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Original Article

Muscle power in children, youth and young adults who acquired HIV perinatally

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Abstract

Objectives: To compare muscle power between youth who acquired HIV perinatally and HIV unexposed uninfected (HUU) youth. **Methods:** We assessed muscle power (relative to body mass, P_{max}/mass), muscle force normalized to body weight (F_{max}/BW), force efficiency, jump height (H_{max}) and velocity (V_{max}) during a single two-legged jump with hands on waist on a force platform (Leonardo) in HIV+ youth (n=35, 9-21 y). Thirty-three and 22 participants returned at 12- and 24-months, respectively. We compared age- and sex-specific z-scores in the HIV+ youth to those in HUU controls (n=716, 9-21 y) adjusting for height and muscle cross-sectional area (MCSA, by pQCT). **Results:** At baseline, z-scores for P_{max}/mass, F_{max}/BW and V_{max} were less than 1 standard deviation lower than HUU after adjusting for height and MCSA ($p<0.05$). P_{max}/mass z-score was negatively associated with level of immunosuppression ($p=0.013$), but this relationship was not significant after adjusting for height and MCSA ($p=0.07$). Z-scores for all mechanography outcomes remained stable over time in HIV+ youth. **Conclusion:** Small deficits in muscle power were apparent in children and youth who acquired HIV perinatally, and the trajectory of muscle power did not change over two years. Further study is needed to identify effective strategies to improve dynamic muscle function in this population.

Keywords: Adolescents, Children, HIV, Mechanography, Muscle Power

Introduction

Improvements in HIV treatment and care have vastly improved outcomes for perinatally HIV+ children. In high-resource countries these children now grow well into adolescence and adulthood[1]. However, many uncertainties surround the effects that chronic HIV infection and exposure to combined antiretroviral therapy (cART) have on youth living with perinatally-acquired HIV as they age. During childhood and adolescence, HIV-infection may be associated with metabolic complications such as lipodystrophy[2] as well as deficits in aspects of health-related fitness including neuromuscular motor skills[3], muscle mass[3] and strength[4] and cardiorespiratory fitness[5]. These deficits may, in turn, lead to poor quality of life in HIV+ children and youth[6,7], and higher risk for reduced musculoskeletal function and frailty in early adulthood[8,9].

Skeletal muscle involvement in HIV+ patients varies with immunological status and treatment[10]; disease- and/or treatment-related loss of muscle mass may contribute to reduced muscle function. Previous studies of muscle function in HIV+ children and adults relied on isokinetic measures of muscle torque[11] or static, isometric measures of muscle strength (e.g., grip strength)[12]. However, dynamic tests such as those used in jumping mechanography may provide more insight into muscle function associated with everyday activities[13,14]. Jumping mechanography derives measurements of muscle force and power from an individual's ground reaction forces during a dynamic jumping

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test[15]. To date, this method has been used only once to assess muscle function in HIV+ children and youth, but comparisons with a healthy cohort were not conducted[7]. Thus, in the present study we first aimed to compare muscle power, as measured with jumping mechanography, between children and adolescents with perinatally acquired HIV and a group of HIV unexposed uninfected (HUU) youth. We hypothesized that mechanography outcomes would be lower in HIV+ as compared with HUU youth. Second, we aimed to examine changes in mechanography outcomes over two years in HIV+ youth. Based on findings in our previous analysis of this cohort[16], we hypothesized that z-scores for mechanography outcomes would not change significantly in HIV+ youth over two years. Lastly, we aimed to describe associations between mechanography outcomes and factors such as level of immunosuppression, virologic control, cART use and physical activity.

Methods

Participants were enrolled in a sub-study of the prospective **C**hildren and women, **A**nti**R**etroviral and **M**arkers of **A**ging (CARMA) cohort. They were children, adolescents and young adults aged 8 to 25 years, who acquired HIV perinatally, and who were receiving regular HIV care (clinic visits every 3 months) at the Oak Tree Clinic in Vancouver, Canada, an interdisciplinary clinic for women and children living with HIV. CARMA enrolled participants between 2009 and 2011 and the primary aim of the sub-study was to evaluate bone health in HIV+ children and adolescents, as described previously[16]. The University of British Columbia Clinical Research Ethics Board approved this study (#H08-01846 and H15-01194). We obtained written informed consent from participants 18 years of age or older, and from the parents or legal guardians, as well as written assent from participants under 18 years of age.

We invited patients to participate if they did not have a history of corticosteroid use (>3 months; relevant to the bone analysis), severe concomitant illness, congenital diseases affecting bone health, and were not currently pregnant. Between 2009 and 2011, 36 of 45 (80%) eligible patients volunteered to participate. Of these, we excluded 1 participant from our analyses as they were older than the upper age range of our HUU controls (21 yrs). Thus, the present analysis includes 35 HIV+ individuals (20 boys, 15 girls; median age 13.9 yrs; range: 8.5 to 21.3 yrs at baseline) with at least one study visit (n=21 with 3 study visits, n=13 with only 2 study visits).

We compared mechanography outcomes in HIV+ youth to those obtained in a cohort of HUU children and youth, data for whom is part of the University of British Columbia's Pediatric Bone and Physical Activity Database[17]. This database includes anthropometry and jumping mechanography outcomes for children and youth aged 9-21 years who were participants in the Healthy Bones Study (HBS) III follow-up[18] (n=398; 211 females; ages 9-21 yrs) and the Fracture and Risk-taking Behaviour Study[19] (n=318; 128 females, 190 males; ages 9-15 yrs). Across both cohorts, participants provided an average of 3 annual mechanography measures (range 1 to 4); however, for the purpose of this analysis we used the first measure for each HUU participant (n=716).

All HUU controls were normally active and none were taking medications known to influence musculoskeletal health. Participants represented a variety of ethnicities, as per the ethnic diversity common to Metro Vancouver[20]. Based on parental report, 56% (n=401) of the HUU cohort was white (both parents or 3 of 4 grandparents born in North America or Europe), 32% (n=227) were Asian (both parents or 3 of 4 grandparents born in Hong Kong, China, India, Philippines, Vietnam, Korea or Taiwan) and 12% (n=88) were of mixed or other ethnicities.

Measurements

We obtained baseline measurements from 28 of the HIV+ participants in February and March 2009, and from 7 participants in 2010. We conducted follow-up visits in February and March of 2010 (n=26) and 2011 (n=29). The average time between baseline and first follow-up was 12.5 (standard deviation (SD)=2.1) months and between first and second follow-up was 12.0 (0.4) months. One HIV+ participant missed the first follow-up, but returned for the second follow-up visit. Clinical and laboratory measures were collected at the Oak Tree Clinic and all other data were collected at the Centre for Hip Health and Mobility, Vancouver Coastal Health Research Institute. The HUU controls underwent the same measurements (with the exception of clinical and laboratory measures) annually from 2008 to 2012.

Clinical and laboratory outcomes

We obtained demographic data (including ethnicity), maturity status (physician-reported Tanner stage and age at menarche), smoking status, antiretroviral treatment history, disease stage (based on the revised HIV Pediatric Classification System from the Center for Disease Control and Prevention[21], CD4 count (nadir, absolute and %) and plasma HIV RNA viral load (pVL) from the patients' medical charts within 3 months of the study visit. We used the $\log_{10}$ of pVL for all analyses. In addition, at the clinic visit closest to the study visit we collected venous blood samples and analyzed for 25 OH-vitamin D (ELISA assay, Immunodiagnostic Systems, Scottsdale, AZ). Trained technicians at the British Columbia Children's Hospital laboratory performed the blood analyses according to standard procedures.

Anthropometry, body composition and muscle cross-sectional area

We measured standing height (stretch stature) to the nearest 0.1 cm with a wall-mounted digital stadiometer (Seca Model 242, Hanover, MD, USA), body mass to the nearest

0.1kg with an electronic scale (Seca Model 840, Hanover, MD, USA). We used the mean of two measures for analysis.

We used a Hologic QDR 4500W bone densitometer (DXA, Hologic Inc, Waltham, MA) to assess total body lean mass (kg) and percent body fat (%). Two experienced technicians acquired and analyzed all DXA scans according to standard procedures and performed daily quality assurance scans. In our laboratory, coefficients of variation (%CV) for repeated measures of lean mass and body fat in 15 healthy adult volunteers were 0.33% and 1.9%, respectively (UBC Children and Youth Physical Activity Research Program, unpublished data).

We used pQCT (Norland/Stratec XCT 3000; Stratec Medizintechnic GmbH, Pforzheim, Germany) to assess muscle cross-sectional area (MCSA, mm^2) at the 50% site of the left tibia, measured proximally from the tibial plafond, as per the HUU cohort[22]. This site primarily captures the soleus and gastrocnemius muscles. One of two trained technicians first acquired a 10-20 mm planar scout scan over the joint line (the minimum scan region required to obtain an image of the tibial plafond for placement of the reference line), and located a standard anatomical reference (the tibial plafond). We then acquired a single 2.3 +/- 0.2 mm slice with a scan speed of 30 mm/sec and a 0.4 mm voxel size. All pQCT scans were analyzed using Stratec software, Version 6.0 by the same trained technicians who acquired the scans. We used Contour mode 1 (-100 mg/cm^3), Peel mode 2 (40 mg/cm^3) and Cort mode 1 (710 mg/cm^3) to determine MCSA.

Physical activity

We used the validated Physical Activity Questionnaire for Children (PAQ-C) and Adolescents (PAQ-A) to estimate leisure-time physical activity[23,24]. A trained research assistant administered the PAQ, a 7-day recall questionnaire that assesses leisure-time moderate to vigorous physical activity (MVPA). We report two physical activity outcomes from the PAQ-C/A: 1) a general physical activity score (1-low active and 5-highly active) and 2) hours/week of MVPA, which provides an estimate of the time spent in common sports and activities[25].

Jumping mechanography

As described previously[17], we used the Leonardo Mechanograph® Ground Reaction Force Plate (GRFP; Novotec Medical GmbH, Germany) to assess muscle function. The mechanics of this device are described in detail elsewhere[15]. Briefly, the GRFP is divided into two sections, which allows for simultaneous measurement of the forces (vertical component only) applied to the right and left legs separately[26]. The sample rate is set to 800 Hz (800 measurements/second for each force sensor). We used the manufacturer's software (Leonardo Mechanography v4.3) for detection, storage and calculation of mechanography outcomes. The software uses force and time data to calculate velocity of the movement (metres/second), power (Watts, W) and jump height (metres) using the approach described by Cavagna[27].

All participants performed a single two-legged countermovement vertical jump (S2LJ) on the GRFP with their hands held static at their waist and their feet

Table 1. Clinical outcomes, anthropometry and descriptive characteristics of HIV+ youth at baseline. Values are presented as mean (standard deviation) except clinical outcomes, which are presented as median (interquartile range).

	Baseline (n=35)
Demographics	
Sex (males/females)	20/15
Age (yrs)	14.1 (3.3)
Ethnicity (Asian/White/Aboriginal/Black/Mixed)	2/7/7/8/11
Disease severity and treatment history*	
CDC stage (N1/N2/A1/A2/B1/B2)	19/6/4/2/2/2
Currently taking cART (Yes/No)	26/9
Ever treated with cART (Yes/No)	31/4
Lifetime months taking cART	99 (59, 146)
$CD4^+$ cells nadir (x 10^6 cells/ mm^3)	325 (213, 400)
$CD4^+$ cells nadir (%)	22 (11, 29)
$CD4^+$ cells (x 10^6 cells/mm^3)	580 (480, 740)
$CD4^+$ cells (%)	30 (24, 38)
Log_{10} HIV pVL in those currently taking cART (n=26)	3.66 (3.66, 3.76)
Log_{10} HIV pVL in those not currently taking cART (n=9)	9.97 (8.21, 10.28)
Anthropometry	
Height (cm)	157.2 (14.7)
Weight (kg)	51.6 (14.6)
BMI (kg/m^2)	20.4 (3.0)
Body composition	
Lean mass (kg)	39.5 (12.7)
Percent body fat	21.4 (8.5)
Muscle CSA (cm^2)	34.5 (9.5)
Maturity	
Girls' Tanner stage (1/2/3/4/5)	4/0/2/4/5
Girls' menarche status (# pre/post)	6/9
Age at menarche (yrs)	12.1 (1.5)
Boys' Tanner stage (1/2/3/4/5)	1/4/3/10/2
Lifestyle factors	
PAQ score (/5)	2.0 (0.5)
MVPA (hrs/week)	6.7 (4.6)
Ever smoked (yes/no)	8/27
Current smoker (yes/no)	6/29
Serum vitamin D (nmol/L)	63.4 (28.7)

CDC=Centers for Disease Control, pVL=plasma HIV RNA viral load, cART =combined antiretroviral therapy, BMI=body mass index, CSA=cross-sectional area, PAQ=physical activity questionnaire, MVPA=moderate to vigorous physical activity.

Table 2. Age- and sex-specific z-scores for anthropometric, body composition and lifestyle outcomes in HIV+ youth at baseline and HIV unexposed uninfected (HUU) controls at first measurement. Values are mean (standard deviation) and p-values indicate whether z-scores are significantly different from HUU controls.

	HIV+ (n=35)	HUU (n=716)	Mean Difference (95% CI)	HIV+ vs. HUU p-value
Anthropometrics				
Height z-score	-0.40 (1.01)	-0.02 (0.99)	-0.38 (-0.73, -0.02)	0.037
Body mass z-score	-0.20 (0.71)	-0.03 (0.98)	-0.17 (-0.43, 0.08)	0.173
BMI z-score	-0.05 (0.66)	-0.02 (1.00)	-0.03 (-0.26, 0.21)	0.824
Body composition				
Lean mass z-score	0.21 (1.02)	0.01 (0.97)	0.20 (-0.15, 0.56)	0.255
Percent body fat z-score	-0.25 (0.83)	-0.09 (0.93)	-0.16 (-0.45, 0.13)	0.273
MCSA z-score*	-0.84 (0.84)	0.01 (0.99)	-0.86 (-1.18, -0.53)	<0.001
Physical activity				
PAQ score z-score	-1.00 (0.99)	-0.009 (1.023)	-1.00 (-1.34, -0.65)	<0.001
MVPA z-score	-0.39 (0.79)	0.05 (1.03)	-0.43 (-0.71, -0.15)	0.004

BMI=body mass index, MCSA=muscle cross-sectional area, PAQ=physical activity questionnaire, MVPA=moderate-to-vigorous physical activity.
**HIV+, n=31; HUU, n=393.*

hip width apart. We chose the hands-on-waist protocol (vs freely moving arms) as this protocol requires less technique and is more suitable for the varied physical activity levels in both our HUU and HIV+ cohorts[28]. The research assistant explained the jumping protocol to all participants in a standardized manner. After hearing the tone (from the computer), participants were asked to initiate a downwards movement and then immediately jump as high as possible using both legs. Participants were instructed to land with both feet on the platform (with each foot on the appropriate side of the middle line) and to remain still until after hearing the tone from the computer signaling the end of the trial. Each participant performed one practice jump and three trial jumps. We used the jump associated with the highest height for analysis.

A number of outcomes are provided by the manufacturer's software; however, the main outcome of interest for the S2LJ are the peak power during lift off phase relative to body mass (P_{max}/mass, W/kg). We also report peak force (F_{max}) normalized to body weight (body mass*force of gravity or max acceleration/g; F_{max}/BW), as this variable is used to calculate force efficiency, which describes the quality of the movement pattern during the S2LJ (e.g., a more efficient movement or jump is one in which more power is generated with less muscle force). Efficiency is calculated as [EFI/((F_{max}/BW/2.4 g)*100)]*100 where EFI is the Esslinger Fitness Index, which is P_{max}/mass compared with the manufacturer's age- and sex-specific reference data provided by the manufacturer, expressed in percent (%) relative to the manufacturer's reference data[29]. Finally, we report jump height (m) and velocity (m/sec). We did not assess reproducibility of mechanography outcomes in our laboratory. However, in a previous study of children aged 7-11 years for the S2LJ using freely moving arms, the coefficient of variation (%CV) ranged from 2.3% (V_{max}) to 13.1% (F_{max}/BW)[26], while in adults aged 19-35 yrs, the CV% ranged from 0.1% (P_{max}) to 6.0% (Efficiency) for the S2LJ with static arms[30]. We recently reported age- and sex-specific reference values for these outcomes[17].

Statistical analysis

As in our previous analysis[16], we first calculated age- and sex-specific z scores to determine if anthropometry, body composition and lifestyle variables differed between HIV+ youth and HUU controls. In HUU controls we calculated age- (whole year, rounded age, e.g., 8.5 to 9.4 yrs categorized as 9 yrs) and sex-specific means (SD) for each anthropometric, body composition, maturity and physical activity outcome using all available data. Thus, for the 716 participants, we included between 1936 and 2011 observations, depending on the outcome variable.

To address our first objective, we utilized LMS-reference curves generated in our HUU youth (using all observations)[17,31] to calculate age- and sex-specific z-scores for mechanography outcomes in HIV+ youth and HUU controls. We used Welch's t test to determine if z-scores in HIV+ youth at baseline were significantly different from z-scores in the HUU cohort. We then fit multivariable regression models to adjust mechanography z-scores for height and MCSA z-scores, which were significantly lower in HIV+ compared with HUU youth (p<0.05, see Results).

To address our second objective (change in z-scores for mechanography outcomes over time) we first determined

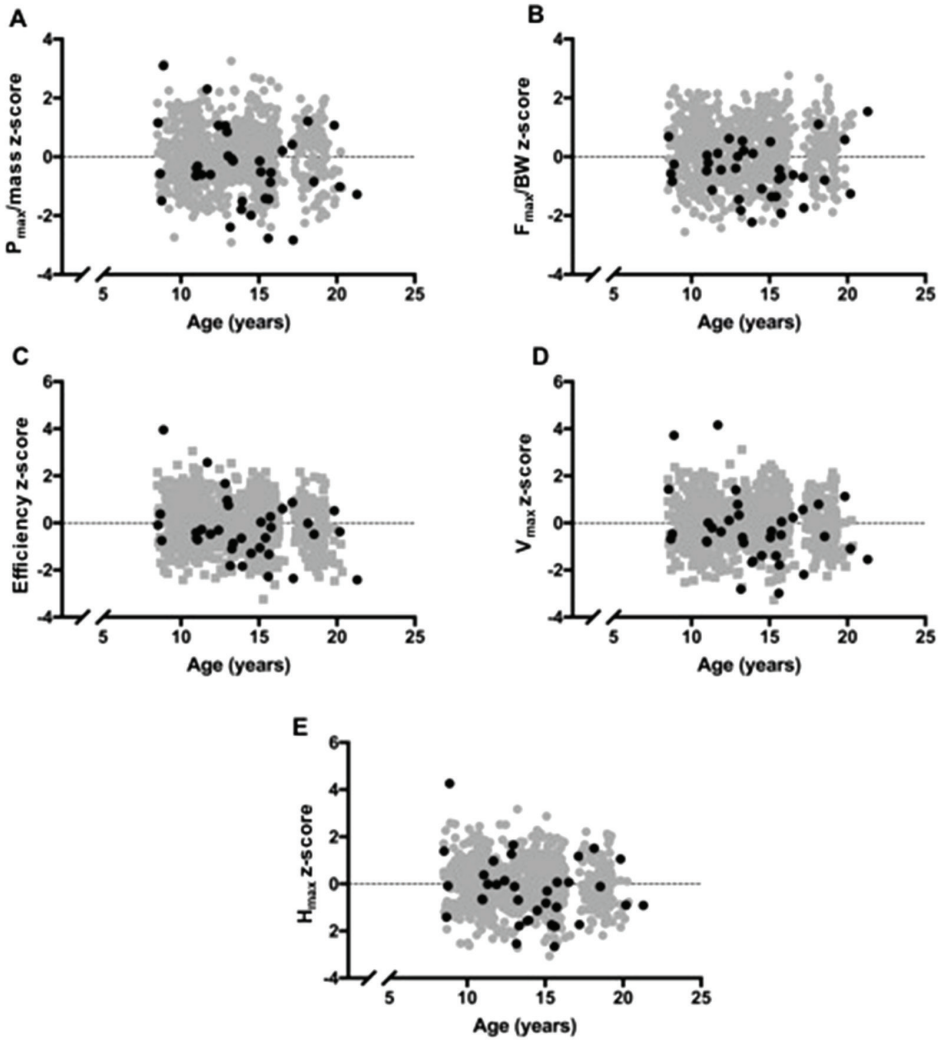

Figure 1. Z-scores for (a) peak muscle power relative to body mass (P_{max}/mass), (b) peak muscle force relative to body weight (F_{max}/BW), (c) maximum jump velocity (V_{max}), (d) maximum jump height (H_{max}) and (e) force Efficiency in HIV+ (black circles, n=35) and HUU (grey circles, n=716) youth at first measurement.

a slope from a linear regression model for each individual; the slope represents the annual change in z-score for each mechanography outcome. We then used a Wilcoxon sign rank test to determine whether the average slope across individuals was different from zero. We performed a similar analysis for anthropometric, body composition and physical activity z-scores.

Finally, we fit a multivariable regression model to identify potential predictors of mechanography outcomes in HIV+ youth at baseline while adjusting for height and MCSA z-scores. Independent variables included antiretroviral treatment (currently taking cART vs. not taking cART), disease stage, CD4+ percentage, peak HIV viral load, physical activity (PA score, MVPA) and vitamin D serum level. We used Stata, Version 10 (StataCorp, TX) for all analyses and we considered $p<0.05$ statistically significant.

Results

Baseline characteristics

At baseline, HIV+ youth were 14 years of age on average, 59% were male and the majority were of mixed ethnicity (32%) (Table 1). At baseline most HIV+ youth were asymptomatic (category N, n=25, 74%) or had mild symptoms of lymphadenopathy, chronic parotitis, dermatitis or recurrent upper respiratory infections (category A, n=5, 15%); a minority had moderate symptoms such as diarrhea and poor weight gain, recurrent herpes zoster infection (shingles) or HIV-related hepatitis (category B, n=4, 12%). None had severe HIV-related disease or AIDS defining illness (category C) at the time of the study but 5 (16%) previously experienced AIDS-defining illnesses such as an opportunistic infection or HIV encephalopathy. Similarly, at baseline, most HIV+ youth

Table 3. Absolute values and z-scores for mechanography outcomes in HIV+ youth at baseline and HIV unexposed uninfected (HUU) controls at first measurement. Values are mean (standard deviation) for unadjusted absolute values and sex- and age-specific z-scores and mean (95% CI) for z-scores adjusted for height and muscle cross-sectional area z-scores.

	HIV+ Unadjusted	HUU Unadjusted*	p-value	HIV+ Adjusted	HUU Adjusted^	p-value
P_{max}/mass (W/kg)	38.2 (7.6)	39.9 (7.6)				
P_{max}/mass z-score	-0.39 (1.33)	0.05 (0.99)	0.060	-0.54 (-0.91, -0.17)	0.15 (0.05, 0.23)	<0.001
F_{max}/BW	2.18 (0.22)	2.39 (0.37)				
F_{max}/BW z-score	-0.47 (0.89)	0.17 (0.98)	<0.001	-0.61 (-0.96, -0.27)	0.31 (0.22, 0.41)	<0.001
Efficiency (%)	97.5 (15.8)	100.2 (13.0)				
Efficiency z-score	-0.28 (1.31)	-0.06 (1.00)	0.338	-0.37 (-0.74, 0.01)	-0.07 (-0.17, 0.03)	0.141
V_{max} (m/sec)	2.22 (0.31)	2.25 (0.28)				
V_{max} z-score	-0.30 (1.50)	-0.02 (1.00)	0.287	-0.47 (-0.85, -0.09)	-0.003 (-0.11, -0.11)	0.020
H_{max} (m)	0.33 (0.08)	0.34 (0.07)				
H_{max} z-score	-0.29 (1.40)	-0.04 (1.01)	0.301	-0.42 (-0.80, -0.04)	-0.06 (-0.16, 0.04)	0.072

P_{max}/mass=Peak muscle power relative to body mass, F_{max}/BW=Peak muscle force relative to body weight, V_{max}=Maximum jumping velocity, H_{max}=Maximum jump height.
**N=716 for unadjusted comparisons, ^N=393 for adjusted comparison due to smaller number of HUU youth with MCSA measurements.*

(n=26, 76%) showed no evidence of immune suppression (absolute CD4>500 cells x 10^6 cells/mm^3 or CD4% >25%) while 7 (21%) had moderate suppression (absolute CD4 200-500 cells x 10^6 cells/mm^3 or CD4% of 15-25%) and 1 had severe immune depression (absolute CD4<200 cells x 10^6 cells/mm^3 or CD4%<15%). Most (74%) of the HIV+ youth were receiving cART at baseline. Three participants initiated cART between visit one and two and two participants initiated cART between visit two and three. Among those treated with cART, 20/25 (80%) had an undetectable HIV plasma viral load (<40 copies/ml) across the entire study period. Lipodystrophy, defined as limb or facial atrophy with or without accumulation of abdominal fat, was clinically observed in seven of the 22 youth who had received at least three years of cART in their lifetime. One HIV+ youth was vitamin D deficient based on recent guidelines (serum vitamin D≤25 nmol/L)[32]. Five of the 35 HIV+ youth (17%) were current smokers at baseline.

Among HIV+ youth, height and MCSA z-scores were significantly lower compared with the HUU controls (Table 2). Z-scores for body mass, BMI, lean mass and percent body fat in HIV+ youth were not significantly different from HUU controls. Maturity status ranged from pre- to post-pubertal in both HIV+ males and females; however, the majority of HIV+ males were Tanner stage 4 or 5 (60%, Table 1). More than half (58%) of the HIV+ females were postmenarcheal with a mean age at menarche of 12.1±1.5 yrs, which was not significantly different from HUU controls (12.5±1.5 yrs) (p=0.539). HIV+ youth were less physically active than HUU controls as per PA Score and MVPA z-scores (Table 2).

At baseline, unadjusted z-scores for F_{max}/BW were significantly lower in HIV+ youth as compared with HUU controls (Table 2, Figure 1); the mean difference was less than 1 standard deviation for all mechanography outcomes. After adjusting for height and MCSA z-scores, P_{max}/mass, F_{max}/BW and V_{max} z-scores were significantly lower in HIV+ youth compared with HUU controls (Table 3). Efficiency did not differ between HIV+ and HUU youth indicating that although the HIV+ youth used less relative force to generate a lower relative power, both groups used a similar quality of movement pattern during the S2LJ.

Change in mechanography z-scores in HIV+ youth

During follow-up, the clinical health of most participants remained stable. Five participants re-initiated cART during the follow-up, as they previously had low adherence to treatment. We present the slopes for z-scores for anthropometric, body composition, physical activity and mechanography outcomes in Table 4. In HIV+ youth, slopes for height, MCSA, PA score and MVPA z-scores were positive and significantly different from zero, suggesting improving trends over time for these parameters. Slopes for all mechanography outcomes were not significantly different from zero suggesting that trajectories in muscle power did not change in this cohort.

Predictors of mechanography outcomes in HIV+ youth

In HIV+ youth at baseline, CD4+ percentage positively predicted z-scores for P_{max}/mass (B=0.068, standard error (SE)=0.026, p=0.013), Efficiency (B=0.073, SE=0.025, p=0.006), V_{max} (B=0.085, SE=0.028, p=0.005) and H_{max}

Table 4. Mean (95% CI) of the slope of z-scores over time in HIV+ youth.

	Slope of z-score over time[a]	p-value
Anthropometry		
Height z-score	0.086 (0.005, 0.167)	0.037
Weight z-score	0.090 (-0.006, 0.186)	0.066
BMI z-score	0.070 (-0.038, 0.178)	0.198
Lean mass z-score	0.079 (-0.027, 0.186)	0.138
Percent body fat z-score	0.067 (-0.069, 0.203)	0.322
MCSA z-score	0.105 (-0.003, 0.216)	0.010
Physical activity		
PAQ score z-score	0.786 (0.408, 1.163)	<0.001
MVPA z-score	0.502 (0.035, 0.969)	0.036
Mechanography		
P_{max}/mass z-score	-0.089 (-0.319, 0.140)	0.434
F_{max}/BW z-score	-0.027 (-0.300, 0.246)	0.841
Efficiency z-score	-0.156 (-0.382, 0.070)	0.169
V_{max} z-score	-0.059 (-0.305, 0.186)	0.627
H_{max} z-score	0.040 (-0.150, 0.231)	0.668

[a] N=33 participants with 0-12 month slopes, 21 participants with 0-12-24 month slopes and 1 participant with a 0-24 month slope.

(B=0.059, SE=0.028, p=0.041) (Figure 2). After adjusting for height and MCSA z-scores, only Efficiency and V_{max} remained significantly associated with CD4+ percentage (p<0.05). We also noted a significant positive association between F_{max}/BW and cART use such that F_{max}/BW was higher among youth currently taking cART compared with those not taking cART (B=0.958, SE=0.350, p=0.011). PA score was not related to any mechanography outcomes in HIV+ youth; however, MVPA was a positive predictor of jump height (B=0.654, SE=0.278, p=0.026). We did not observe significant relationships between other HIV-related outcomes (pVL, CD4 nadir, lifetime months of cART use) and mechanography z-scores in HIV+ youth (data not shown).

Discussion

This is the first prospective study to examine functional measures of muscle power in children and youth living with perinatally-acquired HIV. Compared with a cohort of HUU individuals, HIV+ youth demonstrated significantly lower muscle power (relative to body mass), force relative to body weight and jump height and velocity after adjusting for stature and MCSA. Despite positive trends for height and MCSA across two years in HIV+ youth, trajectories for mechanography outcomes did not change. This suggests that apparent deficits in muscle power, although relatively small in magnitude, may have stabilized over time in this cohort of HIV+ youth.

While muscle power has been characterized in HUU children[13,33] and in other clinical pediatric populations[34-38], to the best of our knowledge, only one previous study investigated muscle power in HIV+ children[11]. Compared with HUU controls, HIV+ children aged 7 to 14 years demonstrated reduced lower limb anaerobic power (measured via the Wingate cycle ergometer test), but similar muscle strength (peak knee extensor torque via isokinetic dynamometry). Unfortunately, relationships between disease-related variables and muscle power were not investigated in this cross-sectional study. However, the authors speculated that smaller muscle mass, more time spent in sedentary behaviours and deficient neuromuscular coordination may underpin lower muscle power in HIV+ youth[11]. In the present study, lower muscle power (relative to body mass) in HIV+ youth was still evident after we adjusted for their smaller MCSA. This is not entirely surprising given that other factors such as fibre type distribution and neuromuscular activation are known to influence muscle power whereas MCSA is more closely related to muscle force[34,39,40]. In the context of musculoskeletal health, future studies that employ mechanography to assess dynamic muscle function in HIV+ youth may benefit from incorporating multiple one-legged hopping to assess maximal muscle force, rather than using the single two-legged jump to assess muscle power. Muscle force provides a better representation of the strains imposed on bone, and in our cohort (data not shown) and others[41] muscle force (via mechanography or MCSA) was more closely associated with bone structure and strength (via pQCT) than was muscle power.

We note several other possible explanations for small deficits in relative muscle power in our cohort of HIV+ children and youth. First, almost one quarter of participants in our study (23%) experienced reduced physical abilities secondary to HIV encephalopathy in infancy and/or to in utero exposure to alcohol or substances of addiction. Second, treatment-related lipodystrophy, including limb muscle atrophy is a common finding in patients treated with antiretrovirals for many years[10], and was clinically observed in one fifth of the HIV+ youth in our study population. In HIV+ men, the presence of lipodystrophy was associated with lower grip strength, a deficit that the authors speculated may be associated with higher levels of systemic inflammation[42]. Further, the magnitude of the difference in grip strength by lipodystrophy status was similar to the difference in grip strength between healthy men aged 50-59 years and men aged 60-69 years[43]. Thus, lipodystrophy in HIV+ individuals may signal an increased risk for early age-related functional declines. Further study is warranted to clarify relationships between muscle mass, power and strength in HIV+ youth with lipodystrophy.

Low levels of physical activity in our cohort of HIV+ youth may also have influenced mechanography outcomes. Although self-reported physical activity was not associated with peak muscle power, leisure-time physical activity was lower in HIV+ youth as compared with the HUU controls. Further, clinically, those HIV+ youth with lipodystrophy in

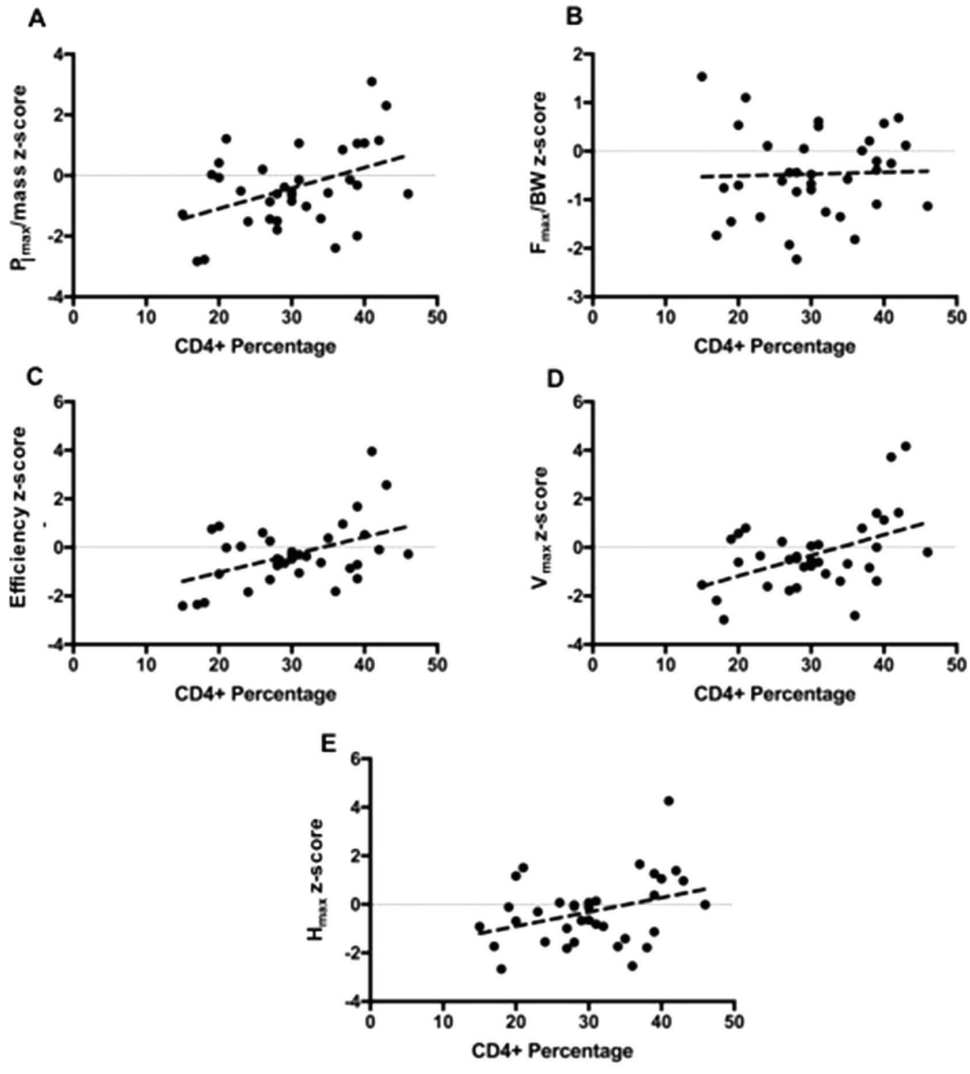

Figure 2. Scatterplots depicting the association between CD4+ percentage and z-scores for (A) peak power relative to body mass (P_{max}/mass), (B) peak muscle force relative to body weight, (C) maximum jump velocity, (D) maximum jump height and (E) force efficiency in HIV+ youth (n=35).

our cohort often reported diffuse leg pain during physical activity, which was a barrier to participation. Future studies of physical activity in relation to muscle function in children and youth living with HIV would benefit from objective monitoring of physical activity with accelerometers to clarify patterns of physical activity (and sedentary time), and how these relate to muscle force and power. In addition, it would be valuable to investigate barriers and facilitators to physical activity in this population. To our knowledge, only one previous study examined physical activity (by questionnaire) in HIV+ youth[44]. In South African children aged 5-9 years, moderate physical activity levels were similar between HUU children and HIV+ children who initiated cART early in life. However, levels of vigorous PA were lower in HIV+ girls compared with their healthy peers[44], which the authors speculated may be due to lower rates of participation in physical education and organized sport among HIV+ girls. As our cohort of HIV+ youth was older than children in the South African study, it is possible that the well documented decline in physical activity during adolescence[45,46] may be accentuated in HIV+ youth. However, we also observed positive trends in physical activity z-scores during our two-year follow-up, which may either suggest improvements in activity behaviours, or indicate regression to the mean in our small cohort. Longitudinal studies of children and youth living with HIV that utilize objective monitoring of physical activity will help to clarify these relationships.

Although most HIV+ youth in our cohort had well-controlled or slow-progressing disease, we observed a significant positive association between level of immunosuppression

and absolute values for peak muscle power, force efficiency and peak jump height velocity. This finding is similar to a study of HIV+ adults in which grip strength was higher among participants with high current T-cell counts[12], and suggests that physical performance is better in HIV+ individuals when disease activity is low. Further study is needed to determine whether immunosuppression directly impacts muscle function, or if the relationship between immunosuppression and muscle function is mediated through effects on overall growth and development.

The effects of cART on muscle function in children who acquired HIV perinatally are not well described. In our cohort, the majority of participants were currently receiving cART and had been on treatment for a median of 126 months (IQR: 65, 151). In this group, peak force relative to body weight tended to be greater as compared with those participants not receiving cART. This is in contrast to the results of Humphries et al.[4] who reported greater muscle strength (assessed by dynamometry) in HIV+ South African children aged 4-8 years not currently receiving cART compared with those on cART. Importantly, our comparison is confounded by the small number of HIV+ participants not currently taking cART, and that of these, only one was cART naïve. Further study is needed to clarify the influence of cART on muscle power during childhood and adolescence.

During our two-year study, changes in z-scores for peak muscle power and other mechanography outcomes were small and not significantly different from zero. This finding suggests that trajectories in these dynamic measures of muscle function did not change over two years in this cohort of HIV+ children and youth. This is similar to our longitudinal analysis of bone outcomes in this sample[16], but as we noted previously our results should be interpreted with caution due to the small sample size and the possibility of regression to the mean. In addition, we were not powered to examine change in mechanography outcomes in HIV+ youth while adjusting for changes in body size, MCSA, maturation and disease-related variables that may influence the trajectory of peak power during growth.

We acknowledge several limitations of our study. First, as we noted previously[16] due to the wide range in ages, ethnicities and maturational status in our small sample of HIV+ youth we must consider the influence of sampling error on our analysis. While our sample included the majority of HIV+ youth in the province of British Columbia who acquired HIV perinatally, it is likely not representative of the population of children and youth living with HIV in other regions. Related to this, we were unable to generate maturity- or ethnic-specific z-scores for mechanography outcomes in the HIV+ youth, nor could we adjust for ethnicity in our analysis due to the heterogeneity in ethnic origins in the HIV+ youth. In our HUU cohort, we recently reported greater values for all mechanography outcomes in Asians compared with whites[17]. Thus, the higher proportion of Asians in the HUU cohort compared with our sample of HIV+ youth, the majority of whom were of mixed ethnicities, may have contributed to the differences in mechanography outcomes observed in the present study. Sampling error may also have increased the chance of of Type I errors, and thus, our results should be interpreted with caution and considered hypothesis generating[16]. Finally, we asked participants to perform the S2LJ with their hands on their waist, which differs from other mechanography studies where children performed the jump with freely moving arms[13,15,29,35]. As described in our previous study[17], we chose this protocol as it is less mechanically challenging and minimizes the influence of coordination on jump parameters[28]. Based on the EFI values in HIV+ and HUU youth, peak power was approximately 10% less in both groups as compared with a European reference sample provided by the manufacturer[29].

In summary, our findings suggest that HIV acquired perinatally may be associated with small deficits in lower limb muscle power relative to body mass. As muscle function directly influences activities of daily living and quality of life, there is a need to better understand the clinical significance of this difference, particularly in HIV+ youth who will live with this chronic disease into adulthood. In adults living with HIV, interventions that targeted increased lower leg muscle power were recommended as a means to improve physical function and quality of life[47], yet few similar programs were implemented in children[48,49]. Thus, further investigation into the effectiveness of physical activity and strength training interventions for enhancing muscle function and quality of life in children and youth who acquired HIV perinatally is warranted.

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