATION

High Resource Settings

ART has resulted in marked improvements in growth among children with HIV in both HRS and LRS, and generally more rapidly for gains in weight than height [9–22]. In HRS, McGrath noted mean increases in HAZ and WAZ of about 0.20 by 2 years after ART

initiation [11]. The PENPACT study demonstrated greater growth recovery after ART initiation, with increases over 4 years of 0.43 and 0.68 for mean HAZ and WAZ, respectively [13]. The pooled analysis of IeDEA cohorts indicated more limited short-term increases in height and weight z-scores in European children, but by 4 years after ART initiation mean HAZ had increased to −0.2 and WAZ to 0.2 [12]. Significantly lower mean HAZ and BMIZ were observed at first pubertal assessment in PHIV boys and girls compared to HIV-exposed uninfected youth (see Table 1); the majority of PHIV youth had likely received ART since early childhood, but often initiated ART with mono or dual therapy [14]. Among highly ART-experienced adolescents in the US, means of −0.30 for HAZ and 0.15 for WAZ were reported [15].

Low Resource Settings

In LRS, the increases in weight and height after ART initiation are somewhat more striking than those in HRS, with increases in mean z-scores after 2 years ranging from 0.4–1.0 in HAZ, and 0.4–1.5 in WAZ (see Table 2) [12,16–18,20]. McGrath reported a mean increase of 0.40 in HAZ and 1.03 in WAZ after 24 months on ART [11]. Among Chinese HIV-infected youth, a 2-year increase of about 0.4 in both HAZ and WAZ was observed, with corresponding decreases in prevalence of stunting from 42% to 34% and in underweight from 21% to 13% [18]. After 5 years on ART, adolescents in the TREAT Asia Pediatric HIV Observational Database (TApHOD) achieved increases in HAZ from −2.3 to −1.6 [17]. Similar improvement was observed in both HAZ and WAZ by 4 years after ART initiation among South African and West African youth [12] (see Table 2). In Ethiopia, ART initiation had dramatic effects on reducing stunting and underweight to less than 20% by two years after starting treatment [22]. Among West African children, catch up growth (attaining z-score>−2) was observed within 2 years in 60–70% of those with initial stunting or underweight, and 90% of those with wasting at the time of ART initiation [20].

PREDICTORS OF GROWTH RECONSTITION AFTER ART INITIATION

The benefits of ART initiation on growth reconstitution are strongest in both high and low resource settings when initiated at younger ages [10,11,18–20,22,23]. McGrath observed greater height and weight gains after ART initiation for younger cohorts than older cohorts, although height gains did not persist beyond 6 months after ART initiation [11]. Jesson also reported lower odds of catch up growth for children >5 years old at ART initiation versus younger children [20]. Schomaker's evaluation of optimal timing of ART initiation suggested better growth reconstitution with earlier ART initiation relative to HIV disease stage (as reflected by CD4 count) among younger children, but inconclusive results among adolescents (age >10 years) [12]. Mixed findings of catch-up growth by sex have been reported [18,20]. Multiple studies have observed that lower initial HAZ was a strong predictor of failure to achieve growth recovery [17,19.20]. Findings regarding association of immunological status (CD4 count, WHO stage) with growth recovery have been inconsistent, often showing no association after accounting for baseline growth measures [12,16,20,22,25]. In addition, catch up growth often appears to stagnate after 1–2 years on ART even among children with virologic suppression [10,26].

The type of initial first-line ART also does not appear to play a major role in growth reconstitution after ART initiation; Melvin observed similar changes in HAZ, WAZ, and BMIZ over 4 years for children randomized to an NNRTI-based regimen and a PI-based regimen [13] who demonstrated viral suppression, and a systematic review indicated no difference in weight gain for NNRTI versus PI-based regimens in models adjusting for baseline weight (although reports from individual studies were somewhat mixed) [12]. However, children on second-line treatment are more likely to experience wasting than those on first-line ART [19]. Use of cotrimoxazole prophylaxis (for prevention of pneumonia, malaria, and other opportunistic infections) along with ART was found to provide benefits in weight recovery in the TaPHOD cohort in Asia, although these benefits did not extend to those with CD4%<10% at ART initiation [27]. Cotrimoxazole use did not appear to confer benefits in height recovery within two years after ART initiation, regardless of CD4% at ART initiation.

Not surprisingly, nutritional supplementation was associated with improved weight and height gain, with about a 0.50 SD improvement among those receiving supplements such as ready to use therapeutic food (RUTF), high energy protein, fortified maize products, and multivitamins [11, 25]. The high variability in types of supplementation across studies makes interpretation somewhat difficult. Among 158 malnourished HIV-infected children and adolescents in Mali participating in a nutritional intervention with RUTF, 74% attained catch-up growth in weight for height within 6 months, but the rates were lower (63%) for those with concurrent stunting at study entry [25]. Social support may also play a role; orphaned children were more likely to have persistent stunting after ART initiation [17].

PUBERTAL DEVELOPMENT IN HIV-INFECTED ADOLESCENTS

Pubertal Onset

While malnutrition is known to slow growth and cause pubertal delay, malnutrition in combination with chronic inflammation can lead to elevated proinflammatory cytokines, reduction in insulin-like growth factor-1 (IGF-1), and altered secretion of growth hormone and gonadotropin-releasing hormone which contribute further to growth deficits and pubertal delays [28,29]. As a result, PHIV youth have significant delays in pubertal onset compared to uninfected children, with greatest delay for those with most severe HIV disease symptoms [23,30,31]. Among PHIV youth in the US, delays in pubertal onset were observed for those with lower CD4 counts or higher viral load as compared to healthier PHIV youth [30]. In a small cross-sectional study conducted in Nigeria, a significantly lower percentage of HIV-infected girls had pubertal onset than an age-matched group of uninfected girls [32]. In longitudinal follow-up of HIV-infected ARROW trial participants in Africa, the observed mean ages at pubertal onset were 12.8 for boys and 11.7 for girls; the estimated mean age at menarche was 14.3 years [31]. These mean ages at onset are substantially later than those in the general US population of 9.3, 9.5, and 12.1 years respectively, and also later than those of PHIV youth in the US [29,30]. Among HIV-infected children and adolescents in Zimbabwe with no prior ART, pubertal delay was reported in 27% of girls and 13% of boys, and 24% of girls aged 15 or older had not yet reached menarche [23].

Later age at ART initiation was associated with significant delays in pubertal onset among both boys and girls, and later age at menarche in girls. Children with lower pre-ART HAZ demonstrated further delays in pubertal onset, even after accounting for age at ART initiation [31]. However, boys who demonstrated response to ART via increases in CD4 counts after ART initiation had earlier pubertal onset than those without such initial ART responses; no benefit of CD4 increase on ART was observed in girls, and pre-ART CD4 was not associated with age at pubertal onset in boys or girls [31].

Sexual Maturity and Final Adult Height

Fewer studies have evaluated sexual maturity among PHIV adolescents. Bellavia et al reported approximately 6 month later mean age at sexual maturity among PHIV compared to PHEU youth in the US [14]. Using a mediation analysis approach, they found that a high percentage of the total effect of HIV infection on age at maturity was mediated by growth measures after pubertal onset, with strongest effects based on both BMIZ and HAZ at age 11 for girls, and HAZ at age 12 for boys. These findings suggest that improving growth during the typical pubertal growth spurt could help normalize timing of sexual maturity. Among African youth, mean ages at maturity were 16.1 years for breast maturity in girls, and 16.9 years for genitalia maturity in boys, which are approximately 9–18 months later than those reported among PHIV youth in the US [31]. The later ages at both pubertal onset and maturity in LRS may be partially attributable to the greater growth deficits, particularly in height, among African adolescents with HIV infection noted previously as compared to those in the US. Decreases of about 9–12cm in final adult height of 18-year olds in Asia were observed relative to WHO growth references, and about half of those classified as stunted at ART initiation remained stunted at age 18 years [33].

IMPLICATIONS OF GROWTH DEFICITS AND DELAYED PUBERTAL DEVELOPMENT

Children with stunting or wasting have significantly elevated risk of mortality and AIDS progression [5,16,34,35]. AIDS-related mortality has increased over the past decade in HIV-infected adolescents, while decreasing in other groups [4]. In developing countries, 14% of childhood deaths are attributable to stunting [5]. Among HIV-infected adolescents, 66% with WHO stage 4 disease were classified as such on the basis of stunting alone [23]. Adolescents with persistent wasting after ART initiation were found to have over 10-fold higher risk of late AIDS or mortality, even after accounting for viral load and other factors; older adolescents were at particularly higher risk of death [34]. Wasting has also been identified as associated with future risk of virologic rebound among adolescents, which contributes to higher risk of mortality [36]. In higher resource settings, mortality rates are low, and wasting was not identified as a predictor of mortality among US adolescents with HIV [37]. Height deficits and pubertal delay have also been shown to be associated with psychosocial health, with increased depression symptoms and links to HIV-related stigma [38,39].

Delayed puberty has implications for bone mineral accrual and maturation, as well as metabolic conditions such as lipodystrophy as adolescents transition to adulthood [15,40–42]. Adolescents with HIV often have alterations in the rate of bone metabolism and

decreases in bone mineral density, which may contribute to higher risk of fractures or osteoporosis in adulthood [40]. Among ART-experienced PHIV adolescents in Asia, 16% had deficient bone mass, which were linked to low BMI, height, and weight z-scores [41].

CHALLENGES

Evaluating height and weight deficits among adolescents initiating ART is currently limited to those who have survived to adolescence in absence of ART, which may induce selection bias. Confounding by indication limits the ability to evaluate effects of ART regimens on pubertal onset and maturity in HRS, where many older adolescents received relatively ineffective mono- or dual-therapy in childhood. Longitudinal evaluations of pubertal development offer several advantages over cross-sectional studies in allowing consideration of each child's pubertal progression and growth measures during adolescence. Due to increased energy needs during adolescence and puberty [19], better documentation of nutritional intake could improve understanding of growth failure, especially in LRS. Other low-cost screening instruments such as mid-upper arm circumference may be useful for identifying those at greatest risk of growth failure [43]. Development of screening tools for assessing growth rates on ART relative to reference standards may also improve identification of growth failures [26].

CONCLUSIONS

Adolescents with HIV have demonstrated impaired growth prior to ART initiation in both high and low resource settings. However, these deficits are much more severe in LRS and persist even years after ART initiation, while HIV-infected adolescents in HRS generally achieve weight recovery. Some improvement in growth status at ART initiation has been noted over time, as children are diagnosed at earlier ages and with less severe HIV disease status. Pre-pubertal growth is intrinsically linked to pubertal onset, and stunted children demonstrate delays in both onset and maturation. The current cohort of HIV-infected adolescents has survived despite often receiving delayed or ineffective ART. As newer WHO treatment guidelines are implemented, growth deficits will hopefully be reduced and translate to other benefits across the health spectrum for adolescents with HIV infection. Early initiation of ART along with nutritional supplementation will be necessary for minimizing growth deficits.

Acknowledgments

Funding: PLW received funding from the Pediatric HIV/AIDS Cohort Study, which is supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from other NIH institutes through cooperative agreements with the Harvard T. H. Chan School of Public Health (HD052102) and Tulane University School of Medicine (HD052104). JJ is a post-doctoral fellow funded by Sidaction, France.

References

Annotations: (*) for special interest and (**) for outstanding

1. [accessed 11/27/17] Number of people living with HIV: Adolescents (10–19). Available at http://aidsinfo.unaids.org

2. World Health Organization. [Accessed 12/1/2017] WHO 2007 Child Growth Standards. Available at: http://www.who.int/childgrowth/standards/en

3. Centers for Disease Control and Prevention. [Accessed 12/1/2017] Growth Charts. 2000. Available at https://www.cdc.gov/growthcharts/cdc_charts.htm

4*. Barlow-Mosha L, Musiime V, Davies MA, et al. Universal antiretroviral therapy for HIV-infected children: a review of the benefits and risks to consider during implementation. J Int AIDS Soc. 2017 Jun 27.20(1):21552. This review highlights benefits of ART initiation on growth and puberty. [PubMed: 28691434]

5*. Goodarz D, Andrews KG, Sudfeld CR, et al. Risk factors for childhood stunting in 137 developing countries: A comparative risk assessment analysis at global, regional, and country levels. PLOS Med. 2016; 13(11):e1002164. This study notes the relative role of HIV as a risk factor for malnutrition versus other risk factors in global context. doi: 10.1371/journal/pmed.1002164 [PubMed: 27802277]

6. WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infections: recommendations for a public health approach. 2. Geneva, Switzerland: WHO; 2016.

7*. Omoni AO, Ntozini R, Evans C, et al. Child growth according to maternal and child HIV status in Zimbabwe. Pediatr Infect Dis J. 2017 Sep; 36(9):869–876. This study demonstrates growth deficits from birth and early childhood in HIV-infected infants. [PubMed: 28198792]

8. Evans C, Chasekwa B, Ntozini R, Humphrey JH, Prendergast AJ. Head circumferences of children born to HIV-infected and HIV-uninfected mothers in Zimbabwe during the pre-antiretroviral therapy era. AIDS. 2016 Sep 24; 30(15):2323–8. [PubMed: 27428746]

9. Achan J, Kakuru A, Ikilezi G, et al. Growth recovery among HIV-infected children randomized to Lopinavir/Ritonavir or NNRTI-based antiretroviral therapy. Pediatr Infect Dis J. 2016 Dec; 35(12): 1329–1332. [PubMed: 27580060]

10. Feucht UD, Van Bruwaene L, Becker PJ, Kruger M. Growth in HIV-infected children on long-term antiretroviral therapy. Trop Med Int Health. 2016 May; 21(5):619–29. [PubMed: 26914715]

11**. McGrath CJ, Diener L, Richardson B, et al. Growth reconstitution following antiretroviral therapy and nutritional supplementation: systematic review and meta-analysis. AIDS. 2015; 29:2009–2023. This is a comprehensive review and meta-analysis of all studies of growth through 2015 in low and high resource settings, both before and after ART initiation. [PubMed: 26355573]

12**. Schomaker M, Leroy V, Wolfs T, et al. IeDEA West and Southern Africa regional collaborations and COHERE in EuroCoord. Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe. Int J Epidemiol. 2017 Apr 1; 46(2):453–465. This is a large pooled cohort analysis including high and low resource settings, uses a sophisticated causal approach to evaluate optimal timing of ART initiation. [PubMed: 27342220]

13*. Melvin AJ, Warshaw M, Compagnucci A, et al. PENPACT-1 (PENTA 9/PACTG 390/ANRS 103) Study Team. Hepatic, renal, hematologic, and inflammatory markers in HIV-Infected children on long-term suppressive antiretroviral therapy. J Pediatric Infect Dis Soc. 2017 Sep 1; 6(3):e109–e115. While this study is fairly small, it is one of few recent evaluations of growth in high resource settings. [PubMed: 28903520]

14**. Bellavia A, Williams PL, DiMeglio LA, et al. International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P219/219C Study, and the Pediatric HIV/AIDS Cohort Study (PHACS). Delay in sexual maturation in perinatally HIV-infected youths is mediated by poor growth. AIDS. 2017 Jun 1; 31(9):1333–1341. This is a large study of sexual maturity in US including both HIV-infected and HIV-exposed uninfected adolescents; a mediation approach is utilized to evaluate the impact of HIV infection via growth deficits on delays in maturity. [PubMed: 28358737]

15*. Jacobson DL, Stephensen CB, Miller TL, et al. Pediatric HIV/AIDS Cohort Study. Associations of low Vitamin D and elevated parathyroid hormone concentrations with bone mineral density in perinatally HIV-Infected Children. J Acquir Immune Defic Syndr. 2017 Sep 1; 76(1):33–42. This study suggests a need for supplementation to address both malnutrition and low bone mineral density. [PubMed: 28797019]

16*. Boettiger DC, Aurpibul L, Hudaya DM, et al. TREAT Asia Pediatric HIV Observational Database. Antiretroviral therapy in severely malnourished, HIV-infected children in Asia. Pediatr Infect Dis J. 2016 May; 35(5):e144–51. Although the focus of this study is on severely malnourished children, the authors also report growth measures prior to ART for entire cohort. [PubMed: 26835972]

17**. Boettiger DC, Sudjaritruk T, Nallusamy R, et al. Non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy in perinatally HIV-Infected, treatment-naïve adolescents in Asia. J Adolesc Health. 2016 Apr; 58(4):451–459. This study focuses specifically on 10–19 year old adolescents, and evaluates height recovery over 5 years of follow-up. [PubMed: 26803201]

18*. Hu R, Mu W, Sun X, et al. Growth of HIV-infected children in the early stage of antiretroviral treatment: a retrospective cohort study in China. AIDS Patient Care STDs. 2016; 30(8):365–370. This is the only recent study in China evaluating growth of HIV-infected children. [PubMed: 27509236]

19*. Cames C, Pascal L, Diack, et al. MAGGSEN Cohort Study Group. Risk factors for growth retardation in HIV-infected Senegalese children on antiretroviral treatment: The ANRS 12279 MAGGSEN Pediatric Cohort Study. Pediatr Infect Dis J. 2017; 36:e87–e92. This study reports growth measures specifically within 10–16 year olds, and notes that wasting and stunting remained high in this age group even after ART initiation. [PubMed: 28187062]

20. Jesson J, Koumakpaï S, Diagne NR, et al. Paediatric WADA IeDEA Collaboration. Effect of age at antiretroviral therapy initiation on catch-up growth within the first 24 months among HIV-infected children in the IeDEA West African Pediatric Cohort. Pediatr Infect Dis J. 2015 Jul; 34(7):e159–68. [PubMed: 25955835]

21. Szubert AJ, Prendergast AJ, Spyer MJ, et al. the ARROW Trial Team. Virologic response and resistance among HIV-infected children receiving long-term antiretroviral therapy without virological monitoring in Uganda and Zimbabwe: Observational analyses within the randomized ARROW trial. PLOS Med. 2017; 14(11):e1002432. [PubMed: 29136032]

22. Ebissa G, Deyessa N, Biadgilign S. Impact of highly active antiretroviral therapy on nutritional and immunologic status in HIV-infected children in the low-income country of Ethiopia. Nutrition. 2016; 32:667–673. [PubMed: 26875999]

23*. McHugh G, Rylance J, Mujuru H, et al. Chronic morbidity among older children and adolescents at diagnosis of HIV infection. J Acquir Immun Defic Syndr. 2016; 73(3):275–281. This is a cross-sectional study of children first identified as HIV positive in adolescence; other comorbidities are reported for these older children along with height and weight deficits.

24**. Adedimeji A, Edmonds A, Hoover D, et al. Characteristics of HIV-Infected children at enrollment into care and at antiretroviral therapy initiation in Central Africa. PLoS One. 2017 Jan 12.12(1):e0169871. This study shows improvement in growth status at ART initiation between 2004 and 2013, coinciding with earlier age at ART initiation. [PubMed: 28081230]

25**. Jesson J, Coulibaly A, Sylla, et al. Evaluation of a nutritional support intervention in malnourished HIV-infected children in Bamako, Mali. J Acquir Immune Defic Syndr. 2017; 76:149–157. This study describes an intervention study for nutritional supplementation among children with malnutrition. [PubMed: 28639991]

26. Keiser O, Blaser N, Davies MA, et al. IeDEA Southern-Africa. Growth in virologically suppressed HIV-positive children on antiretroviral therapy. Pediatr Infect Dis J. 2015; 34:e254–e259. [PubMed: 26192393]

27*. Boettiger DC, Muktiarti D, Kurniati N, et al. Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia) Pediatric HIV Observational Database. Early height and weight changes in children using cotrimoxazole prophylaxis with antiretroviral therapy. Clin Infect Dis. 2016 Nov 1; 63(9):1236–1244. This study addresses the role of concurrent prophylaxis on growth. [PubMed: 27470239]

28. Williams PL, Abzug M, Jacobson DL, et al. Pubertal onset in children with perinatal HIV infection in the era of combination antiretroviral treatment. AIDS. 2013; 27:1959–70. [PubMed: 24145244]

29*. Benyi E, Savendahl L. The physiology of childhood growth: hormonal regulation. Horm Res Paediatr. 2017; 88:6–14. This study describes effects of both malnutrition and chronic inflammation on pubertal development in the general population. [PubMed: 28437784]

30. Munoz-Calvo MT, Argente J. Nutritional and pubertal disorders. Endocr Dev. 2016; 29:153–173. [PubMed: 26680577]

31**. Szubert AJ, Musiime V, Bwakura-Dangarembizi M, et al. ARROW Trial Team. Pubertal development in HIV-infected African children on first-line antiretroviral therapy. AIDS. 2015; 29:609–618. This is a key paper addressing pubertal onset and maturation in low resource settings, including the roles of ART initiation and immunologic status. [PubMed: 25710288]

32. Iloh ON, Iloh KK, Ubesie AC, et al. Comparison of Tanner staging of HIV-infected and uninfected girls at the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria. J Pediatr Endocrinol Metab. 2017 Jun 23. Epub ahead of print. doi: 10.1515/jpem-2016-0356

33*. Bunupuradah T, Kariminia A, Aurpibul L, et al. TREAT Asia Pediatric HIV Observational Database. Final height and associated factors in perinatally HIV-infected Asian adolescents. Pediatr Infect Dis J. 2016 Feb; 35(2):201–4. This is a short communication describing final height based on height after age 18; very few papers on this important topic. [PubMed: 26484429]

34*. Traisathit P, Delory T, Ngo-Giang-Huong N, et al. AIDS-defining events and deaths in HIV-infected children and adolescents on antiretrovirals: a 14-year study in Thailand. J Acquir Immune Defic Syndr. 2017 Oct 14. This study evaluated growth measures as predictors of AIDS and mortality in long-term follow-up. doi: 10.1097/QAI.0000000000001571

35. Sanjeeva GN, Guijal Chebbi P, Pavithra HB, et al. Predictors of mortality and mortality rate in a cohort of children living with HIV from India. Indian J Pediatr. 2016; 83:765–771. [PubMed: 26916891]

36*. Sudjaritruk T, Aurpibul L, Ly PS, et al. Incidence of postsuppression virologic rebound in perinatally HIV-Infected Asian adolescents on stable combination antiretroviral therapy. J Adolesc Health. 2017 Jul; 61(1):91–98. This study identified stunting as a risk factor for virologic rebound. [PubMed: 28343759]

37. Mirani G, Williams PL, Chernoff M, et al. IMPAACT P1074 Study Team. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. Clin Infec Dis. 2015; 61:1850–61. [PubMed: 26270680]

38. Kim MH, Mazenga AC, Yu X, et al. Factors associated with depression among adolescents living with HIV in Malawi. BMC Psychiatry. 2015 Oct 26.15:264. [PubMed: 26503291]

39. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, et al. Perinatally acauired HIV infection in adoolescents from sub-Saharan Africa: a review of emerging challenges. Lancet Infect Dis. 2014; 14:627–639. [PubMed: 24406145]

40*. Eckard AR, Mora S. Bone health in HIV-infected children and adolescents. Curr Opin HIV AIDS. 2016 May; 11(3):294–300. This is an excellent recent review of effects of HIV on bone health. DOI: 10.1097/COH.0000000000000270 [PubMed: 26890208]

41*. Sudjaritruk T, Bunupuradah T, Aurpibul L, et al. Bone-D Study Group. Adverse bone health and abnormal bone turnover among perinatally HIV-infected Asian adolescents with virological suppression. HIV Med. 2017 Apr; 18(4):235–244. This study focuses on HIV-infected adolescents with suppressed viral load, and addresses bone maturation in this subgroup. [PubMed: 27477214]

42. Jiménez B, Sainz T, Díaz L, et al. Madrid Cohort of HIV-Infected Children and Adolescents Integrated in the Pediatric Branch of the Spanish National AIDS Research Network (CoRISpe). Low bone mineral density in vertically HIV-infected children and adolescents: risk factors and the role of T-cell activation and senescence. Pediatr Infect Dis J. 2017 Jun; 36(6):578–583. [PubMed: 28005690]

43*. Mramba L, Ngari M, Mwangme M, et al. A growth reference for mid upper arm circumference for age among school age children and adolescents, and validation for mortality: growth curve construction and longitudinal cohort study. BMJ. 2017; 358:j3423. This study recommends use of mid-upper arm circumferences as an inexpensive reference for evaluating growth failure; the validation includes HIV-infected youth from the ARROW cohort. doi: 10.1136/bmj.j3423 [PubMed: 28774873]

KEY POINTS

- Impaired growth remains a critical issue of concern, particularly in low resource settings, where stunting, wasting and underweight remain common even after years on ART.
- Antiretroviral treatment initiation results in improved growth, with greatest growth recovery in the first years and greater gains in weight than in height.
- The high prevalence of stunting in HIV-infected adolescents translates to delays in pubertal onset and sexual maturity, abnormal bone health, and increased mortality risk.
- The current cohort of HIV-infected adolescents has survived despite often receiving delayed or ineffective ART; recent WHO guidelines for universal ART initiation regardless of age and immunologic status may translate to improved growth and more normalized timing of pubertal development for future cohorts.
- Coordinated efforts for early ART initiation along with nutritional supplementation programs are needed to ensure optimal growth in HIV-infected adolescents.

Table 1

Growth in HIV-infected Adolescents in High Resource Settings Before and After Antiretroviral Treatment Initiation

Author	Country/countries & sample size	Age range	Timing of measurement	Height for age Z-score (mean or median)	Weight for age Z-score (mean or median)	BMI or Weight-for height Z-score (mean or median)
McGrath, 2015 [11]	13 countries (review) n=1810	0–18 years	Before or at ART initiation	−0.9	−0.5	0.3
			6 months after ART	Δ =0.10	Δ =0.19	
			12 months after ART	Δ =0.12	Δ =0.17	
			24 months after ART	Δ =0.18	Δ =0.17	
Schomaker, 2017 [12]	Europe, n=991	1–16 years	Before or at ART initiation	−0.65 (n=767)	−0.07 (n=615)	0.24 (n=474)
			12 months after ART	−0.6 (n=486)	0.1 (n=361)	0.4 (n=307)
			24 months after ART	−0.4 (n=494)	0.1 (n=345)	0.4 (n=289)
			4 years after ART	−0.2 (n=407)	0.2 (n=241)	0.3 (n=218)
Melvin, 2017 [13]	Europe, USA, Argentina, n=99	0–18 years	Before or at ART initiation	−0.98	−0.80	−0.10
			4 years after ART	−0.40 (Δ =0.43)	−0.15 (Δ =0.68)	0.07 (Δ =0.25)
Bellavia, 2017 [14]	USA, n=2086	7–22 years	At baseline pubertal exam age 7 or later	−0.71 boys, −0.58 girls [vs. uninfected: 0.26 boys, 0.13 girls]		0.31 boys, 0.25 girls [vs. uninfected: 0.83 boys, 0.68 girls]
Jacobson, 2017 [15]	USA, n=412	6–17 years	Highly ART-experienced, median=10.7 years	−0.30	0.15	

Δ denotes mean change since ART initiation in growth measure; ART=antiretroviral treatment; BMI=body mass index

Table 2

Growth in HIV-infected Adolescents in Lower Resource Settings Before and After Antiretroviral Treatment Initiation

Author	Country/countries & sample size	Age range	Timing of measurement	Height for age Z-score (mean or median)	Weight for age Z-score (mean or median)	BMI or Weight-for height Z-score (mean or median)
McGrath, 2015 [11]	54 countries (review) n=25,927	0–18 years	Before or at ART initiation	−2.2	−2.1	−1.5
			12 months after ART	Δ =0.23	Δ =0.84	
			24 months after ART	Δ =0.41	Δ =1.03	
Boettiger, 2016 [16]	Asia (mostly Thailand), n=534	10–19 years	Before or at ART initiation	−2.3 (n=418)	−2.6 (n=429)	
			5 years after ART (NNRTI-based)	−1.6		
Boettiger, 2016 [17]	Asia, n=2993	6–14 years	Before or at ART initiation	−2.4	−2.6 (−5.6 among 12% with severe malnutrition, SM)	
			12 months after ART		−2.8 among SM	
			24 months after ART		−2.4 among SM	
Hu, 2016 [18]	China, n=744	0–15 years	Before or at ART initiation	−1.71 (42% stunted)	−1.06 (21% underweight)	
			12 months after ART	−1.46 (38% stunted)	−0.68 (14% underweight)	
			24 months after ART	−1.30 (34% stunted)	−0.60 (13% underweight)	
Cames, 2017 [19]	Senegal, n=244	2–16 years, median=9.5	Before or at ART initiation	46% stunted (45% in 10–16 yr olds)		41% wasted (47% in 10–16 yr olds)
			At enrollment (median duration on ART=2.9 years)	30% stunted (42% in 10–16 yr olds)		33% wasted (52% in 10–16 yr olds
Jesson, 2015 [20]	West Africa, n=2004	<10 years old at ART initiation	Before or at ART initiation	−1.98 (48% stunted)	−2.05 (51% underweight)	−1.31 (33% wasted)
Schomaker, 2017 [12]	Southern Africa, N=16,230	1–16 years	Before or at ART initiation	−2.24 (n=8545)	−1.46 (n=8189)	−0.56 (n=4905)
			12 months after ART	−2.0 (n=3772)	−1.0 (n=3366)	−0.2 (n=2206)
			24 months after ART	−1.8 (n=3359)	−0.9 (n=2730)	−0.3 (n=1893)
			4 years after ART	−1.6 (n=2335)	−0.9 (n=1532)	−0.3 (n=1255)
	West Africa, n=3355	1–16 years	Before or at ART initiation	−1.98 (n=2125)	−1.94 (n=2002)	−1.4 (n=1125)
			12 months after ART	−1.8 (n=885)	−1.4 (n=835)	−0.9 (n=489)

Author	Country/countries & sample size	Age range	Timing of measurement	Height for age Z-score (mean or median)	Weight for age Z-score (mean or median)	BMI or Weight-for height Z-score (mean or median)
			24 months after ART	−1.5 (n=758)	−1.2 (n=628)	−1.0 (n=415)
			4 years after ART	−1.3 (n=460)	−1.1 (n=320)	−1.1 (n=227)
Szubert, 2017 [21]	Uganda, Zimbabwe, n=1206	0–17 years	Before or at ART initiation	−2.4	−2.2	
Ebissa, 2016 [22]	Ethiopia, n=556	5–10 years	Before or at ART initiation	64% stunted	55% underweight	15% wasted
			24 months after ART	<20%	<20%	Almost 0%
McHugh, 2016 [23]	Zimbabwe, n=385	6–15 years	At HIV diagnosis	−1.2	−1.1	
Adedimeji, 2017 [24]	Central Africa, n=3246	0–15 years	At enrolment to care, n=3246		−1.8 (45% underweight)	
			At ART initiation, n=2058		−1.9 (47% underweight, decreased from 56% in 2004–05 to 36% in 2012–13)	

Δ denotes mean change since ART initiation in growth measure; ART=antiretroviral treatment; BMI=body mass index

Curr Opin HIV AIDS. Author manuscript; available in PMC 2019 May 01.