

## Increased Left Ventricular Posterior Wall End-Diastolic Thickness in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection

### To the Editors:

At least a third of HIV-infected infants have slow progressing disease and even without HIV treatment have a 50% probability of surviving to adolescence.<sup>1,2</sup> Hence, substantial numbers of adolescents, infected before interventions to prevent mother-to-child HIV transmission became available, are presenting to clinical services with undiagnosed HIV in sub-Saharan Africa. A high burden of cardiac disease was recently described among vertically infected adolescents who attended HIV outpatient clinics in Harare, Zimbabwe. In that study, left ventricular (LV) hypertrophy,

defined as a maximal wall thickening  $z$ -score  $>2$  of the LV interventricular septum, the LV posterior wall (LVPW), or both, was observed in 67% (74/110) of the participants. Multivariate analysis showed no association with the participant's age, sex, stunting, wasting, body mass index (BMI), New York Heart Association (NYHA) functional status, World Health Organization (WHO) HIV stage, CD4 count, duration or type of antiretroviral therapy (ART), and LV hypertrophy.<sup>3</sup>

In the general population, LVPW thickness increases with age in healthy adults, occurs in insulin-dependent diabetes mellitus in the absence of overt cardiac disease, in the morbidly obese, persisting despite weight loss, and in patients with chronic inflammatory conditions, including rheumatoid arthritis and systemic lupus erythematosus.<sup>4</sup> In HIV-uninfected children, increased LVPW thickness is described to exist in association with elevated inflammatory biomarkers<sup>5</sup> and in myocarditis.<sup>6</sup> Among HIV-infected children, a small increase in LVPW thickness in early life predisposes these children to myocardial ischemia, and all-cause mortality,<sup>4,5</sup> and in the general population increased LV mass is an independent predictor of cardiovascular mortality in adults.<sup>7</sup> Given the significance of increased LVPW thickness among these groups, we specifically investigated the clinical associations of LVPW thickening among the previously described cohort of vertically infected adolescents.<sup>3</sup>

One hundred and ten adolescents aged 10–19 (median 15) years were consecutively recruited from 2 HIV outpatient clinics in Harare. Participant demographics and clinical features were recorded, and transthoracic echocardiography was performed as previously described.<sup>3</sup> Echocardiographic parameters were expressed as a deviation from the body surface area-corrected mean using pediatric reference ranges; an LVPW  $z$ -score  $>2$  was regarded as abnormal. Associations among clinical variables (age, sex, height-for-age  $z$ -score (stunting), weight-for-age  $z$ -score (wasting), BMI, WHO stage, CD4 count, NYHA functional status, duration and type of ART, and LVPW

thickness were assessed, and variables showing an association at significance level  $P < 0.1$  were included in a multivariate logistic regression analysis, where  $P < 0.05$  was considered significant. Ethical approval was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee, Medical Research Council of Zimbabwe, and the Biomedical Research and Training Institute Institutional Review Board, Harare. The participants gave their assent to participate, and written informed consent in either English or Shona was obtained from their guardians.

The clinical characteristics of the study participants have been described previously.<sup>3</sup> Briefly, 78 (71%) had been taking ART for a median of 20 [interquartile range (IQR) 5–40] months, 90% of whom were on the first-line ART regimen [2 nucleoside reverse transcriptase inhibitors (including stavudine or zidovudine) and a nonnucleoside reverse transcriptase inhibitor]. The median CD4 count was 384 cells per microliter (IQR 171–578), 87% (96/110) had WHO stage 3 or 4 disease, and the median BMI  $z$ -score was  $-0.69$  (IQR  $-1.81$ – $0.11$ ). The median LVPW thickness  $z$ -score was  $+1.82$  (IQR  $0.69$ – $2.63$ ), with a  $z$ -score  $>2$  in 48 (44%) and  $>3$  in 17 (15%) participants. An LVPW thickness  $z$ -score  $>2$  was associated with an ART duration of  $>12$  months [odds ratio (OR) 2.60,  $P = 0.06$ ], BMI  $<18.5$  kg/m<sup>2</sup> (OR 2.31,  $P = 0.04$ ), and wasting (weight-for-age  $z$ -score  $<-2$ ) (OR 2.00,  $P = 0.07$ ). After adjusting for age, sex, stunting (height-for-age  $z$ -score  $<-2$ ), WHO HIV staging, CD4 count, NYHA functional status, and ART regimen, the LVPW thickness was associated with a longer ART duration (adjusted OR 3.16, 95% confidence interval 1.10–9.05) and low BMI (adjusted OR 3.46, 95% confidence interval 1.25–9.60).

The high prevalence of LVPW thickening in this cohort is striking, and contrasts with the pattern seen in HIV-infected younger children in the pre-ART era. The P<sup>2</sup>C<sup>2</sup> study in the United States followed up HIV-infected children (median age 2.1 years) for a median of 5 years. The LVPW was thinned at baseline in HIV-infected

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children compared with that in HIV-negative controls (mean z-score  $-0.31$ ,  $P = 0.003$ )<sup>8</sup> and reached a nadir between 2 and 6 years, but it was normalized by 7 years of age. This pattern was attributed to an early myocardial insult causing LV dilatation in younger HIV-infected children, with a delayed LV hypertrophic response restoring LV thickness by late childhood.<sup>9</sup> Where present, LVPW thickening at baseline was associated with increased all-cause 5- and 10-year mortalities.<sup>10</sup>

The reason for the high prevalence of LVPW thickening in older children with longstanding HIV, compared with that in HIV-infected adults, age-matched HIV-negative children, and younger HIV-infected children remains unclear, but infers chronic myocardial damage. Prolonged exposure to HIV may cause direct damage through viral invasion of cardiac myocytes,<sup>11</sup> HIV-induced transcriptional activation of myocyte cellular genes, and HIV proteins, such as gp120, which has a negative inotropic effect.<sup>12</sup> LVPW thickening has been associated with inflammatory conditions in adults and in children; this includes rheumatoid arthritis, systemic lupus erythematosus, and myocarditis.<sup>4-6,13</sup> Chronic untreated HIV infection also causes systemic immune activation, and the high prevalence of LVPW thickening in our cohort with longstanding untreated HIV infection may result from chronic HIV-mediated inflammation.<sup>14</sup> Most of the larger studies investigating the relationship between HIV and cardiac structure and function have been conducted in Western populations. Genetic and environmental differences in the Zimbabwean group examined here may be partly responsible for our unexpected findings. Pathogens such as viruses (cytomegalovirus, adenovirus, and Coxsackie B), toxoplasma, and cryptococcus, which can affect cardiac function, may be more common in sub-Saharan Africa.

In this study, 71% of the adolescents were receiving ART, and the longer duration of treatment was associated with LVPW thickening. Data on the relationship between ART exposure and LVPW thickness are mixed. Among younger HIV-infected chil-

dren, ART seems to be cardioprotective, limiting LV structural and functional impairment,<sup>15</sup> and the use of zidovudine by 63% (124/196) of HIV-infected children in the P2C2 study may explain the observed lower rates of LVPW thickening. Studies in HIV-infected adults have shown a more varied response to ART, but are limited by their cross-sectional nature. Thymidine analogs, including zidovudine and stavudine, have been associated with mitochondrial toxicity, blunted myocardial hypertrophy, and impaired cardiac function early in life.<sup>16,17</sup>

LVPW thickening was also associated with a reduced BMI in this study. Studies of HIV-negative children with protein energy malnutrition show mixed results with both increased and decreased LV mass being proportionate to body surface.<sup>18-20</sup> However, there are few data concerning the relationship between LVPW thickness and BMI in the context of HIV infection, where the mechanism of wasting is known to be different, and specific micronutrient deficiencies, neuroendocrine abnormalities, and a correlation between HIV viral load and poor growth have been identified.<sup>21</sup> It is possible that these factors limiting general growth in HIV-infected children have a concurrent effect on the development of cardiac tissue.

The study had several limitations including the use of US and European echocardiographic reference values, use of M-mode echocardiography, which may overestimate wall thickening compared with that of 2D imaging, and the cross-sectional study design, which has inherent issues of reverse causality. Nevertheless, it is the first study to demonstrate a high prevalence of increased LVPW thickness and an association with a low BMI and duration of receipt of ART among the growing cohort of HIV-infected adolescents with vertically acquired disease. Further prospective studies are required to investigate pathological mechanisms, reversibility, and prognostic implications of LVPW thickening and to investigate the effect of ART exposure at different stages of child-

hood on the long-term cardiac function in adolescence.

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## CD4 T-Lymphocyte Percentages Corresponding to CD4 T-Lymphocyte Count Thresholds in a New Staging System for HIV Infection

### To the Editors:

For epidemiologic surveillance of HIV infection in the United States, until this year, the staging system for adults (published in 2008) had been separate from the classification system for children (published in 1994).<sup>1,2</sup> To design a single staging system for both adults and children based primarily on absolute CD4 T-lymphocyte counts, we retained the age-specific CD4 count thresholds used to define the boundaries between stages 1, 2, and 3 (called “immunologic categories” rather than “stages” in the 1994 classification for children). Values greater than or equal to the upper threshold indicate stage 1, values less than the upper threshold but greater than or equal to the lower threshold indicate stage 2, and values less than the lower threshold indicate stage 3 (AIDS). For children aged <1 year, the lower and upper CD4 count thresholds are 750 and 1500 (cells/μL); for children aged 1 to <6 years, they are 500 and 1000; for children aged 6 to <13 and for adults and adolescents aged 13 or older, they are 200 and 500.

Those staging/classification systems used both the absolute CD4 count and the CD4 percentage of total lymphocytes to classify cases into stages; if the CD4 count and the CD4 percentage indicated different stages, the more

advanced of the 2 stages was selected. If one of these measurements was not available, the classification was based solely on the other measurement. The lower and upper CD4 percentage thresholds in those staging/classification systems were 15% and 25% for all 3 age groups of children, and 14% and 29% for adults and adolescents.<sup>1,2</sup> In developing an updated staging system, we reassessed the relationship between the CD4 counts and the CD4 percentages and selected the mean CD4 percentage corresponding to each CD4 count threshold.

We analyzed pairs of CD4 counts and CD4 percentages from 2 data sources: (1) the National HIV Surveillance System (NHSS) of the Centers for Disease Control and Prevention (data received by March 31, 2013) and (2) the HIV Research Network (HIVRN), a consortium of 19 facilities providing care to HIV-infected patients. Because data from these 2 sources may overlap to an unknown extent, we analyzed them separately to avoid duplicating observations in a single analysis. After testing several models of the relationship between CD4 counts and CD4 percentages, we concluded that a linear regression model of their natural logarithmic transformations would be best, with the logarithm of the CD4 percentage as the dependent variable predicted by the logarithm of the CD4 count:  $\log(\text{CD4 percentage}) = \text{Intercept} + \text{Slope} \times \log(\text{CD4 count})$ . We calculated the mean CD4 percentage predicted by each CD4 count threshold by placing each CD4 count threshold in the regression equation with the estimated Intercept and Slope (regression coefficient), and taking the antilogarithm of the result.

The results from HIVRN data were similar to those from NHSS data (Table 1). Rounded to the nearest whole percentage, the lower and upper CD4 percentage thresholds derived from NHSS data were as follows:

- For children aged <1 year: 26% and 34%.
- For children aged 1 to <6 years: 22% and 30%.
- For children aged 6 to <13 years: 14% and 24%.
- For adults and adolescents aged ≥13 years: 14% and 26%.