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Patterns of linear growth among children and adolescents living with HIV on antiretroviral therapy in Zimbabwe and Zambia

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Abstract

Background Adolescents with HIV (AWH) frequently exhibit impaired growth, which manifests as stunting and wasting. We studied trajectories in leg-length (appendicular), sitting (axial), and standing height among AWH on antiretroviral therapy (ART), determining peak height velocity (PHV) and age at PHV (aPHV).

Methods Analyses used VITALITY trial data from Zimbabwe and Zambia (PACTR20200989766029), which recruited AWH (11-19 years) established on ART to determine whether vitamin D_3/calcium supplementation improves bone health. The study enrolled participants between January and December 2021. Weight-for-age and height-for-age z-scores (WAZ/HAZ) were calculated from 12-weekly anthropometry over 96 weeks. Height trajectory analyses used SuperImposition by Translation And Rotation (SITAR) methods adjusting for height, tempo (aPHV) and velocity. Linear associations between vitamin D/calcium supplementation, HIV-specific factors, WAZ, HAZ, and SITAR parameters were determined.

Results Overall, 842 participants (53·2% female; median age 15·5 [IQR:13·2-17·9] years), were taking ART for median 9·8(IQR:6·3–12·3) years. Mean(SD) HAZ was 1·21(1·05) in females, -1·68(1·05) in males. Overall, 251(29·8%) AWH were stunted (HAZ < -2) and 253(30%) wasted (WAZ < -2). Standing, appendicular and axial aPHVs were: Female 13·4, 13·3, 13·9 years; Males 15·3, 15·0, 15·8 years. Unsuppressed viral-load(VL) and delayed ART initiation (age > 4-years) were associated with later aPHV and shorter axial height in females. In all, unsuppressed VL had a more negative effect on aPHV for axial (Females: β = 0·39 years [95%CI:0·12,0·65]; Males: β = 0·45 [95%CI:0·10,0·80]) than appendicular growth (Females: β = 0.31 [95%CI 0·08,0·53]; Males: β = 0·2 [95%CI:-0·17,0·56]). Conversely, delayed ART initiation was more negatively related to aPHV for appendicular (Females: β = 0·25 [95% CI:0·08,0·43]; Males: β = 0·63 [95%CI:0·32, 0·93] than axial growth (Females: β = 0·13 [95%CI:-0·08,0·34]; Males: β = 0·56 [95%CI:0·28,0·86]. Lower HAZ and WAZ were associated with lower height, later aPHV and lower PHV. At 48-week vitamin-D_3/calcium supplementation had no effect on the growth pattern.

Conclusion Unsuppressed viral load and delayed ART-initiation predicted later aPHV. Stunting and wasting were associated with attenuated growth velocity and later aPHV. Adolescents with HIV experience persistent linear growth impairments, potentially persisting into adulthood.

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Introduction

In 2024, 2.38 [1.83-2.97] million young people (from birth to 19 years of age) were living with HIV worldwide, with 60% residing in east and southern Africa [1]. The availability of antiretroviral therapy (ART) has dramatically improved life expectancy [2], such that children diagnosed with HIV, who would otherwise have died in early childhood, are now reaching adolescence and adulthood [3]. Although immediate ART is recommended to all children perinatally-infected with HIV, the coverage of ART is suboptimal with only 57% of children with HIV aged 0-14 years accessing ART [4].

Adolescence is an important period for skeletal growth, marked by rapid height gains (the 'growth spurt') with bones lengthening, widening, and laying down mineral until epiphyseal growth plates fuse. During this period, an estimated 15% of final adult stature is accrued encompassing both axial (spinal) and appendicular (long bone) growth [5]. However, the low calcium and vitamin D intakes observed in sub-Saharan Africa (SSA) can compromise bone growth [6], contributing to stunting, which is common among children living with HIV in the region, despite ART [7]. In addition to malnutrition affecting up to 57% of children and adolescents in east and southern Africa [8], HIV-induced chronic inflammation and delayed ART initiation can contribute to impaired growth [5, 9].

Adolescence represents a potential window of opportunity for interventions to correct growth deficits [9]. Despite the clinical benefits of ART in promoting health and survival, the impact of ART on growth patterns during adolescence has been inconsistently reported. Growth parameters include *size* (an individual's height in centimetres), peak height *velocity* (the rate of linear growth each year), and *tempo* (the age at peak height velocity [10]. While some studies suggest that early ART initiation may facilitate 'catch-up growth' [11], the relationship between age at ART initiation and age at peak height velocity remains unclear [12]. Furthermore, inconsistent associations between HIV viral load and growth patterns in individuals receiving ART have been reported [11, 13]. As such, understanding these potentially modifiable HIV-specific factors and their relationships with parameters of growth, might help inform strategies to reduce growth deficits and improve bone health later in life. This study aimed to understand growth characteristics [*size*, age at peak height velocity (*tempo*), and peak growth *velocity*] in adolescents living with HIV (AWH), and determine the associations between HIV-specific factors as well as vitamin D/calcium supplementation, with these growth characteristics.

Methods

Study design and participants

A pre-planned secondary analysis was conducted using data from The vitamin D for adolescents with HIV to reduce musculoskeletal morbidity and immunopathology (VITALITY) trial; Pan African Clinical Trials Registry PACTR20200989766029 [14]. This was a Phase III, individually randomized, double-blind, placebo-controlled trial of high-dose vitamin D_3 (20,000 IU per week) and calcium carbonate (500 mg daily) versus placebo. The trial enrolled 842 adolescents aged 11-19 years living with HIV recruited from HIV public sector outpatient clinics in Harare, Zimbabwe and Lusaka, Zambia, between January and December 2021. Those included had been perinatally infected with HIV and taking ART for at least six months. Exclusion criteria included: being acutely unwell, taking tuberculosis treatment, being pregnant or breastfeeding, or having a history of either thyrotoxicosis, chronic renal disease, hypercalcemia, a phosphate metabolism disorder, or osteomalacia. Participants were followed up for 96 weeks and this analysis used all prospectively collected longitudinal data.

Procedures

At baseline, a researcher-administered questionnaire, pre-programmed using Open Data Kit (ODK) on to electronic tablets, was used to collect socio-demographic characteristics (age, sex, and household assets reflecting socioeconomic status [SES]) and clinical data including HIV history [age at ART initiation and current ART regimen]. Dietary calcium and vitamin D intakes were assessed using a dietary diversity questionnaire based on that of the Food and Agriculture Organization of the United Nations (FAO) questionnaire adapted to Zimbabwe and Zambia, and focussing on foods rich in calcium and vitamin D (legumes, dairy, eggs, meat/poultry, and fish) [15]. Using the FAO food composition tables, dietary vitamin D and calcium intakes were estimated based on frequency of consumption and portion size (Supplementary Table 1) [16]. In this age group, the Institutes of Medicine (U.S.) recommended daily dietary reference intake for adequate calcium and vitamin D is 1300 mg and 15 µg respectively, with values < 150 mg and < 4 µg indicating very low consumption [17]. Tanner pubertal

staging and anthropometry measurements were assessed (by trained nurses) in boys using testicular volume (orchidometer) and in girls using breast development and menarche age, with pubic hair development evaluated in both sexes to classify each participant into one of five levels of pubertal development [18, 19].

Anthropometry assessments

Participants underwent measurement of height (in centimetres) and weight (in kilogrammes) barefoot and in light clothing, at 12 weekly intervals over two years. A wall-mounted Seca 222 stadiometer was used to measure height (Seca Mechanical Floor Scales Class III, Seca Precision for health, Hamburg, Germany). For standing height, the participant stood with both heels together with buttocks, and scapulae touching the vertical backboard of the stadiometer. To measure sitting (axial) height, the participant sat straight on a standardized measurement stool with their back and buttocks touching the backboard of the stadiometer. Axial height was calculated as total sitting height minus stool height. Appendicular height (leg-length) was calculated by subtracting axial height from standing height. These three height assessments [standing, axial, and appendicular height] were performed at each time point in triplicate, recorded to the nearest 0.1 cm, with the median of the three measured used for analyses. Anthropometry z-scores were calculated using UK reference data, due to lack of local reference data [20]. Stunting and wasting were classified as standing height and weight for age z-scores < -2 respectively.

Blood tests

At baseline, blood samples (5 ml) were collected in EDTA tubes from which HIV viral load testing was performed using the Qiagen rotor gene Q in Zambia and the Roche COBAS Ampliprep/COBAS Taqman48 in Zimbabwe. HIV viral load suppression was defined as a viral load < 60 copies/mL. Baseline concentration for vitamin D metabolite [25-hydroxyvitamin; 25(OH)D] was analysed at the Bioanalytical Facility, University of East Anglia (Norwich, UK) using Liquid chromatography Tandem Mass Spectrometry (LC-MS/MS) [21].

Data analysis

Data were cleaned, checked and analysed using RStudio [22]. All quantitative variables were summarised using mean ± standard deviation (SD) if normally distributed, or otherwise as median with an interquartile range (IQR). Categorical variables were summarised as frequencies with percentages. Quintiles of SES were derived from a principal component analysis of participant-reported household assets.

The Super Imposition by Translation and Rotation (SITAR) method was used to model linear growth, measured by appendicular, axial, and standing height [23]. SITAR is a longitudinal regression model which uses a natural cubic spline to model a mean growth curve, together with three non-linear random effects which summarise individual departures from this curve. The random effects are measures of size (in centimetres) (higher values indicating being taller); tempo (in years) (higher and lower values indicating having older or younger than average age at peak height velocity (aPHV) respectively) and velocity (in centimetres/year) (higher values indicating a greater growth velocity). The SITAR mean velocity curve represents the first derivative of the mean growth curve showing changes in growth intensity by age. In addition, the mean peak height velocity (PHV) and aPHV were determined from the velocity curve as a point of maxima. Separate models were fitted for appendicular, axial, and standing height; all height models were stratified by sex. Evaluation of model fit was performed by looking at the Bayesian Information Criterion (BIC), the percentage variance in the crude height measurement explained by the SITAR mean curve, and the residual SDs [23].

Individual level parameters of growth were determined from the predicted SITAR random effects for size, tempo, and velocity. Firstly, descriptive Pearson linear correlation coefficients (r) between the growth parameters were determined. Secondly, the variations (SDs) in the SITAR random effects (growth parameters) were generated to quantify heterogeneity in growth between participants. Thirdly, associations between a priori variables measured at baseline and the three random SITAR growth parameters were evaluated in linear regression models. The univariate analyses each generated unconditional regression coefficients with 95% confidence intervals which are free of 'table two fallacy'. A priori defined independent variables included socioeconomic status (SES), dietary calcium and vitamin D intakes, malnutrition indicators [baseline height for age (HAZ), weight for age (WAZ), and BMI for age (BMIZ) z-score], and, HIV-specific factors (age at ART initiation, tenofovir disoproxil fumarate (TDF)-containing ART regimen, and HIV viral load). In addition, the associations between the trial intervention (vitamin D_3 [20000 IU weekly dose] and calcium carbonate [500-mg daily dose] supplemented for 48 weeks) and growth parameters were estimated.

In sensitivity analyses, all linear regression analyses between a priori independent variables and SITAR growth parameters for height, tempo and velocity, and similarly between trial arm and these growth parameters, were repeated, stratified by country. In addition, anthropometry z-scores derived from WHO reference values

were used as exposures to SITAR growth parameters for height, tempo and velocity.

To further determine whether growth deficits in the cohort persisted to the cessation of linear development, sequential HAZ measurements performed at 12 weekly intervals over 96 weeks were fitted with a natural cubic spline model (with five degrees of freedom) stratified by sex to determine HAZ trajectories by age.

Comparison of age at PHV and PHV were performed against three published studies to have previously used SITAR methods in Africa, among HIV-negative adolescents, to determine pubertal delay and the strength of growth velocity in our study population (Supplementary Table 2).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, or in the decision to submit the paper for publication.

Results

The study population

The analyses describe 842 participants enrolled and followed up for 96 weeks, during which a median of 6 (IQR: 4-8) height assessments per participant were recorded. Of those enrolled, 745 (88.5%) participants had the maximum nine data points, with 97 censored [died ($n=5$), lost to follow up ($n=39$), and withdrawn ($n=53$)] (Supplementary Fig. 1 and Supplementary Table 3).

At baseline, the median age was 15.5 (IQR: 13.2–17.9) years; 53.2% ($n=448$) were female and mean (SD) standing heights were 154.4 cm (SD = 12.7) and 151.6 cm (SD = 9.6) for males and females respectively. Stunting and wasting were more commonly seen in males (stunting 42.4% and wasting 37.6%) compared to females (stunting 19.2% and wasting 23.4%). Most participants were in Tanner stages IV ($n=207$; 24.6%) and V ($n=261$; 31.1%), with a higher proportion of females ($n=170$; 38%) compared to males ($n=91$; 23.2%) in Tanner stage V. Two thirds ($n=560$) of participants reported eating dairy products either once or twice ($n=284$; 33.7%) or less than once ($n=276$; 32.6%) per week. Most participants were estimated to be consuming between 4–6 µg of dietary vitamin D ($n=496$; 58.9%) and less than 150 mg ($n=639$; 75.9%) of calcium daily. Three quarters of the AWH had 25(OH)D < 75 nmol/L. On average, participants had been initiated on ART at a median age of 5.5 [IQR: 3.9–9.2] years, spending a median 65.1% [IQR: 39.6–81.6] of their life being spent on ART such that a quarter ($n=241$; 24.9%) of AWH started ART when they were younger than 3.9 years (Table 1). The median duration of ART use was 9.8 (IQR: 6.3–12.3) years and 81.7% ($n=688$) were taking a TDF-containing ART regimen. Overall, at baseline, 164/839 (19.5%) had an HIV viral load ≥ 60 copies/mL.

Modelling growth using SITAR

For all height regions, mean SITAR growth curves plateaued at greater heights in males compared to females (Fig. 1). For the three mean SITAR curves, at least 98.2% and 99.0% of the variance in the crude individual height curves were explained by the SITAR models for males and females respectively, indicating a good model fit.

Standing height

The mean age at which peak standing height velocity was reached was 13.4 (SD = 1.2) and 15.3 (SD = 1.4) years for females and males respectively, with a mean difference between sexes of 1.9 [95% CI: 1.7–2.1] years (Table 2). The corresponding peak standing height velocities were 5.5 (SD = 0.43) and 7.6 (SD = 0.53) cm/year for females and males. The SITAR standing height parameters showed positive correlations between size and tempo, which were stronger in females ($r=0.34$) than males ($r=0.22$), suggesting AWH who were older at PHV (increased tempo) were likely to be taller. Negative correlations between velocity and size [females: −0.56; males: −0.09] provide evidence that taller standing height was correlated with lower standing height velocity (taller AWH grew more slowly). Further negative correlations between tempo and velocity [females: −0.07; males: −0.21] provide evidence that older age at peak standing height velocity is associated with lower standing height velocity in both sexes (AWH with a later age at peak height velocity than the average grew more slowly).

Comparatively, SITAR derived estimates for peak standing height velocity (age at peak standing height velocity) from rural and urban South Africa ranged from 11.4–12.4 years (6.7 −7.7 cm/year) and 13.5 −14.9 years (8.7—9.1 cm/year) for females and males respectively (Supplementary Table 2).

Appendicular height

SITAR adjusted mean growth and velocity curves for appendicular height determined age at peak appendicular velocity as 13.3 (SD = 1.1) and 15.0 (SD = 1.7) years in females and males respectively; mean between sex difference 1.7 [95% CI: 1.5–1.9] years. The peak appendicular height velocity was 4.1 (SD = 0.72) and 4.5 (SD = 0.33) cm/year in females and males respectively (Table 2). In both males and females, correlations showed older age at peak appendicular height (increased tempo) was associated with lower appendicular height velocity [female: −0.53; male: −0.42]. Additionally, a taller appendicular height (size) was correlated with lower appendicular

Table 1 Descriptives of baseline socio-demographic, growth and HIV characteristics stratified by sex

	Total (*n* = 842)	Male (*n* = 394)	Female (*n* = 448)
Socio-demographic characteristics			
Age, *median (IQR)*	15.5 (13.2–17.9)	15.7 (13.3–17.9)	15.3 (13.1–17.7)
Currently enrolled in school, *n (%)*	713 (84.7)	326 (82.7)	387 (86.4)
Socio-Economic Status quintiles, *n (%)*			
Q_1 (low)	170 (20.2)	89 (22.6)	81 (18.1)
Q_2	167 (19.8)	76 (19.3)	91 (20.3)
Q_3	175 (20.8)	70 (17.8)	105 (23.4)
Q_4	162 (19.2)	82 (20.8)	80 (17.9)
Q_5 (high)	168 (19.9)	77 (19.5)	91 (20.3)
Dairy consumption, *n (%)*			
Never	100 (11.9)	51 (12.9)	49 (10.9)
< 1/week	276 (32.8)	133 (33.8)	143 (31.9)
1–2 times/week	284 (33.7)	136 (34.6)	148 (33.0)
3–5 times/week	92 (10.9)	36 (9.1)	56 (12.5)
Almost every day	90 (10.7)	38 (9.6)	52 (11.6)
Daily dietary vitamin D intake (µg), *n (%)*			
< 4	173 (20.6)	86 (21.8)	87 (19.4)
4- < 6	496 (58.9)	228 (57.9)	268 (59.8)
6- < 8	161 (19.1)	75 (19.0)	86 (19.2)
8 +	12 (1.4)	5 (1.3)	7 (1.6)
Daily dietary calcium intake (mg), *n (%)*			
< 150	639 (75.9)	305 (77.4)	334 (74.6)
150–299	129 (15.3)	57 (14.5)	72 (16.1)
300 +	74 (8.8)	32 (8.1)	42 (9.4)
Tanner stage, *n (%)*			
I	77 (9.2)	34 (8.7)	43 (9.6)
II	129 (15.4)	84 (21.4)	45 (10.1)
III	166 (19.8)	90 (22.9)	76 (17.0)
IV	207 (24.6)	94 (23.9)	113 (25.3)
V	261 (31.1)	91 (23.2)	170 (38.0)
25(OH)D < 75 nmol/L, *n (%)*	637 (75.6)	283 (71.8)	354 (79.0)
Growth characteristics			
Standing height (cm), *mean (SD)*	152.8 (11.2)	154.4 (12.7)	151.6 (9.6)
Axial height (cm), *mean (SD)*	78.6 (5.7)	78.7 (6.4)	78.4 (5.0)
Appendicular height (cm), *mean (SD)*	74.3 (6.4)	75.9 (7.1)	73.0 (5.4)
Height for age z-score, *mean (SD)*	−1.43 (1.08)	−1.68 (1.05)	−1.21 (1.05)
Weight for age z-score, *mean (SD)*	−1.42 (1.22)	−1.90 (1.10)	−1.01 (1.17)
Height for age z-score < −2, *n (%)*	251 (29.8)	147 (37.3)	104 (23.2)
Weight for age z-score < −2, *n (%)*	253 (30.0)	167 (42.4)	86 (19.2)
BMI for age z-score < −2, n (%)	105/838 (12.5)	75/392 (19.1)	30/446 (6.7)
HIV clinical characteristics			
Age at ART initiation (years), *median (IQR)*	5.5 (4.9–9.2)	5.2 [4.8–8.5]	5.7 [4.9–9.6]
Starting ART at age > 4 years (lower quartile), *n (%)*	210 (24.9)	101 (25.6)	109 (24.3)
Percentage life on ART [a], *median (IQR)*	65.1 (39.6–81.6)	66.9 (43.9–82.4)	63.3 (36.0–80.9)
ART duration, *median (IQR)*	9.8 (6.3–12.3)	10.2 (6.6–12.5)	9.2 (5.7–12.0)
Current TDF-containing ART regimen, *n (%)*	688 (81.7)	320 (81.2)	368 (82.1)
Viral load (≥ 60 copies/ml), *n (%) [n = 839]*	165 (19.6)	84 (21.3)	81 (18.1)

[a] Percentage life on ART reflects the number of years lived since ART initiation expressed as a percentage of current age, *SD* Standard deviation, *IQR* Interquartile range, *µg* micrograms, *mg* milligrams, *25(OH)D* 25-hydroxyvitamin D, *BMI* Body mass index, *ART* Antiretroviral therapy, *TDF* Tenofovir disoproxil fumarate

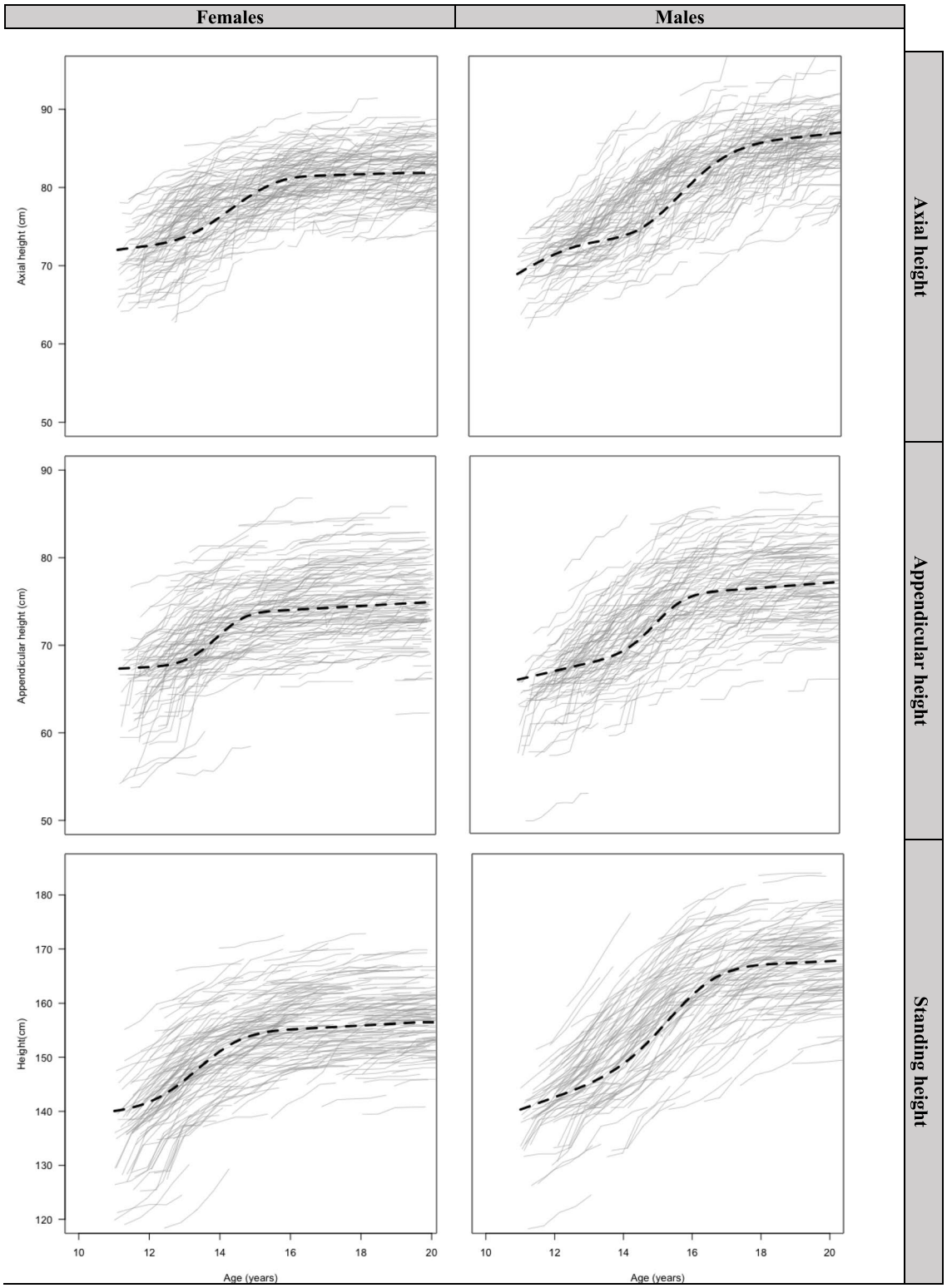


Fig. 1 Axial, appendicular and standing height SITAR growth curves by sex, fitted with the mean SITAR curve. Legend: Crude individual growth curves (in grey) for axial (top row), appendicular (middle row), and standing heights (bottom row) fitted with the mean SITAR growth curve (dashed black lines) for female (left) and males (right)

Table 2 SITAR models summary statistics and random-effects correlations for axial, appendicular and standing height, stratified by sex

	Females			Males		
	Axial height	**Appendicular height**	**Standing height**	**Axial height**	**Appendicular height**	**Standing height**
Mean growth parameters						
Tempo, *i.e.*, Age at peak height velocity (years)	13.9	13.3	13.4	15.8	15.0	15.3
Velocity, *i.e.*, Peak height velocity (cm/year)	3.5	4.1	5.5	4.5	4.5	7.6
SITAR model summary statistics						
SITAR curve degrees of freedom	3	3	4	3	3	4
Percentage of variance explained (%)	99	99.6	99.5	98.2	99.5	99.3
Model residuals SD (cm)	0.51	0.32	0.40	0.56	0.37	0.48
Correlations between growth parameters (r)						
Size-Tempo	0.50	0.52	0.34	0.33	0.49	0.22
Size-Velocity	−0.44	−0.58	−0.56	−0.42	−0.46	−0.09
Tempo-Velocity	−0.19	−0.53	−0.07	0.08	−0.42	−0.21
Variance						
Size SD (cm)	4.0	4.9	7.2	3.9	5.3	8.3
Tempo SD (years)	1.4	1.1	1.2	1.6	1.7	1.4
Velocity SD (proportion)	0.63	0.72	0.43	0.32	0.33	0.53

Percentage of variance explained in the SITAR adjusted curves for females and males, *SD* Standard deviation. Model residual SD reflects the standard deviation of the model prediction error terms (unexplained variance), such that a higher percentage of variance explained implies a lower model residual SD. Correlations between growth parameters were estimated using the Pearson correlation coefficient

height velocity [females: −0.58; males: −0.46], and an older age at peak appendicular height [females: 0.52; males: 0.49].

Axial height

SITAR adjusted mean and velocity curves for axial height determined age at peak axial height was 13.9 (SD = 1.4) and 15.8 (SD = 1.6) years in females and males respectively; mean difference: 1.9 [95% CI: 1.7–2.1] years (Fig. 2 and Table 2). Peak axial height velocity was 3.5 (SD = 0.63) and 4.5 (SD = 0.32) cm/year in females and males respectively. In both sexes, correlations showed that being taller axially (size) was associated with (i) older age at peak axial height (increased tempo) [female 0.50; male 0.33 years] and (ii) lower axial height velocity [female −0.44; male: −0.42 cm/year]. Among females, older age at peak axial height was associated with lower axial height velocity [correlation: -0.19] whilst the opposite, albeit weakly was seen in males [correlation: 0.08].

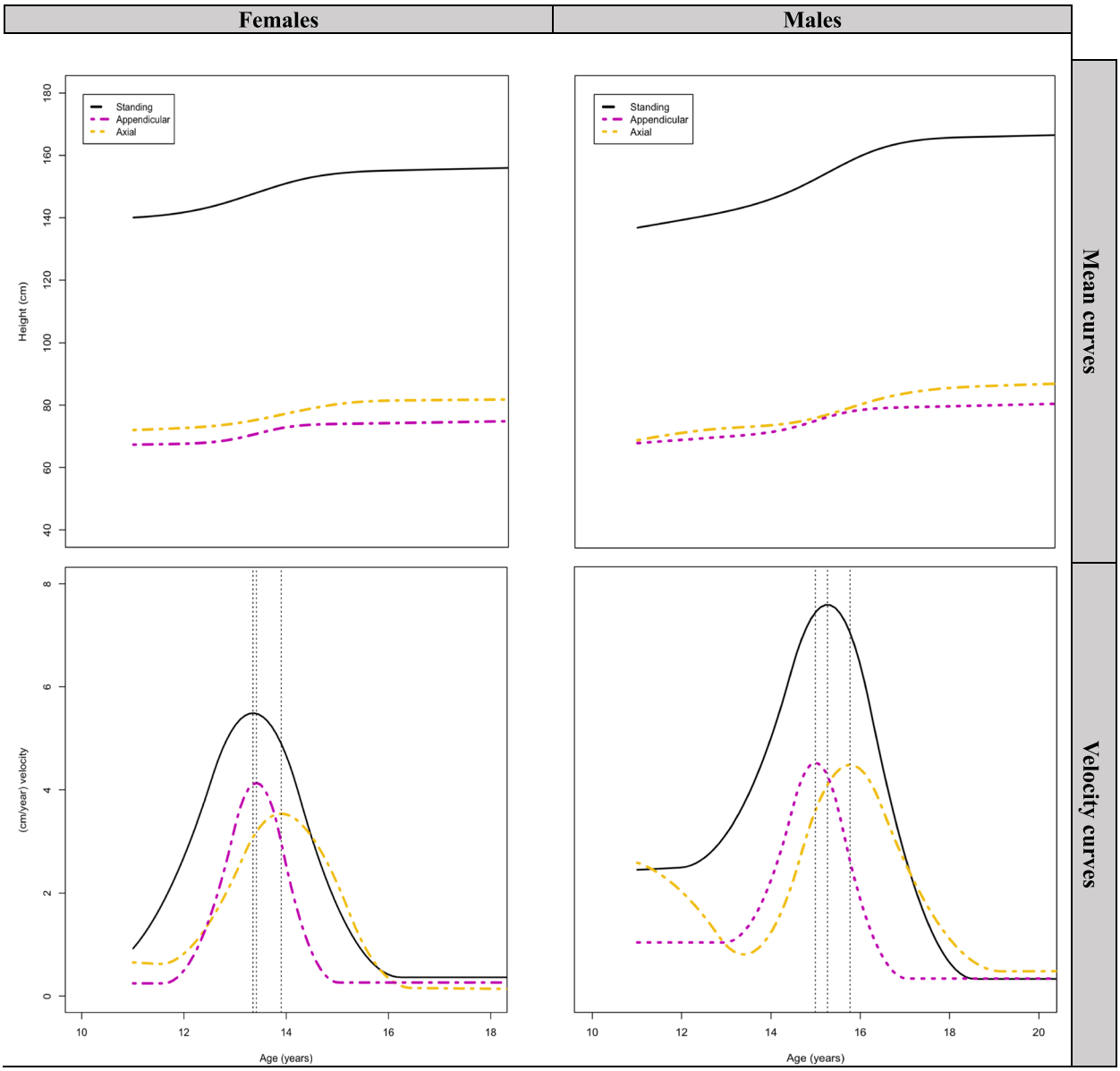
Associations between anthropometry z-scores, socio-economic, diet and HIV characteristics and SITAR growth parameters

Size (centimetres)

In both female and male AWH, higher baseline HAZ and WAZ were each associated with greater standing, axial, and appendicular height (Fig. 3). Furthermore, greater baseline BMIZ was associated with: (i) increased axial height in both males [β: 0.66 cm, 95%CI: 0.29, 1.04] and females [β:1.18 cm, 95%CI: 0.80, 1.56], and (ii) standing height in females [β:1.21 cm, 95%CI: 0.58, 1.85]. Use of TDF at baseline was positively associated with standing height among females [β: 2.01 cm, 95%CI: 0.28, 3.73]; this association was also observed for standing, appendicular, and axial height in males. Greater dietary vitamin D intake showed a positive association with standing [β: 1.41 cm, 95%CI: 0.42, 2.41] and appendicular height [β: 0.94 cm, 95%CI: 0.23, 1.65] among females, and axial size [β: 0.78 cm, 95%CI: 0.23, 1.32] in males. Greater dietary calcium intake was weakly associated with greater standing height in females, but lower standing height in males.

Tempo (years): age at peak height velocity

Higher baseline HAZ and WAZ were associated with negative tempo (*i.e.*, younger aPHV and earlier pubertal timing) for standing and axial height in both females and males (Fig. 3). For example, in males, greater HAZ was associated with an earlier axial tempo, −0.65 [95%CI: −0.77, −0.53], suggesting an SD increase in baseline HAZ results in peak axial velocity occurring 7.8 months earlier than on average in AWH. Sex-based differences in the association between baseline HAZ and appendicular tempo were seen. In males, each SD increase in HAZ was associated with younger age at peak appendicular velocity, by on average 3.2 months earlier than the mean (−0.27 [95%CI: −0.41, −0.13]). By contrast in females, each SD increase in baseline HAZ was associated with older age at peak appendicular velocity, by on average

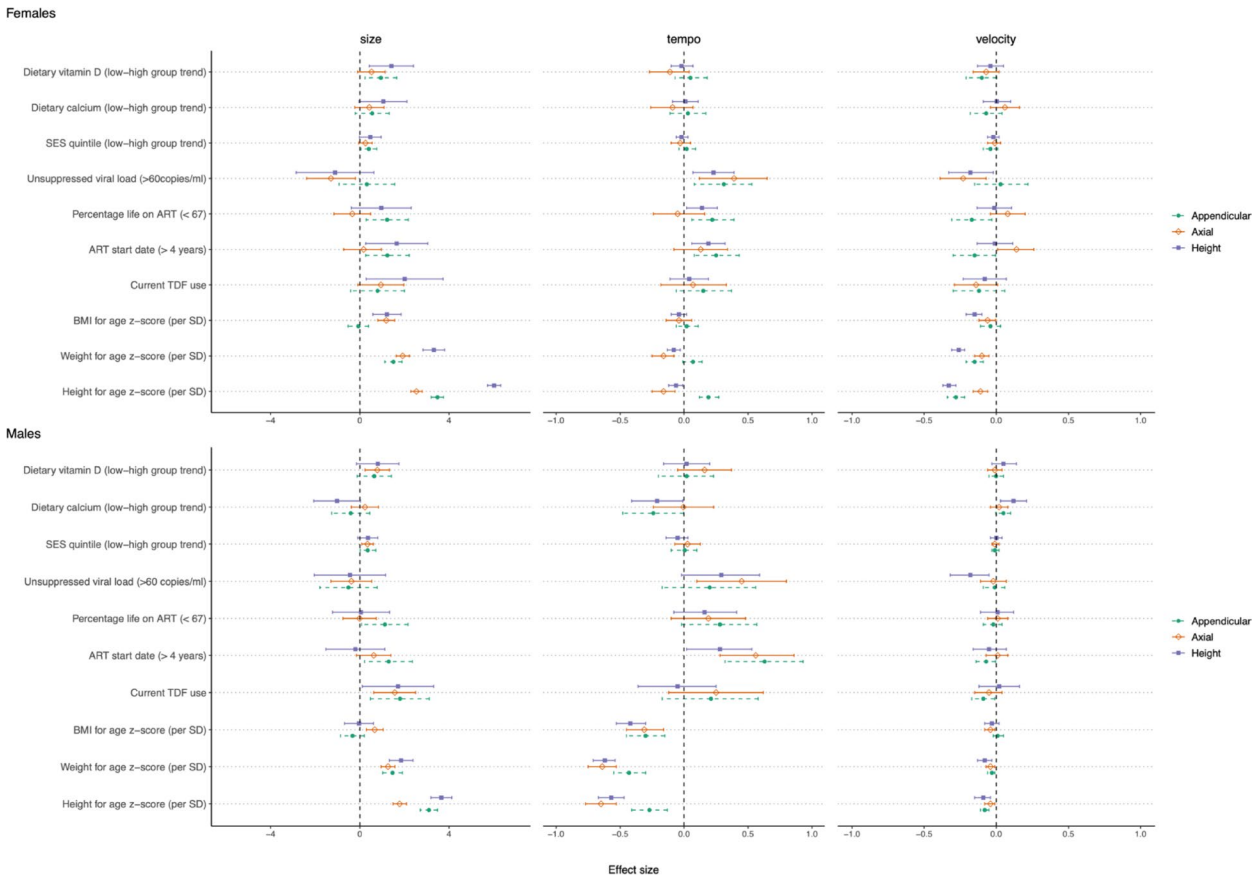


The top and bottom rows are showing mean and velocity curves respectively for standing (black), appendicular (purple) and axial (yellow) height.

Fig. 2 Mean and velocity curves for axial, appendicular and standing height for females and males. Legend: The top and bottom rows are showing mean and velocity curves respectively for standing (black), appendicular (purple) and axial (yellow) height

2.3 months later than the mean (0.19 [95%CI: 0.12, 0.27]). Among males, greater baseline BMIZ was associated with earlier age at peak height velocity for standing (−0.42 [95%CI: −0.53, −0.30], axial [−0.31 [95%CI: −0.45, −0.16] and appendicular height [−0.30 [95%CI: −0.45, −0.15]).

Participants who had delayed ART initiation until after four years of age were likely to have delayed tempo, particularly for appendicular height in both females [β: 0.25; 95%CI: 0.08, 0.43] and males [β: 0.63, 95%CI 0.32, 0.93], translating to a delay in age at peak appendicular height velocity of three and seven months respectively. A similar pattern was observed in females with those who had spent < 67% of their life on ART (67% being the median in males and females) having axial and standing height tempo delayed by on average 2.6 [β: 0.22; 95%CI: 0.06, 0.39] and 1.7 [β: 0.14; 95%CI: 0.02, 0.26] months respectively. In addition, unsuppressed viral load was associated with delayed axial height tempo in both sexes [Females: 0.39; 95%CI: 0.12, 0.65.; Males: 0.45; 95%CI: 0.10, 0.80], corresponding to a delayed tempo of 4.7 and 5.4 months



SES: Socioeconomic status; TDF; Tenofovir disoproxil fumarate; ART: Antiretroviral therapy; BMI: Body mass index; SD: Standard deviation

Fig. 3 Univariable linear regression models [β (95% CI)] for the association between demographic and anthropometry z-scores and SITAR growth parameters [size, timing of puberty (tempo) and velocity] showing a beta [95% CI] effect size. Legend: A forest plot showing univariate linear associations between dietary intake, socioeconomic status, HIV factors and malnutrition indicators with SITAR growth parameters [size (left), tempo (middle) and velocity (right) for appendicular (green), axial (orange) and standing (purple) heights. SES: Socioeconomic status; TDF; Tenofovir disoproxil fumarate; ART: Antiretroviral therapy; BMI: Body mass index; SD: Standard deviation

in females and males respectively, relative to those virally suppressed.

Velocity (cm/year): peak height velocity (cm/year)

Higher baseline HAZ and WAZ were inversely associated with velocity most notably for standing height, with a much stronger relationship in females than males. For example, in females, the univariable association between baseline HAZ and standing height velocity was −0.33 [95%CI: −0.37, −0.28], indicating a reduction in standing height velocity (i.e., slower growth) for each SD gain in baseline HAZ. Females who had been on ART for < 67% of their life were likely to have lower appendicular velocity [β: −0.17, 95%CI: −0.31, −0.03] compared to those above the median. In addition, unsuppressed viral load was associated with lower standing height velocity in both females [β: −0.18, 95%CI: −0.33, −0.02] and males [β: −0.18; 95%CI: −0.32, −0.05]. Lower axial height velocity [β: −0.23, 95%CI: −0.39, −0.07] was also noted in females with unsuppressed viral loads when compared to those virally suppressed.

No association were observed between trial arm and any of the SITAR growth parameters (Supplementary Table 4). Furthermore, HAZ trajectories over 96 weeks, stratified by sex, showed persistent negative estimates with age, particularly after the age of 19 in both sexes (Supplementary Fig. 2). In addition, no association was observed between baseline vitamin D status [25(OH) D < 75 nmol/L and SITAR growth parameters (Supplementary Fig. 3). The sensitivity analyses showed no country differences in the associations between a priori exposures and SITAR growth parameters (data not shown). Moreso, use of WHO growth reference values showed consistent prevalence of stunting ($n = 231$; 27.4%) and wasting ($n = 251$; 30.2%), as well as consistent associations between anthropometry z-scores and SITAR growth parameters (Supplementary Fig. 4).

Discussion

This study is the first to use SITAR growth modelling to understand appendicular, axial, and standing heights in an African adolescent population living with HIV through to the cessation of linear growth. Our findings demonstrate prolonged growth periods and persistent growth impairments resulting in deficits that appear to carry through into adulthood. Age at peak height velocity occurred relatively late with lower velocity in appendicular, axial, and standing heights among AWH. Our findings identify novel observations that adolescents with an unsuppressed viral load, those delayed when initiating ART, and those who spent a smaller proportion of life on ART (whilst living with HIV), were more likely to experience pubertal delay and slower growth (i.e., less intense peaks in velocity). The negative effect of an unsuppressed viral load was more pronounced on axial than appendicular growth whereas, initiating ART at an older age and spending a smaller proportion of life on ART appeared more detrimental to appendicular growth. Whilst greater dietary vitamin D intake was associated with taller size/stature, the randomised controlled trial showed that a single year of vitamin D and calcium supplementation during adolescence was insufficient to recover impairments in linear growth.

Our novel findings show that adolescents followed up through to cessation of linear growth, who (i) start ART at a later age, and (ii) who have unsuppressed viral loads were more likely to have delayed aPHV and experience less intense growth. Consistent with other studies [4], we further identified delayed aPHV and lower PHV among AWH for all skeletal regions when compared to published reports in HIV negative adolescents [24]. The potential reasons for growth failure among AWH are multifactorial including chronic inflammation, opportunistic infections, gastrointestinal illness, and nutrient malabsorption. The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) cohort, which includes participants with a median age of eight years at baseline, also reported that lower HAZ and BMIZ were associated with delayed aPHV among females and less intense PHV [5]. Our findings extend these results, showing that these relationships are sustained through from childhood and into adolescence. This means that AWH experience persistent growth impairments until cessation of linear growth resulting in deficits that will carry into adulthood and later life [25].

The current study further identified a positive association between dietary vitamin D intake and higher overall stature as reported in other studies [26]. However, the 48-week randomized controlled trial showed that a single year of supplementation during adolescence is insufficient to recover impairments in linear growth. These paradoxical findings may be explained by the dietary vitamin D questionnaire inadvertently capturing overall nutritional status, including protein-rich foods, with those who reported higher vitamin D intakes being healthier and less stunted/wasted. Furthermore, the observational analyses may have been confounded by social deprivation, closely linked to dietary patterns, whereas the trial was randomised [27]. In addition, the study observed sex dimorphism in the weak associations between calcium intake and height, as previously highlighted in other studies [28], partly explained by sex-specific changes in timing of puberty.

During growth, appendicular precedes axial development [29]. Whilst unsuppressed viral load had a more pronounced negative effect on axial than appendicular height, later initiation of ART and more lifetime lived with HIV and not exposed to ART appeared more detrimental to appendicular growth. As such, it is possible that delay in ART initiation among children, with a reported median age at ART initiation of six years (comparable to estimates across sub-Saharan Africa) [4], concurs with the temporal sequencing of growth. Impaired appendicular growth, may be explained by hepatic resistance to growth hormone or growth hormone deficiency, which is commonly seen in AWH [30], and to which the epiphyseal plates of the appendicular skeleton are sensitive. Alternatively, the axial skeleton contains predominantly trabecular bone, which may be more vulnerable to viral replication and chronic inflammation increasing bone turnover and impairing growth [31].

Study strengths include a large sample size from two settings covering a wide age-range, with older participants followed up until cessation of linear growth. Assessment of nutrition indicators and HIV specific factors allowed nuanced understanding of their effects on SITAR growth parameters. Nonetheless, lack of local anthropometric reference data meant the need to use UK data to determine undernutrition, [20] possibly resulting in misclassification. While dietary data were collected using a standardised tool, food portions and frequency food items are often poorly recalled leading to inaccuracies in determining dietary vitamin D intake. In addition, data were not captured on ART regimen changes, preventing assessment of effects on growth outcomes. Moreso, measurement of growth hormone and markers of inflammation, which were not collected in the trial, could have provided additional insights into mechanisms underlying growth patterns in AWH. The study lacked comparator data from HIV negative adolescents which could have allowed for local comparison of PHV and age at PHV.

In conclusion, this is the first study to highlight, in adolescents resident in east and southern Africa, the intricate interplay between HIV and its treatment, anthropometric indicators, dietary factors and linear growth. We observed delayed ART initiation, spending a smaller proportion of life on ART and having an unsuppressed viral load were associated with delayed aPHV for appendicular, axial, and standing heights. The study further identified that HIV infection and its treatment negatively affected the appendicular and axial regions differently. We confirmed low HAZ, WAZ, and BMIZ were associated with delayed puberty and lower peak growth velocity highlighting the importance of nutrition in growth of AWH. While in observational data higher dietary vitamin D intake was associated with increased stature, in trial data calcium and vitamin D supplementation did change growth parameters, suggesting dietary vitamin D intake may reflect a proxy measure for overall nutrition, and/or a single year of supplementation during adolescence is insufficient to recover linear growth. Taken together these findings highlight the need for holistic care approaches to address ART initiation, viral suppression and nutritional status to improve growth outcomes in AWH, to prevent growth deficits persisting into adulthood.

Abbreviations

25(OH)D	25-hydroxyvitamin-D
aPHV	Age at peak height velocity
ART	Antiretroviral therapy
AWH	Adolescence living with HIV
BMIZ	Body mass index z-score
BIC	Bayesian Information Criterion
DEQAS	Vitamin D external quality assessment
EDTA	Ethylenediaminetetraacetic acid
FAO	Food and Agriculture Organization of the United Nations
HAZ	Height for age z-score
HCHEC	Harare Central Hospital Ethics committee
HIV	Human immunodeficiency virus
IOM	Institute of Medicine
IQR	Interquartile range
LC-MS/MS	Liquid chromatography Tandem Mass Spectrometry
PHV	Peak height velocity
SD	Standard deviation
SITAR	SuperImposition by Translation And Rotation
SES	Socio economic status
TDF	Tenofovir disoproxil fumarate
VITALITY	Vitamin D for adolescents with HIV to reduce musculoskeletal morbidity and immunopathology
VL	Viral load
WAZ	Weight for age z-score

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Clinical trial
The VITALITY trial was first registered at The Pan African Clinical Trials Registry (PACTR202009897660291||http://www.pactr.org/) on 3 September 2020. The VITALITY trial protocol is publicly available.

Authors' contributions
The study was conceived by TM, CLG. Design: TM, HM, NVD, VS, LK, RAF, CLG. Data acquisition: TM, TB, VS, NVD, HBM, MC. Analysis: TM, AM, NIM, CLG. Interpretation: TM, AM, KAW, NIM, RAF, CLG. Manuscript drafting: TM, AM, CLG. Manuscript revision: TM, HM, NVD, RAF, CLG. All authors take responsibility for their contributions outlined above and have read and approved the final manuscript.

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Data availability
De-identified datasets including individual participant data and a data dictionary used and/or analysed during the current study are available from the corresponding author on reasonable request through the London School of Hygiene and Tropical Medicine (LSHTM) DataCompass repository (DOI: 10.17037/DATA.00003868).

Declarations

Ethics approval and consent to participate
All methods were carried out in line with the Declaration of Helsinki and written informed consent was obtained from guardians with written assent from participants aged <18 years. Participants aged 18 years or older and emancipated minors (those aged below 18 years who are married or have children) provided independent informed consent [32]. The study was approved by the Biomedical Research and Training Institute Institutional Review Board (reference AP158/2020), the Harare Central Hospital Ethics committee (reference HCHEC 030320/12), the Medical Research Council of Zimbabwe (reference A/2626), the University of Zambia Biomedical Research Ethics Committee (reference 1116-2020), and the London School of Hygiene and Tropical Medicine Ethics Committee (reference 22030).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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