Global Variations in Pubertal Growth in Adolescents Living with Perinatal HIV

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BACKGROUND

Adolescents living with perinatally acquired HIV experience puberty later than HIV-exposed uninfected young people[1].

This study describes factors associated with timing of the adolescent growth spurt in adolescents living with HIV, including differences between geographical regions.

INCLUSION CRITERIA

The CIPHER Cohort Collaboration pooled observational data from 1994-2015 across 12 paediatric HIV cohort networks in 48 countries.

Adolescents living with perinatally acquired HIV were eligible for inclusion in this analysis if they:

- **initiated combination ART (cART) before age 10 years**,
- **had ≥4 height measurements aged 8-18 years** including ≥1 measurement aged ≥12 years for females and ≥14 years for males (based on expected age at peak height velocity),
- had **height and weight measurements at ART initiation** (within 6 months before to 1 month after).

STATISTICAL ANALYSIS

Height-for-age (HAZ) and BMI-for-age z-scores (zBMI) were calculated using the WHO Growth Standard[2] and WHO 2007 growth reference[3].

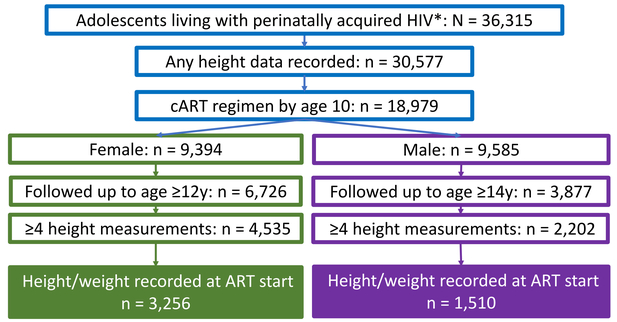
We used SITAR (Super Imposition by Translation And Rotation) models[4] to model height from age 8-18 years separately in males and females.

- SITAR models can be used to estimate 3 parameters which represent how an individual differs from the average growth of all patients in terms of mean height, timing and intensity* of the pubertal growth spurt.

Multivariable linear regression models were then used to explore characteristics associated with timing of the adolescent growth spurt.

* A more intense growth spurt is one which may be short in duration but during which the adolescent grows rapidly. Less intense growth spurts occur over longer periods of time, with less rapid growth.

SAMPLE CHARACTERISTICS



*entered care before age 10 years, with no known non-vertical route of HIV infection and were followed beyond age 10 years

Figure 1: Flow diagram

- 18,979 adolescents initiated cART by age 10 years, 49.5% were female (Fig 1).
- 3,256 females and 1,510 males had sufficient data to be included in the multivariable models.
- Those excluded were more likely to be from sub-Saharan Africa and/or to have started ART at a younger age.

Table 1: Characteristics of adolescents included in the analysis

	Botswana & South Africa	Eastern & Southern Africa*	Western & Central Africa	Europe & North America	Asia - Pacific	Latin America & Caribbean
	Median[IQR] or n(%)					
	n=815	n=2,456	n=307	n=506	n=504	n=178
Year of birth	1998[96,00]	1999[98,00]	1998[96,99]	1996[94,98]	1999[98,00]	1998[96,00]
Female sex	552(68%)	1,736(71%)	208(68%)	297(59%)	343(68%)	120(67%)
At ART initiation:						
Calendar year	2005[04,07]	2006[05,08]	2005[05,06]	2001[99,03]	2005[03,06]	2003[01,04]
Age (years)	7.9[6.0,8.9]	8.2[7.0,9.2]	8.2[6.9,9.1]	5.5[2.7,7.9]	6.9[5.3,8.1]	4.4[2.0,7.1]
First regimen						
PI + ≥2NRTI	42(5%)	50(2%)	32(10%)	251(50%)	5(1%)	69(39%)
NNRTI + ≥2NRTI	773(95%)	2,391(97%)	275(90%)	231(46%)	497(99%)	106(60%)
3 NRTIs **	0	15(1%)	0	24(5%)	2(0%)	3(2%)
Height-for-age z-score	-1.9[-2.7,-1.2]	-2.1[-3.0,-1.2]	-1.6[-2.6,-0.7]	-0.9[-1.7,0.1]	-2.4[-3.3,-1.5]	-1.8[-2.7,-1.1]
Weight-for-age z-score	-1.6[-2.5,-0.9]	-1.9[-2.9,-1.1]	-1.9[-3.0,-1.0]	-0.4[-1.2,0.4]	-2.2[-3.3,-1.2]	-1.3[-2.4,-0.5]
BMI-for-age z-score	-0.6[-1.3,0.2]	-0.7[-1.5,0.0]	-1.3[-2.2,-0.5]	0.2[-0.6,1.0]	-0.9[-0.6,1.0]	-0.3[-1.2,0.5]

*excluding Botswana and South Africa, **including Abacavir

VARIATIONS IN TIMING OF PUBERTAL GROWTH SPURT

- In **females**, being born in more recent calendar years (p=0.002) and higher zBMI at ART initiation (p=0.015) were independently associated with earlier growth spurts (Table 2).
- Timing of the growth spurt also varied by region and HAZ (p=0.017); overall **females** in Sub-Saharan Africa and those with lower HAZ at ART experienced later growth spurts (Fig 2).
  - In Asia-Pacific, for every 1SD decrease in HAZ, the **female** growth spurt occurred 3.5 (95%CI 2.2, 4.7) months later, compared to 1.3 (0.8,1.7) months in other regions.

- In **males**, higher zBMI at ART initiation was associated with an earlier growth spurt (p=0.005) (Table 2).
- **Males** with both lower HAZ and older age at ART start experienced later growth spurts (Fig 3).
- Differences across regions were also observed (p<0.001); the growth spurt occurred 9 months earlier in **males** in Asia-Pacific and Latin America, compared to Eastern and Southern Africa (Table 2).

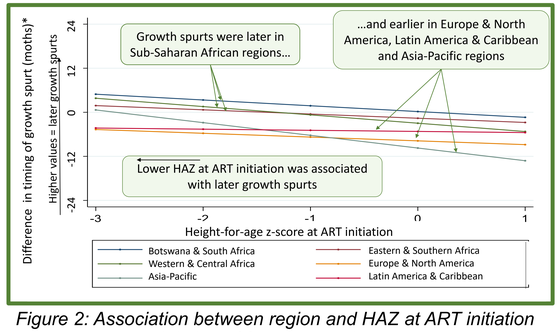


Figure 2: Association between region and HAZ at ART initiation and timing of female growth spurts

* On the y-axis, 0 represents the average time of the growth spurt across all females included in the analysis. Lower values represent earlier growth spurts and higher values represent later growth spurts. Lines represent differences by region and HAZ in timing for an adolescent born in 1999, who initiated an NNRTI regimen at age 7 years with a zBMI=-1.

Table 2: Multivariable analysis for timing of pubertal growth spurt

	Female			Male		
	Coef	95% CI	P-value	Coef	95% CI	P-value
Year of birth (per 1 year increase)	-0.5	-0.8, -0.2	0.002	-0.2	-0.8, 0.4	0.563
Region						
Botswana & South Africa				-1.1	-3.7, 1.4	<0.001
Eastern & Southern Africa				ref		
Western & Central Africa	HAZ x region p=0.017** (see Fig 2)			-0.7	-4.5, 3.1	
Europe & North America				-6.6	-10.6,-2.5	
Asia-Pacific				-8.5	-11.7,-5.4	
Latin America & Caribbean				-8.8	-13.9,-3.6	
HAZ at ART start (per 1SD decrease*)				Age X HAZ p=0.009 (see Fig 3)		
Age at ART start (per 1 year increase)	0.3	0.0, 0.6	0.074			
Initial PI regimen	0.0	-2.4, 2.6	0.991	1.4	-2.0, 4.7	0.427
zBMI at ART start (per 1SD increase)	-0.5	-0.9, -0.1	0.015	-0.9	-1.5, -0.3	0.005

Coefficients represent the difference in months in the timing of the pubertal growth spurt. Negative values indicate an earlier growth spurt, and positive a later growth spurt. *The relationship between timing of male growth spurts and HAZ was found to be non-linear and best fitting model obtained when HAZ was transformed as exp(-HAZ/SD(HAZ)). ** In a separate model, excluding the Asia-Pacific region, there was no evidence that the association between timing of the growth spurt and HAZ differed across other regions (p=0.584)

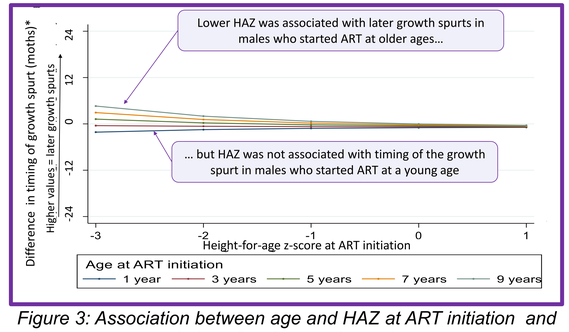


Figure 3: Association between age and HAZ at ART initiation and timing of male growth spurts

* On the y-axis, 0 represents the average time of the growth spurt across all males included in the analysis. Lower values represent earlier growth spurts and higher values represent later growth spurts. Lines represent differences by age and HAZ at ART start in timing for an adolescent born in 1999 in Easter and Southern Africa, who initiated an NNRTI regimen with a zBMI=-1.

CONCLUSIONS

- Starting ART when stunted was associated with a delayed pubertal growth spurt in females globally, irrespective of age at ART. In males being stunted was only associated with timing in those who started ART at an older age.
- Growth spurts were later in Sub-Saharan Africa in both males and females.
- Longer term follow-up is important to understand the impact of these delays on outcomes later in life.

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