

# Early cardio-pulmonary disease in children despite very early ART: Evidence from the CHER trial cohort



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## Background

Untreated HIV infection in children is associated with chronic progressive pulmonary and cardiac disease [1,2]

The degree to which early antiretroviral therapy (ART) prevents this is unclear [3,4]

- 1) Ferrand, Rashida A., Sujal R. Desai, Charlotte Hopkins, Caroline M. Elston, Susan J. Copley, Kusum Nathoo, Chiratidzo E. Ndhlovu et al.. "Chronic lung disease in adolescents with delayed diagnosis of vertically acquired HIV infection." *Clinical infectious diseases* 55.1 (2012): 145-152.
- 2) Starc, T. J., Lipshultz, S. E., Easley, K. A., Kaplan, S., Bricker, J. T., Colan, S. D., ... & Schluchter, M. D., et al. "Incidence of cardiac abnormalities in children with human immunodeficiency virus infection: the prospective P 2 C 2 HIV study." *The Journal of pediatrics* 141.3 (2002): 327-335.
- 3) Crothers, K. HIV infection and risk for incident pulmonary diseases in the antiretroviral therapy era. *Am J Respir Crit Care Med*, 2011. 183(3): 388.
- 4) Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med*. 2012;13(8):453-68. PMID: 22413967.

## Background

Maximal oxygen consumption ( $\text{VO}_2\text{max}$ ) is the gold standard measure of cardiovascular and respiratory fitness and a sensitive marker of early cardiovascular or respiratory disease [5]

5) Carlson, David J. "VO2max: the gold standard?." *CHEST Journal* 108.3 (1995): 602-603.

## Aim

To estimate  $\text{VO}_2\text{max}$  in perinatally-HIV-infected primary-school-aged children who initiated LPVr-based ART in the first few months of life in a well-resourced trial setting

## Methods

Cross-sectional analysis, observational design

Cape Town participants in CHER trial <sup>[6,7]</sup> who initiated LPVr-based ART at median **9.1** (IQR: 7.4 – 12.0) *weeks of age*

HIV-uninfected control group from the same communities and socio-economic background

Standardized 3-minute exercise step test to estimate VO<sub>2</sub>max using a previously validated formula for healthy school-age children <sup>[8]</sup>

- 6) Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, Jean-Philippe P, McIntyre JA. Early antiretroviral therapy and mortality among HIV-infected infants. *New England Journal of Medicine* 2008; 359(21): 2233-2244.
- 7) Cotton MF, Violari A, Otwombe K, Panchia R, Dobbels E, Rabie H, Josipovic D, Liberty A, Lazarus E, Innes S, Janse van Rensburg A, Pelsler W, Truter H, Madhi S, Handelsman E, Jean-Philippe P, McIntyre JA, Gibb DM, Babiker AG on behalf of the CHER Study Team. Early limited antiretroviral therapy is superior to deferred therapy in HIV-infected South African infants: results from the CHER (Children with HIV Early antiRetroviral) Randomized Trial. *Lancet* 2013; 382(9904): 1555–1563.
- 8) Jacks, Dean E., Robert Topp, and Justin B. Moore. "Prediction of VO<sub>2</sub> Peak Using a Sub-maximal Bench Step Test in Children (Revised\*)." *Clinical Kinesiology* 66.3 (2012): 74.

## Methods

Estimated  $\text{VO}_2\text{max}$  corrected for fat-free body mass  
(measured by dual energy X-ray absorptiometry - DXA)

Entered into multivariate linear regression as the dependent variable, with the following as independent variables:

- Age
- Gender
- Vertebral bone mineral density z-score measured by DXA as a **surrogate marker of chronic malnutrition** [9]
- Fasting lipids as a **surrogate marker for extremely high refined carbohydrate + low protein diet** [10], which may reduce exercise tolerance and increase muscle tiredness [11]

9) Gordon, C. M. (2003). Normal bone accretion and effects of nutritional disorders in childhood. *Journal of Women's Health, 12*(2), 137-143.

10) Ma, Y., Li, Y., Chiriboga, D. E., Olendzki, B. C., Hebert, J. R., Li, W., ... & Ockene, I. S. (2006). Association between carbohydrate intake and serum lipids. *Journal of the American College of Nutrition, 25*(2), 155-163.

11) de Queiroz, K. B., Rodovalho, G. V., Guimarães, J. B., de Lima, D. C., Coimbra, C. C., Evangelista, E. A., & Guerra-Sá, R. (2012). Endurance training blocks uncoupling protein 1 up-regulation in brown adipose tissue while increasing uncoupling protein 3 in the muscle tissue of rats fed with a high-sugar diet. *Nutrition research, 32*(9), 709-717.

## Results

<b>Demographics and clinical characteristics</b> presented as median (interquartile range)	HIV-infected n = 77	Uninfected controls n = 48	Unadjusted p-value (2-tailed)
Age at study visit (years)	7.7 (7.6 – 7.8)	8.5 (7.8 – 8.7)	<0.0001
Gender (male/female)	44% / 56%	63% / 38%	0.05
Cumulative time on ART (years)	7.1 (6.7 – 7.4)	---	---
Dominant ART regimen (ZDV / 3TC / LPVr)	91% / 97% / 96%	---	---
Proportion with undetectable HIV RNA PCR viral load (<150 copies/ml)	95%	---	---
Cumulative time with undetectable HIV RNA PCR viral load (years)	5.2 (2.4 – 5.6)	---	---
Current CD4 (cells/mm <sup>3</sup> )	1115 (848 – 1432)	---	---
Maximum WHO clinical stage ever reached (1 or 2 / 3 / 4)	10% / 40% / 49%	---	---

## Results

<b>Demographics and clinical characteristics</b> presented as median (interquartile range)	<b>HIV-infected</b>  n = 77	<b>Uninfected controls</b>  n = 48	<b>Unadjusted p-value (2-tailed)</b>
<b>Weight-for-age z-score</b>	<b>-0.4</b> <b>(-1.0 – 0.3)</b>	<b>-0.2</b> <b>(-1.0 – 1.1)</b>	<b>0.13</b>
<b>Height-for-age z-score</b>	<b>-0.8</b> <b>(-1.3 – 0.1)</b>	<b>-0.3</b> <b>(-1.1 – 0.3)</b>	<b>0.12</b>
<b>Body mass index-for-age z-score</b>	<b>0.1</b> <b>(-0.5 – 0.7)</b>	<b>0.1</b> <b>(-0.5 – 1.2)</b>	<b>0.26</b>
<b>Waist-to-height ratio</b>	<b>0.46</b> <b>(0.44 – 0.49)</b>	<b>0.45</b> <b>(0.43 – 0.48)</b>	<b>0.25</b>
<b>Fat-free body mass (kg)</b>	<b>17.5</b> <b>(16.0 – 19.8)</b>	<b>18.8</b> <b>(17.0 – 20.9)</b>	<b>0.007</b>
<b>Vertebral bone mineral density z-score</b>	<b>-0.4</b> <b>(-1.1 – +0.1)</b>	<b>-0.3</b> <b>(-0.9 – +0.3)</b>	<b>0.14</b>



## Results

<b>Demographics and clinical characteristics</b> presented as median (interquartile range)	HIV-infected n = 77	Uninfected controls n = 48	Unadjusted p-value (2-tailed)
<b>Total cholesterol (mmol/L)</b>	4.2 (3.7 – 4.8)	3.5 (3.1 – 4.0)	<0.0001
<b>LDL cholesterol (mmol/L)</b>	2.5 (2.0 – 2.9)	1.9 (1.6 – 2.4)	<0.0001
<b>Triglyceride-HDL cholesterol ratio</b>	0.7 (0.5 – 1.0)	0.4 (0.3 – 0.7)	<0.0001
<b><i>Unadjusted</i> VO<sub>2</sub>max (ml/min/kg)</b>	53 (46 – 59)	51 (43 – 57)	0.21

## Results

<b>Multiple linear regression</b>	<b>Difference in VO<sub>2</sub>max (ml/min/kg fat-free body mass) (95% confidence interval)</b>	<b>p-value (2-tailed)</b>
<b>Gender (male versus female)</b>	<b>-8.1 (-11.9 to -4.3)</b>	<b>&lt;0.0001</b>
<b>Age (per year increase)</b>	<b>-2.5 (-6.9 to 1.8)</b>	<b>0.26</b>
<b>Vertebral bone mineral density z-score (per unit increase)</b>	<b>-1.8 (-3.7 to 0.1)</b>	<b>0.06</b>
<b>LDL cholesterol (per mmol/L increase)</b>	<b>3.4 (0.7 to 6.2)</b>	<b>0.01</b>
<b>HIV-infected versus uninfected</b>	<b>-5.4 (-10.1 to -0.6)</b>	<b>0.03</b>

After adjustment, **HIV+ children had a significantly lower VO<sub>2</sub>max** per kg fat-free body weight

## Conclusion

**While early ART offers substantial benefit, it may not entirely prevent chronic non-infectious pulmonary and cardiac disease in perinatally-infected children**

## Limitations

- **Cross-sectional analysis**
- **Observational design**

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