

# Effects of HIV Infection on Pulmonary Artery Pressure in Children



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## ABSTRACT

**Background:** Pulmonary hypertension may complicate human immunodeficiency virus (HIV) infection and result in right ventricular (RV) failure and premature death. There are limited data of the effects of childhood HIV infection or antiretroviral therapy (ART) on pulmonary artery pressure (PAP).

**Objectives:** To establish if there is an association between childhood HIV infection or its treatment and pulmonary artery pressure.

**Methods:** The study conducted a cross-sectional study of 102 HIV-infected (48 ART-naïve, 54 ART-exposed) and 51 HIV-uninfected children in Jakarta, Indonesia, to estimate PAP using echocardiography parameters: tricuspid regurgitation peak velocity (TRV), left ventricular systolic index and diastolic eccentricity index (EI), and RV systolic function, assessed by tricuspid annulus plane systolic excursion. The association between either ART-naïve or ART-exposed HIV and PAP was explored using general linear modelling adjusted for potential confounders.

**Results:** ART-exposed HIV-infected children had higher TRV (adjusted difference: 0.36 m/s; 95% confidence interval [CI]: 0.12 to 0.60;  $p = 0.003$ ) and diastolic EI (adjusted difference 0.06; 95% CI: 0.01 to 0.11;  $p = 0.02$ ) than did uninfected children. The EI in ART-exposed children was significantly higher than normal. ART-naïve HIV-infected children had a lower tricuspid annulus plane systolic excursion (adjusted difference:  $-2.2$  mm; 95% CI:  $-3.73$  to  $-0.71$ ;  $p = 0.004$ ), despite no difference in TRV (adjusted difference: 0.18 m/s; 95% CI:  $-0.06$  to 0.43 m/s;  $p = 0.14$ ). Seven (13%) ART-exposed and 4 (8.3%) ART-naïve HIV-infected children had pulmonary hypertension. Within-HIV group comparisons showed that accounting for lower respiratory tract infections attenuated the lower RV systolic function in ART-naïve children but not in ART-exposed children (difference:  $-1.1$  mm; 95% CI:  $-2.8$  to 0.7 mm;  $p = 0.22$ ), but not the higher left ventricular eccentricity indexes in the ART-exposed children (systolic difference: 0.07; 95% CI: 0.02 to 0.12;  $p = 0.007$ ; diastolic difference: 0.08; 95% CI: 0.02 to 0.14;  $p = 0.006$ ).

**Conclusions:** ART-exposed HIV infection is associated with higher estimated PAP. Reduced RV systolic function is seen in ART-naïve HIV infection. Lower respiratory tract infection partly explains lower systolic RV function in ART-naïve relative to ART-exposed HIV infection.

Human immunodeficiency virus (HIV) infection in children continues to be a global epidemic [1]. Although the incidence has declined in some countries, particularly due to effective prevention of vertical transmission, new cases are continuing to increase in low-to-middle income countries, where coverage of antiretroviral therapy (ART) is inadequate and only reaches about 30% to 40% of HIV-infected children [2]. In 2013, there were approximately 630,000 children living with HIV globally, with most of these children residing in Africa and Asia [2]. Despite these challenges, the life expectancy of HIV-infected children has been increasing with a shift in the medical focus from acute to chronic complications related to the disease and its treatment [3].

Pulmonary hypertension is one of the chronic complications associated with HIV infection, and which may result in premature death due to right ventricular (RV) failure [4]. The exact prevalence of pulmonary hypertension in HIV-infected children is unknown and data in children are limited to case reports or survey [5]. Prevalence estimates of pulmonary hypertension in adults, mostly from developed countries, vary from 0.5% to 9.9%. Since these figures are derived from studies involving only symptomatic patients, this may underestimate the magnitude of the problem [6]. Unfortunately, data from the developing world are even more scanty. These populations are also more prone to chronic pulmonary infections which may potentiate the development of pulmonary

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hypertension [6]. Furthermore, whether HIV-associated pulmonary hypertension is attributable to the virus or viral component itself or to ART remains unclear. Animal and in vitro studies suggest that ART may either prevent or induce the development of pulmonary hypertension [7]. Given the limited data in children, we aimed to investigate the effects of HIV infection in children on noninvasively estimated pulmonary artery pressure (PAP) with particular attention to delineate the effects of ART-naïve HIV infection from ART-exposed HIV infection.

## METHODS

### Study design and population

We performed a cross-sectional analysis of children enrolled in a cohort study investigating the cardiovascular manifestations of HIV infection. The cohort was established in June 2013 in Jakarta, Indonesia. We enrolled 114 vertically-acquired HIV-infected children (56 ART-naïve, 58 ART-exposed) from the outpatient clinics and wards of Cipto Mangunkusumo National General Hospital, Koja District Hospital, and the Indonesian Planned Parenthood Association clinic, Jakarta, Indonesia. In our setting at that time (years 2013 to 2015), HIV screening in pregnancy was not routinely performed resulting in detection of HIV later in childhood and these children remaining untreated for months or even years. Children with congenital heart disease were excluded from this study. We also recruited 51 uninfected children as a reference group.

Of the 155 subjects enrolled, echocardiography was successful for 153 children (48 ART-naïve HIV infected, 54 ART-exposed HIV infected, 51 uninfected). Of the 48 ART-naïve HIV-infected children, 4 patients had previously received ART for <3 months, but had been off treatment for at least 5 years at the time of study enrollment. So, although these children had experienced ART previously, for this particular research question we considered them naïve for treatment. Not all children with echocardiograms had sufficient tricuspid regurgitation (TR) to estimate the RV systolic pressure, leaving 44 ART-naïve, 38 ART-exposed, and 31 uninfected children with suitable data for measurement of TR jet velocity.

Informed consent was obtained from every child parents or guardians. This study was approved by the Ethics Committee of Faculty of Medicine University of Indonesia.

### Diagnosis of HIV infection

HIV infection was diagnosed according to World Health Organization criteria/Centers of Disease Control guidelines (positive HIV polymerase chain reaction in those <18 months, HIV serology in those >18 months) [8]. Subjects were classified as ART-exposed if they had been started on highly active ART regimen at the time of study enrolment for at least 2 weeks. Clinical and immunologic staging were defined based on World Health Organization criteria [8].

### Outcome measurements

We performed cardiac ultrasound and measured several echocardiographic parameters to estimate PAP [9]. These included assessment of septal curvature (left ventricular [LV] diastolic and systolic eccentricity index) and the peak velocity of the TR jet. In the setting of normal RV volume loading, the LV eccentricity index is a measure of the RV pressure relative to the LV pressure. In the absence of RV outflow obstruction, RV pressure is determined by PAP. The LV eccentricity index was defined as the ratio of the anterior-posterior (parallel to septum) to septal-lateral (perpendicular to septum) diameters measured in the parasternal short-axis view at the level of the LV papillary muscles at both end-diastole and end-systole. A ratio >1 was considered abnormal [10]. The TR jet velocity was used as a measure of the RV systolic pressure to estimate the corresponding PAP. A TR jet velocity >3.4 m/s or TR jet velocity of 2.9 to 3.4 m/s with LV diastolic or systolic eccentricity index >1.1 was considered abnormal and indicative of pulmonary hypertension [11]. LV systolic function was measured using the biplane Simpson method [12]. The RV systolic function was assessed by measuring the systolic excursion of the tricuspid annulus at the lateral wall (tricuspid annulus plane systolic excursion [TAPSE]) using M-mode.

### Possible confounders and intermediary variables

For the associations between HIV infection or treatment status with PAP parameters, we a priori considered age and postnatal secondhand smoking exposure as potential confounders, as both variables were considered likely to be associated with HIV infection and PAP. The association between smoking and pulmonary hypertension has been described previously [13], and HIV-infected children were likely to have parents who smoked. With regard to possible intermediary variables, we considered that degree of inflammation as reflected by high-sensitivity C-reactive protein (hs-CRP) level, lung infection, and decreased LV systolic function may mediate the association between HIV infection or treatment and increased PAP. Lower respiratory tract infection (LRTI) was defined as an International Classification of Diseases-Tenth Revision-coded hospital diagnosis of pneumonia or respiratory tuberculosis, which was diagnosed based on hospital records. A diagnosis of pneumonia included pulmonary infections due to *Pneumocystis jirovecii*. Tuberculosis infection was established by a Mantoux test, radiological features, or supporting bacteriologic evidence (positive acid-fast bacilli smear, serology, or culture).

We collected data regarding smoking exposure using a standardized questionnaire. Plasma hs-CRP was measured in the certified clinical pathology clinic of Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

### Data analysis

Baseline characteristics were first described according to HIV infection/treatment status and presented as mean  $\pm$

**TABLE 1.** Baseline characteristics of study subjects with available echocardiograms

	ART-Naïve HIV (n = 48)	ART-Exposed HIV (n = 54)	Non-HIV (n = 51)	p Value
Age, yrs*	3.6 (0.6–11.4)	5.4 (0.6–12.2)	6.4 (2.4–14.0)	<0.001
Male	22 (46)	25 (46)	24 (47)	0.99
Low socioeconomic status	20 (43)	31 (57)	10 (20)	0.001
Parental smoking exposure after birth				
Mother	4 (9)	6 (11)	0 (0)	0.06
Father/other household members	36 (75)	47 (87)	34 (67)	0.047
Parental smoking exposure in pregnancy				
Mother	7 (16)	8 (15)	1 (2.0)	0.04
Father/other household members	36 (75)	45 (83)	35 (69)	0.21
Family history of CVD	15 (33)	14 (26)	3 (6)	0.004
Body weight (n = 149), kg	12.9 ± 7.0	17.4 ± 6.1	22.5 ± 9.5	<0.001
Body height (n = 145), cm	92.7 ± 19.3	104.8 ± 16.9	116.5 ± 17.7	<0.001
Body mass index (n = 145), kg/m <sup>2</sup>	14.3 ± 2.4	15.4 ± 2.4	15.9 ± 2.8	0.01
Systolic BP, mm Hg	101.0 ± 11.2	99.9 ± 10.5	102.3 ± 9.6	0.51
Diastolic BP, mm Hg	62.5 ± 9.7	60.7 ± 7.7	61.1 ± 7.4	0.50
Hemoglobin level (n = 132), g/dl	109 (69–150)	115 (42–141)	127 (102–146)	<0.001
hs-CRP, nmol/l	37 (0–2,759)	48 (371–5,507)	5 (0–155)	<0.001
Lower respiratory tract infection <sup>†</sup>	33 (69)	20 (37)	0 (0)	<0.001
Pneumonia	10 (21)	5 (9)	0 (0)	<0.001
Tuberculosis	31 (65)	19 (35)	0 (0)	<0.001
HIV clinical stage 3 or 4	43 (94)	30 (60)	—	<0.001
CD4% (n = 67)	10 (0–49)	30 (4–79)	—	<0.001
LVIDd, mm	31.0 ± 6.3	32.7 ± 4.9	33.4 ± 4.1	
LVEF, %	61.3 ± 13.2	63.1 ± 9.7	67.7 ± 5.4	
TR jet velocity, m/s	a. 2.49 ± 0.61	b. 2.68 ± 0.50	c. 2.32 ± 0.38	‡
Systolic eccentricity index	d. 1.01 ± 0.10	e. 1.06 ± 0.11	1.03 ± 0.06	‡
Diastolic eccentricity index	1.03 ± 0.10	1.09 ± 0.14	1.04 ± 0.06	‡
TAPSE, mm	16.5 ± 3.5	18.9 ± 4.2	20.2 ± 3.3	‡

Values are median (range), n (%), or mean ± SD.  
ART, antiretroviral therapy; BP, blood pressure; CVD, cardiovascular disease; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LV, left ventricular; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVIDd, left ventricular internal diameter at end-diastole; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.  
\*Kruskal-Wallis test.  
<sup>†</sup>Pneumonia or pulmonary tuberculosis.  
<sup>‡</sup>See Table 2.

SD, median (range), or proportion, as appropriate. The distributions of numeric and categorical variables across groups (ART-naïve HIV infected, ART-exposed HIV infected, uninfected) were assessed using the 1-way analysis of variance or Kruskal-Wallis and chi-square tests, respectively.

We performed general linear modelling with HIV or treatment status as a fixed factor and each PAP parameter as separate dependent variables to evaluate the effects of either ART-naïve or ART-exposed HIV infection on echocardiographic estimates of PAP. The same models were used for further adjustment of potential confounders. To obtain an insight about possible mechanisms underlying the association, we made a graphical presentation of the effects of adding each potential intermediary variable on the final (confounder adjusted) model. Exploration of LRTI as a possible explanation for pulmonary hypertension was

restricted to HIV groups only because LRTI, as defined previously, was not present in the uninfected children.

Findings are presented as crude and adjusted mean difference with 95% confidence interval (CI) and p values. A 95% CI not including zero, which corresponds with a 2-sided p value of <0.05, was considered statistically significant. We performed statistical analyses using SPSS version 19 (IBM Corporation, Armonk, NY) and RStudio 0.98.507 for Mac (RStudio, Boston, MA).

## RESULTS

The baseline characteristics of subjects with available echocardiographic measurements are described in Table 1. The ART-naïve HIV-infected children were younger and smaller compared with the other groups. Children with HIV infection also had significantly lower socioeconomic

**TABLE 2.** Effects of HIV infection on pulmonary artery pressure–associated parameters

	Crude			Model 1			Model 2		
	Mean Difference	95% CI	p Value	Mean Difference	95% CI	p Value	Mean Difference	95% CI	p Value
<b>TR jet velocity</b>									
Non-HIV	Ref.			Ref.					
ART-naïve HIV	0.17	−0.07 to 0.40	0.17	0.17	−0.08 to 0.41	0.19	0.18	−0.06 to 0.43	0.14
ART-exposed HIV	0.36	0.13 to 0.59	0.003	0.36	0.13 to 0.59	0.003	0.36	0.12 to 0.60	0.005
<b>Eccentricity index (systolic)</b>									
Non-HIV	Ref.			Ref.			Ref.		
ART-naïve HIV	−0.02	−0.06 to 0.02	0.25	−0.03	−0.07 to 0.02	0.27	−0.03	−0.08 to 0.01	0.12
ART-exposed HIV	0.03	−0.01 to 0.07	0.13	0.03	−0.01 to 0.07	0.15	0.03	−0.01 to 0.07	0.13
<b>Eccentricity index (diastolic)</b>									
Non-HIV	Ref.			Ref.			Ref.		
ART-naïve HIV	−0.015	−0.06 to 0.03	0.53	0.01	−0.06 to 0.04	0.78	−0.01	−0.06 to 0.04	0.73
ART-exposed HIV	0.05	0.005 to 0.10	0.03	0.06	0.01 to 0.11	0.02	0.06	0.01 to 0.11	0.02
<b>TAPSE</b>									
Non-HIV	Ref.			Ref.			Ref.		
ART-naïve HIV	−3.64	−5.15 to −2.12	<0.001	−2.20	−3.63 to −0.77	0.003	−2.22	−3.73 to −0.71	0.004
ART-exposed HIV	−1.26	−2.73 to 0.22	0.10	−0.71	−2.04 to 0.63	0.30	−0.83	−2.24 to 0.57	0.24

Model 1: adjusted for age; Model 2: adjusted for age and postnatal secondhand smoking (maternal and other household members). CI, confidence interval; other abbreviations as in Table 1.

level and were more heavily exposed to second hand smoking. No sex differences were found between HIV and treatment status groups. The median duration of ART was 2.5 (range 0.1–9.9) years.

The associations between ART-naïve or ART-exposed HIV infection and PAP and associated RV function are shown in Table 2. Although the ART-naïve HIV-infected children tended to have higher PAP than did uninfected children, as indicated by their TR jet velocity, the differences were not statistically significant, neither in crude analysis (difference: 0.17 m/s;  $p = 0.17$ ) nor in adjusted analysis (difference: 0.18 m/s;  $p = 0.14$ ). The LV eccentricity index did not differ from uninfected children. However the ART-naïve HIV-infected children had significantly reduced RV systolic function (indicated by lower TAPSE) compared with the uninfected reference group (crude difference: −3.64 mm;  $p < 0.001$ ). This difference remained after adjustment for age and postnatal smoking exposure (difference: −2.2 mm;  $p = 0.004$ ). LV ejection fraction explained some of the reduction in RV systolic function in ART-naïve HIV infection (Figure 1). Compared with ART-exposed HIV-infected children, the ART-naïve children tended to have lower TAPSE (adjusted difference: −1.5 mm,  $p = 0.07$ ) and the difference was partially explained by LRTI (adjusted difference: −1.1 mm;  $p = 0.22$ ).

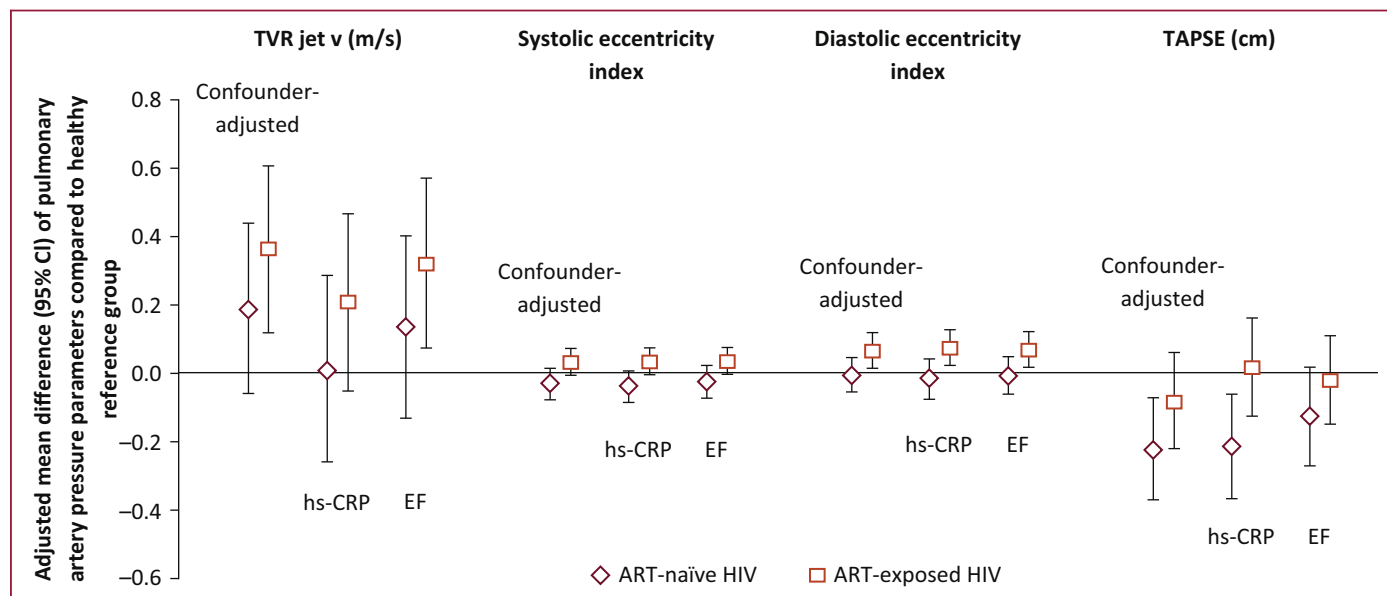
ART-exposed HIV-infected children had higher estimated systolic PAPs compared with uninfected children (Table 2), reflected in higher TR jet velocity in both crude (difference: 0.36 m/s;  $p = 0.003$ ) and adjusted (difference:

0.36 m/s;  $p = 0.005$ ) analyses. The elevated PAP was also suggested by their higher diastolic eccentricity index (adjusted difference: 0.06;  $p = 0.02$ ). Excluding that children receiving ART for <6 months ( $n = 10$ ) did not substantially change these findings (adjusted TR jet velocity difference: 0.28 m/s; 95% CI: 0.03 to 0.53;  $p = 0.03$ ; adjusted LV diastolic eccentricity index difference: 0.05; 95% CI: 0.01 to 0.10;  $p = 0.03$ ). Degree of systemic inflammation (hs-CRP level) did attenuate the relation between higher TR jet velocity and ART-exposed HIV infection (Figure 1).

Within the HIV groups, the ART-exposed children had a higher systolic (adjusted difference: 0.07; 95% CI: 0.02 to 0.11;  $p = 0.006$ ) and diastolic (0.07; 95% CI: 0.01 to 0.13;  $p = 0.02$ ) eccentricity index than did the ART-naïve children, and the difference in TR jet velocity did not reach statistical significance (0.20; 95% CI: −0.09 to 0.48;  $p = 0.17$ ). These differences did not change by further LRTI adjustment (systolic eccentricity index: 0.07; 95% CI: 0.02 to 0.12;  $p = 0.007$ ; diastolic index (0.08; 95% CI: 0.02 to 0.14;  $p = 0.006$ ). Seven (13%) ART-exposed HIV-infected children met the echocardiographic criteria for pulmonary hypertension, compared with 4 (8.3%) and 1 (2%) in the ART-naïve HIV-infected and reference groups, respectively.

## DISCUSSION

This study showed that ART-exposed HIV infection is associated with elevated PAP, as demonstrated by either an elevated TR jet velocity or an abnormal LV eccentricity



**FIGURE 1. Explanatory models for the effects of HIV infection and pulmonary artery pressure.** ART = antiretroviral therapy; EF = ejection fraction; TAPSE = tricuspid annular plane systolic excursion; TVR = tricuspid valve regurgitation.

index, whereas no statistically significant differences in these 2 echo parameters were found in ART-naïve HIV-infected children compared with uninfected children. However, the ART-naïve HIV-infected children had reduced RV systolic function, as reflected by a reduction in TAPSE. Approximately 13% of ART-exposed and 8% of ART-naïve HIV-infected children had echocardiographic evidence of pulmonary hypertension. Within-HIV group comparisons showed that LRTI contributed to the reduced RV function in the ART-naïve HIV-infected children, but to not the abnormal LV eccentricity indexes in ART-exposed children.

To our knowledge, this is the first clinical study investigating pulmonary hypertension among HIV-infected children with standardized echocardiographic measurements. Previous data are limited to anecdotal case reports [5] or questionnaire data from specialists caring for HIV-infected children [14]. The latter survey concluded that pulmonary hypertension among HIV-infected children was probably underestimated because of lack of routine assessment [14]. Moreover, we had the unique opportunity to delineate the effects of ART-naïve HIV infection from ART-exposed infection.

Our study revealed that, compared with uninfected children, the ART naïve HIV-infected children did not have higher estimated PAPs compared with uninfected control subjects, albeit in the setting of reduced RV systolic function. There has been no previous human study showing a clear association between HIV and pulmonary hypertension per se, and many early attempts to demonstrate HIV in the lung vasculature have failed [15]. Based on animal studies, a current hypothesis is that pulmonary hypertension develops due to pulmonary vascular inflammation and

remodeling in response to HIV protein (Nef, Tat, gp120) [6]. Therefore, it may be expected that the ART-naïve HIV-infected children would have higher PAP than would uninfected children as well as would ART-exposed children, in whom HIV replication is at least partially suppressed. Our findings did not confirm this hypothesis, and there are a number of possible explanations as for why. Firstly, reduced RV systolic function in the ART naïve HIV-infected group would lead to the generation of a lower RV systolic pressure, and therefore lower TR jet velocity. Similarly, the LV eccentricity index may be reduced in the setting of reduced RV systolic function. Finally, our ART-naïve HIV-infected children comprised a smaller group of younger patients, with a further reduction in sample size due to mortality. It is possible that any lung pathology due to HIV infection would be at an earlier stage of the disease process because of the younger age of the ART-naïve group.

The finding that ART-exposed HIV-infected children showed signs of elevated PAP raises concerns about the possible dual effects of ART on the pulmonary vasculature. To date, the possible effects of ART on HIV associated pulmonary hypertension remains controversial and evidence has been sparse. Although highly active ART is highly effective in controlling HIV replication, and therefore possibly decreased burden of pulmonary hypertension, data in adults suggest that increased survival of pulmonary hypertensive HIV patients treated with highly active ART is more attributable to CD4+ count and improved cardiac index, rather than direct effects on the pulmonary vasculature [4].

In contrast, other studies have suggested that some ART drugs may lead to the development of pulmonary

arterial hypertension through mechanisms that are not completely understood. Ritonavir, a protease inhibitor, has been suggested to inhibit bradykinin-dependent vasorelaxation, while in vitro, other ART drugs decrease the synthesis of nitric oxide, a potent pulmonary vasodilator, increase reactive oxygen species, and activate extracellular signal-regulated kinase 1/2, signaling molecules involved in the regulation of cell division and differentiation [6]. As our ART-exposed HIV-infected children seemed to have partially controlled HIV infection with chronic (40%) or acute (10%) lung infections, it is difficult to discern the interaction of effect among ART, HIV infection, and lung infection on pulmonary hypertension.

Our study was limited by the fact that we did not have the opportunity to perform invasive cardiac catheterization to confirm the presence of pulmonary hypertension. We were unable to obtain complete echocardiography for all children, particularly the sicker ART-naïve HIV-infected patients. Therefore, we may have underestimated the true effect of ART-naïve HIV infection. The measurements were also incomplete for TR jet velocity, as not all children had sufficient TR to accurately estimate PAP. However, children with no or minimal TR are less likely to have pulmonary hypertension. Moreover, with the available measurements, we did observe a difference in TR jet velocity between ART-exposed HIV-infected children and uninfected children.

With regard to possible underlying mechanisms, the degree to which lung co-infection contributes to HIV-associated increased PAP remains unclear. There is also a possibility of an interaction with HIV infection. For example, it has been demonstrated in animal models that concurrent pulmonary infection with *Pneumocystis jirovecii* increases the risk of pulmonary arteriopathy and hypertension by causing immune activation, which contributes to HIV-1 replication and cytokine dysregulation [7]. In our HIV patients, LRTI largely explained the relatively reduced RV systolic function with ART-naïve HIV, but not the higher TR jet velocity in ART-exposed HIV infection. This suggests that, apart from LRTI, other factors, such as viral protein or the ART drugs, may play a pathogenic role. As previously suggested [7], LRTI and other co-infections are likely to act as an effect modifier that can potentiate the development of pulmonary hypertension. Further research is needed to clarify whether the effects of LRTI are attributable to a specific type of pathogen or to nonspecific lung inflammation.

## CONCLUSIONS

In conclusion, ART-exposed HIV infection is associated with elevation of estimated PAP, while ART-naïve HIV infection appears to be associated with reduced RV systolic function. LRTI contributes to the reduced RV systolic function in the ART-naïve children. There are a number of clinical implications of our study. Our findings emphasize

that ongoing surveillance for pulmonary hypertension is warranted, even following treatment with ART. Although vertically acquired HIV infection in the developed world is largely preventable, our findings in ART-naïve HIV-infected children are particularly relevant in low-resource settings in which the burden of vertically acquired HIV infection is highest.

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