Supplementary data

Supplement S1 – SITAR growth model

Linear growth was modelled using Super Imposition by Translation And Rotation (SITAR) models [1]. SITAR quantifies differences in growth via three parameters that represent average height, timing and intensity of the adolescent growth spurt (i.e. the period of rapid gains in height typically observed during adolescence). SITAR models can explain up to 99% of the variation between individuals' growth [1] and can be summarised as:

$$y_{it} = a_i + h\left(\frac{t - b_i}{exp^{-c_i}}\right)$$

where the outcome y_{it} represents the height of individual *i* at age *t* and h() is a natural cubic spline of height over age. In our analysis, a spline with 4 degrees of freedom was used (models with >4 degrees of freedom failed to converge). Parameters a_i, b_i and c_i are random effects representing differences between the population average and an individual's average height, timing and intensity. Larger values of a_i indicate taller height, on average, throughout adolescence and larger b_i indicates later growth spurts. c_i represents intensity and a shrinking or stretching of the age scale. Large values of c_i indicate steeper, more rapid, growth spurts with higher growth velocity while lower values result in a shallower curve.

All height measurements (in centimetres) from age 8 (or after start of ART if later) to <19 years were included. Log transformations of age and height were considered but the untransformed data provided the best fit based on adjusted Bayesian information criterion.

Growth velocity curves were estimated by taking the first derivative of the mean height curves.

1. Cole TJ, Donaldson MD, Ben-Shlomo Y. **SITAR—a useful instrument for growth curve analysis**. *International journal of epidemiology* 2010; 39(6):1558-1566.

Table S1: Characteristics of females included and excluded from analysis

	All	East & Southern Africa (excluding Botswana & South Africa)	Botswana & South Africa	West & Central Africa	Europe & N America	Asia-Pacific	Central & South America, & the Caribbean (n=241)
	(n=6,732)	(n=3,747)	(n=1,176)	(n=397)	(n=3747)	(n=534)	
				Median[IQR] or n(%)			
All							
Included	3,230 (48%)	1,706(46%)	553(47%)	211(53%)	297(47%)	342(64%)	121(50%)
Excluded	3,502(52%)	2,041(54%)	623(53%)	186(47%)	340(53%)	192(36%)	120(50%)
Year of birth							
Included	1999[1997,2000]	1999[1998,2000]	1998[1997,2001]	1998[1997,1999]	1997[1995,1999]	1999[1998,2000]	1999[1997,2000]
Excluded	2000[1998,2001]	2000[1999,2001]	1999[1998,2000]	1998[1997,1999]	1999[1996,2001]	2000[1998,2001]	1998[1997,2000]
At ART initiation							
Age (years)							
Included	7.7[6.0,8.9]	8.1[6.8,9.1]	7.8[5.8,8.8]	8.0[6.6,9.0]	5.3[2.4,7.8]	6.5[5.0,7.9]	4.1[1.7,7.1]
Excluded	7.4[5.5,8.8]	7.9[6.4,9.0]	7.2[5.3,8.6]	7.6[6.2,8.9]	3.7[0.8,6.8]	6.1[4.3,7.9]	6.1[3.8,8.1]
PI regimen							
Included	266(8%)	23(1%)	29(5%)	17(8%)	143(48%)	4(1%)	50(41%)
Excluded	363(10%)	16(1%)	53(9%)	60(32%)	203(60%)	11(6%)	20(17%)
HAZ							
Included	-2.0[-2.9,-1.1]	-2.1[-3.0,-1.2]	-2.0[-2.7,-1.2]	-1.6[-2.6,-0.6]	-1.0[-1.7,0.0]	-2.3[-3.3,-1.5]	-1.8[-2.7,-0.9]
Excluded	-2.0[-3.0,-1.1]	-2.0[-2.9,-1.0]	-2.1[-3.1,-1.3]	-2.0[-2.7,-1.3]	-0.2[-1.4,0.4]	-2.2[-3.4,-1.4]	-1.8[-2.1,-1.0]
BMIz							
Included	-0.6[-1.5,0.1]	-0.7[-1.5,0.3]	-0.5[-1.3,0.2]	-1.3[-2.2,-0.4]	0.1[-0.6,0.9]	-0.9[-1.7,-0.1]	-0.4[-1.2,0.6]
Excluded	-0.6[-1.4,0.2]	-0.7[-1.6,0.1]	-0.3[-1.0,0.5]	-1.1[-2.1,-0.3]	0.4[-0.7,1.3]	-0.8[-2.3,0.2]	-0.5[-0.9,-0.2]

In total, 6732 females were born ≥ 12 years prior to end of follow-up and potentially eligible for the analysis. 3230 had complete data at ART initiation and at least 4 heights recorded during follow-up and were included in analysis. In this table, characteristics of the 3230 included are compared to 3502 who were excluded due to missing data. HAZ and BMI at ART initiation was available for 1519 and 1476 females, respectively, excluded from the models. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index -for-age z-score; HAZ Height-for-age z-score; IQR Interquartile range; PI boosted protease inhibitor

Table S2 Characteristics of males included and excluded from analysis

	All	East & Southern Africa (excluding Botswana & South Africa)	Botswana & South Africa	West & Central Africa	Europe & N America	Asia & Pacific	Central & South America, & the Caribbean (n=144)
	(n=3,879)	(n=1,975)	(n=765)	(n=208)	(n=477)	(n=310)	
				Median[IQR] or n(%)			
All							
Included	1,493(38%)	704(36%)	263(34%)	100(48%)	208(44%)	160(52%)	58(40%)
Excluded	2,386(62%)	1,271(64%)	502(66%)	108(52%)	269(56%)	150 (48%)	86(60%)
Year of birth							
Included	1998[1996,1999]	1998[1997,1999]	1997[1996,1999]	1997[1996,1998]	1996[1993,1997]	1998[1997,1999]	1998[1996,1998]
Excluded	1998[1997,1999]	1999[1998,1999]	1998[1997,1999]	1997[1995,1997]	1997[1995,1999]	1999[1997,2000]	1998[1997,1999]
At ART initiation							
Age (years)							
Included	8.0[6.6,9.1]	8.4[7.4,9.3]	8.1[6.4,9.1]	8.6[7.6,9.4]	5.7[3.2,8.0]	7.1[5.9,8.2]	5.3[3.2,7.4]
Excluded	7.9[6.3,9.0]	8.4[7.2,9.2]	7.3[6.0,8.7]	8.4[7.4,9.1]	4.4[1.3,7.0]	7.0[5.6,8.2]	5.7[4.0,7.5]
PI regimen							
Included	182(12%)	27(4%)	13(5%)	14(14%)	108(52%)	1(1%)	19(33%)
Excluded	270(11%)	20(2%)	38(8%)	38(35%)	151(56%)	5(3%)	18(21%)
HAZ							
Included	-1.8[-2.8,-1.0]	-2.1[-2.9,-1.2]	-1.8[-2.7,-1.1]	-1.6[-2.7,-0.8]	-0.8[-1.4,0.1]	-2.5[-3.3,-1.6]	-1.8[-2.7,-1.2]
Excluded	-2.0[-3.0,-1.1]	-2.1[-3.0,-1.1]	-2.1[-3.0,-1.3]	-2.2[-2.9,-1.2]	-0.8[-1.7,0.1]	-2.3[-3.2,-1.5]	-1.7[-2.7,-1.1]
BMIz							
Included	-0.7[-1.6,0.2]	-0.8[-1.8,0.0]	-0.7[-1.4,0.2]	-1.5[-2.2,-0.7]	0.3[-0.5,1.1]	-1.0[-1.9,-0.1]	-0.3[-1.5,0.3]
Excluded	-0.7[-1.6,0.1]	-0.8[-1.8,0.0]	-0.4[-1.1,0.3]	-1.4[-2.6,-0.7]	0.2[-0.5,0.7]	-1.0[-2.4,-0.4]	-0.3[-1.3,0.3]

In total 3879 males were born ≥ 14 years prior to end of follow-up and potentially eligible for the analysis. 1493 had complete data at ART initiation and at least 4 heights recorded during follow-up and were included in analysis. In this table characteristics of the 1493 included are compared to 2386 who were excluded due to missing data. HAZ and BMI at ART initiation was available for 1218 and 1183 males, respectively, excluded from the models. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index -for-age z-score; HAZ Height-for-age z-score; IQR Interquartile range; PI boosted protease inhibitor

Table S3: Availability of height data

	Number of height measurements				Age at latest height measurement			
	Median	IQR	Min	Max	Median	IQR	Min	Max
<u>Females</u>								
All	27	[18,38]	4	108	13.9	[12.8,15.2]	12.0	19.0
Region								
East & Southern Africa	29	[19,41]	4	108	13.6	[12.7,14.8]	12.0	19.0
Botswana & South Africa	27	[22,34]	4	79	14.0	[12.9,15.7]	12.0	19.0
West & Central Africa	20	[12,46]	4	102	13.6	[12.7,14.7]	12.0	18.7
Europe & North America	19	[12,27]	4	66	15.4	[13.8,16.8]	12.0	19.0
Asia-Pacific	29	[19,41]	4	93	14.2	[13.0,15.2]	12.0	19.0
Central & South America, & the Caribbean	24	[18,36]	8	69	14.3	[13.1,16.6]	12.1	19.0
<u>Males</u>								
All	33	[23,44]	4	116	15.3	[14.6,16.4]	14.0	19.0
Region								
East & Southern Africa	37	[24,50]	4	116	15.1	[14.5,16.1]	14.0	19.0
Botswana & South Africa	34	[29,39]	5	77	15.5	[14.7,17.2]	14.0	19.0
West & Central Africa	26	[16,64]	5	97	15.0	[14.5,15.6]	14.0	18.5
Europe & North America	23	[16,30]	4	52	16.4	[15.3,17.6]	14.0	19.0
Asia-Pacific	36	[26,48]	11	106	15.1	[14.5,16.0]	14.0	19.0
Central & South America, & the Caribbean	30	[25,37]	14	70	15.4	[14.8,16.6]	14.0	18.9

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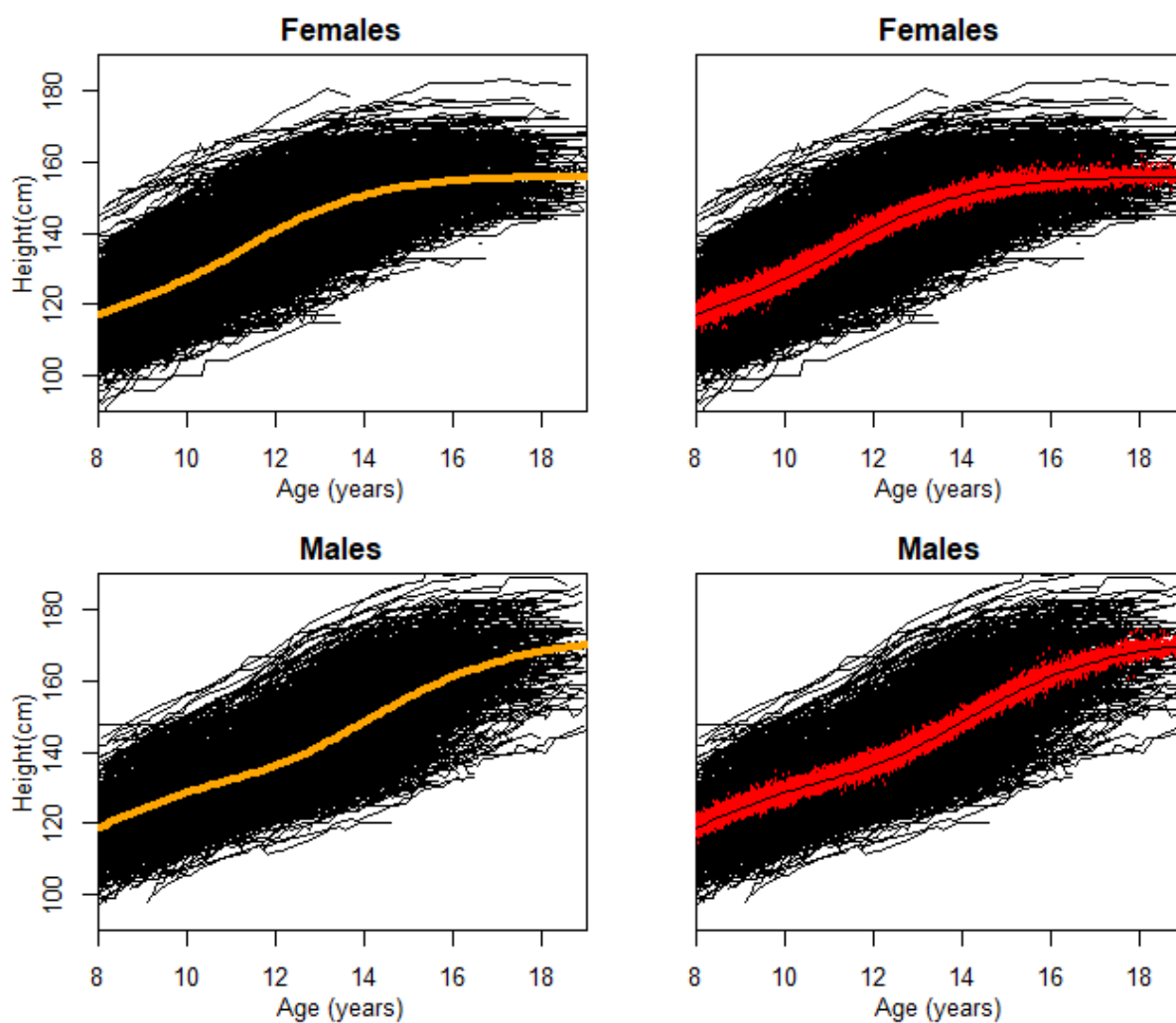
On the left, individual growth trajectories are shown along with a fitted spline. In females, the residual standard deviation (RSD) around this curve was 7.9 cm, and in males it was 8.4 cm. On the right SITAR adjusted height measurements are shown in red. In females, the RSD after adjustment was 0.9 cm, and it was 1.0 cm in males, corresponding to a reduction in variation of 97.9% and 98.0%, respectively.

Figure S1: Individual height trajectory and SITAR adjusted height measurements

Table S4: Regional variations in average height, timing, and intensity of the pubertal growth

	Females				Males			
	Coef.	Lower 95% CI	Upper 95% CI	p-value	Coef.	Lower 95% CI	Upper 95% CI	p-value
a - average height								
East & Southern Africa	ref				ref			
Botswana & South Africa	3.602	2.752	4.452	<0.001	1.557	0.103	3.011	0.036
West & Central Africa	4.979	3.712	6.246	<0.001	3.671	1.521	5.820	0.001
Europe & North America	8.299	7.207	9.390	<0.001	9.345	7.757	10.933	<0.001
Asia-Pacific	0.395	-0.633	1.424	0.451	-1.214	-2.976	0.547	0.177
Central & South America, & the Caribbean	4.284	2.651	5.918	<0.001	0.643	-2.105	3.391	0.647
b –timing of growth spurt								
East & Southern Africa	ref				ref			
Botswana & South Africa	0.434	0.306	0.563	<0.001	-0.003	-0.267	0.261	0.980
West & Central Africa	0.221	0.029	0.413	0.024	0.038	-0.353	0.428	0.850
Europe & North America	-0.370	-0.536	-0.205	<0.001	-0.494	-0.783	-0.206	0.001
Asia-Pacific	-0.009	-0.165	0.147	0.912	-0.337	-0.657	-0.017	0.039
Central & South America, & the Caribbean	-0.310	-0.558	-0.063	0.014	-0.946	-1.445	-0.447	<0.001
c –Intensity of growth spurt								
East & Southern Africa	ref				ref			
Botswana & South Africa	-0.002	-0.023	0.018	0.825	0.033	0.007	0.059	0.013
West & Central Africa	0.037	0.007	0.068	0.016	0.027	-0.012	0.065	0.178
Europe & North America	0.095	0.069	0.121	<0.001	0.111	0.082	0.139	<0.001
Asia-Pacific	0.060	0.035	0.084	<0.001	0.139	0.107	0.170	<0.001
Central & South America, & the Caribbean	0.076	0.037	0.116	<0.001	0.094	0.044	0.143	<0.001

Table S5: Multivariable analysis of association between characteristics at ART initiation and timing of the pubertal growth in females

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa	ref					
Botswana & South Africa	-1.102	0.375	-2.94	0.003	-1.838	-0.366
West & Central Africa	-0.869	0.731	-1.19	0.235	-2.303	0.565
Europe & North America	-1.640	0.323	-5.08	<0.001	-2.273	-1.007
Asia-Pacific	-1.754	0.414	-4.24	<0.001	-2.565	-0.943
Central & South America, & the Caribbean	-2.160	0.473	-4.57	<0.001	-3.087	-1.233
Initiated ART on PI based regimen	0.047	0.100	0.47	0.639	-0.149	0.243
HAZ at ART initiation (FP comp 1)	-0.067	0.009	-7.76	<0.001	-0.084	-0.050
HAZ at ART initiation (FP comp 2)	-0.011	0.001	-7.57	<0.001	-0.014	-0.008
Age at ART initiation (FP comp 1)	-0.015	0.003	-4.81	<0.001	-0.021	-0.009
Age at ART initiation (FP comp 2)	0.006	0.001	4.82	<0.001	0.004	0.009
BMIz at ART initiation	0.009	0.047	0.20	0.841	-0.083	0.102
Year of birth (FP comp 1)	-0.291	0.041	-7.10	<0.001	-0.372	-0.211
Region X Age at ART initiation						
Botswana & South Africa X Age FP Comp 1	0.016	0.005	3.32	0.001	0.007	0.026
West & Central Africa X Age FP Comp 1	0.016	0.009	1.69	0.091	-0.003	0.034
Europe & North America X Age FP Comp 1	0.012	0.005	2.33	0.020	0.002	0.022
Asia-Pacific X Age FP Comp 1	0.015	0.005	2.80	0.005	0.005	0.026
Central & South America, & the Caribbean X Age FP Comp 1	0.019	0.008	2.49	0.013	0.004	0.034
Botswana & South Africa X Age FP Comp 2	-0.007	0.002	-3.30	0.001	-0.011	-0.003
West & Central Africa X Age FP Comp 2	-0.007	0.004	-1.74	0.082	-0.014	0.001
Europe & North America X Age FP Comp 2	-0.005	0.002	-2.17	0.030	-0.009	0.000
Asia-Pacific X Age FP Comp 2	-0.006	0.002	-2.64	0.008	-0.011	-0.002
Central, & South America, & the Caribbean X Age FP Comp 2	-0.008	0.003	-2.25	0.024	-0.014	-0.001
BMIz at ART initiation X Age at ART initiation						
BMIz X Age FP Comp 1	-0.001	0.001	-0.52	0.600	-0.002	0.001
BMIz X Age FP Comp 2	0.000	0.000	0.37	0.708	-0.001	0.001
Region X Year of birth						
Botswana & South Africa	0.282	0.073	3.88	<0.001	0.139	0.425
West & Central Africa	0.128	0.157	0.81	0.416	-0.181	0.437
Europe & North America	0.261	0.094	2.79	0.005	0.077	0.445
Asia-Pacific	0.316	0.101	3.12	0.002	0.118	0.514
Central & South America, & the Caribbean	0.328	0.139	2.36	0.019	0.055	0.600

A multivariable linear regression model was used to analyse factors associated with a parameter representing timing of the pubertal growth spurt estimated using SITAR. Coefficients represent differences in timing (in years) with lower values indicating earlier growth spurts and higher values indicating later growth spurts. Age and HAZ (transformed as -HAZ/SD(HAZ), where SD(HAZ)=1.5) at ART initiation were modelled using second order fractional polynomials (FP(3 3) and FP(-1 -1), respectively) and year of birth as a first degree fractional polynomial (FP(3)). Model includes interactions between region and age at ART initiation (LRT, p=0.0002), BMIz and age at ART initiation (p=0.0250) and region and year of birth (p<0.001). Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index -for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor

Table S6: Multivariable analysis of association between characteristics at ART initiation and intensity of the pubertal growth in females

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa	ref					
Botswana & South Africa	-0.224	0.062	-3.61	0.000	-0.346	-0.102
West & Central Africa	-0.151	0.104	-1.45	0.146	-0.355	0.053
Europe & North America	-0.104	0.059	-1.76	0.078	-0.219	0.012
Asia-Pacific	0.136	0.081	1.68	0.093	-0.023	0.296
Central & South America, & the Caribbean	-0.258	0.096	-2.68	0.007	-0.447	-0.069
Initiated ART on PI based regimen	-0.014	0.016	-0.90	0.369	-0.045	0.017
HAZ at ART initiation	-0.003	0.003	-1.00	0.319	-0.010	0.003
Age at ART initiation	0.008	0.002	3.73	0.000	0.004	0.012
BMIz at ART initiation (FP comp 1)	0.093	0.026	3.61	0.000	0.042	0.143
BMIz at ART initiation (FP comp 2)	-0.038	0.011	-3.53	0.000	-0.059	-0.017
Year of birth	-0.015	0.003	-4.82	0.000	-0.021	-0.009
Region X HAZ at ART initiation						
Botswana & South Africa	-0.003	0.008	-0.42	0.673	-0.019	0.013
West & Central Africa	0.020	0.010	1.98	0.048	0.000	0.041
Europe & North America	0.006	0.009	0.64	0.521	-0.012	0.025
Asia-Pacific	0.025	0.009	2.81	0.005	0.008	0.043
Central & South America, & the Caribbean	-0.015	0.015	-0.98	0.327	-0.045	0.015
Region X year of birth						
Botswana & South Africa	0.018	0.005	3.73	0.000	0.009	0.028
West & Central Africa	0.018	0.009	2.00	0.046	0.000	0.036
Europe & North America	0.021	0.005	4.01	0.000	0.011	0.031
Asia-Pacific	-0.001	0.007	-0.17	0.865	-0.014	0.012
Central & South America, & the Caribbean	0.029	0.008	3.60	0.000	0.013	0.045

A multivariable linear regression model was used to analyse factors associated with a parameter representing the intensity of the pubertal growth spurt estimated using SITAR. Lower values indicating lower intensity growth spurts and higher values indicating and more intense and rapid growth spurts. BMIz (transformed as -BMIz/SD(BMIz), where SD(BMIz)=1.5) at ART initiation was modelled using a second order fractional polynomials (FP(2 3)). Model includes interactions between region and HAZ at ART initiation (LRT, p<0.001) and region and year of birth (p=0.0187). Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor

Table S7: Multivariable analysis of association between characteristics at ART initiation and timing of the pubertal growth in males

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa	ref					
Botswana & South Africa	-0.509	0.846	-0.60	0.548	-2.169	1.151
West & Central Africa	-4.923	1.512	-3.26	0.001	-7.889	-1.958
Europe & North America	-2.112	0.734	-2.88	0.004	-3.551	-0.672
Asia-Pacific	-3.135	1.019	-3.08	0.002	-5.135	-1.135
Central & South America, & the Caribbean	-3.485	1.664	-2.09	0.036	-6.750	-0.220

|	Coef.	Std error	t-value	p-value	Lower 95% CI	Upper 95% CI
Initiated ART on PI based regimen	-0.002	0.176	-0.01	0.992	-0.347	0.343
HAZ at ART initiation (FP comp 1)	-0.014	0.060	-0.23	0.817	-0.133	0.105
HAZ at ART initiation (FP comp 2)	-0.125	0.417	-0.30	0.764	-0.944	0.693
Age at ART initiation (FP comp 1)	0.035	0.011	3.04	0.002	0.012	0.057
Age at ART initiation (FP comp 2)	-0.015	0.005	-3.18	0.002	-0.025	-0.006
BMIz at ART initiation	0.000	0.033	-0.01	0.992	-0.066	0.065
Year of birth	-0.155	0.057	-2.70	0.007	-0.267	-0.042
Region X year of birth						
Botswana & South Africa	0.047	0.079	0.59	0.553	-0.108	0.201
West & Central Africa	0.502	0.151	3.31	0.001	0.204	0.799
Europe & North America	0.198	0.073	2.73	0.006	0.056	0.341
Asia-Pacific	0.244	0.095	2.57	0.010	0.058	0.431
Central & South America & the Caribbean	0.247	0.159	1.55	0.121	-0.065	0.559
HAZ at ART initiation X Age at ART initiation						
HAZ FP Comp 1 X Age FP Comp 1	0.002	0.001	1.79	0.073	0.000	0.004
HAZ FP Comp 1 X Age FP Comp 2	-0.001	0.000	-1.87	0.062	-0.002	0.000
HAZ FP Comp 2 X Age FP Comp 1	-0.017	0.008	-2.18	0.029	-0.032	-0.002
HAZ FP Comp 2 X Age FP Comp 2	0.007	0.003	2.28	0.023	0.001	0.014

A multivariable linear regression model was used to analyse factors associated with a parameter representing timing of the pubertal growth spurt estimated using SITAR. Coefficients represent differences in timing (in years) with lower values indicating earlier growth spurts and higher values indicating later growth spurts. Age and HAZ (transformed as -HAZ/SD(HAZ) at ART initiation were modelled using second order fractional polynomials (FP(3 3) and FP(-1 -0.5), respectively). Model includes interactions between region and year of birth (LRT, p=0.0014) and HAZ and age at ART initiation (p=0.0387). Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor

Table S8: Multivariable analysis of association between characteristics at ART initiation and intensity of the pubertal growth in males

|	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa	ref					
Botswana & South Africa	0.028	0.014	2.05	0.041	0.001	0.055
West & Central Africa	0.021	0.020	1.03	0.305	-0.019	0.060
Europe & North America	0.090	0.022	4.00	<0.001	0.046	0.134
Asia-Pacific	0.134	0.017	7.92	<0.001	0.101	0.168

Central & South America, & the Caribbean	0.083	0.028	2.98	0.003	0.028	0.137
Initiated ART on PI based regimen	-0.006	0.018	-0.33	0.745	-0.041	0.029
HAZ at ART initiation	0.007	0.004	2.00	0.046	0.000	0.015
Age at ART initiation	-0.001	0.003	-0.28	0.782	-0.008	0.006
BMIz at ART initiation	-0.025	0.012	-2.10	0.036	-0.048	-0.002
Year of birth	-0.004	0.003	-1.21	0.227	-0.010	0.002
BMIz at ART initiation X Age at ART initiation	0.003	0.002	2.19	0.028	0.000	0.006

A multivariable linear regression model was used to analyse factors associated with a parameter representing the intensity of the pubertal growth spurt estimated using SITAR. Lower values indicating less intense growth spurts and higher values indicating more intense and rapid growth spurts. Model includes an interaction between BMIz and age at ART initiation (LRT, p=0.0277). Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor

Timing of female growth spurt

Intensity of female growth spurts
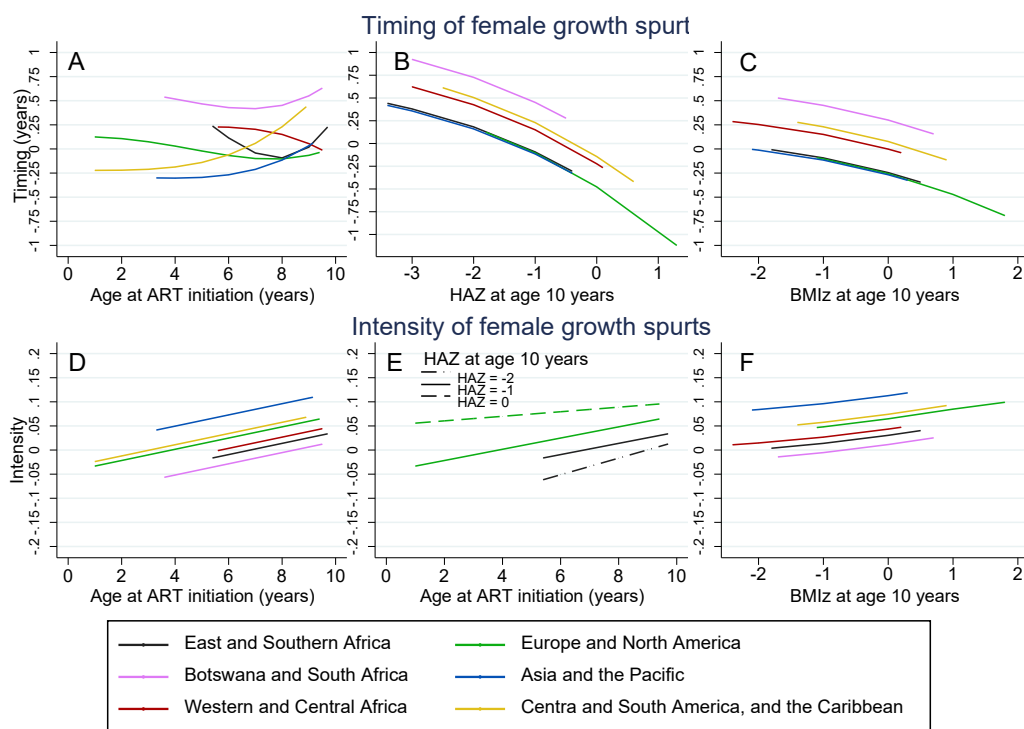
On the y-axes, 0 represents the average time (A-C) and average intensity (D-F) of the growth spurt across all females in the analysis. Lower values represent earlier/less intense growth spurts and higher values later/more intense growth spurts. For example, A demonstrates that increasing age at ART is associated with later growth spurts, though there is some variation by region. D shows that increasing age at ART initiation is associated with more intense growth spurts. Lines represent differences in timing/intensity across regions for adolescents born in 1999, who initiated an NNRTI regimen, with a BMIz of -1 (in panels A, B, D, E), HAZ of -1 (A, C, D, F) at age 8 years (B, E, F). Lines are restricted to the 10th-90th percentile of age, HAZ and BMIz observed in each region. The interaction between HAZ and age for timing (panel E) is illustrated for adolescents in East and Southern Africa and Europe and North America. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; NNRTI Non-nucleoside reverse transcriptase inhibitor

Figure S2: Female pubertal growth: Multivariable associations between region, age at ART initiation, HAZ and BMIz at age 10 years and the timing and intensity of the pubertal growth spurt in females in the CIPHER global cohort collaboration, 1994-2015.
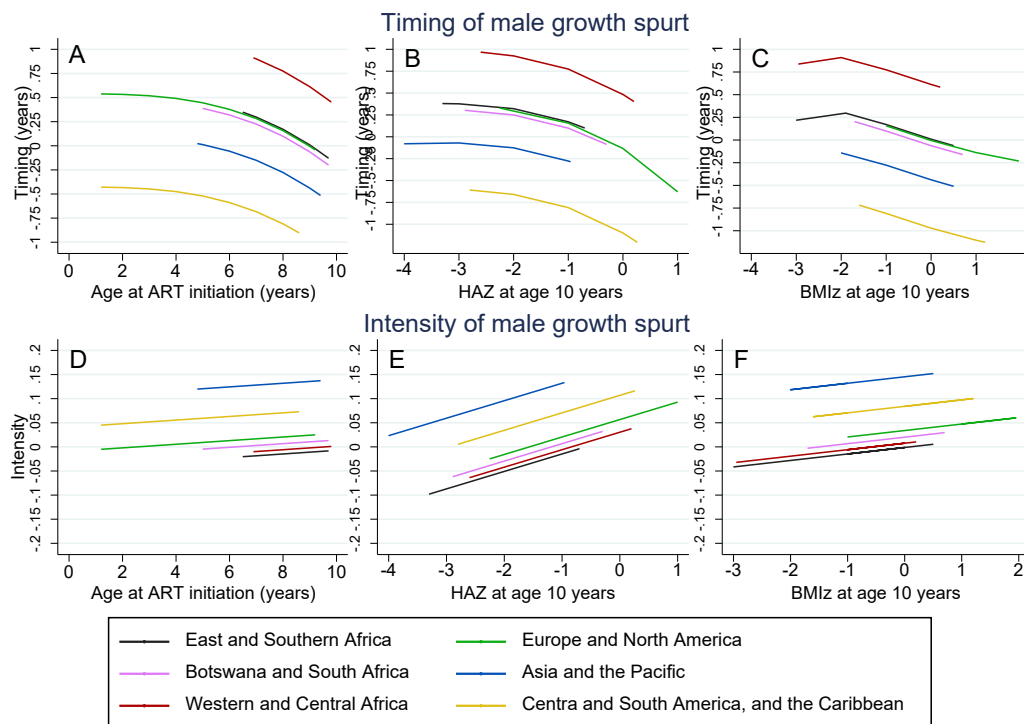
On the y-axes, 0 represents the average time (A-C) and average intensity (D-F) of the growth spurt across all males in the analysis. Lower values represent earlier/less intense growth spurts and higher values later/more intense growth spurts. For example, A demonstrates that increasing age at ART is associated with later growth spurts up to around age 7, and earlier growth spurts after age 7 years. D shows that increasing age at ART initiation is associated with more intense growth spurts. Lines represent differences in timing/intensity across regions for males born in 1998, who initiated an NNRTI regimen, with a BMIz of -1 (in panels A, B, D, E), HAZ of -1 (A, C, D, F) at age 8 years (B, C, E). Lines are restricted to the 10th-90th percentile of age, HAZ and BMIz observed in each region. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; NNRTI Non-nucleoside reverse transcriptase inhibitor

Figure S3: Male pubertal growth: Multivariable associations between region, age at ART initiation, HAZ and BMIz at age 10 years and the timing and intensity of the pubertal growth spurt in males in the CIPHER global cohort collaboration, 1994-2015.

Table S9: Multivariable analysis of association between characteristics at age 10 years and timing of the pubertal growth in females

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa	ref					
Botswana & South Africa	-2.104	0.639	-3.29	0.001	-3.357	-0.851
West & Central Africa	0.406	1.094	0.37	0.710	-1.738	2.550
Europe & North America	-0.017	0.560	-0.03	0.975	-1.116	1.081
Asia-Pacific	-1.397	0.773	-1.81	0.071	-2.913	0.119
Central & South America, & the Caribbean	-1.811	0.953	-1.9	0.058	-3.679	0.058
Initiated ART on PI based regimen	0.047	0.100	0.47	0.639	-0.149	0.243
HAZ at age 10 years (FP comp 1)	0.018	0.002	10	<0.001	0.015	0.022
HAZ at age 10 years (FP comp 2)	-0.467	0.032	-14.65	<0.001	-0.529	-0.404
Age at ART initiation (FP comp 1)	-0.016	0.003	-5.38	<0.001	-0.021	-0.010
Age at ART initiation (FP comp 2)	0.007	0.001	5.37	<0.001	0.004	0.009
BMIz at age 10 years (FP comp 1)	0.004	0.002	2.41	0.016	0.001	0.008
BMIz at age 10 years (FP comp 2)	-0.155	0.027	-5.69	<0.001	-0.208	-0.102
Year of birth (FP comp 1)	0.384	0.328	1.17	0.241	-0.259	1.027
Year of birth (FP comp 2)	-1.105	0.533	-2.07	0.038	-2.150	-0.060
Region X Year of birth						
Botswana & South Africa X year FP comp 1	1.318	0.487	2.71	0.007	0.363	2.273
West & Central Africa X year FP comp 1	-1.065	0.884	-1.2	0.228	-2.799	0.668
Europe & North America X year FP comp 1	-0.874	0.453	-1.93	0.054	-1.764	0.015
Asia-Pacific X year FP comp 1	0.001	0.631	0	0.998	-1.236	1.239
Central & South America, & the Caribbean X year FP comp 1	0.388	0.765	0.51	0.612	-1.112	1.887
Botswana & South Africa X year FP comp 2	-1.629	0.782	-2.08	0.037	-3.162	-0.097
West & Central Africa X year FP comp 2	2.028	1.657	1.22	0.221	-1.221	5.277
Europe & North America X year FP comp 2	2.184	0.832	2.62	0.009	0.552	3.816
Asia-Pacific X year FP comp 2	0.451	1.065	0.42	0.672	-1.636	2.538
Central & South America, & the Caribbean X year FP comp 2	-0.159	1.290	-0.12	0.902	-2.688	2.369
Region X Age at ART initiation						
Botswana & South Africa X Age FP Comp 1	0.011	0.005	2.29	0.022	0.002	0.021
West & Central Africa X Age FP Comp 1	0.018	0.010	1.82	0.069	-0.001	0.037
Europe & North America X Age FP Comp 1	0.012	0.005	2.36	0.018	0.002	0.022

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Asia-Pacific X Age FP Comp 1	0.014	0.005	2.62	0.009	0.004	0.025
Central & South America, & the Caribbean X Age FP Comp 1	0.016	0.008	2.06	0.040	0.001	0.030
Botswana & South Africa X Age FP Comp 2	-0.005	0.002	-2.2	0.028	-0.009	0.000
West & Central Africa X Age FP Comp 2	-0.008	0.004	-1.86	0.063	-0.015	0.000
Europe & North America X Age FP Comp 2	-0.005	0.002	-2.27	0.023	-0.009	-0.001
Asia-Pacific X Age FP Comp 2	-0.006	0.002	-2.43	0.015	-0.010	-0.001
Central, & South America, & the Caribbean X Age FP Comp 2	-0.006	0.003	-1.83	0.068	-0.013	0.000

A multivariable linear regression model was used to analyse factors associated with a parameter representing timing of the pubertal growth spurt estimated using SITAR. Coefficients represent differences in timing (in years) with lower values indicating earlier growth spurts and higher values indicating later growth spurts. Age, HAZ (transformed as -HAZ/SD(HAZ), where SD(HAZ)=1.3) at age 10 years, and BMIz (transformed as -BMIz/SD(BMIz), where SD(BMIz)=1.1) at age 10 years and year of both were modelled using second order fractional polynomials (FP(3 3) , FP(-1 -1), FP(-1 -0.5) and FP (3 3) respectively). Model includes interactions between region and age at ART initiation (LRT, p=0.0029), and region and year of birth (p<0.0001). 3088 females with data available at age 10 years were included in the model. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor

Table S10: Multivariable analysis of association between characteristics at age 10 years and intensity of the pubertal growth in females

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa						
Botswana & South Africa	-0.207	0.059	-3.51	0.000	-0.322	-0.091
West & Central Africa	-0.187	0.102	-1.83	0.068	-0.388	0.014
Europe & North America	-0.162	0.058	-2.77	0.006	-0.277	-0.047
Asia-Pacific	0.075	0.078	0.96	0.337	-0.078	0.228
Central & South America, & the Caribbean	-0.251	0.097	-2.6	0.009	-0.441	-0.062
Initiated ART on PI based regimen	-0.018	0.016	-1.07	0.284	-0.050	0.015
HAZ at age 10 years (FP comp 1)	-0.009	0.002	-4.36	0.000	-0.013	-0.005
HAZ at age 10 years (FP comp 2)	0.142	0.020	6.98	0.000	0.102	0.181
Age at ART initiation	0.032	0.005	6.69	0.000	0.022	0.041
BMIz at age 10 years (FP comp 1)	-0.001	0.000	-3.74	0.000	-0.002	-0.001
BMIz at age 10 years (FP comp 2)	0.020	0.004	4.59	0.000	0.012	0.029
Year of birth	-0.015	0.003	-4.84	0.000	-0.021	-0.009
Region X year of birth						
Botswana & South Africa	0.017	0.005	3.47	0.001	0.007	0.027
West & Central Africa	0.018	0.009	2	0.046	0.000	0.036
Europe & North America	0.018	0.005	3.4	0.001	0.008	0.028
Asia-Pacific	0.001	0.006	0.1	0.917	-0.012	0.013
Central & South America & the Caribbean	0.027	0.008	3.21	0.001	0.010	0.043
HAZ at age 10 ears X Age at ART initiation						
HAZ FP Comp 1 X Age	0.001	0.000	3.66	0.000	0.000	0.001
HAZ FP Comp 2 X Age	-0.011	0.002	-4.53	0.000	-0.016	-0.006

A multivariable linear regression model was used to analyse factors associated with a parameter representing the intensity of the pubertal growth spurt estimated using SITAR. Lower values indicating lower intensity growth spurts and higher values indicating and more intense and rapid growth spurts. HAZ transformed as -HAZ/SD(HAZ), where SD(HAZ)=1.3) and BMIz (transformed as -BMIz/SD(BMIz), where SD(BMIz)=1.1) at age 10 years were modelled using a second order fractional polynomials (both FP(-1 -0.5)). Model includes interactions between region and year of birth (LRT, p=0.001) and age at ART initiation and HAZ at age 10 years (p<0.001). 3088 females with data available at age 10 years were included in the model. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor

Table S11: Multivariable analysis of association between characteristics at age 10 years and timing of the pubertal growth in males

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa	-0.038	0.858	-0.04	0.964	-1.721	1.644
Botswana & South Africa	-4.424	1.540	-2.87	0.004	-7.445	-1.403
West & Central Africa	-1.806	0.741	-2.44	0.015	-3.260	-0.353
Europe & North America	-2.909	1.035	-2.81	0.005	-4.939	-0.879
Asia-Pacific	-2.585	1.749	-1.48	0.140	-6.016	0.847
Initiated ART on PI based regimen	-0.019	0.182	-0.1	0.917	-0.376	0.338
HAZ at age 10 years (FP comp 1)	-0.433	0.133	-3.26	0.001	-0.693	-0.173
HAZ at age 10 years (FP comp 2)	-0.191	0.144	-1.33	0.184	-0.473	0.091
Age at ART initiation (FP comp 1)	-0.001	0.000	-3.24	0.001	-0.001	0.000
BMIz at age 10 years (FP comp 1)	1.618	0.478	3.38	0.001	0.680	2.557
BMIz at age 10 years (FP comp 2)	-0.896	0.265	-3.38	0.001	-1.416	-0.376
Year of birth	-0.144	0.059	-2.46	0.014	-0.259	-0.029
Region X year of birth						
Botswana & South Africa	-0.003	0.080	-0.04	0.970	-0.159	0.153
West & Central Africa	0.457	0.154	2.96	0.003	0.155	0.760
Europe & North America	0.163	0.072	2.25	0.024	0.021	0.305
Asia-Pacific	0.224	0.096	2.32	0.020	0.035	0.413
Central & South America & the Caribbean	0.146	0.165	0.88	0.378	-0.178	0.470

A multivariable linear regression model was used to analyse factors associated with a parameter representing timing of the pubertal growth spurt estimated using SITAR. Coefficients represent differences in timing (in years) with lower values indicating earlier growth spurts and higher values indicating later growth spurs. Age, HAZ (transformed as -HAZ/SD(HAZ), where SD(HAZ)=1.3) and BMIz (transformed as -HAZ/SD(BMIz), where SD(BMIz)=1.1) at age 10 years were modelled using fractional polynomials (FP(3), FP(0 -0.5) and FP(0.5 1), respectively). Model includes interaction between region and year of birth (LRT, p=0.004). 1427 males with data available at age 10 years were included in the model. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor

Table S12: Multivariable analysis of association between characteristics at age 10 years and Intensity of the pubertal growth in males

	Coef.	Standard error	t-value	p-value	Lower 95% CI	Upper 95% CI
Region						
East & Southern Africa	ref					
Botswana & South Africa	0.021	0.014	1.58	0.115	-0.005	0.048
West & Central Africa	0.009	0.020	0.45	0.655	-0.030	0.048
Europe & North America	0.035	0.022	1.57	0.116	-0.009	0.079
Asia-Pacific	0.147	0.016	8.9	0.000	0.114	0.179
Central & South America, & the Caribbean	0.085	0.028	3.1	0.002	0.031	0.139
Initiated ART on PI based regimen	-0.010	0.018	-0.56	0.577	-0.044	0.025
HAZ at age 10 years	0.036	0.004	8.15	0.000	0.027	0.045
Age at ART initiation	0.004	0.003	1.13	0.258	-0.003	0.010
BMIz at age 10 year	0.013	0.005	2.97	0.003	0.005	0.022
Year of birth	-0.004	0.003	-1.23	0.217	-0.010	0.002

A multivariable linear regression model was used to analyse factors associated with a parameter representing the intensity of the pubertal growth spurt estimated using SITAR. Lower values indicating less intense growth spurts and higher values indicating more intense and rapid growth spurts. 1427 males with data available at age 10 years were included in the model. Abbreviations: ART Antiretroviral therapy; BMIz Body Mass Index-for-age z-score; HAZ Height-for-age z-score; PI boosted protease inhibitor