HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

J Allergy Clin Immunol. 2020 May ; 145(5): 1473–1476. doi:10.1016/j.jaci.2019.12.890.

Immune imbalance and activation are associated with lower lung function in youth with perinatally-acquired HIV

Engi F. ATTIA, MD MPH[a], **Denise JACOBSON, PhD MPH**[b], **Wendy YU, MPH**[b], **Claudia S. CROWELL, MD MPH**[a,c], **Elizabeth MALECHE-OBIMBO, MBChB MMed MPH**[d], **Paige L. WILLIAMS, PhD MS**[b], **T. Eoin WEST, MD MPH**[a], **Sandra K. BURCHETT, MD MSc**[e,f], **Meyer KATTAN, MD**[g], **Andrew A. COLIN, MD**[h], **Sherry ESKANDER, MBBCh MSc**[i], **Michael H. CHUNG, MD MPH**[a], **Kristina CROTHERS, MD**[a], **William T. SHEARER, MD PhD**[j,*,†] **Pediatric HIV/AIDS Cohort Study**

[a]University of Washington, Seattle, WA, US

[b]Harvard T.H. Chan School of Public Health, Boston, MA, US

[c]Seattle Children's Hospital, Seattle, WA, US

[d]University of Nairobi, Nairobi, Kenya

[e]Boston Children's Hospital, Boston, MA, US

[f]Harvard Medical School, Boston, MA, US

[g]Columbia University Medical Center, New York City, NY, US

[h]University of Miami, Miami, FL, US

[i]Coptic Hospital and Coptic Hope Center for Infectious Diseases, Nairobi, Kenya

Corresponding Author: Engi F. Attia, MD MPH, 325 Ninth Avenue, Campus Box 359762, Harborview Medical Center, Seattle, WA 98144, Phone: +1 206 744 3244, Fax: +1 206 744 8584, eattia@uw.edu.

*This work is dedicated to the memory of Dr. William T. Shearer. He was the senior mentor for this manuscript and participated with great joy in conducting the study and composing early drafts. It is of great solace to us all that he spent his last days working on this, and other, passion projects.

†Deceased: October 9, 2018.

The following institutions, clinical site investigators and staff participated in conducting PHACS AMP and AMP Up in 2018, in alphabetical order: **Ann & Robert H. Lurie Children's Hospital of Chicago**: Ellen Chadwick, Margaret Ann Sanders, Kathleen Malee, Yoonsun Pyun; **Baylor College of Medicine**: William Shearer, Mary Paul, Chivon McMullen-Jackson, Mandi Speer, Lynnette Harris; **Bronx Lebanon Hospital Center:** Murli Purswani, Mahboobullah Mirza Baig, Alma Villegas; **Children's Diagnostic & Treatment Center**: Lisa Gaye-Robinson, Sandra Navarro, Patricia Garvie; **Boston Children's Hospital:** Sandra K. Burchett, Michelle E. Anderson, Adam R. Cassidy; **Jacobi Medical Center**: Andrew Wiznia, Marlene Burey, Ray Shaw, Raphaelle Auguste; **Rutgers - New Jersey Medical School:** Arry Dieudonne, Linda Bettica, Juliette Johnson, Karen Surowiec; **St. Christopher's Hospital for Children:** Janet S. Chen, Maria Garcia Bulkley, Taesha White, Mitzie Grant; **St. Jude Children's Research Hospital**: Katherine Knapp, Kim Allison, Megan Wilkins, Jamie Russell-Bell; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Heida Rios, Vivian Olivera; **Tulane University School of Medicine**: Margarita Silio, Medea Gabriel, Patricia Sirois; **University of California, San Diego**: Stephen A. Spector, Megan Loughran, Veronica Figueroa, Sharon Nichols; **University of Colorado Denver Health Sciences Center**: Elizabeth McFarland, Carrie Chambers, Emily Barr, Mary Glidden; **University of Miami:** Gwendolyn Scott, Grace Alvarez, Juan Caffroni, Anai Cuadra

Disclosure Statement: The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or U.S. Department of Health and Human Services. No conflicts of interest were declared by any authors.

[j]Baylor College of Medicine and Texas Children's Hospital, Houston, TX, US

Capsule Summary:

High CD8 T-cells and low CD4/CD8 are associated with lower lung function among youth living with perinatally-acquired HIV, despite antiretroviral therapy and CD4 preservation/reconstitution. Understanding these underlying mechanisms is critical to mitigate lung function impairment.

Keywords

Adolescents; youth; perinatally-acquired HIV; chronic lung disease; immune imbalance; immune activation; CD8 T-cells; CD4/CD8 ratio; lung function; FEV_1

To the Editor:

Contemporary reports indicate a high burden of impaired lung function among youth living with perinatally-acquired HIV (YLPHIV) worldwide. The prevalence of impaired lung function is estimated to be 33% among YLPHIV in the U.S.-based Pediatric HIV/AIDS Cohort Study (PHACS),[1] and up to 45% among YLPHIV in several sub-Saharan African countries.[2,3]

Little is known about the pathophysiologic mechanisms underlying impaired lung function among YLPHIV. Persistent immune imbalance and activation, reflected by a low (reversed) CD4/CD8 ratio, are linked with chronic lung disease (CLD) among adults living with HIV despite antiretroviral therapy (ART) and CD4 T-cell reconstitution.[4] In this study, we determined whether immune imbalance and activation based on a high CD8 T-cell count and low CD4/CD8 ratio were associated with lower lung function, as measured by forced expiratory volume in one second (FEV_1), among YLPHIV and explored whether FEV_1 differed between YLPHIV living in the U.S. and Kenya.

We performed a cross-sectional analysis of 10-21 year-old YLPHIV in the multi-site U.S.-based pulmonary sub-study of the PHACS Adolescent Master Protocol[1] and in a cohort study in Nairobi, Kenya.[3] Both studies collected pre- and post-bronchodilator spirometry, CD4 and CD8 T-cell counts, demographics and anthropometric data. We obtained spirometry in both cohorts according to American Thoracic Society standards and used NHANES III reference equations to calculate percent-predicted values for FEV_1 ($\%FEV_1$). Institutional review boards at Baylor College of Medicine, Harvard T.H. Chan School of Public Health, University of Washington, University of Nairobi/Kenyatta National Hospital, and participating U.S. sites approved the studies. Participants and guardians provided written consent/assent.

We compared characteristics between 188 U.S. and 49 Kenyan YLPHIV, using Chi-square and Wilcoxon rank-sum tests for categorical and continuous variables. We fit linear regression models to evaluate mean differences in $\%FEV_1$ among U.S. compared to Kenyan youth, adjusted for age and sex. Because immunologic markers may differ by ethnicity/race and be potential confounders of the relationship between setting (U.S. vs Kenya) and FEV_1, we additionally adjusted for CD8 T-cells ("CD8" from here forward) or CD4/CD8 in

separate models.[5] Conversely, CD8 and CD4/CD8 may be on the causal pathway between setting and FEV_1 by way of the association of these immunologic markers with environmental exposures and timing of ART initiation. To further evaluate the relationship of CD8 and CD4/CD8 with FEV_1, we calculated Spearman partial correlations of CD8 and CD4/CD8 with pre- and post-bronchodilator $\%FEV_1$, adjusted for age and sex in U.S. and Kenyan youth separately. In sensitivity analyses, we restricted models to black U.S. and Kenyan YLPHIV. Because immune imbalance and activation may be triggered by infections, we also stratified the CD4/CD8 ratio by prior pulmonary tuberculosis.

U.S. youth were older, on average, than Kenyan youth (17 vs 13 years); 42% of U.S. youth and 51% of Kenyan youth were male (Table I). Active tobacco use was reported by 10% of U.S. youth, but Kenyan youth reported more exposure to passive smoking and nearly universal indoor combustible fuel use. Prior pulmonary tuberculosis was less common among U.S. compared to Kenyan youth. Although U.S. youth initiated ART at a median age of three years compared to eight years among Kenyan youth, U.S. and Kenyan youth had similar nadir and recent CD4, and similar proportions were receiving ART. Nonetheless, the median [interquartile range] CD4/CD8 was lower in Kenyan than U.S. youth (0.65 [0.42, 0.94] vs 0.91 [0.55, 1.25], p=0.004), driven by higher CD8 in Kenyan compared to U.S. youth (1098 cells/μL [849, 1473] vs 722 [514, 930], p<0.001).

Pre- and post-bronchodilator $\%FEV_1$ were significantly lower among Kenyan compared to U.S. youth. On average, Kenyan YLPHIV had 9.6% (95% CI 3.8, 15.4) lower pre-bronchodilator $\%FEV_1$ and 8.3% (2.7, 14.0) lower post-bronchodilator $\%FEV_1$ than U.S. YLPHIV, after adjusting for age and sex. These differences were attenuated in models also adjusted for CD8 (pre-bronchodilator: −5.2 [−11.6, 1.2], p=0.11; post-bronchodilator: −4.5 [−10.7, 1.8], p=0.16) or CD4/CD8. Differences persisted in analyses restricted to black U.S. and Kenyan youth.

In U.S. youth, higher CD8 correlated with lower pre- and post-bronchodilator $\%FEV_1$ (r= −0.19, p=0.01; r= −0.16, p=0.03) after adjusting for age and sex; when restricted to black youth, correlations remained negative at r= −0.11 (p=0.23) and r= −0.13 (p=0.14), respectively. In Kenyan youth, correlations were in the same direction (r= −0.22, p=0.15 and r= −0.24, p=0.12). Correlations of lower CD4/CD8 with lower $\%FEV_1$ were similar. The distribution of CD4/CD8 was similar among youth with and without prior pulmonary tuberculosis across settings.

In summary, Kenyan YLPHIV had lower $\%FEV_1$ than U.S. YLPHIV. Higher CD8 and lower CD4/CD8 were associated with lower pre-bronchodilator and post-bronchodilator $\%FEV_1$, even in the setting of CD4 preservation/reconstitution.

Lower lung function, especially lower post-bronchodilator $\%FEV_1$, may represent CLD that manifests with irreversible airflow limitation. Imaging studies among YLPHIV in sub-Saharan Africa suggest that obliterative bronchiolitis may represent a unique etiology of CLD.[2,3] Bronchiectasis is also common, especially in light of prior pulmonary infections.[2] Asthma also contributes to CLD, potentially via mechanisms linked to immune

reconstitution or CD8 subsets; asthma-chronic obstructive pulmonary disease overlap may also play a role.[6,7]

HIV infection and associated chronic immune activation during critical periods of immune system and organ development are likely to influence end-organ injury in YLPHIV, including CLD.[2] Although most experience CD4 reconstitution and decline in CD8 with contemporary ART, some maintain persistently elevated CD8 and depressed CD4/CD8. As CD8 counts can be higher in alveolar fluid than in peripheral circulation, persistent activation of residual pulmonary CD8 T-cells may be important in CLD.[8] This may be particularly relevant for youth who initiate ART at older ages and do not experience a sufficient decline in CD8. Further, low peripheral CD4/CD8 is associated with CLD among adults living with HIV,[4] and was correlated with lower $\%FEV_1$ in our cohort of YLPHIV.

Importantly, Kenyan YLPHIV had lower $\%FEV_1$ than U.S. YLPHIV. Measured risk factors, such as pulmonary infections, tobacco and combustible fuel smoke exposure, and age at ART initiation, as well as unmeasured factors, including disease severity, delayed HIV diagnosis/treatment, nutritional status and socioeconomic status likely contribute to observed differences in $\%FEV_1$. However, these factors may also impact CD8 and, consequently, the CD4/CD8 ratio. Notably, we found no difference in CD4/CD8 among youth with and without prior pulmonary tuberculosis, suggesting that HIV-related immune imbalance and activation may play a bigger role.[9] Although adjusting for CD8 or CD4/CD8 attenuated differences in $\%FEV_1$, even in models restricted to black youth, this should be interpreted cautiously because the mechanistic pathway between these immunologic parameters and FEV_1 remains unclear.

Despite the additional inherent limitations of the small sample size, cross-sectional nature of our study, use of NHANES reference equations and lack of an HIV-uninfected comparison group, a substantial strength is that we leveraged data from existing, well-characterized prospective cohorts that collected comparable exposure and outcome data in distinctly different settings. Our findings suggest that chronic immune imbalance and activation may contribute to CLD in YLPHIV despite ART and CD4 reconstitution/preservation. As more children living with HIV are surviving into adolescence and adulthood, it is imperative to understand risk factors and mechanisms of lung function impairment among youth living with HIV to guide efforts to mitigate the global CLD burden.

Acknowledgments:

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS. The study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Institute of Dental and Craniofacial Research, the National Cancer Institute, the National Institute on Alcohol Abuse and Alcoholism, the Office of AIDS Research, and the National Heart, Lung, and Blood Institute through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) (Principal Investigator: George R Seage III; Program Director: Liz Salomon) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Ellen Chadwick; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson).

Funding Sources: E.F.A. has received the following funding for research reported in this publication: National Heart, Lung, and Blood Institute of the National Institutes of Health (F32 HL123031, K23 HL129888); INTERSECT-Ellison Fellowship; and the Pediatric HIV/AIDS Cohort Study (PHACS) New Investigator Award. PHACS is supported by the *Eunice Kennedy Shriver* National Institute Of Child Health & Human Development (NICHD) with co-funding from the National Institute Of Dental & Craniofacial Research (NIDCR), the National Institute Of Allergy And Infectious Diseases (NIAID), the National Institute Of Neurological Disorders And Stroke (NINDS), the National Institute On Deafness And Other Communication Disorders (NIDCD), Office of AIDS Research (OAR), the National Institute Of Mental Health (NIMH), the National Institute On Drug Abuse (NIDA), and the National Institute On Alcohol Abuse And Alcoholism (NIAAA), through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) and the Tulane University School of Medicine (HD052104). For the remaining authors, no funding sources were declared.

Abbreviations:

ART	antiretroviral therapy
CLD	chronic lung disease
FEV_1	forced expiratory volume in one second
$\%FEV_1$	percent-predicted forced expiratory volume in one second
NHANES III	National Health and Nutrition Examination Survey III
PHACS	Pediatric HIV/AIDS Cohort Study
YLPHIV	youth living with perinatally-acquired human immunodeficiency virus
U.S.	United States of America

REFERENCES

1. Shearer WT, Jacobson DL, Yu W, Siberry GK, Purswani M, Siminski S, et al.; for the Pediatric HIV/AIDS Cohort Study. Long-term pulmonary complications in perinatally HIV-infected youth. J Allergy Clin Immunol 2017;140:1101–11.e17. [PubMed: 28279683]
2. Ferrand RA, Desai SR, Hopkins C, Elston CM, Copley SJ, Nathoo K, et al. Chronic lung disease in adolescents with delayed diagnosis of vertically acquired HIV infection. Clin Infect Dis 2012;55:145–52. [PubMed: 22474177]
3. Attia EF, Maleche-Obimbo E, West TE, Ndukwe-Wambutsi L, Kiptinness C, Cagle A, et al. Adolescent age is an independent risk factor for abnormal spirometry among people living with HIV in Kenya. AIDS 2018;32:1353–9. [PubMed: 29794491]
4. Triplette M, Attia EF, Akgun KM, Soo Hoo GW, Freiberg MS, Butt AA, et al. A Low Peripheral Blood CD4/CD8 Ratio Is Associated with Pulmonary Emphysema in HIV. PLoS One 2017;12:e0170857. [PubMed: 28122034]
5. Mandala WL, Ananworanich J, Apornpong T, Kerr SJ, MacLennan JM, Hanson C, et al. Control lymphocyte subsets: can one country's values serve for another's? J Allergy Clin Immunol 2014;134:759–61.e8. [PubMed: 25171870]
6. Foster SB, Lu M, Thompson B, Rich KC, Matukas LM, Mason R, et al. Association between HLA inheritance and asthma medication use in HIV positive children. AIDS 2010;24:2133–5. [PubMed: 20613458]
7. Dakhama A, Collins ML, Ohnishi H, Goleva E, Leung DY, Alam R, et al. IL-13-producing BLT1-positive CD8 cells are increased in asthma and are associated with airway obstruction. Allergy 2013;68:666–73. [PubMed: 23573812]
8. Neff CP, Chain JL, MaWhinney S, Martin AK, Linderman DJ, Flores SC, et al. Lymphocytic alveolitis is associated with the accumulation of functionally impaired HIV-specific T cells in the

lung of antiretroviral therapy-naive subjects. Am J Respir Crit Care Med 2015;191:464–73. [PubMed: 25536276]

9. Alvarez P, Mwamzuka M, Marshed F, Kravietz A, Ilmet T, Ahmed A, et al. Immune activation despite preserved CD4 T cells in perinatally HIV-infected children and adolescents. PLoS One 2017;12:e019033

Table I.

Characteristics of YLPHIV in U.S. vs Kenyan cohort*

	U.S. YLPHIV (n=188)	Kenya YLPHIV (n=49)	p-value
Age (years)	17 (14 – 19)	13 (11 – 15)	<0.001
Male	79 (42)	25 (51)	0.26
Black race/ethnicity	138 (73)	49 (100)	--
Tobacco Exposure			
Active tobacco use	16 (9)	0 (0)	0.01
Passive smoking	18 (10)	11 (22)	
No smoking	144 (81)	38 (78)	
Indoor combustible fuel use	--	40 (82)	--
Prior pulmonary infection			
Bacterial pneumonia	87 (46)	19 (39)	0.35
Tuberculosis	3 (2)	14 (29)	<0.001
Self-reported asthma (ever)	63 (34)	2 (4)	<0.001
HIV-related variables^			
CD4 T-cell count (cells/μL)	635 (458 – 783)	667 (453 – 843)	0.45
CD8 T-cell count (cells/μL)	722 (514 – 930)	1098 (849 – 1473)	<0.001
CD4/CD8 ratio	0.91 (0.55 – 1.25)	0.65 (0.42 – 0.94)	0.004
Nadir CD4 T-cell count (cells/μL)	335 (148 – 473)	269 (193 – 482)	0.85
HIV-1 RNA ≤400 copies/mL	127 (69)	--	--
Currently receiving ART	165 (89)	46 (94)	0.33
Duration of ART (years)	13 (10 – 14)	5 (3 – 8)	<0.001
Age at ART initiation (years)	3 (1 – 5)	8 (5 – 11)	<0.001
Percent-predicted FEV_1 (%FEV_1) results			
Pre-bronchodilator %FEV_1	98 (85 – 109)	86 (76 – 100)	0.003
Post-bronchodilator %FEV_1^	100 (88 – 113)	93 (83 – 104)	0.006

*Results presented as median (interquartile range) or n (%).

^HIV-related variables available for 185 U.S. youth; post-bronchodilator %FEV_1 available for 183 U.S. youth; no missing data points for Kenyan youth.

ART: antiretroviral therapy, %FEV_1: percent-predicted forced expiratory volume in one second; YLPHIV: youth living with perinatally-acquired human immunodeficiency virus,