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Educational delays among children living with perinatally-acquired HIV in Johannesburg, South Africa

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ABSTRACT

Little is known about how growing up with HIV impacts educational outcomes in sub-Saharan African children. We evaluated if South African children living with HIV (CLWH) were in the appropriate school grade-for-age compared to uninfected control children. We observed higher rates of not being in the correct grade-for-age in CLWH compared with controls (OR 3.32, 95% CI: 2.07-5.34), adjusted for study site, sex, whether the child's biological father was alive, and caregiver education. Initiation of ART before 6 months of age reduced but did not eliminate this association. Whether these associations are due to biological factors or other social and environmental determinants, and how best to support CLWH to achieve educational goals, warrants further investigation.

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Introduction

Currently an estimated 1.8 million children <15 years are living with HIV (CLWH) worldwide, including 1.2 million in Eastern and Southern Africa (UNAIDS, 2017). The success of antiretroviral therapy (ART), particularly when started in the first year of life, has transformed HIV from an acute, fatal disease to a lifelong chronic condition (Hazra, Siberry, & Mofenson, 2010). However, CLWH face a range of complicated issues, including morbidity associated with lifelong HIV infection and ART, and challenges associated with stigma, discrimination, disclosure of a child's diagnosis, and adherence.

Education is universally recognized to be important for child development, and educational achievement is a predictor of later life health and economic productivity (Link & Phelan, 1995). As CLWH age into adolescence and adulthood, it is important to monitor milestones related to school and employment (Abrams et al., 2018; Mofenson & Cotton, 2013; Sohn & Hazra, 2013). In limited resource settings, there have been studies of educational outcomes in children affected by HIV, defined as having lost one or both parents to HIV/AIDS or living with an HIV-infected parent (Guo, Li, & Sherr, 2012; Orkin, Boyes, Cluver, & Zhang, 2014; Pufall et al., 2014). A review of 23 studies found educational disadvantages among children affected by HIV for various outcomes, including reduced school enrollment, attendance, and performance as well as lower educational attainment (Guo et al., 2012). However, there are few studies of educational outcomes among CLWH on modern antiretroviral regimens who initiated ART at early ages, particularly in sub-Saharan Africa, which bears 90% of the pediatric HIV epidemic (UNAIDS, 2017). Initiating ART early in the first year or life regardless of clinical symptoms and regardless of CD4 status has been recommended by the World Health Organization since 2008 (Organization, 2006, 2010).

In this study, we investigated whether or not children were in the appropriate grade-for-age in a cohort of school-aged CLWH and controls in South Africa. In addition, we evaluated whether or not there were differences in educational outcomes between CLWH who initiated ART early (<6 months of age) vs. later (≥6 months of age).

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Materials and methods

Study population

Data for this study came from a cross-sectional sample of CLWH and uninfected controls enrolled in Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study (CHANGES), a longitudinal cohort study of CLWH and HIV-uninfected controls 4–9 years of age at entry into the study in Johannesburg, South Africa (Ramteke et al., 2017). In brief, CHANGES was conducted at two sites: Empilweni Services and Research Unit (ESRU) at Rahima Moosa Mother and Child Hospital and Perinatal HIV Research Unit (PHRU) at Chris Hani Baragwanath Hospital. CLWH previously initiated ART before 3 years of age and had previously participated in clinical trials at these sites (Coovadia et al., 2010; Coovadia et al., 2015; Cotton et al., 2013; Kuhn et al., 2012; Murnane et al., 2017; Violari et al., 2008). HIV-uninfected controls were recruited from children accessing outpatient health services at the two study sites and from siblings and household members of the CLWH. This analysis was conducted using data from the last visit in CHANGES between May 1, 2017 and August 31, 2018. The Institutional Review Boards of Columbia University, New York, NY, USA, and the University of the Witwatersrand, Johannesburg, South Africa approved the study. Children's guardians provided informed consent and children over 7 years of age provided assent.

Measurements

Socio-demographic information and medical history were obtained through structured interview with the caregiver. Whether the child currently attended school and the child's current grade were also ascertained during the interview. The primary outcome in this study was whether children were in the appropriate grade-for-age calculated based on the South African Schools Act 84 of 1996. For example, the appropriate grade-for-age of a child aged five and turning six by June 30th in the calendar year of admission to school (January 1 to December 31) would be grade 1. If a child fell behind in school, did not currently attend school or attended a special needs school, they were considered to not be in the appropriate grade-for-age. Secondary outcomes included whether the child had ever failed a year at school and school non-attendance (number of days of school missed in the past month because of a health problem). Also included in the interview were questions on whether the child has been hospitalized since the last visit (yes/no) and whether the child misses school to go to the doctor or hospital (never, almost never, sometimes, often, almost always).

At the same study visit at which caregiver interview was obtained, plasma HIV-RNA levels (lower limit of detection 40 copies/ml) were measured by the Abbott RealTime HIV-1 Assay (Abbott Park, Illinois, USA). CD4 counts and percentages were measured by the Tru-Count Method (BD Biosciences, Germany) for CLWH.

Statistical Analysis

Characteristics and educational outcomes were compared between groups using parametric t-tests for continuous variables that met standard assumptions and the chi-squared or Fisher's exact tests for categorical variables. To evaluate factors associated with not being in the appropriate grade-for-age in all children, unadjusted odds ratios (ORs) and confidence intervals (95% CIs) were estimated using logistic regression. Characteristics marginally associated with not being in the appropriate grade-for-age (p-value <0.10) were included in a multivariable model to estimate adjusted ORs (aORs). The analysis was repeated among CLWH only including additional HIV-specific factors, including age at ART initiation (<6 months of age vs. ≥6 months of age). All p-values are 2-tailed and p-values <0.05 were considered statistically significant. Statistical calculations were performed using SAS version 9.4 (Cary, North Carolina, USA).

Results

Study participants

A total of 480 CLWH and 130 controls were included in this analysis. Approximately 20% of the controls were siblings or household members of CLWH and 80% were accessing outpatient health services at sites. Their characteristics are shown in Table 1. Children were an average of 10.8 years of age (range 7.0-14.0 years) and mean age was similar in both groups (10.8 vs. 10.8 years, $p = 0.51$). There were fewer boys in the CLWH group compared to the control group (45.6 vs. 58.5%, $p = 0.009$). The primary caregiver was the biological mother for 84.8% of CLWH and 96.2% of controls (<0.001). A smaller proportion of biological mothers (93.1 vs. 98.5%, $p = 0.07$) and fathers (83.3 vs. 90.8%, $p = 0.09$) were alive for CLWH compared to controls. A similar proportion of CLWH and controls had a foreign-born parent (18.5 vs. 17.7%, $p = 0.82$). About half of caregivers for CLWH and controls completed high school (52.9 vs. 45.4%, $p = 0.13$). Most CLWH and controls lived in a house (67.3 vs. 63.1%, $p = 0.37$). Others lived in a flat, shack, rented room, outbuilding,

Table 1. Clinical and demographic characteristics of children living with HIV (CLWH) vs. controls

	CLWH ($n = 480$)	Controls ($n = 130$)	P
Age (years), Mean (SD)	10.8 (1.3)	10.8 (1.7)	0.51
Age (years), Range	7.8–14.0	7.5–14.1	-
Sex, N (%)			0.009
Male	219 (45.6)	76 (58.5)	
Female	261 (54.4)	54 (41.5)	
Biological mother's HIV status, N (%)			-
HIV-positive	480 (100.0)	43 (33.1)	
HIV-negative	0 (0.0)	84 (64.6)	
Unknown	0 (0.0)	3 (2.3)	
Mother is primary caregiver, N (%)			<0.001
Yes	407 (84.8)	125 (96.2)	
No	73 (15.2)	5 (3.8)	
Biological mother is alive, N (%)			0.07
Yes	447 (93.1)	128 (98.5)	
No	31 (6.5)	2 (1.5)	
Unknown	2 (0.4)	0 (0.0)	
Biological father is alive, N (%)			0.09
Yes	400 (83.3)	118 (90.8)	
No	67 (14.0)	9 (6.9)	
Unknown	13 (2.7)	3 (2.3)	
Child has a foreign-born parent, N (%)			0.82
Yes	89 (18.5)	23 (17.7)	
No	391 (81.5)	107 (82.3)	
Caregiver educational attainment, N (%)			
No school / did not finish high school	254 (52.9)	59 (45.4)	0.13
Completed high school	226 (47.1)	71 (54.6)	
Child lives in a house, N (%)			0.37
Yes	323 (67.3)	82 (63.1)	
No	157 (32.7)	48 (36.9)	
Caregiver lost job in past 6 months, N (%)			0.003
Yes	51 (10.6)	3 (2.3)	
No	429 (89.4)	127 (97.7)	
Child admitted to hospital since last visit, N (%)			0.23
Yes	6 (1.3)	4 (3.1)	
No	474 (98.8)	126 (96.9)	
Child misses school to go to the doctor or hospital, N (%)			
Never	90 (19.2)	44 (34.1)	<0.001
Almost never	7 (1.5)	6 (4.7)	
Sometimes	306 (65.4)	79 (61.2)	
Often	58 (12.4)	0 (0.0)	
Almost always	7 (1.5)	0 (0.0)	

or hostel. Similar proportions of CLWH and controls had been admitted to the hospital since the last visit (1.3% vs. 3.1%, $p = 0.23$). 13.9% of caregivers of CLWH reported that children had to miss school to go to the doctor or hospital "often" or "almost always" compared to 0% of controls.

All CLWH previously initiated ART before 3 years of age, including 82% before 1 year of age. The median age at ART initiation was 4.4 months of age (IQR: 2.0-9.1 months); 303 (63.1%) initiated ART <6 months of age and 177 (36.7%) initiated ART ≥6 months of age. Current mean CD4 percentage was 36.1 ± 6.7% and 429 (89.9%) had a suppressed HIV RNA <40 copies/mL. Most children (60.4%) were currently on a lopinavir/ritonavir-based ART regimen, with 37.1% on an efavirenz-based regimen and 2.5% on another regimen.

HIV and education

Overall, 45.8% of CLWH were not in the appropriate grade-for-age compared to 30.0% of controls ($p < 0.01$). As shown in Table 2, CLWH were twice as likely to not be in the appropriate grade-for-age compared to controls (OR: 1.97, 95% CI: 1.30-2.99) in unadjusted analyses. Compared to girls, boys were twice as likely not to be in the appropriate grade-for-age (OR: 1.90, 95%CI: 1.37-2.63). Not having a living biological father vs. having one (OR: 1.62, 95% CI: 0.99-2.62) and less caregiver education (not completing high school vs. completing high school) were also associated with not being in the correct grade-for-age (OR: 1.46, 95% CI: 1.06-2.02). Whether or not the child had a living biological mother, had their biological mother as their primary caregiver, had a foreign-born parent, or lived in a house were not associated with not being in the appropriate grade-for-age. Among controls, there was no difference in being in the appropriate grade-for-age between those with an HIV-positive mother and those with an HIV-negative mother (data not shown).

As shown in Table 2, after adjusting for site, sex, whether the child's biological father was alive, and caregiver education, CLWH were more likely not to be in the appropriate grade-for-age compared to uninfected children (aOR: 3.32, 95% CI: 2.07-5.34). Educational delay was more common in boys (aOR: 2.01, 95% CI: 1.42-2.85) and more common among children whose caregivers who did not complete high school compared to those who did (aOR: 1.56, 95% CI: 1.11-2.21). There was no interaction between HIV status and sex (interaction term $p = 0.79$).

Similar proportions of CLWH and controls had ever failed a year at school (29.8 vs. 23.1%, $p = 0.32$). Among CLWH, 12.8%, 7.1%, and 4.8% missed 1, 2, and 3 days of school in the past month because of a health problem, respectively, compared to 7.8%, 2.6%, and 2.6% of controls ($p = 0.003$).

Age at ART initiation and education

Stratifying by age at ART initiation, 55.9% who initiated ART >6 months ever had educational delay compared to 39.9% who initiated ≤6 months ($p = 0.0007$). Among all children, those who initiated ART >6 months (aOR: 4.01; 95% CI: 2.39-6.72) and who initiated ≤6 months (aOR: 2.72, 95% CI: 1.62-4.57) were more likely to have educational delays than uninfected controls, adjusted for site, sex, whether the child's biological father was alive, and caregiver education.

As shown in Table 3, among CLWH only, initiating ART >6 months was associated with not being in the

Table 2. Factors associated with not being in the appropriate grade-for-age, all children.

Factor	n/N (%)	Unadjusted OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
HIV status					
CLWH	220/480 (45.8)	1.97 (1.30, 2.99)	0.001	3.32 (2.07, 5.34)	<0.0001
Controls	39/130 (30.0)	1.00		1.0	
Site					
ESRU	175/365 (48.0)	1.77 (1.26, 2.47)	0.0009	2.61 (1.78, 3.84)	<0.0001
PHRU	84/245 (34.3)	1.00		1.0	
Age in years		0.99 (0.89, 1.11)	0.91		
Sex					
Male	149/295 (50.5)	1.90 (1.37, 2.63)	0.0001	2.01 (1.42, 2.85)	<0.0001
Female	110/315 (34.9)	1.00			
Biological mother is primary caregiver					
No	33/78 (42.3)	0.99 (0.61, 1.61)	0.98		
Yes	226/532 (42.5)	1.00			
Biological mother is alive					
No	16/33 (48.5)	1.30 (0.65, 2.63)	0.46		
Yes	241/575 (41.9)	1.00			
Biological father is alive					
No	40/76 (52.6)	1.62 (0.99, 2.62)	0.051	1.50 (0.90, 2.50)	0.12
Yes	211/518 (40.7)	1.00			
Highest caregiver grade completed					
No school / did not finish high school	147/313 (47.0)	1.46 (1.06, 2.02)	0.021	1.56 (1.11, 2.21)	0.012
Completed high school	112/297 (37.7)	1.00			
Child lives in a house					
No	94/205 (45.9)	1.23 (0.88, 1.73)	0.23	–	–
Yes	165/405 (40.7)	1.00			
Has a foreign-born parent					
Yes	48/112 (42.9)	1.02 (0.67, 1.54)	0.92		
No	211/498 (42.4)	1.0			

*The adjusted model includes all variables with $p < 0.10$ in unadjusted analysis.

appropriate grade-for-age, adjusted for sex, site, whether the child's biological father was alive, current ART regimen, and whether the child has been told his/her HIV status (aOR: 1.74, 95% CI: 1.05-2.88). In the adjusted analysis, male CLWH were more likely not to be in the correct grade compared to females (aOR: 1.67, 95% CI: 1.08-2.57). Those who had not been told his/her HIV status were also more likely not to be in the correct grade-for-age (aOR: 1.87, 95% CI: 1.18-2.95).

Discussion

In a cohort of children in South Africa, we observed higher rates of not being in the correct grade-for-age in CLWH compared with uninfected children. All CLWH had started treatment within the first 3 years of life, most prior to 1 year of age, and were maintained in care, mostly well-suppressed on ART. Although all CLWH had poorer educational outcomes than controls regardless of the timing of ART initiation, those who initiated ART early had better outcomes than those initiating ART later.

Few studies have assessed educational outcomes in CLWH. A study of children aged 6–17 in Zimbabwe did not find any association between HIV status and being in the correct grade-for-age, defined as being more than two years behind in school (Pufall et al., 2014). Of interest, a mixed-methods study of primary school children in Zimbabwe found that children who were one or more class grades behind in school due to illness were more likely to be HIV-infected compared to children who were not (Bandason et al., 2013). A recent study in Rwanda found that HIV-positive children were twice as likely to be overage for their grade compared to HIV-unaffected children (Henning et al., 2018). These studies did not specify whether children with HIV were on ART or virologically suppressed. In our cohort, caregivers of CLWH reported that their children had to miss school for medical visits more often than caregivers of controls.

Comparable to other studies in this age group, boys in our cohort had more educational delay than girls. A community-based study of children aged 4–13 years conducted in HIV-affected communities in South Africa and Malawi found boys with HIV to be less often in the correct grade-for-age (Hensels et al., 2016). Among CLWH, children who had not been told their HIV status were more likely not to be in the correct grade-for-age. The decision of how and when to disclose HIV status to children is complex and necessitates a developmentally appropriate process; this finding may reflect delays in child development. In addition, there may be unmeasured family or household dynamics or psychosocial circumstances that affect both disclosure of HIV status as well as educational outcomes (Finnegan et al., 2019; Hayfron-Benjamin, Obiri-Yeboah, Ayisi-Addo, Siakwa, & Mupepi, 2018; Kalembo, Kendall, Ali, & Chimwaza, 2019; Kiwanuka, Mulogo, & Haberer, 2014).

Table 3. Factors associated with not being in the appropriate grade-for-age, children living with HIV (CLWH).

Factor	n/N (%)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P*
Age at ART initiation					
≥6 months	99/177 (55.9)	1.91 (1.31, 2.78)	0.0007	1.74 (1.05, 2.88)	0.032
<6 months	121/303 (39.9)	1.0		1.0	
Age in years		1.00 (0.87, 1.14)	0.98		
Sex					
Male	121/219 (55.3)	2.02 (1.40, 2.91)	0.0002	1.67 (1.08, 2.57)	0.021
Female	99/261 (37.9)	1.0		1.0	
Site					
ESRU	136/235 (57.9)	2.63 (1.82, 3.81)	<0.0001	1.96 (0.99, 3.87)	0.054
PHRU	84/245 (34.3)	1.0		1.0	
Biological mother is primary caregiver					
No	32/73 (43.8)	0.91 (0.55, 1.50)	0.71	–	–
Yes	188/407 (46.2)	1.0			
Biological mother is alive					
No	202/447 (45.2)	1.29 (0.62, 2.68)	0.49	–	–
Yes	16/31 (51.6)	1.0			
Biological father is alive					
No	176/400 (44.0)	1.57 (0.93, 2.64)	0.09	1.57 (0.85, 2.90)	0.15
Yes	37/67 (55.2)	1.0			
Highest caregiver grade completed					
No school / did not finish high school	125/254 (49.2)	1.34 (0.93, 1.92)	0.12	–	–
Completed high school	95/226 (42.0)	1.0			
Child lives in a house					
No	142/323 (44.0)	1.26 (0.86, 1.85)	0.24	–	–
Yes	78/157 (49.7)	1.0			
Has a foreign born parent					
Yes	177/391 (45.3)	1.13 (0.71, 1.79)	0.60	–	–
No	43/89 (48.3)	1.0			
Current plasma HIV RNA (copies/ml)					
Not suppressed >40	26/48 (54.2)	1.45 (0.79, 2.63)	0.23	–	–
Suppressed <40	193/429 (45.0)	1.0			
Current CD4 percentage (%)		1.00 (0.97, 1.03)	0.99	–	–
Current ART regimen					
EFV-based	103/178 (57.9)	2.15 (1.47, 3.15)	<0.0001	0.86 (0.44, 1.68)	0.67
LPV/r-based	113/290 (39.0)	1.0		1.0	
Other	4/12 (33.3)	0.78 (0.23, 2.66)	0.70	0.78 (0.17, 3.51)	0.75
Child has been told his/her HIV status					
No	120/222 (54.1)	1.82 (1.27, 2.63)	0.001	1.87 (1.18, 2.95)	0.008
Yes	100/255 (39.2)	1.0		1.0	
Don't know	0/3 (0.0)	–		–	
Pre-treatment HIV RNA (copies/ml)					
<100,000	20/35 (57.1)	1.0		1.0	
100,000-340,000	23/65 (35.4)	0.41 (0.18, 0.95)	0.04	0.40 (0.16, 0.99)	0.047
340,000-750,000	33/68 (48.5)	0.71 (0.31, 1.61)	0.41	0.92 (0.37, 2.27)	0.85
≥750,000	113/245 (46.1)	0.64 (0.31, 1.31)	0.22	0.73 (0.33, 1.59)	0.42
Pre-treatment CD4 percentage (%)		0.96 (0.95, 0.98)	<0.0001	0.97 (0.96, 1.00)	0.054

*The adjusted model includes all variables with $p < 0.10$ in unadjusted analysis.

It is unclear whether these associations are due to actual biological factors or other social and environmental factors. A review of children affected by HIV and educational outcomes emphasized incorporating measures of individual and contextual factors, such as caregiver gender and poverty, in studies of educational outcomes (Guo et al., 2012). We adjusted for sociodemographic variables to the best of our ability in our study. In addition, many of the children in our control group came from the same family or households as CLWH. One potential mechanism for poorer educational outcomes among CLWH is neurodevelopmental impairment, a major co-morbidity associated with HIV (Chiriboga, Fleishman, Champion, Gaye-Robinson, & Abrams, 2005; Koekkoek et al., 2006; Patel et al., 2009; van Arnhem et al., 2013). Studies have found higher rates of cognitive impairment in CLWH compared with controls (Abubakar, Van Baar, Van de Vijver, Holding, & Newton, 2008; Boivin et al., 1995; McGrath et al., 2006; Msellati et al., 1993). It is possible that earlier ART may mitigate these effects. There is a growing body of evidence that indicates early ART may have benefits for a number of clinical outcomes including growth, virologic control, and neurodevelopment (Laughton et al., 2012; Shiau et al., 2013; Shiau et al., 2017). This is the first study to report on the timing of ART initiation and educational outcomes in CLWH who were initiated on ART in the first few years of life and well-maintained on treatment. However, even early and prolonged treatment did not completely mitigate these outcomes. Further studies evaluating long-term outcomes of starting ART even earlier (in the neonatal period) are warranted.

Our study is limited by a single educational outcome, albeit an important one. Future studies should include other more extensive educational outcomes, including academic achievement, other aspects of school performance, and completion of primary and secondary school. In addition, other family or contextual factors (e.g., distance to school, school quality) that might support or impede school attendance and academic achievement should be included, as well as other measures of socioeconomic status associated with access to education. These factors may potentially be related to the differences observed by study site. Of note, we did observe that CLWH missed school for scheduled appointments for monitoring HIV more often than controls. Our study was also limited in that our control group included siblings of CLWH and other children affected by HIV.

In conclusion, educational delay appears to be greater in CLWH, particularly those who have delayed treatment initiation. Progressing through school in a timely manner is important for school performance, school completion, and the onset of other life transitions for adolescents. School disengagement can place children at risk for other behaviors, such as substance use, early sexual debut, or gang involvement, resulting in poorer psychological, physical, social, and economic health. Regardless of underlying cause, interventions to improve timely progression through school are needed. In addition, accommodations to healthcare visits (i.e., After school or weekend medical appointments) may minimize school absences.

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Disclosure statement

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