Pulmonary Complications of HIV-1 in Youth: The PHACS AMP Study

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ABSTRACT*

Background: Perinatally HIV-infected youth (PHIV) may have an increased risk of asthma compared to perinatally HIV-exposed uninfected youth (PHEU), particularly after antiretroviral therapy. Prior studies have diagnosed asthma by history, asthma medications, and physician examination. The present multi-center study used pulmonary function tests (PFTs) to compare the prevalence of obstructive (OBS) and restrictive (RES) pulmonary air flow patterns in PHIV and PHEU.

Methods: PFT results were compared by HIV status using a Chi-square test. PHIV and PHEU youth were evaluated for evidence of OBS, RES, and reversible (REV) airway patterns by PFTs without and with bronchodilators. Flow loop (3-5 repeats) PFTs from 11 PHACS/AMP PFT laboratories were evaluated centrally by two blinded pediatric pulmonologists for acceptability. Predicted values were calculated as the percent of normal values based on age-sex-race adjusted reference values in healthy children. Pulmonary disease status from pre-bronchodilator results was defined as OBS only (FEV1 < 80% or FEV1/FVC < 80% or FEF < 65%), OBS+RES (FVC1 < 80% and FEV1/FVC < 80%), RES only (FVC < 80% and FEV1/FVC ≥ 80%), or normal (not RES or OBS). Reversible airway function was defined as a >10% increase in FEV1 after bronchodilator.

Results: Of the 216 PHIV and 151 PHEU who had a PFT test, 188 (87%) and 132 (87%) produced reproducible and acceptable PFT test results, respectively. A post-bronchodilator PFT was available on 183/188 PHIV and 126/132 PHEU. Of those with evaluable PFTs, the median age was 15.9 (range 10-21) years of age with 45% male and 68% African-American. The prevalence of pulmonary function abnormalities was similar for HIV and HEU youth (P=0.52). Abnormal PFT results for HIV vs. HEU were: 42 (22%) vs. 28 (21%) had OBS, 2 (1%) vs. 0 (0%) had OBS+RES, and 18 (10%) vs. 17 (13%) had RES PFT abnormalities; 126 (67%) and 87 (66%) had normal results, respectively. PHIV had a lower prevalence of reversibility than HEU youth (9% versus 17%, P=0.052). Similarly, OBS PHIV had a lower rate of reversibility than OBS PHEU: 12/40 (30%) vs. 13/26 (50%), P = 0.10, trend.

Conclusions: The rate of pulmonary function abnormalities is similar in both HIV and HEU youth, but reversibility of OBS is lower in PHIV groups.

BACKGROUND

In a previous analysis among 451 perinatally HIV-infected (PHIV) and 237 perinatally HIV-exposed uninfected children (PHEU) in the Adolescent Master Protocol (AMP)of the Pediatric HIV/AIDS Cohort Study (PHACS), we studied the cumulative incidence of asthma. (Siberry et al 2012) Asthma was defined as a reported diagnosis of asthma or asthma medication use at ≥ 3 years of age. The unadjusted cumulative incidence of developing asthma by 15 years old was 37% in the PHIV and 29% in the PHEU (**Fig. 1**). . The hazard ratio was 1.37 (1.01, 1.86, P= 0.046) (Siberry et al, 2012)

Figure 1: Time to Development of Asthma in PHIV and HEU children

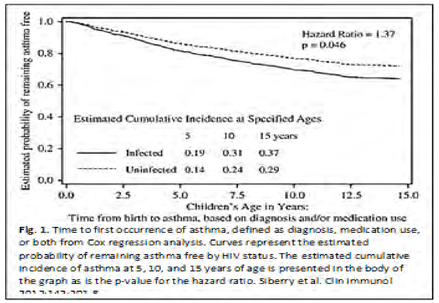

Fig. 1. Time to first occurrence of asthma, defined as diagnosis, medication use, or both from Cox regression analysis. Curves represent the estimated probability of remaining asthma free by HIV status. The estimated cumulative incidence of asthma at 5, 10, and 15 years of age is presented in the body of the graph as is the p-value for the hazard ratio. Siberry et al. Clin Immunol

BACKGROUND (CONTD)

HLA typing of patients in WITS revealed a remarkable prominence of HLA-A68 in patients with HIV and asthma by independent multivariate analysis with a significant hazard ratio of 4.76 (p=0.006). By contrast, none of the HIV patients who inherited the HLA-Cw6 antigen developed asthma (Foster et al 2010). Earlier evidence suggested that the increase in cumulative incidence of asthma in PHIV was associated with an increase in CD4 cell counts (Foster et al 2008).

OBJECTIVES

- Obtain pulmonary function tests (PFTs) to compare PHIV and PHEU on the prevalence of:
  1) Obstructive and restrictive airway disease
  2) Reversible airway function post bronchodilator inhalation

METHODS

Study Population

- There were 370 children (PHIV=218, PHEU =152) enrolled into the pulmonary study, and all but 3 had a PFT performed. PFTs were evaluable among 188 of 216 (87%) PHIV and 132 of 151 (87%) of HEU.
- **Parent study:** PHIV and PHEU youth enrolled in the PHACS-AMP protocol were recruited to enroll into the Pulmonary Substudy at 13 clinical sites.
- **Exclusion criteria**: Participants were excluded if they had acute/ symptomatic asthma could not follow instructions and perform PFTs, had a known history of cardiac arrhythmia and /or hypertension, were pregnant or gave birth within the last six weeks.

Pulmonary Function Tests

- **PFTs** were performed pre-and post bronchodilation with albuterol inhalation. Flow loops (3-5 repeats) PFTs for each participant were evaluated centrally by two pediatric pulmonologists who were blinded to HIV status to determine if the PFT was evaluable.
- **Predicted values:** Predicted values were calculated as the percent of normal values based on age-sex-race adjusted reference values in healthy children National Institutes of Health. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. August 2007.NIHPublication No. 07-4051, http://www.nhlbi.nih.gov,guidelines/asthma/index.htm. .
- **Definition of obstruction (OBS) and/or restrictive (RES) disease status based on predicted values: (mutually exclusive groups):**
  - **OBS only:** FEV1 < 80% or FEV1/FVC < 80% or FEF 25-75% <65%
  - **OBS+RES:** FVC < 80% and FEV1/FVC < 80%
  - **RES only:** FVC < 80% and FEV1/FVC ≥ 80%
  - **Normal:** Not RES or OBS
- **Reversibility**: Reversible (REV) airway function was defined as a >10% increase in FEV1 after bronchodilator (albuterol).
- **Analysis:** PFT results were compared by HIV status using a Kruskal Wallis, Wilcoxon test or Chi-square test.
- **Pulse Oximetry:** ≥ 95% saturation defined as normal.

RESULTS

Table 1A: The PHIV were older (median 16.8 yrs. vs. 14.7yrs.) than PHEU. While the two groups did not differ significantly by race/ethnicity and sex, the proportion of blacks tended to be greater and the proportion of males lower in the PHIV.

Table 1B: The prevalence of PFT-defined restrictive and/or obstructive pulmonary disease was similar between PHIV and PHEU (p=0.52). The prevalence of abnormal PFTs differed by race/ethnicity (p= 0.003) and sex (p=0.011) with non-Hispanic whites more likely to have a normal PFT. Males had a higher prevalence of restrictive disease.

Table 1C: As a group, PHIV had a lower prevalence of reversibility than the PHEU group (9% versus 17%, p=0.052). Reversibility in those PHIV and PHEU cohorts with obstructive flow-type patterns again demonstrated less reversal of obstructive air flow patterns with PHIV (P = 0.10, trend).

Pulse oximetry tests were normal in all study subjects.

Table 1A: Characteristics by HIV Status of Children with Evaluable PFT – by column percent

Characteristic	Category	PHIV (N=188)	PHEU (N=132)	P-Value
Age (Years)	Median (Q1, Q3)	16.8 (14.2, 18.8)	14.7 (12.8, 16.6)	<0.001
Race/Ethnicity N (%)	Non-Hispanic White/Other	13 (7%)	12 (9%)	0.230
	Black	136 (72%)	81 (61%)	
	Hispanic	38 (20%)	38 (29%)	
	Not known/not reported	1 (1%)	1 (1%)	
Male Sex	*N (%)*	79 (42%)	66 (50%)	0.158
Pre-bronchodilator FEV1 FVC	Median (Q1, Q3)	98 (85, 109) 100 (89, 110)	97 (84, 105) 99 (88, 109)	0.42 0.39

Table 1B: Prevalence of Restrictive/Obstructive Pulmonary Disease by HIV Status and Socioeconomic Status – by row percent

Characteristic	Category	Obstructive	Restrictive	Restrictive + obstructive	Normal	P-Value
		(N=70)	(N=35)	(N=2)	(N=213)	
Cohort	Infected	42 (22%)	18 (10%)	2 (1%)	126 (67%)	0.52
	Uninfected	28 (21%)	17 (13%)	0 (0%)	87 (66%)	
Age (years)	Median (Q1, Q3)	15.8 (13.7, 18.3)	15.9 (13.7, 17.7)	17.2 (14.1, 20.3)	15.9 (13.7, 18.2)	0.90
Race/ Ethnicity N (%)*	Non-Hispanic White/Other	1 (4%)	3 (12%)	0 (0%)	21 (84%)	0.003
	Black	51 (24%)	14 (6%)	1 (0%)	151 (70%)	
*2 unknown	Hispanic White/Other	18 (24%)	17 (22%)	1 (1%)	40 (53%)	
Sex N (%)	Male	37 (26%)	8 (6%)	2 (1%)	98 (68%)	0.011
	Female	33 (19%)	27 (15%)	0 (0%)	115 (66%)	

Table 1C: Prevalence of Reversibility from PFT by HIV Status – by column percent

Characteristic	Category	Infected (N=188)	Uninfected (N=132)	Total (N=320)	P-Value
>=10% increase in FEV1 post-bronchodilators for total group	Yes	17 (9%)	21 (17%)	38 (12%)	0.052
	No	166 (91%)	105 (83%)	271 (88%)	
For Obstructive Sub-group		N = 40	N = 26	N = 66	
	Yes	12 (30%)	13 (50%)	25 (38%)	0.10
	No	28 (70%)	13 (50%)	41 (62%)	

Asthma in HIV Infection as a Public Health Threat

The number of adolescents and young adults living with HIV since birth worldwide is growing. In the year 2012, the U.S. alone estimated that there were 10,500 HIV-infected adolescents and young adults, and globally, there is a cohort of greater than 6 million adolescents and young adults who have been living with HIV infection since birth and are aging into young adulthood (CDC HIV Surveillance Report 2012), portending an enormous number of patients at risk for pulmonary complications demanding improved diagnostic, primary prevention and therapeutic strategies. Given the worldwide prevalence of HIV infection (30+ million) a significant increase in the pulmonary complications of asthma predicts an enormous number of patients will need this complication to be much better defined so that new therapies can be created for HIV and asthma

SUMMARY

- PHIV and PHEU had a similar prevalence of restrictive and/or obstructive pulmonary disease based on PFT.
- Both PHIV and PHEU had an equally high prevalence of abnormal lung function.
- PHIV had a lower rate of reversibility of obstructive pulmonary air flow (total group and OBS only).

CONCLUSIONS

- The lower rate of reversibility in PHIV compared to PHEU raises the possibility that respiratory symptoms in PHIV are misclassified as asthma.
- The difference in reversibility of obstructive airflow patterns suggests a previously unknown pathology in the lung tissue of HIV-infected patients.
- Further study is warranted to determine the nature and pathogenesis of the observed pulmonary function abnormalities, possibly including a sensitized cellular component that damages the lungs.

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