Muscle strength in young children perinatally infected with HIV who were initiated on antiretroviral therapy early

J Potterton,[1] PhD; **R Strehlau,**[2] MB BCh; MSc; **S Shiau,**[3] PhD; **N Comley-White,**[1] MSc Physiotherapy; **L Kuhn,**[4] PhD; **S Arpadi,**[4] MD

[1] *Department of Physiotherapy, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[3] *Department of Biostatistics and Epidemiology, Rutgers University, Piscataway, New Jersey, USA*
[4] *Gertrude H. Sergievsky Center, Columbia University Irving Medical Center, New York, USA*

Corresponding author: J Potterton (joanne.potterton@wits.ac.za)

Background. As children with perinatally acquired HIV (PHIV) are living longer, long-term physical sequelae of the disease are becoming more pertinent. Muscle strength is known to be adversely affected in adults infected with HIV but little is known about the muscle strength of children with PHIV.
Objectives. To determine the muscle strength of children perinatally infected with HIV compared with an uninfected control group. Associations between clinical and anthropometric variables and muscle strength were investigated.
Methods. In this cross-sectional descriptive study, 175 children who acquired HIV perinatally and 171 children who were HIV-uninfected had their muscle strength assessed by hand-held dynamometry and the 'make test'. Clinical data were extracted from the children's clinic files. Height and weight were assessed using a stadiometer and a digital scale, respectively. Children were between the ages of 5 and 11 years of age at assessment. The children living with HIV had all been initiated on antiretroviral treatment (ART) at a young age (mean (standard deviation (SD)) 8.7 (6.7) months) and their disease was well controlled.
Results. Despite the children with HIV presenting with significantly lower height, weight and body mass index (BMI) for age *z*-scores, there was no statistical difference in muscle strength between the two groups. BMI and Tanner staging were associated with muscle strength in both groups.
Conclusions. Children who are initiated on ART at an early age and whose disease is well controlled are able to attain near-normal muscle strength. Longitudinal follow-up of these children as they go through puberty is warranted.

As countries around the world strive to achieve optimal management of people exposed to and living with HIV, more children are being tested for HIV, accessing antiretroviral therapy (ART) and living longer.[1] More attention now needs to be paid to the long-term effects of the disease and long-term medication use. Perinatally acquired HIV (PHIV) infection results in long-term inflammation which can give rise to distinctive chronic clinical complications that cause severe multisystem morbidity and may be evident throughout childhood.[1]

Myopathy and muscle weakness in adults living with HIV have been described;[2] however, very little research has been done on the muscle strength of children infected with HIV. It has been hypothesised that HIV may cause reduced muscle strength which then subsequently delays gross motor function and participation in age-appropriate sport and recreational activities.[3-5] HIV is associated with protein malabsorption,[6] depletion of protein reserves, and abnormal protein metabolism.[7] These protein metabolism abnormalities can also lead to decreased muscle bulk, which may affect muscle strength.[8] Skeletal muscle involvement can occur at any stage of HIV infection, both in individuals on ART and those who are not on treatment, and may be one of the first manifestations of the disease.[9] Myopathies in HIV are classified as follows: HIV-associated myopathies and related conditions; muscle complications of ART; opportunistic infections and tumour infiltrations of skeletal muscle; and rhabdomyolysis.[9]

The few studies investigating muscle strength in children infected with HIV have been small and have found conflicting results. Somarriba *et al.*[10] found that a small sample of HIV-infected children from Miami presented with relatively weaker lower limb muscle strength than their HIV-negative counterparts; however, Ramos *et al.*[5] found no differences in muscle strength (the maximum force a muscle can generate against a resistance) but small deficits in muscle power (product of dynamic muscular force and muscle contraction velocity) in their comparative study conducted in Puerto Rico. Macdonald *et al.*[11] also demonstrated relatively small deficits in muscle power in HIV-infected Canadian children but did not assess muscle strength.

The aim of the present study was to determine the muscle strength of primary-school-aged children perinatally infected with HIV and initiated on ART at an early age.

Methods

This study was nested within the CHANGES Bone Study which monitored a cohort of children living with HIV and children without

HIV infection enrolled into the study between the ages of 5 and 11 years in Johannesburg, South Africa (SA).[12] At a cross-sectional visit, 175 children living with HIV and 171 children without HIV, from the same socioeconomic background, were assessed for muscle strength. A sample of convenience was used; children attending the clinic together with their caregivers were invited to participate.

Muscle strength was assessed objectively using a MicroFET-ll hand-held dynamometer (Hoggan Scientific LLC, USA). The assessment takes less than a minute per muscle group to perform, and the results have been shown to be valid and reliable in children as young as 2 years of age.[13]

Muscle strength was assessed using a 'make test'. Measurements included shoulder abduction, shoulder forward flexion, elbow flexion, elbow extension, hip flexion, hip extension, knee flexion, knee extension, ankle plantar flexion and ankle dorsiflexion. Each measurement was taken three times and the maximum reading was recorded. A standard protocol for positioning and dynamometer placement was followed with all children. Shoulder and elbow values were summed to give an overall upper limb score and hip, knee and ankle scores were summed to give a lower limb score. All measurements were done by a physiotherapist trained in the assessment technique with experience working with children.

Clinical and anthropometric data were extracted from data collected routinely as part of the CHANGES Bone Study visit. Body mass index (BMI) was calculated (weight (kg) divided by height (m^2) and sexual maturity was determined using Tanner staging.

We compared measurements of children living with HIV with those of children without HIV infection. Descriptive statistics were used to summarise and report the data from the two groups. A linear regression univariate correlation analysis was done to investigate associations between anthropometric and clinical data, the sum of upper-limb muscle strength and the sum of lower-limb muscle strength outcomes. Sex-stratified analyses are reported. The results were reported as coefficient estimates (p-value).

Ethical clearance was obtained from the Human Research Ethics Committee (medical) at the University of the Witwatersrand (ref. no. M120871). The parent or legal guardian accompanying the child signed the informed consent and children older than 7 years with sufficient mental capability gave assent prior to any testing being done.

Results

The results for 175 children living with HIV and 171 children without HIV were analysed. The two groups were well matched for age (p=0.88) and sex (p=0.23). Table 1 shows the anthropometric and clinical data of the participants.

Table 1. Anthropometric and clinical characteristics of participants			
Characteristic or measurement	Children with PHIV (N=175), n (%)*	Children without HIV (N=171), n (%)	p-value
Sex			
Male	84 (48.0)	93 (54.4)	0.239
Female	91 (52.0)	78 (45.6)	
Age (years), mean (SD)	9.3 (1.9)	9.2 (1.9)	0.877
Anthropometric measurement			
WAZ, mean (SD)	−0.79 (0.96)	−0.14 (1.15)	0.001
Underweight	15 (8.6)	3 (1.8)	0.006
HAZ, mean (SD)	−1.00 (1.42)	−0.53 (0.90)	<0.001
Stunted	29 (16.6)	7 (4.1)	<0.001
BMI (kg/m²), mean (SD)	16.0 (2.3)	16.7 (3.0)	0.016
BAZ, mean (SD)	−0.33 (1.18)	−0.01 (1.24)	0.015
Tanner stage 1	135 (77.1)	134 (78.4)	0.798
Lab test results closest to day of assessment			
Viral load (copies/mL)		NA	NA
TND or LDL (≤20 or ≤40)	133 (76.0)		
21 - 1 000	33 (18.9)		
>1 000	9 (5.1)		
Range	16.5 - 2 358.0	NA	NA
CD4 count (cells/uL)			
Mean (SD)	1 029.0 (353.4)	NA	NA
Median (IQR)	1 019.0 (764.0 -1 270.0)	NA	NA
<750	39 (22.3)	NA	NA
750 - 1 000	47 (26.9)		
>1 000	89 (50.9)		
CD4 %			
Range	9.81 - 56.59	NA	NA
Mean (SD)	37.43 (7.36)	NA	NA
Median (IQR)	37.63 (32.78 - 42.65)	NA	NA
Age at ART start (months), mean (SD)	8.7 (6.7)	NA	NA

PHIV = perinatally acquired HIV; SD = standard deviation; WAZ = weight-for-age z-score; HAZ = height-for-age z-score; BAZ = BMI-for-age z-score; TND = target not detected; LDL = lower than detectable limit; IQR = interquartile range; ART = antiretroviral therapy.
*Unless otherwise specified.

Significant differences were noted in weight-for-age *z*-score (WAZ) and the frequency of underweight (WAZ <−2SD below mean on World Health Organization Growth Charts) between the two groups, with the children living with HIV being more likely to be underweight. Children infected with HIV also had significantly lower height-for-age *z*-scores (HAZ) and were more likely to be stunted. The BMI scores for the children living with HIV were also significantly lower than the control group.

Children living with HIV were initiated on ART at a mean age of 8.7 months and the majority were virally suppressed, with mean CD4 T-cell percentage in the normal range (37.43%) at the time of testing.

There were no significant differences between the two groups for muscle strength in either the upper (*p*=0.984) or lower (*p*=0.845) limbs. Table 2 shows the muscle strength for all muscle groups tested.

BMI and Tanner staging were associated with muscle strength in both the upper and lower limb. Children with a higher BMI and higher BMI-for-age *z*-score (BAZ) and children who were Tanner stage 2 or higher had a stronger association with muscle strength for both groups of children combined, as well as for the children living with HIV alone. Table 3 shows the results of the univariate regression analysis for the children living with HIV.

Discussion

Children living with PHIV who started ART early in life and have well-controlled disease have muscle strength comparable with otherwise healthy controls. The HIV-infected children in this study were all initiated on ART relatively early in life and their disease was well controlled. Early initiation of ART has been identified as a

key priority to improve long-term outcomes of infants infected with HIV.[14] Muscle strength values for both groups were slightly lower than those reported by McKay *et al.*[15] in their normative reference values of strength and flexibility for 1 000 adults and children in Australia. Normative values for SA children from a similar socioeconomic situation are not available.

Ramos *et al.*[5] also found no difference in the muscle strength of their small group of HIV-infected adolescents compared with a control group, although muscle power was significantly lower in the HIV-infected children. The mean age of the children in their study was similar to the current study and all study participants were perinatally HIV-infected. The mean CD4% count was lower (25%) compared with that of the children in the current study (37.43%). Macdonald *et al.*[11] showed small deficits in muscle power in their HIV-infected children compared with a control group; however, they did not assess muscle strength. The HIV-infected children in their study also had lower levels of physical activity than the HIV unexposed uninfected (HUU) controls.

The findings of this study were different to results reported by Somarriba *et al.*,[10] who found weaker lower-limb muscle strength in children infected with HIV compared with uninfected controls. The children in their study were older, not all were on ART, their mean CD4% was lower (28% compared with 37.43% in the current study) and not all were perinatally infected with HIV.

Humphries *et al.*[16] assessed muscle strength in a small group (*n*=32) of young HIV-infected children between 4 and 6 years of age in SA. This study was conducted when access to antiretrovirals in SA was much more limited. The muscle strength of the children in the current study, who had better access to ART from a young age and whose disease was well controlled, was considerably better.

Table 2. Muscle strength of children living with HIV v. controls			
Muscle strength measurements in newtons, mean (SD)	Children with PHIV (*N*=175), *n* (%)	Children without HIV (*N*=171), *n* (%)	*p*-value
R shoulder abduction	52.2 (17.2)	53.9 (19.3)	0.389
L shoulder abduction	47.0 (17.3)	48.6 (18.8)	0.414
R shoulder flexion	35.8 (19.2)	35.7 (20.5)	0.943
L shoulder flexion	35.4 (19.5)	34.6 (19.2)	0.720
R elbow flexion	71.2 (21.0)	69.5 (24.7)	0.485
L elbow flexion	69.0 (21.8)	68.5 (24.7)	0.825
R elbow extension	68.9 (19.6)	70.5 (21.0)	0.482
L elbow extension	68.9 (20.2)	69.2 (22.0)	0.901
R hip flexion	100.2 (28.3)	104.2 (29.3)	0.197
L hip flexion	101.0 (30.2)	108.4 (32.6)	0.029
R hip extension	107.8 (36.1)	109.1 (36.2)	0.743
L hip extension	102.5 (32.1)	102.3 (31.2)	0.958
R knee flexion	84.6 (25.8)	88.7 (27.9)	0.162
L knee flexion	85.9 (25.8)	90.9 (28.0)	0.090
R knee extension	102.9 (33.6)	104.5 (37.5)	0.668
L knee extension	105.9 (34.2)	109.5 (39.4)	0.362
R plantar flexion	93.4 (63.5)	84.2 (55.4)	0.155
L plantar flexion	88.7 (59.0)	81.0 (53.6)	0.208
R dorsi flexion	67.3 (32.8)	65.5 (31.6)	0.603
L dorsi flexion	65.3 (33.8)	63.9 (31.8)	0.702
Upper-limb score	449.6 (125.1)	449.9 (135.7)	0.984
Lower-limb score	1 108.2 (338.7)	1 115.6 (359.0)	0.845
Sum of hip and knee muscle measurements	790.6 (220.3)	817.3 (234.2)	0.276
Sum of ankle muscle measurements	314.3 (182.2)	295.1 (166.1)	0.312

SD = standard deviation; PHIV = perinatally acquired HIV; R = right; L = left.

Table 3. Results from univariate linear regression analyses, controlling for age at measurement and sex for children with PHIV

Anthropometric measurement and lab measurement	Outcomes for all children with PHIV (N=175)*		Outcomes for male children with PHIV (N=84)*		Outcomes for female children with PHIV (N=91)*	
	Upper-limb sum	Lower-limb sum	Upper-limb sum	Lower-limb sum	Upper-limb sum	Lower limb sum
Age at ART start (months)	–0.5 (0.715)	0 (0.997)	2.8 (0.177)	6.9 (0.234)	–3.1 (0.133)	–5.9 (0.303)
HAZ	3.2 (0.623)	–2.3 (0.898)	17.5 (0.216)	33.0 (0.404)	–0.3 (0.968)	–9.8 (0.645)
Stunted (ref: not stunted)	–38.9 (0.126)	–42.3 (0.549)	–28.2 (0.430)	–15.2 (0.875)	–50.3 (0.168)	–51.3 (0.623)
BMI (kg/m²)	22.2 (<0.001)	52.0 (<0.001)	20.7 (0.004)	43.8 (0.030)	23.0 (<0.001)	55.5 (<0.001)
BAZ	37.1 (<0.001)	83.5 (<0.001)	45.5 (<0.001)	89.7 (0.013)	34.1 (<0.001)	78.9 (0.003)
Tanner stage 1 (ref: >1)	–121.7 (<0.001)	–251.4 (0.004)	–118.6 (0.006)	–218.5 (0.074)	–123.2 (0.006)	–293.0 (0.017)
CD4 count (cells/uL)						
750 -1 000 (ref: <750)	22.0 (0.415)	10.7 (0.885)	8.4 (0.808)	4.4 (0.963)	38.9 (0.356)	7.5 (0.948)
<1 000 (ref: <750)	17.1 (0.481)	33.5 (0.616)	35.9 (0.263)	71.1 (0.423)	2.1 (0.953)	-9.8 (0.923)
Viral load (copies/mL)						
21 - 1 000 (ref: LDL)	3.5 (0.882)	65.1 (0.331)	43.8 (0.164)	116.0 (0.192)	–33.4 (0.356)	–6.6 (0.949)
>1 000 (ref: LDL)	–59.5 (0.154)	–48.4 (0.677)	–75.3 (0.257)	–164.6 (0.379)	–57.5 (0.298)	32.4 (0.832)

PHIV = perinatally acquired HIV; ART = antiretroviral therapy; HAZ = height-for-age *z*-score; BMI = body mass index; BAZ = BMI-for-age *z*-score; LDL = lower than detectable limit.
*p-values in brackets.

It is interesting to note that although not significantly different, the muscle strength of the hip and knee tended to be lower in the children living with HIV but the strength of both dorsi and plantar flexors was higher in this group. This was possibly to compensate for their more proximal muscle weakness. One other study that assessed muscle strength in SA children with HIV only included those with HIV encephalopathy (HIVE). Naik *et al.*[17] also found that the plantar flexors of the children with HIVE were stronger than those of their HIV-negative peers who had cerebral palsy.

We and others have reported that children living with HIV tend to have less vigorous physical activity.[11,18] Sedentary behaviour is an additional risk factor for muscle weakness.

Despite being well managed, the children infected with HIV still presented with significantly lower anthropometric scores. WAZ and HAZ scores, as well as BMI and BAZ were all significantly lower than the HIV-negative control group. Growth in children infected with HIV has been an area of concern for many years, and further studies of how best to address these concerns are needed. Growth and development in children are strong determinants of muscle strength, often more so than chronological age;[19] this is confirmed in our study with BMI and BAZ being significantly associated with upper- and lower-limb muscle strength.

Some of the children enrolled in the control group of this study were exposed to HIV *in utero* but uninfected (HEU). The growth and development of HEU children is a contentious topic, with some studies suggesting that exposure to HIV and ART *in utero* may have detrimental effects on the long-term health outcomes of children.[20,21] This factor could explain why the muscle strength of the children in the control group was lower than has been found in other HUU groups.

Conclusions

The results of this study suggest that children infected with HIV who are well managed, have the potential to perform well in assessments of muscle strength compared with their uninfected peers. The muscle strength of children, both infected and uninfected, in this community needs to be investigated further. Future studies would do well to include children who are infected with HIV, exposed to HIV *in utero* but uninfected, as well as an unexposed uninfected control group.

1. Lowenthal E, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand R. Perinatal acquired HIV infection in adolescents from sub-Saharan Africa: A review of emerging challenges. Lancet Infect Dis 2014;14:627-639. https://doi.org/10.1016/S1473-3099(13)70363-3
2. Gomes-Neto M, Rodriguez I, Lédo AP, Vieira JP, Brites C. Muscle strength and aerobic capacity in HIV-infected patients: A systematic review and meta-analysis. J Acquir Immune Defic Syndr 2018;79(4):491-500. https://doi.org/10.1097/qai.0000000000001835
3. Baillieu N, Potterton J. The extent of delay of language, motor, and cognitive development in HIV-positive infants. J Neurol Phys Ther 2008;32:118-121. https://doi.org/10.1097/npt.0b013e3181846232
4. Potterton J, Hilburn N, Strehlau R. Developmental status of pre-school children receiving cART – a descriptive cohort study. Child Care Health Dev 2016;42(3):410-414. https://doi.org/10.1111/cch.12321
5. Ramos E, Guttierez-Tessoonniere S, Conde J, et al. Anaerobic power and muscle strength in human immunodeficiency virus-positive preadolescents. PM R 2012;4(3):171-175. https://doi.org/10.1016/j.pmrj.2011.11.009
6. Arpadi SM. Growth failure in children with HIV infection. J Acquir Immune Defic Syndr 2000;25(Suppl 1):S37-S42. https://doi.org/10.1097/00042560-200010001-00006
7. Jahoor F, Abramson S, Heird W. The protein metabolic response to HIV infection in young children. Am J Clin Nutr 2003;78(1):182-189. https://doi.org/10.1093/ajcn/78.1.182

8. O'Brien K, Tynan AM, Nixon S, Glazier RH. Effects of progressive resistive exercise in adults living with HIV/AIDS: Systematic review and meta-analysis of randomised trials. AIDS Care 2008;20(6):631-653. https://doi.org/10.1080/09540120701661708

9. Authier FJ, Chariot P, Gherardi RK. Skeletal muscle involvement in human immunodeficiency virus (HIV)-infected patients in the era of highly active antiretroviral therapy (HAART). Muscle Nerve 2005;32:247-260. https://doi.org/10.1002/mus.20338

10. Somarriba G, Lopez-Mitnik G, Ludwig D, et al. Physical fitness in children infected with the human immunodeficiency virus: Associations with highly active antiretroviral therapy. AIDS Res Hum Retroviruses 2013;29(1):112-120. https://doi.org/10.1089/aid.2012.0047

11. Macdonald HM, Nettlefold L, Maan EJ, Cote H, Alimenti A, CIHR Emerging Team Grant on HIV Therapy and Aging (CARMA). Muscle power in children, youth and young adults who acquired HIV perinatally. J Musculoskelet Neuronal Interact 2017;17(2):27-37.

12. Ramteke SM, Shiau S, Foca M, et al. Patterns of growth, body composition, and lipid profiles in a South African cohort of human immunodeficiency virus-infected and uninfected children: A cross-sectional study. J Pediatric Infect Dis Soc 2018; 7(2):143-150. https://doi.org/10.1093/jpids/pix026

13. Gajdosik C. The ability of very young children to produce reliable isometric force measurements. Pediatr Phys Ther 2005;17(4):251-257. https://doi.org/10.1097/01.pep.0000186507.74151.78

14. Penazzato M, Irvine C, Vicari M, et al. A global research agenda for pediatric HIV. J Acquir Immune Defic Syndr 2018;78(suppl1):S10-S15. https://doi.org/10.1097%2FQAI.0000000000001743

15. McKay M, Baldwin J, Ferreira P, Simic M, Vanicek N, Burns J. Normative reference values for strength and flexibility of 1,000 children and adults. Neurology 2017;88(1):36-43. https://doi.org/10.1212/wnl.0000000000003466

16. Humphries C, Potterton J, Mudzi W. A pilot study to investigate the muscle strength of children infected with HIV. Int J Ther Rehabil 2014;21(1):19-24. https://doi.org/10.12968/ijtr.2014.21.1.19

17. Naik T, Potterton J, Firth G, Wilson KS, Humphries CR. A comparison of the clinical presentation of with HIV infected (HIVE) to uninfected (CP) children with spastic diplegia in South Africa. Vulnerable Child Youth Stud 2018;13(3):195-206. https://doi.org/10.1080/17450128.2017.1417657

18. Wong M, Shiau S, Yin M, et al. Decreased vigorous physical activity in school-aged children with human immunodeficiency virus in Johannesburg, South Africa. J Pediatr 2016;172:103-109. https://doi.org/10.1016/j.jpeds.2016.01.034

19. Hogrel J, Decostre V, Alberti C, et al. Stature is an essential predictor of muscle strength in children. BMC Musculoskelet Disord 2012;13(176). https://doi.org/10.1186/1471-2474-13-176

20. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL. HIV-exposed uninfected children: A growing population with a vulnerable immune system? Clin Exp Immunol 2014;176(1):11-22. https://doi.org/10.1111/cei.12251

21. Jumare J, Datong P, Osawe S, et al. Compromised growth among HIV-exposed uninfected compared with unexposed children in Nigeria. Pediatr Infect Dis J 2019;38(3):280-286. https://doi.org/10.1097/inf.0000000000002238