Can Metabolomics and Quantitative CT Improve Endotyping and Phenotyping of Chronic Lung Disease Among Youth with HIV?

Engi F. Attia, MD MPH ATSF
Assistant Professor
Pulmonary, Critical Care and Sleep Medicine
Adjunct Assistant Professor, Department of Global Health
University of Washington School of Medicine

Outline

Background

Chronic lung disease (CLD)

- HIV
- Children and Adolescents

CLD phenotypes and endotypes in YLWH

Research at the Hope Center

Next steps and future directions

Summary

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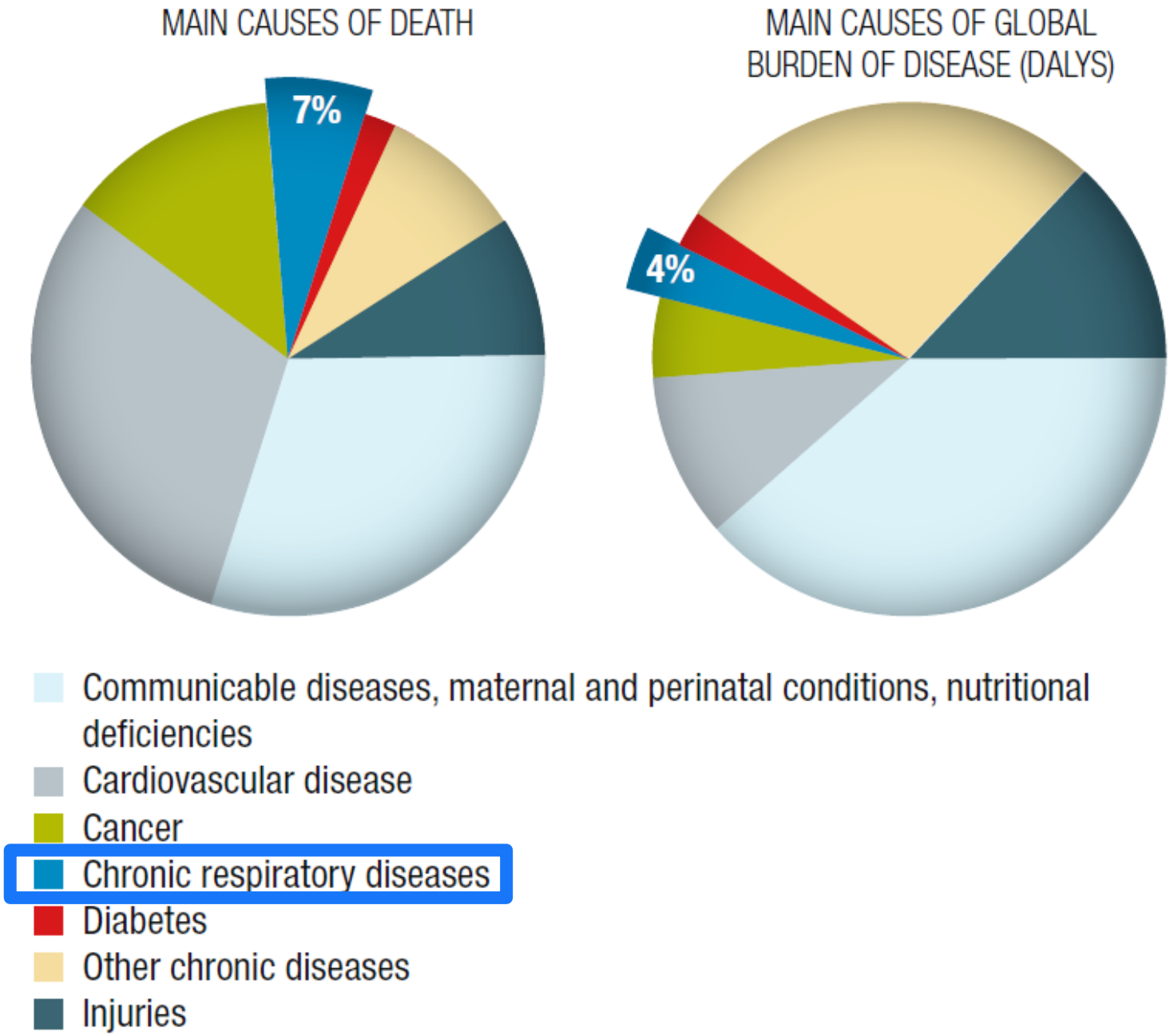
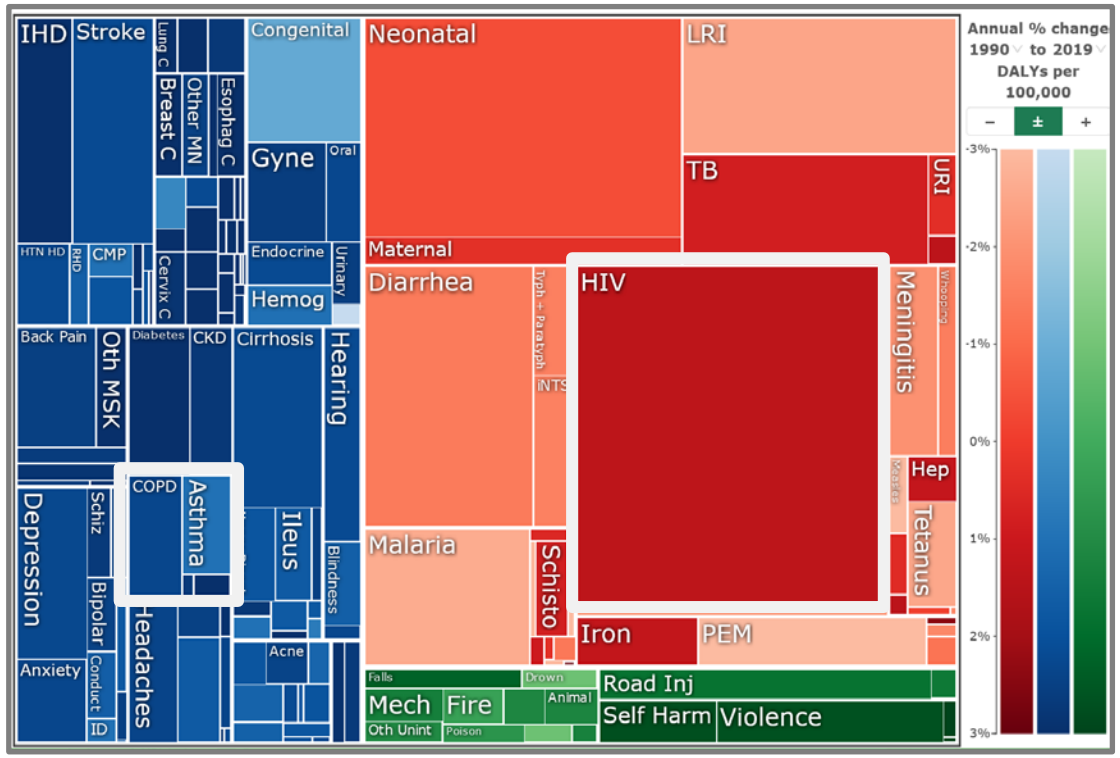
Globally, chronic lung disease (CLD) accounts for 7% of deaths and 4% of DALYs

http://www.who.int/respiratory/publications/global_surveillance/en/index.html

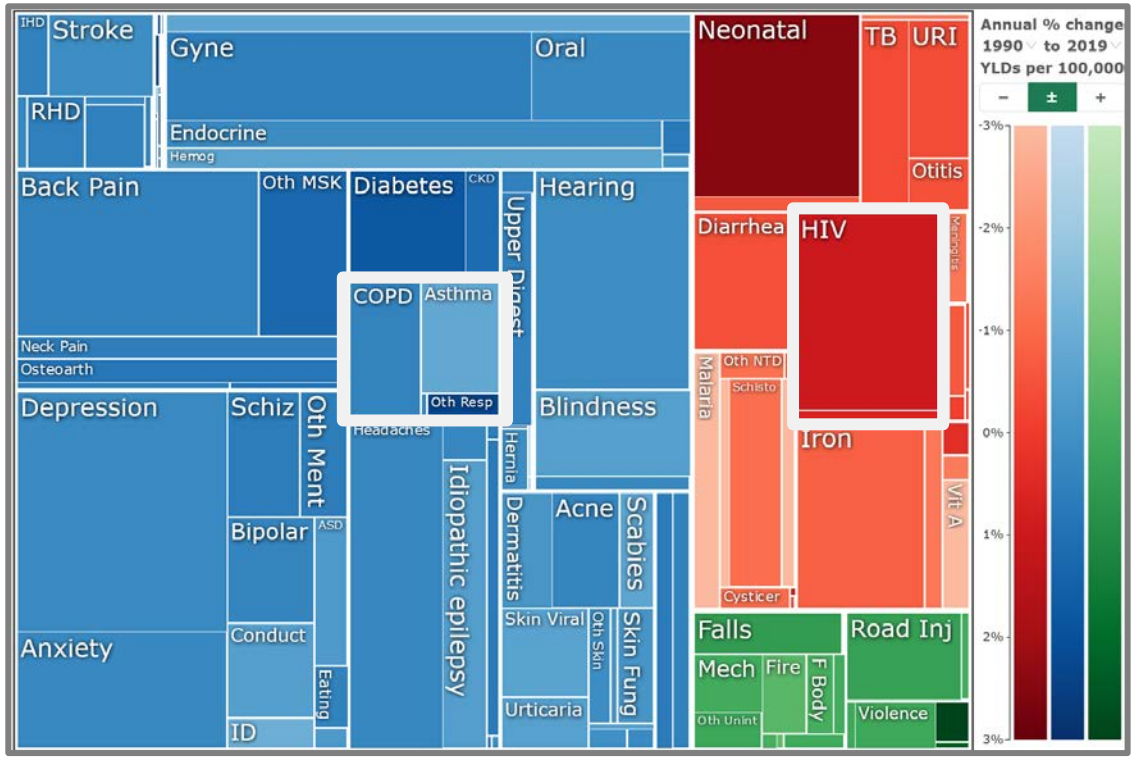


CLD and HIV in Kenya

DALYs



YLD



https://vizhub.healthdata.org/gbd-compare/

Shift in HIV-related pulmonary complications toward CLD among youth with HIV (YLWH)

Majority have ≥1 chronic respiratory symptom

Hypoxia after submaximal exercise (12-38%)

Radiographic abnormalities common (>50%)

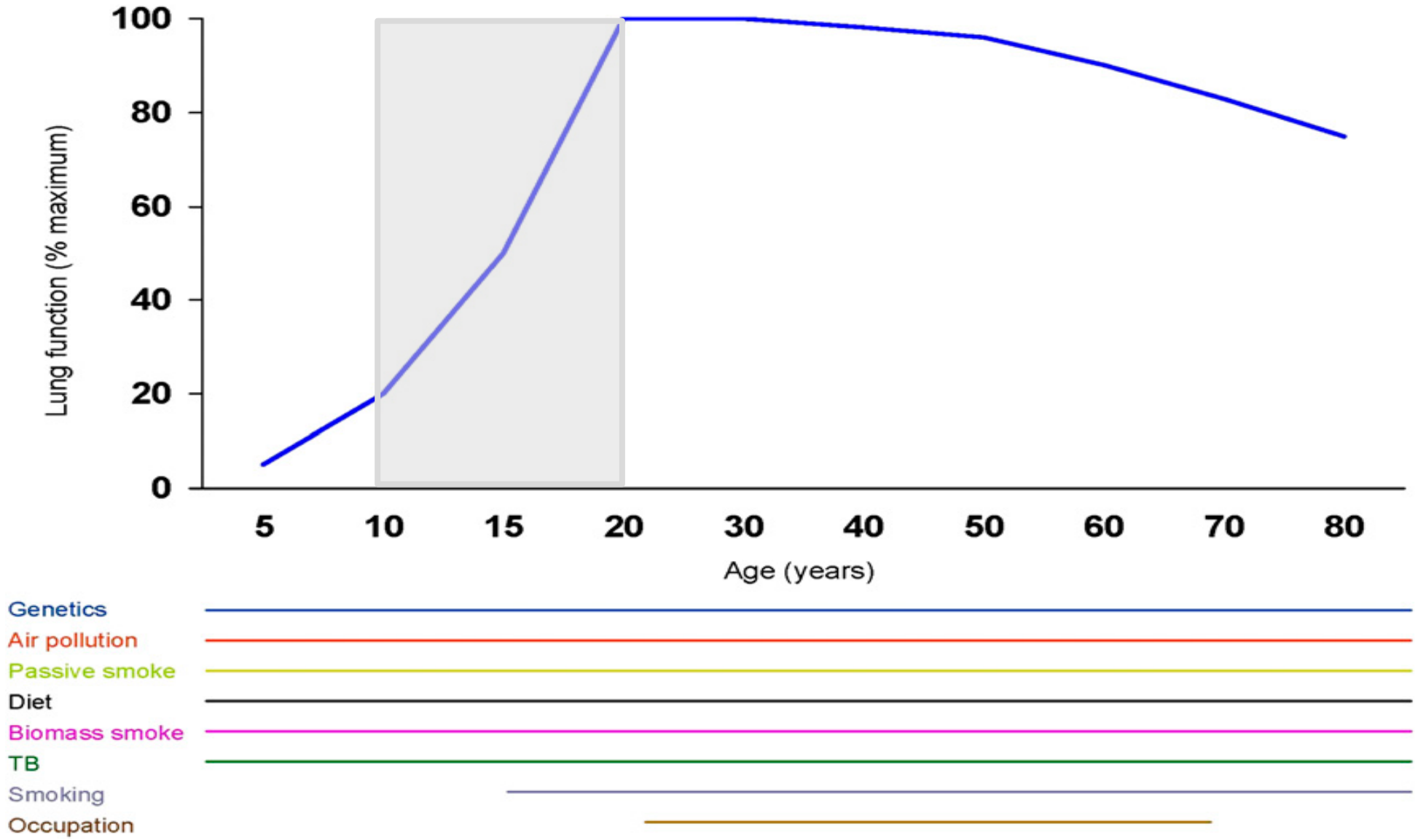
Prevalence of impaired lung function:

- Up to 45% in several sub-Saharan African countries
- ~33% in the U.S.

Ferrand *CID* 2012; Rylance *AIDS* 2016; Mwalukomo *J Ped Infect Dis Soc* 2016; Githinji *Ann ATS* 2017; Shearer *JACI* 2017; Attia *AIDS* 2018

Pathophysiology of CLD in youth with perinatally-acquired HIV

- Early life factors linked with impaired lung function later in life
  - Fetal oxygen/nutrient delivery
  - Low weight at birth and during childhood
  - Malnutrition
  - Inhaled pollutants


100
80
60
40
20
0
Lung function (% maximum)
5
10
15
20
30
40
50
60
70
80
Age (years)
Genetics
Air pollution
Passive smoke
Diet
Biomass smoke
TB
Smoking
Occupation

Pathophysiology of CLD in youth with perinatally-acquired HIV

- Early life factors linked with impaired lung function later in life
  - Fetal oxygen/nutrient delivery
  - Low weight at birth and during childhood
  - Malnutrition
  - Inhaled pollutants
- Unique consideration in YLWH → longstanding HIV during critical periods of lung, immune development
  - Associated with greater prevalence of end-organ injury
  - Chronic inflammation, immune activation, endothelial activation, etc.

Youth disproportionately affected by HIV

- In 2022, ~1.65 million youth aged 10-19 years old were living with HIV (140,000 new infections)
- Between 2005 and 2016, number of youth:
  - Living with HIV **increased by 30%**
  - Dying due to HIV-related illnesses **tripled**
- Most YLWH live in LMICs
  - 85% in sub-Saharan Africa; 73% of new infections
- >1 million additional YLWH anticipated by 2030 (~183,000 annual new HIV infections)

https://data.unicef.org/topic/hivaids/adolescents-young-people/

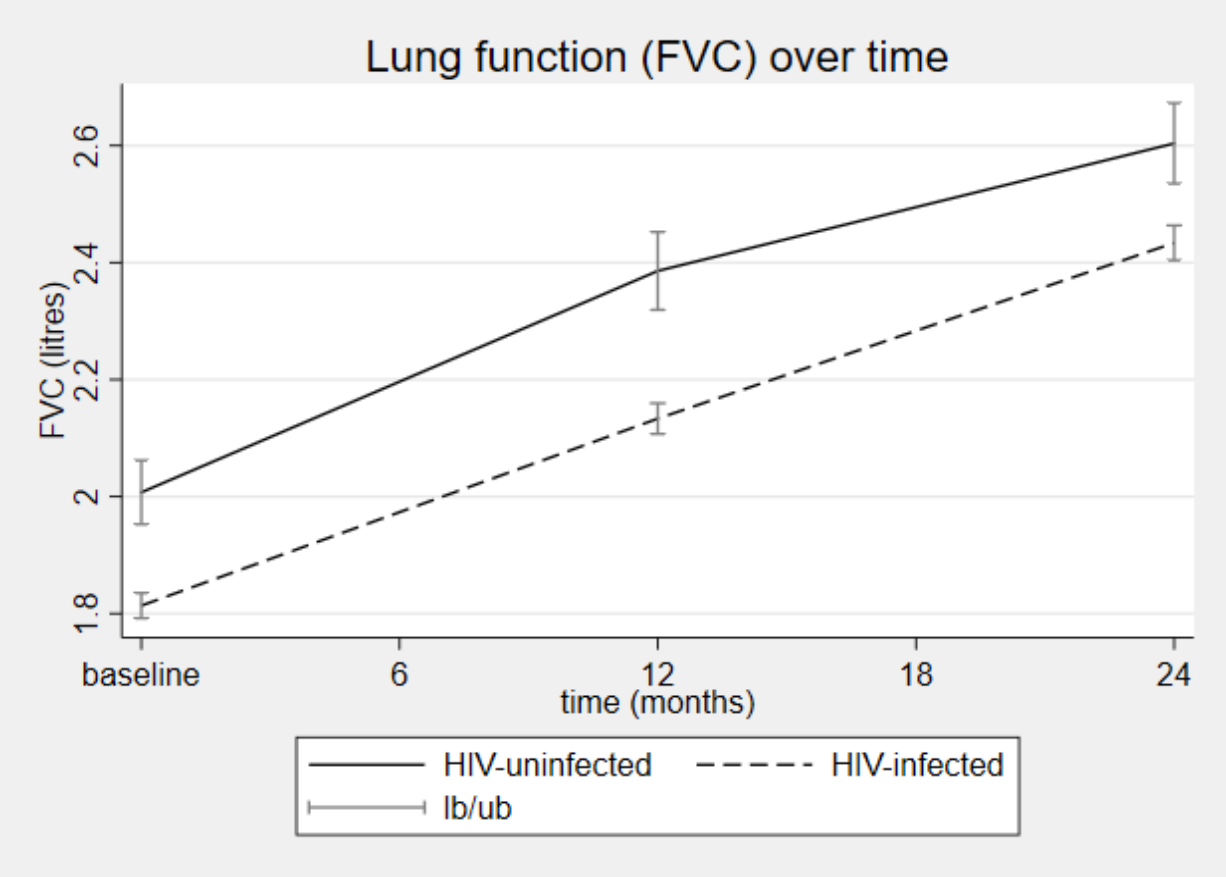
AIDS

Adolescent age is an independent risk factor for abnormal spirometry among people living with HIV in Kenya

Adolescent age is associated with a 3-fold risk* of abnormal lung function among people with HIV

***aOR 3.2** (95%CI 1.5–7.0) adjusted for CD4, BMI, WHO HIV stage, TB, paraffin/kerosene, smoking

Lung growth lags in YLWH, despite ART initiation at 4 yrs old



Longitudinal changes in spirometry in South African youth with PHIV on ART

Githinji *Clin Infect Dis* 2020;70(3):483-90

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Phenotypes

Observable characteristics

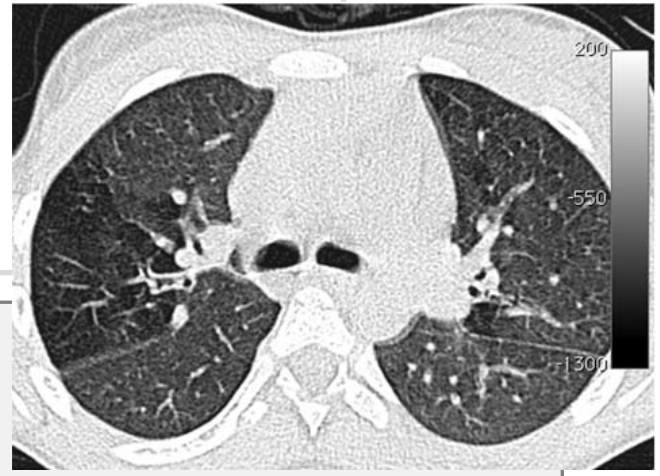
- Symptoms
- Physical exam

Commonly available clinical data

- Spirometry (pre-/post-bronchodilator) +/- plethysmography
- Chest imaging
- Laboratory values, including blood IgE, eos
- 6MWT
- History – exposures, risk factors

MAJOR ARTICLE HIV/AIDS

Chronic Lung Disease in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection



116 participants
- Mean age: 14 ± 2.6 years (HIV dx: 12 years)
- 69% receiving ART

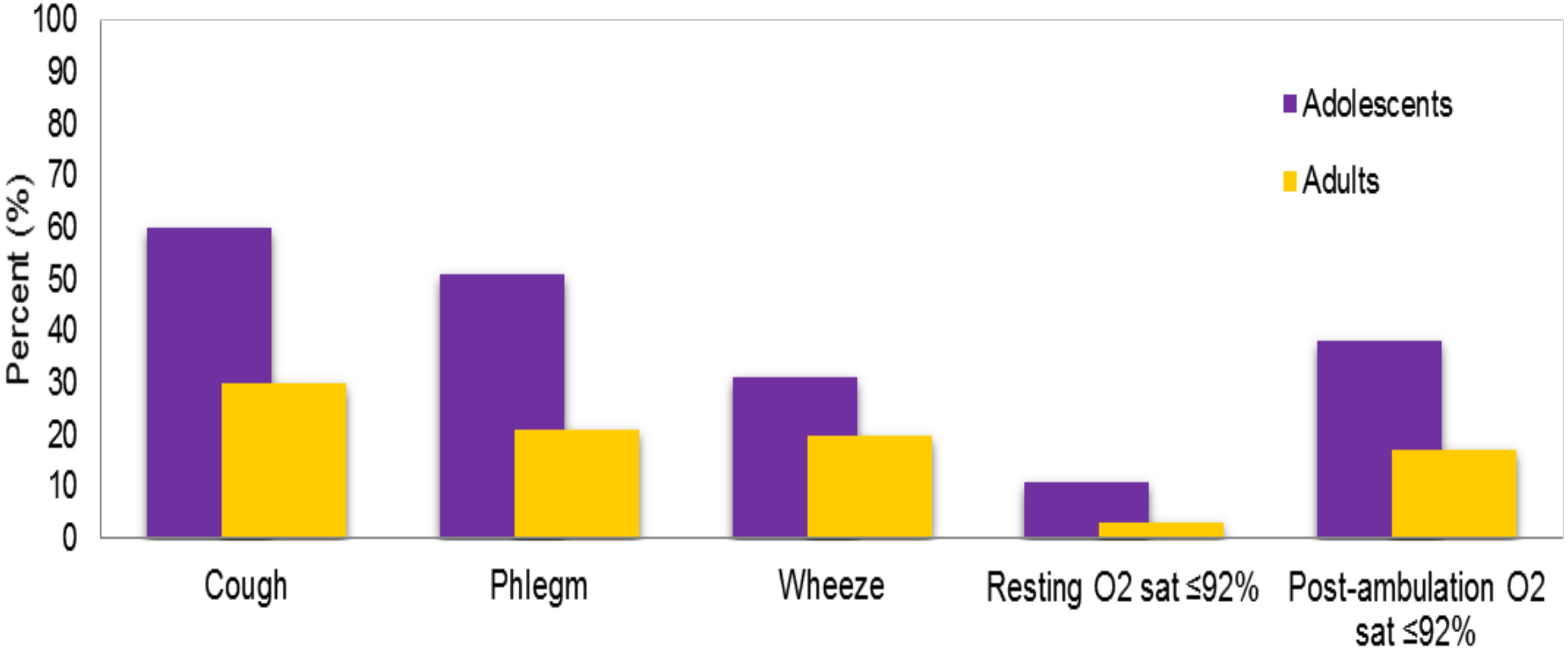
Chronic cough (66%), reduced exercise tolerance (21%), multiple respiratory infections in past year (41%), hypoxemia with exercise (29%)

41% with FEV_1 <80% predicted; poor bronchodilator response

31/56 (55%) had mosaic attenuation on HRCT → obliterative bronchiolitis?

Ferrand *Clin Infect Dis* 2012;55:145-52

YLWH had significantly more chronic respiratory symptoms and oxygen desaturation than adults with HIV



Attia *AIDS* 2018;32:1353-9

YLWH had a high prevalence of abnormal spirometry patterns

	Adolescents (10-19 yo) *n* = 52	Adults (≥20 yo) *n* = 372	*P*-value
Abnormal spirometry, %	40	17	<0.001
Airflow limitation			
Pre-BD FEV1/FVC <LLN, %	23	10	0.008
Post-BD FEV1/FVC <LLN, %	27	7	<0.001
FEV1 <LLN, %	27	11	0.001
FVC <LLN, %	17	8	0.02

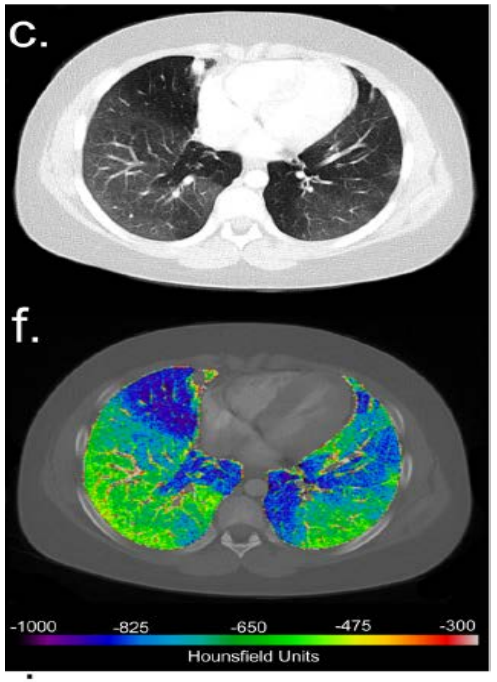
Attia *AIDS* 2018;32:1353-9

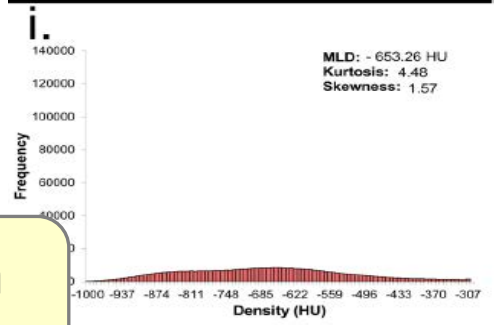
European Radiology

Quantitative CT analysis for bronchiolitis obliterans in perinatally HIV-infected adolescents—comparison with controls and lung function data

Using semi-automated lung segmentation for CTs from 78 YLWH and16 uninfected youth, YLWH had greater:

- Mean lung density, mass
- Ventilation heterogeneity
- High- (HU >-810) and low-attenuation (HU <-950) regions





Low attenuation areas and ventilation heterogeneity correlated with lower FEV1/FVC (airflow limitation) → obliterative bronchiolitis?

BUT greater % of high-attenuation than low-attenuation areas → higher lung density may reflect inflammation

Phenotypes of CLD in YLWH remain poorly understood

Airway-predominant		Parenchymal, vascular
Obliterative/constrictive bronchiolitis	Post-TB lung disease	Interstitial diseases – fibrosis, LIP
Bronchiectasis	Recurrent infections – TB, bacterial, viral	Pulmonary hypertension
Asthma		
Asthma/COPD overlap?		

Endotypes

Distinct from clinical phenotypes

→ Link clinical expression of disease to driving mechanisms of disease

'A subtype of disease defined functionally and pathologically by a molecular mechanism or by treatment response…'

Heterogeneity of CLD and genetic and environmental factors

→ Multiomics: **metabolomics**, genetics, epigenetics, **immunologic assays**, transcriptomics, lipidomics

→ Distinct endotypes may (co)-exist

→ Associated with clinical features and reflect differing molecular causes, responses to therapies

Anderson *Lancet* 2008;372:1107-19
Chung *Curr Opin Allergy Clin Immunol* 2023;23:199–204

Little is known about endotypes of CLD among YLWH

Among PHIV adolescents, **early ART initiation** and **improved nutrition** were associated with better lung function

PHIV school-age children who initiated **ART in infancy** had **lung function near population norms**

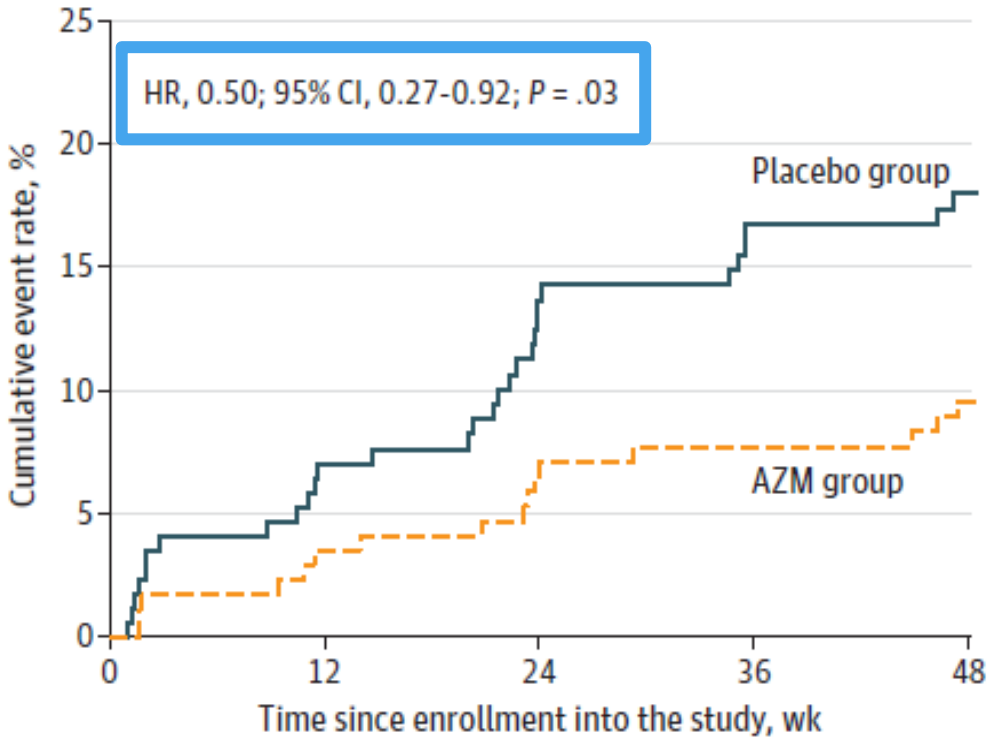
Pre-ART pneumonia, growth deficits and air pollution exposure → lower lung function

Rylance PLoS One 2019; Hameiri-Bowen AIDS 2021; Attia JAIDS 2022

Original Investigation | Pulmonary Medicine

Effect of Once-Weekly Azithromycin vs Placebo in Children With HIV-Associated Chronic Lung Disease

The BREATHE Randomized Clinical Trial



- Randomized 347 youth with HIV-CLD to weekly azithromycin x48 weeks
  - No difference in zFEV1
  - ↓ exacerbations (12.1 vs 24.7/100 p-y)
- Azithromycin resistance on NP swabs/ sputum (*S.pneumo*, *S.aureus*)
- Preserved bacterial diversity; decreased *H.flu* and *Moraxella* → improved lung function?

Ferrand *JAMA Network Open* 2020;3:e2028484, Abotsi *ERJ Open Res* 2021;8:00491-2021, Abotsi *Microbiome* 2023;11:29

THE JOURNAL OF Allergy AND Clinical Immunology

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

Among 49 Kenyan and 188 US youth with PHIV

- FEV1 % predicted was significantly lower among Kenyan compared to US youth
- Higher CD8 and lower CD4/CD8 were associated with lower FEV1 % predicted, even in the setting of CD4 preservation/reconstitution

JAIDS
JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME

Endothelial activation, innate immune activation, and inflammation are associated with airflow limitation and obstruction among adolescents with HIV

Among 50 Kenyan YLWH, biomarkers of endothelial activation, immune activation, and chronic inflammation were associated with lower post-BD $zFEV_1/FVC$ → potential mechanistic pathways

Individual biomarkers
sVCAM-1, sICAM-1, sCD163, sTREM-1, CD4/CD8, SAA

Factors representing endothelial and immune/monocyte activation

High prevalence of post-BD airflow obstruction (28%) and mosaic attenuation (48%), suggestive of **obliterative bronchiolitis phenotype**
→ Associated with **immune activation (sCD14) endotype**

Metabolomic profiling is emerging as a tool to identify signatures unique to lung diseases

Metabolic pathways have been implicated in heterogeneous CLD pathophysiology:

→ Pyrimidine, lipid, fatty acid metabolism, glycolysis, mitochondrial beta-oxidation and the TCA cycle

Metabolomic profiling has NOT been performed among YLWH and CLD

Nambiar Respirology 2020; Lorente Crit Care 2021; Kelly Biochimica 2017

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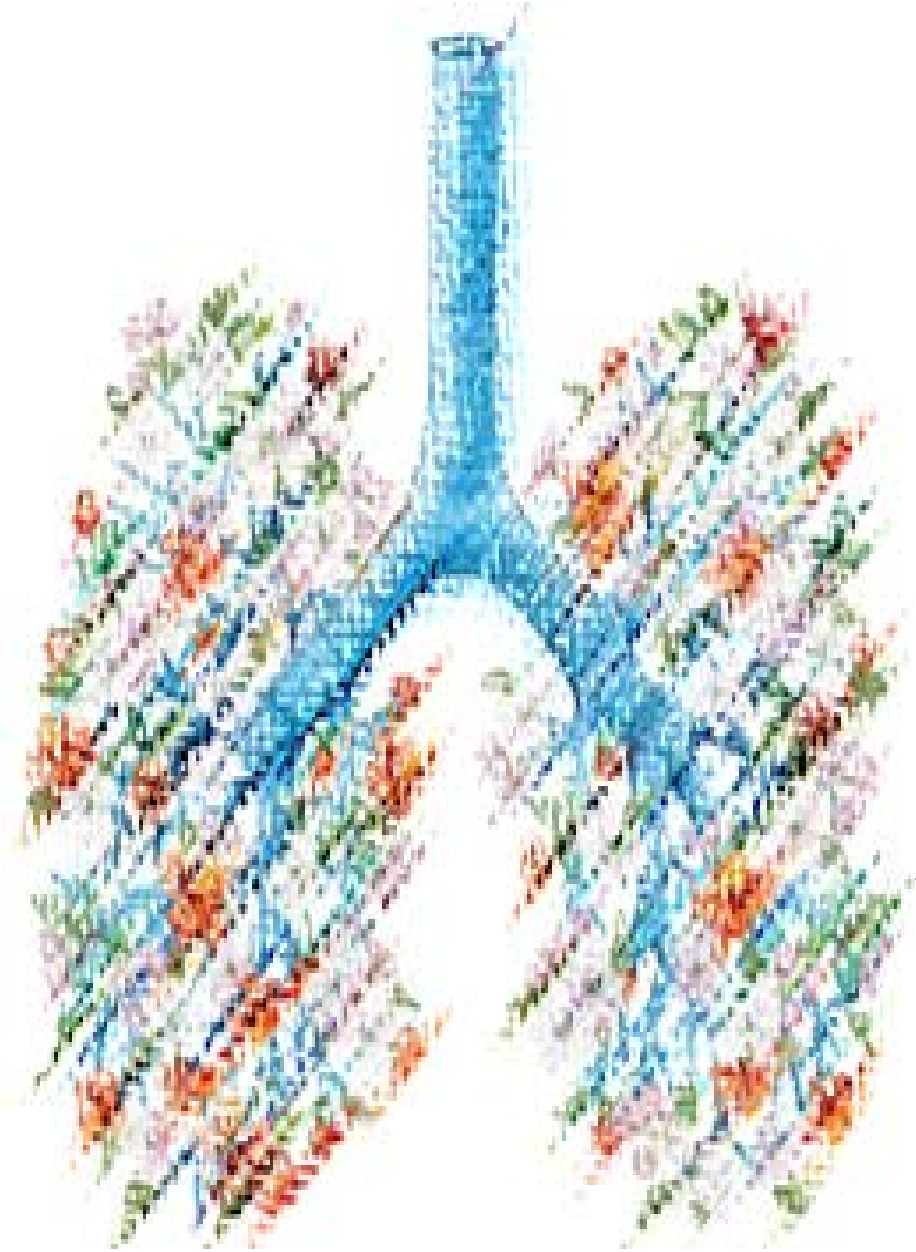

NIH K23 CDA

BREATHE II Study

PHENOTYPING AND ENDOTYPING:

IMAGING, BIOMARKERS, AND LONGITUDINAL SPIROMETRY IN YLWH AND HIV- YOUTH

Research Objectives

- Compare phenotypes, risk factors of CLD in YLWH and HIV- youth
  - Baseline spirometry, chest CTs
- Determine whether HIV is associated with CLD and diminished growth of lung function over time
- Determine whether endotypes identified by immunological assays (chronic inflammation, immune activation and HIV severity) and metabolomic profiling are associated with increased risk of:
  - Prevalent CLD
  - Diminished lung function over time

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Study Site & Population

165 YLWH and 170 HIV-uninfected youth with adequate quality spirometry enrolled July 2017 – December 2018

Inclusion criteria

- Age 10-19 yo
- YLWH in care at the Hope Center
- Uninfected youth from surrounding area in Nairobi

Exclusion criteria

- Acute respiratory infection
- Severe illness
- Recent TB diagnosis
- Pregnancy

Key Study Procedures

Pre- & post-BD spirometry
- Baseline + 6, 12 & 24 (→48) mos
- Global GLI ref eqns

HRCT in YLWH
- Inspiratory, expiratory
- Clinical assessment
- Quantitative measures

Biomarker & metabolite analysis
- Inflammation, immune imbalance/ activation, endothelial activation
- CD4, CD8
- Metabolomic profiling

Ambient PM2.5
- NASA satellites
- Linked to home address
- Accounts for temp/humidity at spirometry

Preliminary Results

Select baseline characteristics	YLWH (n=165)	HIV- (n=170)	p-value
Male, n (%)	93 (56)	64 (37)	0.001
Age, median (IQR)	16 (13, 18)	14 (12, 16)	<0.001
HIV-related variables			
Current ART, n (%)	165 (100)	–	
Duration of ART (years), median (IQR)	8 (2, 11)	–	
Current CD4 count (cells/μL), median (IQR)	576 (359, 787)	917 (707, 1104)	<0.001
Current CD4/CD8 ratio, median (IQR)	0.74 (0.37, 1.03)	1.45 (1.12, 1.83)	<0.001
Prior pneumonia, n (%)	54 (32)	40 (24)	0.08
Prior pulmonary TB, n (%)	21 (13)	1 (1)	<0.001
BMI-for-age z-score, median (IQR)	-0.4 (-1.2, 0.2)	-0.1 (-0.8, 0.6)	0.008
Height-for-age z-score, median (IQR)	-1.2 (-1.8, -0.5)	-0.5 (-1.2, 0.1)	<0.001
Aggregate indoor biofuel burning (hrs/wk)	10 (3, 23)	14 (4, 28)	0.003
Secondhand cigarette smoke exposure, n (%)	40 (24)	30 (18)	0.14
Ambient $PM_{2.5}$ (PPM), median (IQR)	43.2 (26.1, 52.2)	48.5 (30.4, 56.8)	0.003
Any respiratory symptoms, n (%)	101 (61)	83 (49)	0.02
Cough	57 (34)	33 (19)	0.002

	YLWH	HIV-	Adjusted difference*
	mean z-score (95% CI)		difference (95% CI)
Pre-bronchodilator			
$zFEV_1$	-0.92 (-1.08, -0.76)	-0.74 (-0.87, -0.60)	-0.19 (-0.42, 0.03)
zFVC	-0.83 (-0.98, -0.68)	-0.64 (-0.77, -0.50)	**-0.23 (-0.44, -0.02)**
$zFEV_1$/FVC	-0.15 (-0.31, 0.01)	-0.15 (-0.29, 0.00)	0.01 (-0.23, 0.25)
Post-bronchodilator			
$zFEV_1$	-0.75 (-0.91, -0.59)	-0.54 (-0.68, -0.41)	**-0.24 (-0.46, -0.02)**
zFVC	-0.82 (-0.98, -0.67)	-0.62 (-0.77, -0.48)	**-0.24 (-0.45, -0.02)**
$zFEV_1$/FVC	0.14 (0.00, 0.29)	0.21 (0.08, 0.34)	-0.06 (-0.27, 0.16)

YLWH have significantly lower $zFEV_1$ and zFVC compared to HIV- youth

*linear regression models adjusted for age, sex, BMI-/height-for-age z-scores, inhaled exposures (secondhand smoke, hrs/wk biofuel burning, ambient $PM_{2.5}$)

HIV is independently associated with **any abnormal spirometry** pattern and **PRISm** among youth

	YLWH	HIV-	Adjusted* relative risk
	n (%)		RR (95% CI)
Any abnormal pattern	**40 (25)**	**29 (18)**	**1.63 (1.04, 2.56)**
Pre-BD			
Airflow obstruction	8 (5)	10 (6)	--
PRISm	**31 (20)**	**19 (12)**	**2.06 (1.22, 3.50)**
Post-BD			
Airflow obstruction	3 (2)	4 (3)	--
PRISm	25 (17)	12 (8)	--

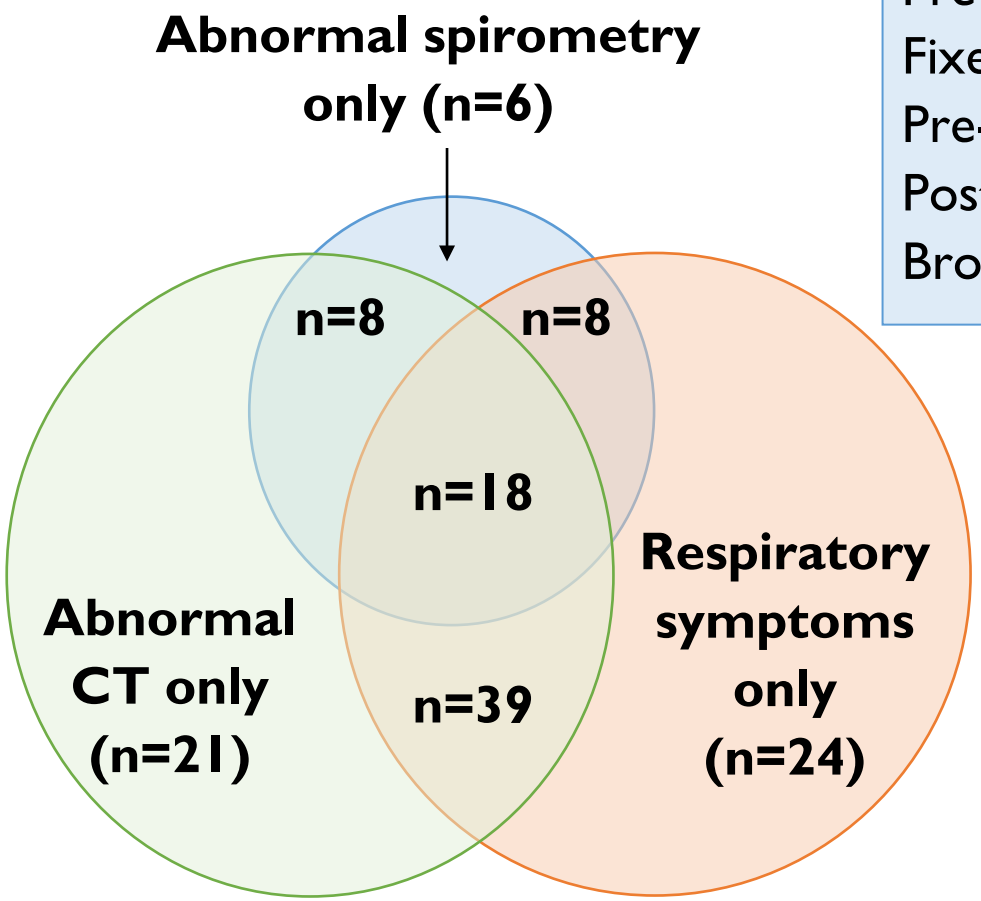
*adjusted for age, sex, BMI/height-for-age z-score, inhaled exposures (secondhand smoke, hrs/wk biofuel burning, ambient PM2.5) in modified Poisson regression model with robust error variance

Abnormal spirometry, chest CT and respiratory symptoms among YLWH

(n=152 with complete data)

CT Abnormalities (n=91)

Nodules, n=52
Mosaic attenuation, n=41
Bronchiectasis, n=16
Lymphadenopathy, n=15
Linear scars, n=14
Groundglass, n=9
Bronchial wall thickening, n=7
Consolidation, n=8
Emphysema, n=8

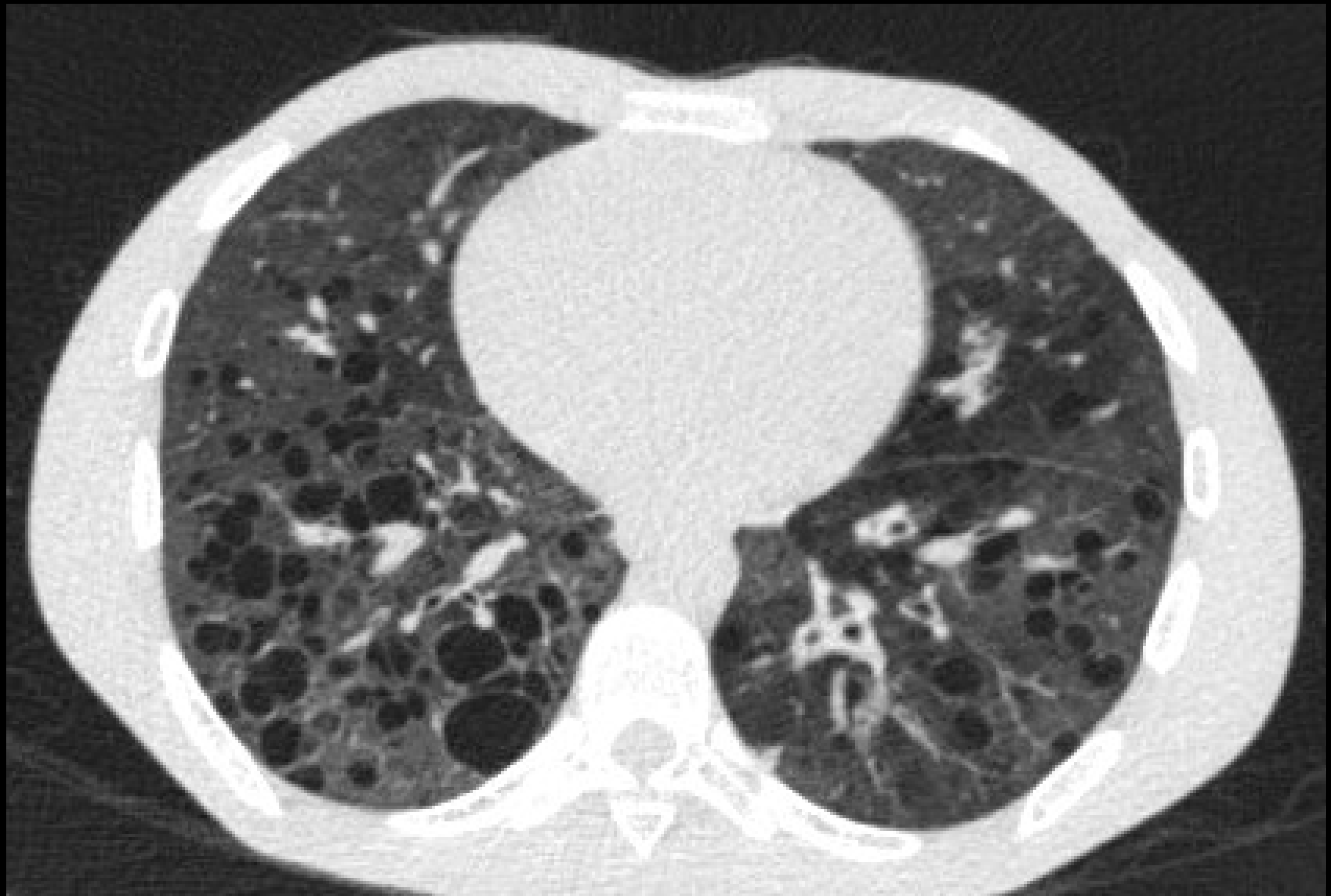


Abnormal Spirometry (n=40)

Pre-BD airflow obstruction, n=8
Fixed airflow obstruction, n=3
Pre-BD PRISm, n=31
Post-BD PRISm, n=25
Bronchodilator response, n=13

Presence of Respiratory Symptoms (n=94)

Cough, n=55
Sputum production, n=34
Wheezing, n=35
Chest tightness, n=40
Breathlessness, n=14



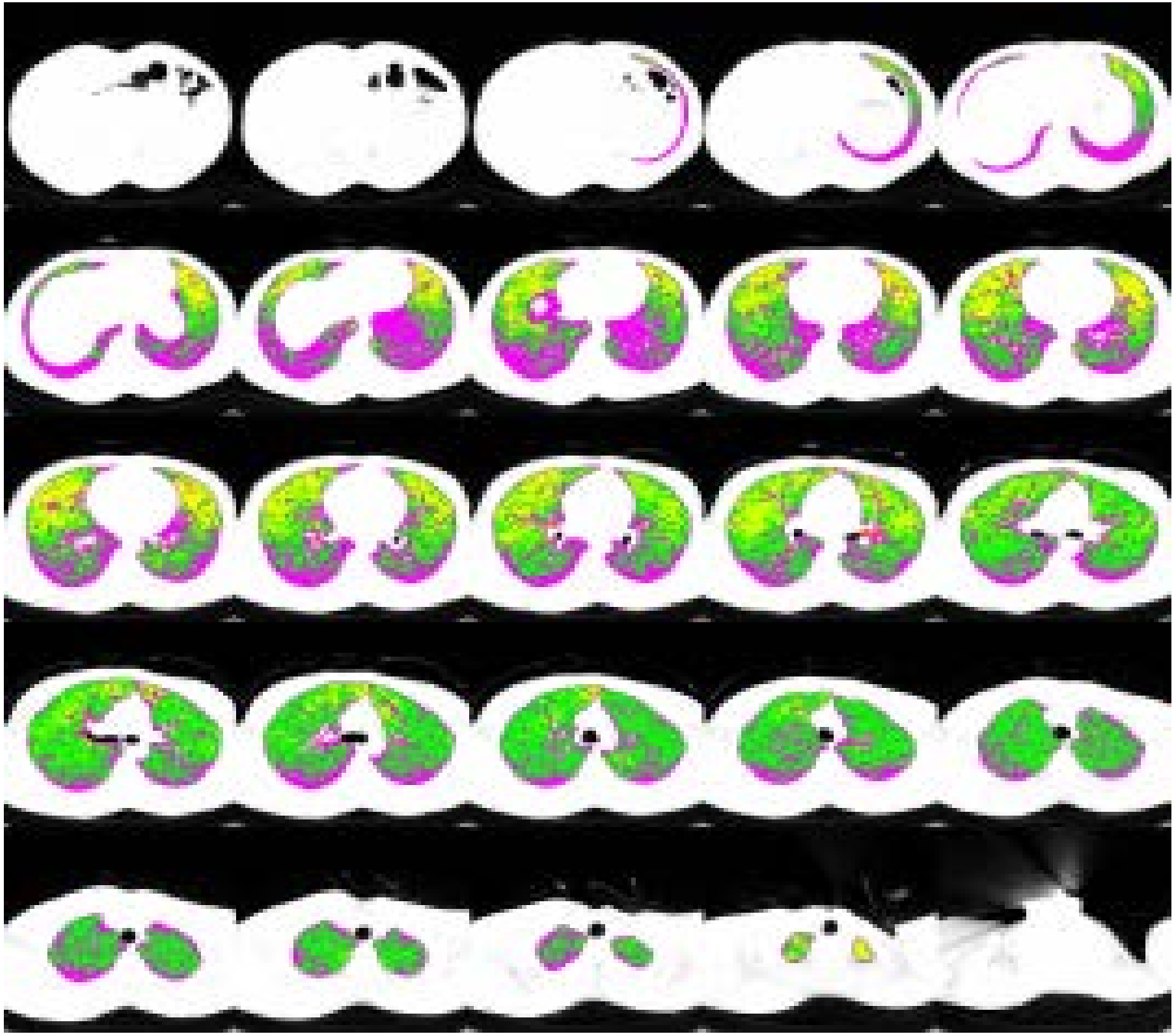
Quantitative CT Metrics → parametric response mapping

NORMAL
Voxels ABOVE -950 HU on inspiration
Voxels ABOVE -856 HU on expiration

FUNCTIONAL LOW DENSITY AREA (fSAD)
Voxels ABOVE -950 HU on inspiration
Voxels BELOW -856 HU on expiration

PERSISTENT LOW DENSITY AREA (Emph)
Voxels BELOW -950 HU on inspiration
Voxels BELOW -856 HU on expiration

INSPIRATION HIGH DENSITY AREA (PD)
Voxels ABOVE -810 HU on inspiration



Quantitative CT metrics	Any abnormal spirometry (n=47)	Normal spirometry (n=92)	
	median (IQR)		p-value
Whole lung volume (expiratory)	2.18 (1.70, 2.71)	2.24 (1.86, 3.01)	<0.001
Mean expiratory HU	-655.31 (-691.57, -614.63)	-662.46 (-694.57, -623.61)	0.01
Whole lung volume (inspiratory)	2.93 (2.30, 3.53)	3.78 (3.05, 4.68)	<0.001
Mean inspiratory HU	-733.43 (-756.63, -698.61)	-760.66 (-778.24, -738.34)	<0.001
PRM - normal lung	53.05 (24.21, 66.92)	68.37 (45.64, 74.88)	<0.001
PRM - parenchymal disease (PD)	31.88 (21.03, 65.87)	19.07 (14.24, 31.82)	<0.001

Quantitative CT metrics but NOT qualitative findings **differ** by abnormal spirometry among YLWH

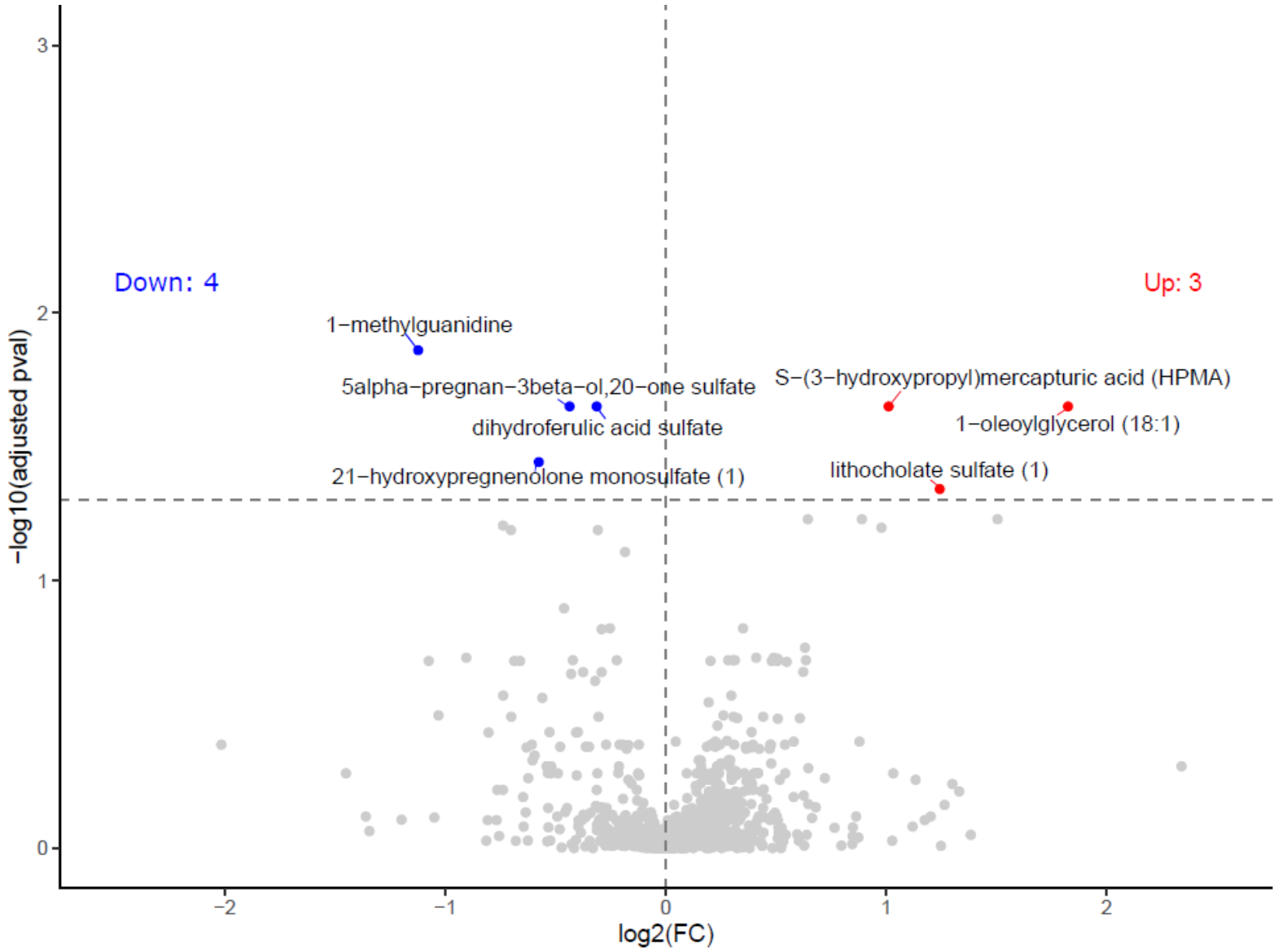
Among YLWH but not HIV- youth, higher levels of
- sCD14
- sICAM-1
- sVCAM-1

(Factor 2) were associated with abnormal spirometry, including PRISm

	YLWH		HIV-	
Serum biomarkers	Adjusted* RR (95% CI)	p-value	Adjusted* RR (95% CI)	p-value
Any abnormal spirometry pattern				
Factor 1 *(IL-6, ET-1)*	0.76 (0.56, 1.03)	0.08	0.96 (0.51, 1.81)	0.9
Factor 2 *(sCD14, sICAM-1, sVCAM-1)*	**1.32 (1.03, 1.70)**	**0.03**	0.90 (0.63, 1.30)	0.6
Factor 3 *(CRP, SAA)*	**1.31 (1.04, 1.67)**	**0.03**	**1.86 (1.38, 2.50)**	**<0.001**

*adjusted for age, sex, BMI/height-for-age z-score, inhaled exposures (secondhand smoke, hrs/wk biofuel burning, ambient PM2.5) in modified Poisson regression model with robust error variance

Among YLWH, distinct metabolomic profiles of
- oxidative stress
- pyrimidine metabolism
are associated with respiratory abnormalities and low FEV1



Conclusions

HIV → Proportionally lower **$zFEV_1$ and zFVC**
→ Greater risk of **abnormal spirometry, PRISm**

→ after accounting for age, sex, growth parameters and inhaled pollutants

Among **YLWH**:

Substantial **heterogeneity and overlap** in manifestations of CLD; challenging to identify clinical subtypes

High density areas (**parenchymal disease**) on quantitative CT may be informative for identifying phenotypes of CLD

Endotypes with **metabolic pathways** of **oxidative stress and pyrimidine metabolism** and **endothelial and immune activation** were associated with **respiratory abnormalities**

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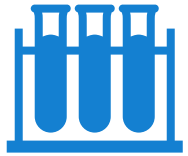
Toward identifying phenotypes and endotypes…

Phenotyping

Personalized attenuation thresholds; additional quantitative chest CT analyses

Longitudinal lung function data analysis (group-based trajectory modeling)

Endotyping



Additional proteomic, epigenetic, microbiome profiling

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In summary…

- **CLD is an important complication of HIV** among youth
- Manifestations of CLD are **heterogeneous** and **overlapping**
  → challenging to identify clinical phenotypes and endotypes

Among **YLWH**:

Obliterative bronchiolitis and **CLD represented by areas of parenchymal disease** may represent clinical **phenotypes** relevant in HIV

Important **endotypes** of HIV-related CLD and impaired lung function may include:

- **Immune/endothelial activation, inflammation**
- **Metabolomic pathways of oxidative stress and pyrimidine metabolism**

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SEATTLE CHILDREN'S
UNIVERSITY OF HAWAI'I AT MĀNOA
UNIVERSITY OF WASHINGTON/FRED HUTCH
CENTER FOR AIDS RESEARCH

pHACS
Pediatric HIV/AIDS Cohort Study
A Study of the National Institutes of Health

TREE
TREATMENT RESEARCH AND EXPERT EDUCATION

Coptic Hope Centre

INTERSECT
International Respiratory and Severe Illness Center
INTERSECT-Ellison Fellowship

Division of Pulmonary & Critical Care Medicine
Lakshminarayan Fellow Fund Endowment Grant

Thomas Francis, Jr. Global Health Travel Fellowship
University of Washington
DEPARTMENT OF GLOBAL HEALTH

Thrasher Research Fund
Medical research grants to improve the lives of children
Early Career Award

Declaration: No conflicts of interest

Questions?

eattia@uw.edu

@engiattia