Lung disease in HIV: Causes and consequences

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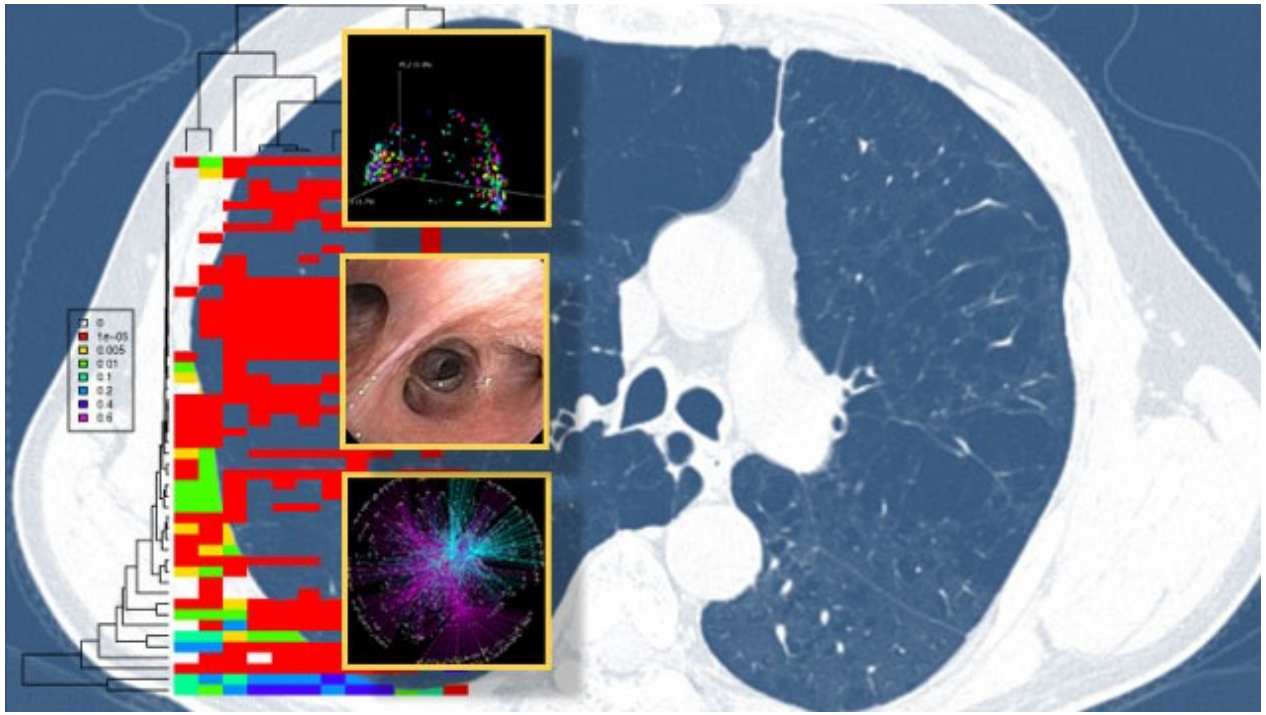
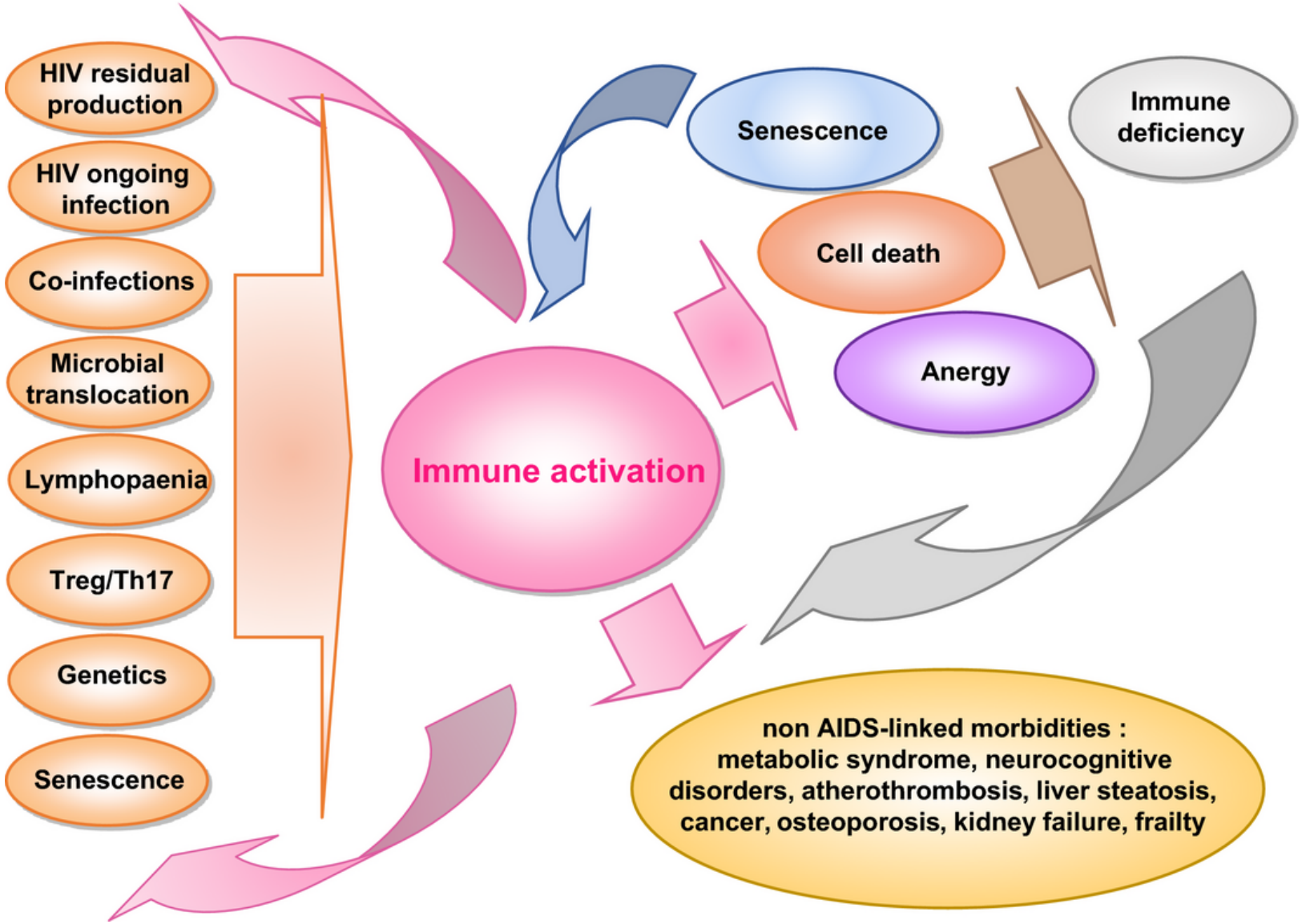


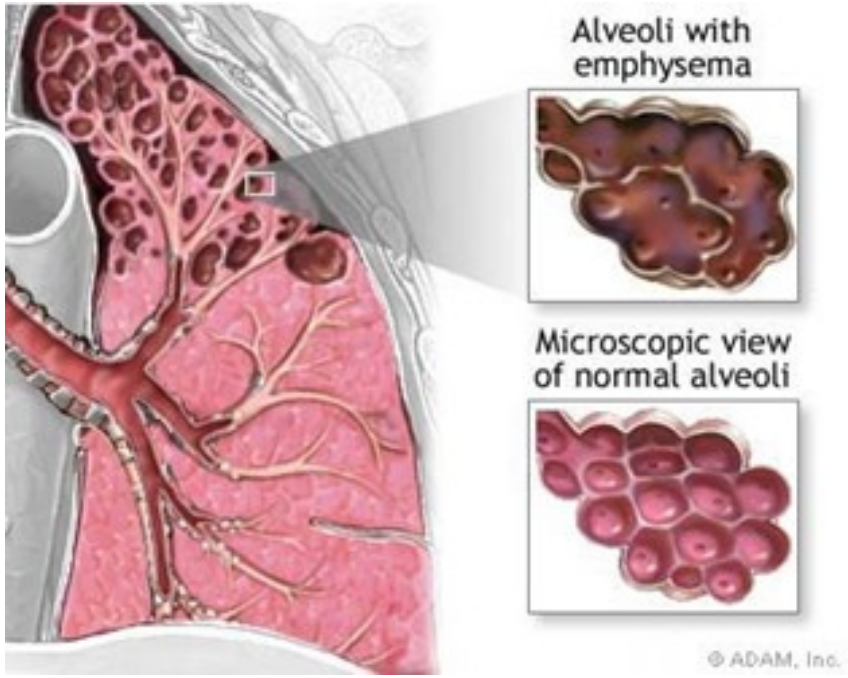
Pulmonary co-morbidities in HIV?



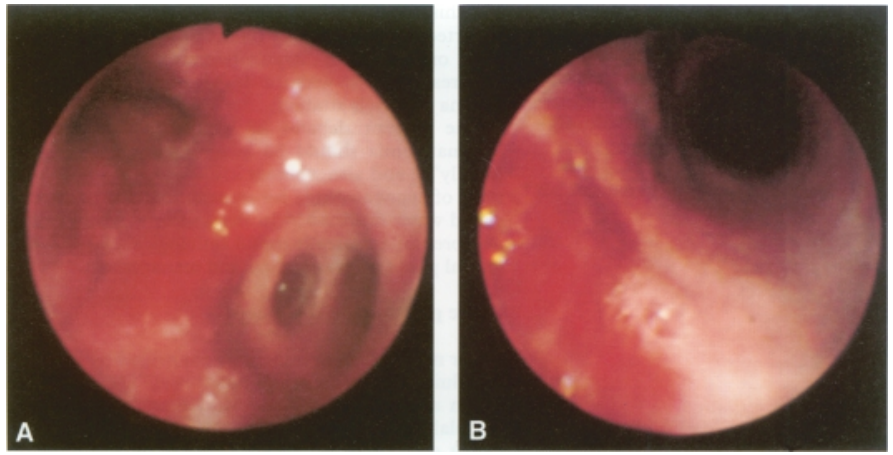
Younas M et al, HIV Med, 2015

Outline

- Scope of the problem
  - Pre-ART
  - Post-ART
- Phenotypes of COPD
  - Epidemiology
  - Contribution of HIV
  - Biomarkers
- Potential role of the microbiome
- Approach to therapy



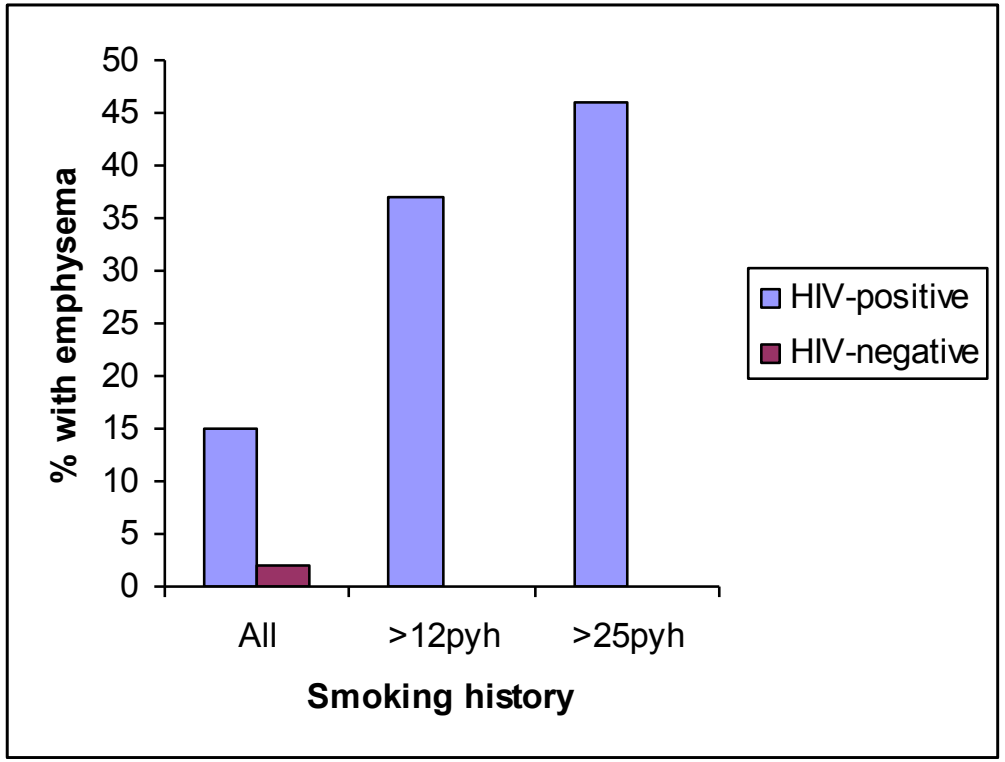
Lung disease leading cause of mortality in early HIV epidemic

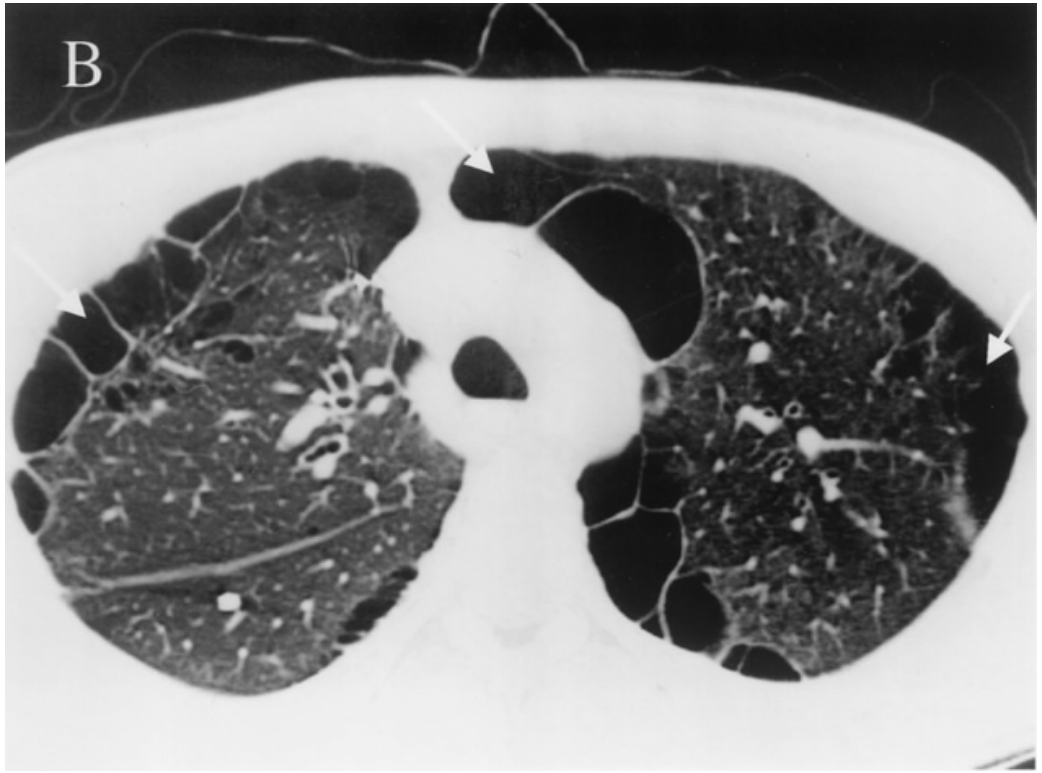


<u>Infections</u>:
Pneumocystis pneumonia
Tuberculosis
Bacterial pneumonia

<u>Neoplasms</u>:
Kaposi sarcoma
Lymphoma

COPD and HIV Pre-ART: Increased prevalence even in those without AIDS, primarily emphysema

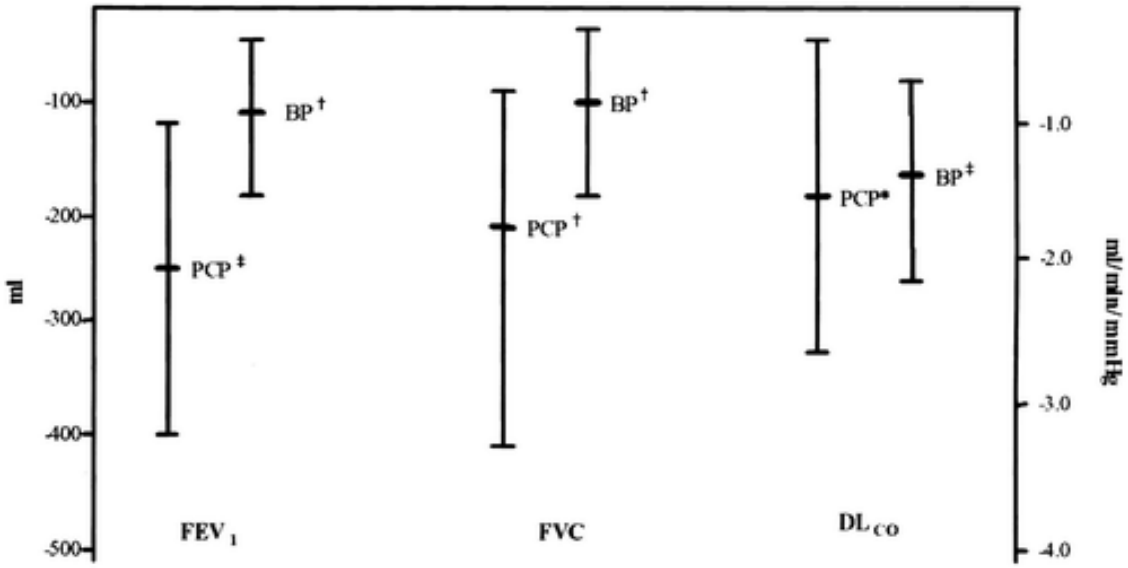




Kuhlman et al. *Radiology* 1989;173:23-6; Diaz et al. *Ann Int Med* 2000;132:369-72
Diaz et al. *Chest* 2003;123:1977-82

Pulmonary Complications of HIV Study (PCHIS)

- >1,300 HIV+ and HIV- men
- HIV+ individuals:
  - More common respiratory symptoms
  - Abnormal diffusing capacity (DLco)
  - Progressive COPD-like changes after pneumonia (PCP & bacterial)
  - HIV independent risk

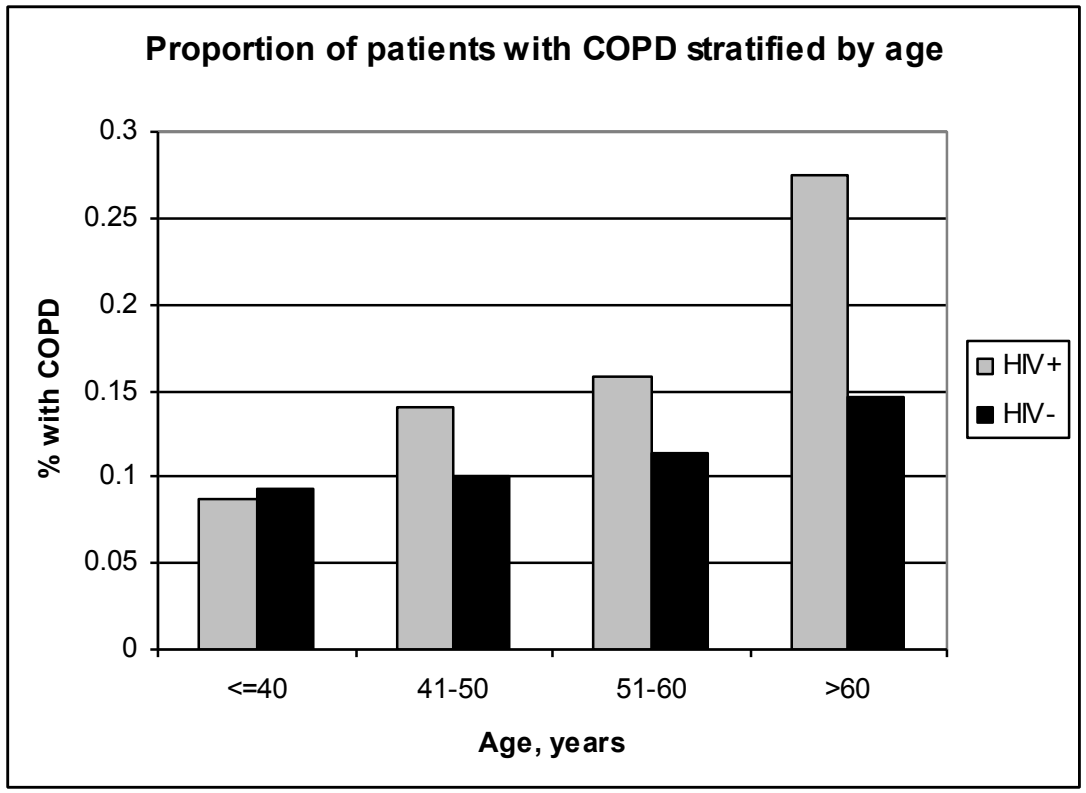


Wallace JM et al. Chest, 1997; Rosen MJ et al. AJRCCM, 1995; Morris A et al. AJRCCM, 2000

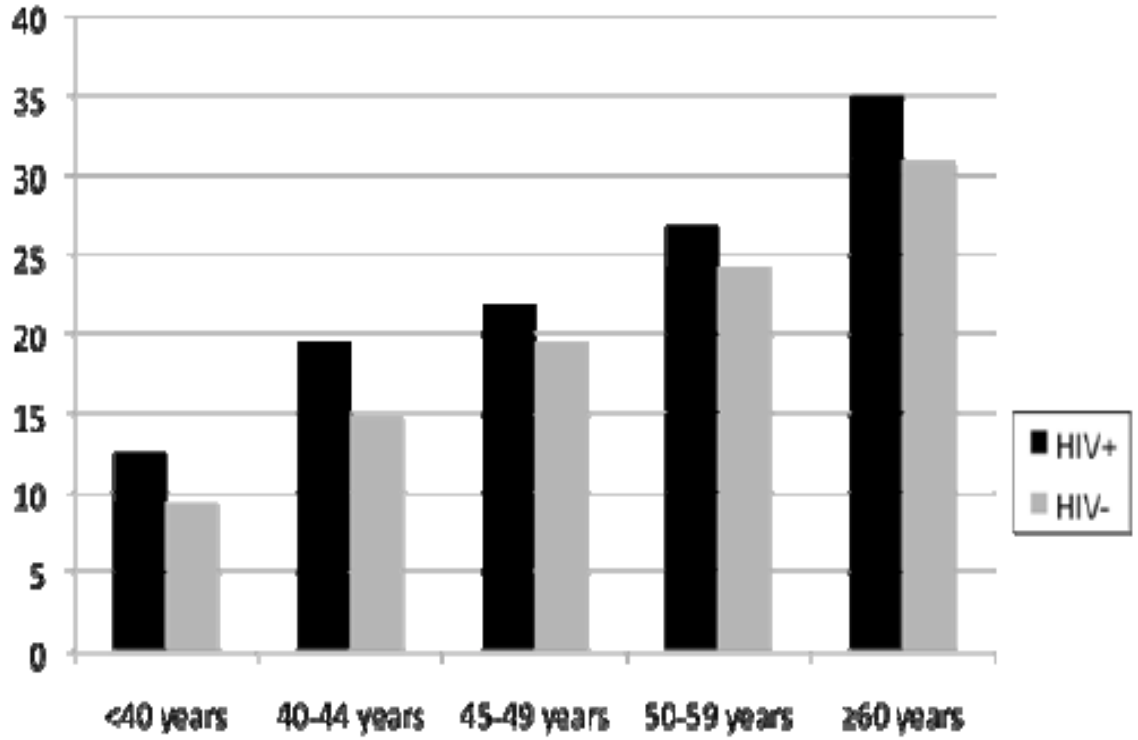
What do we know about COPD in the ART era?

COPD is more common in HIV+ Veterans

COPD prevalence



COPD incidence per 1,000 person-yrs

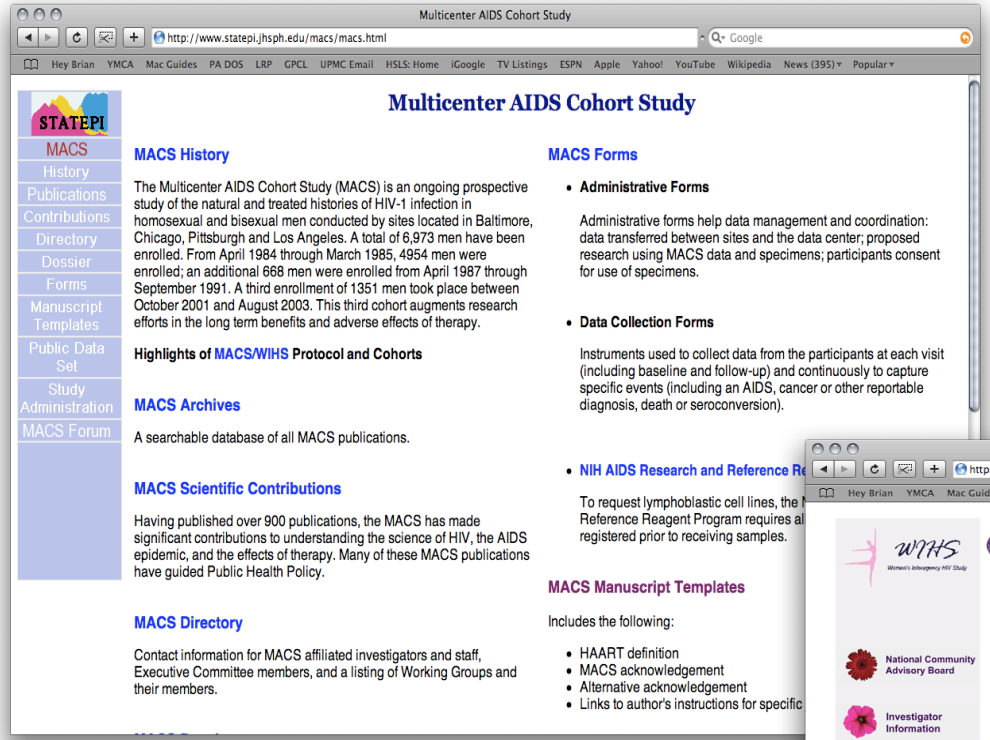


-Based on self report or chart review

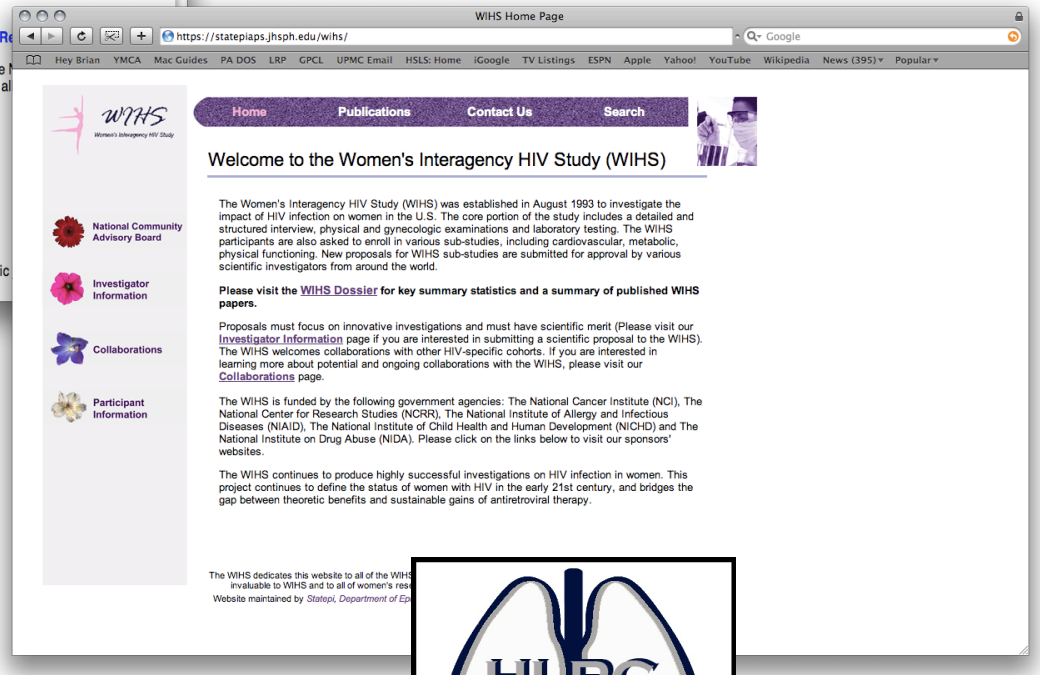
Crothers et al. *Chest*, 2006

Crothers et al. *AJRCCM*, 2011

Multicenter AIDS Cohort Study (MACS)



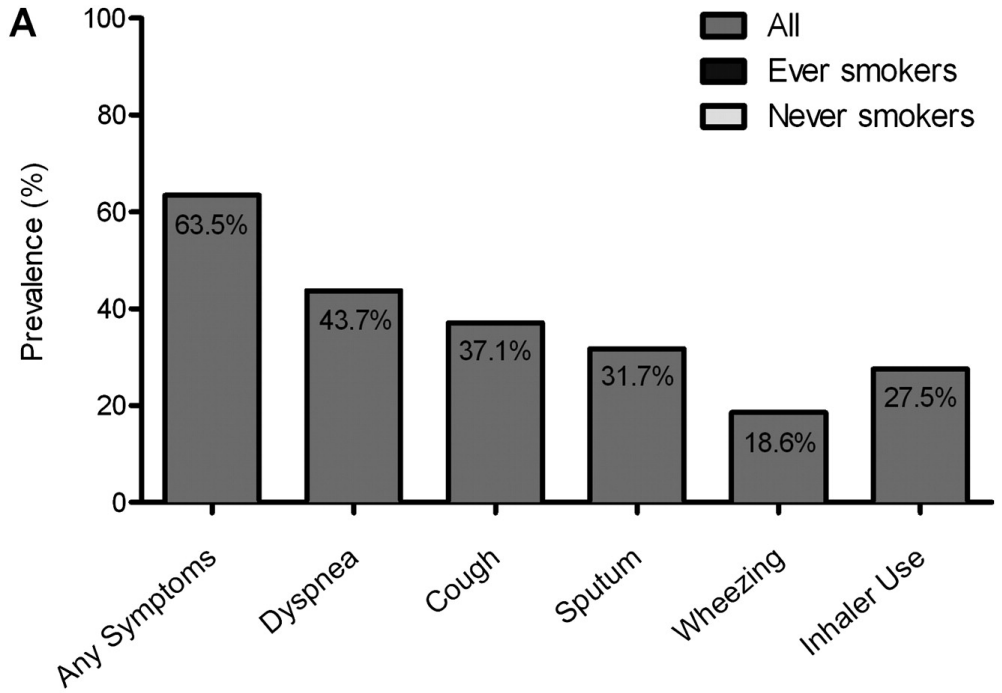
Women's Interagency HIV Study (WIHS)

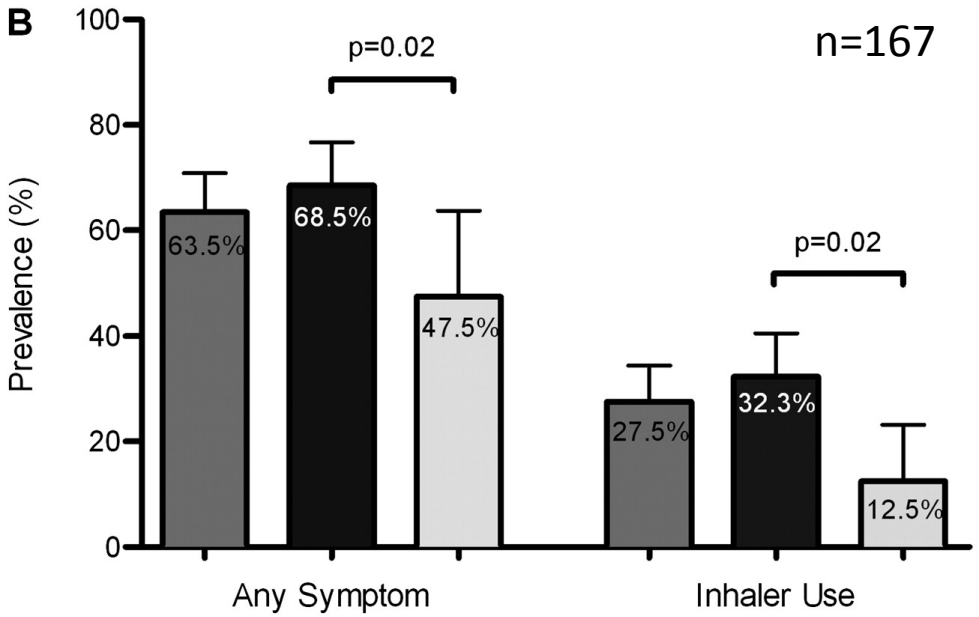


Pittsburgh Clinical Trials Unit

University of Washington

HLRC
HIV Lung Research Center



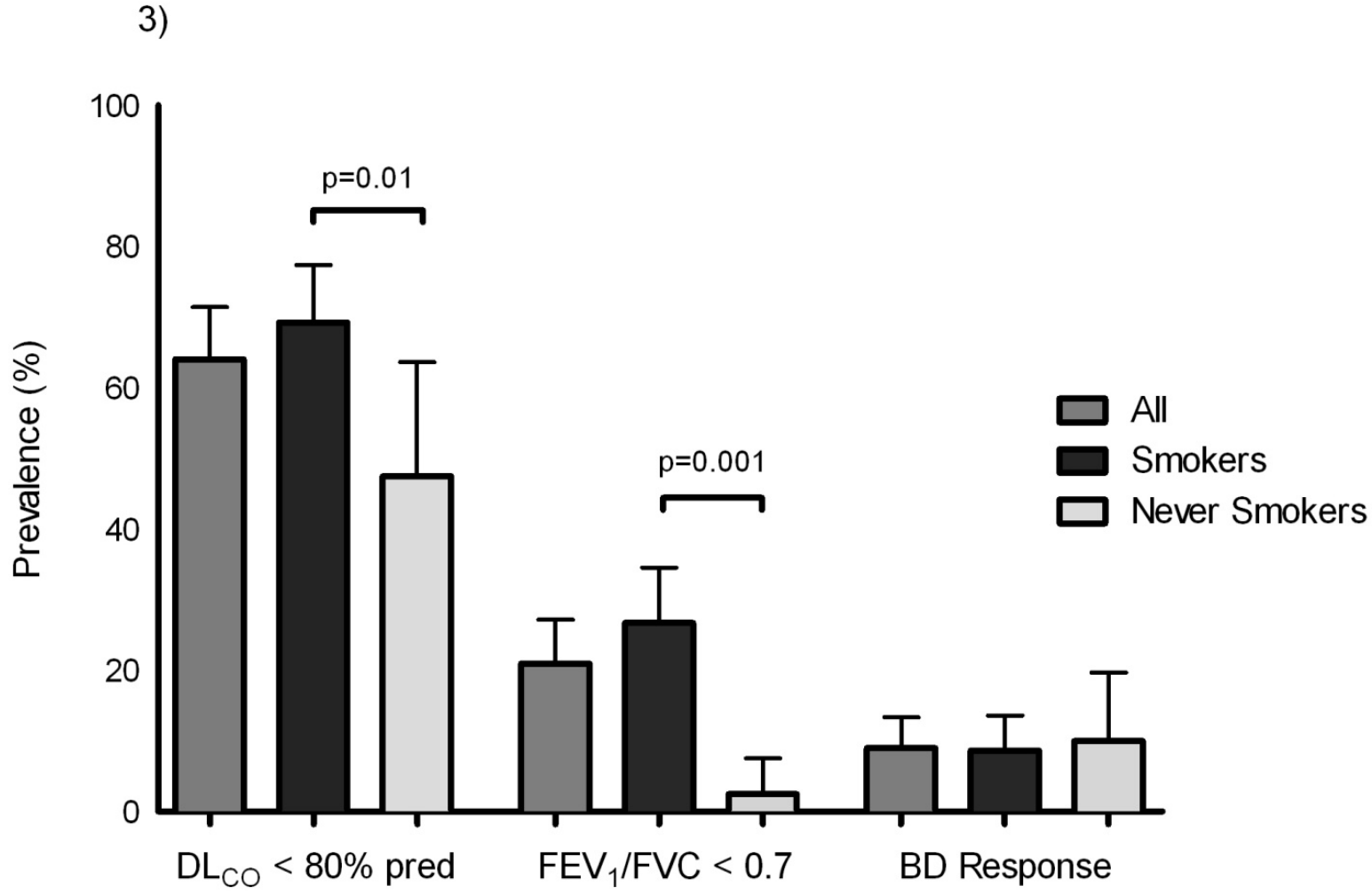


Respiratory symptoms and inhaler use common in HIV+ outpatients

Only 15% had prior PFTs

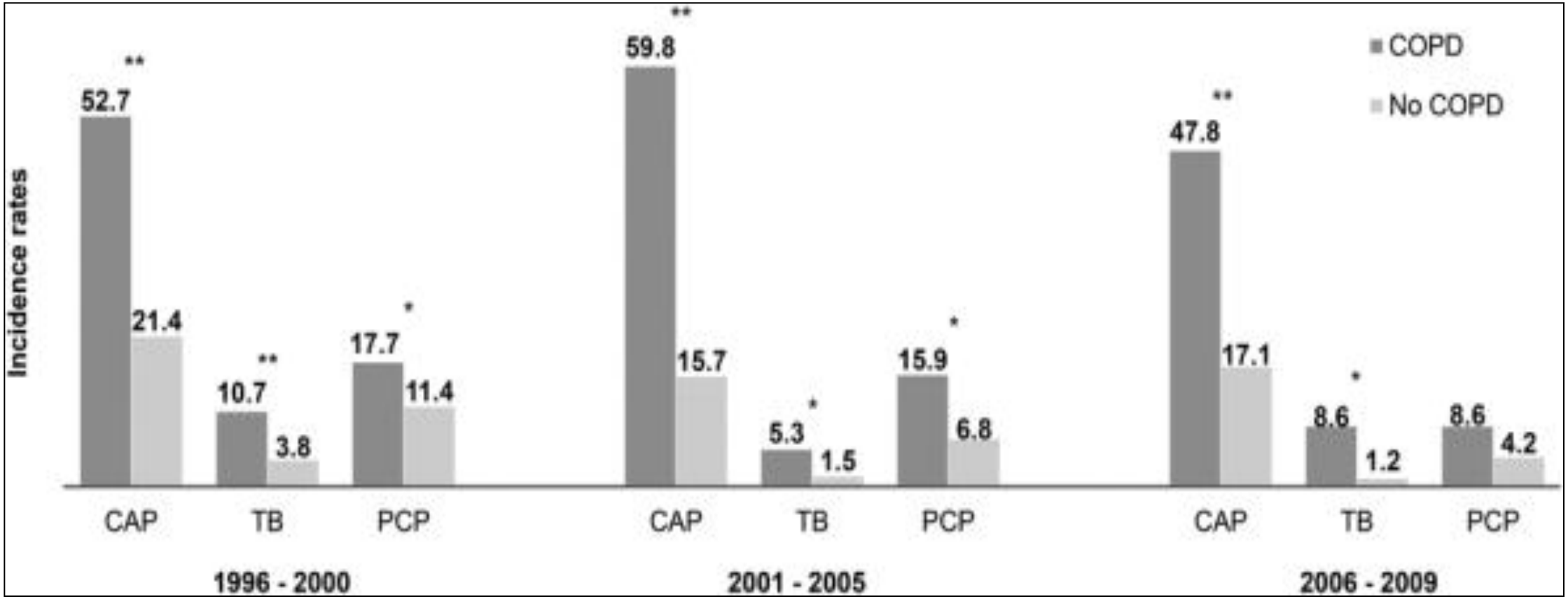
Gingo, M et al. *AJRCCM*, 2010

Pulmonary function abnormalities are common



Gingo et al. AJRCCM 2010

Increased risk of pneumonia in HIV+ COPD



CAP, TB, and PCP in all ART eras

Attia EF et al, JAIDS, 2015

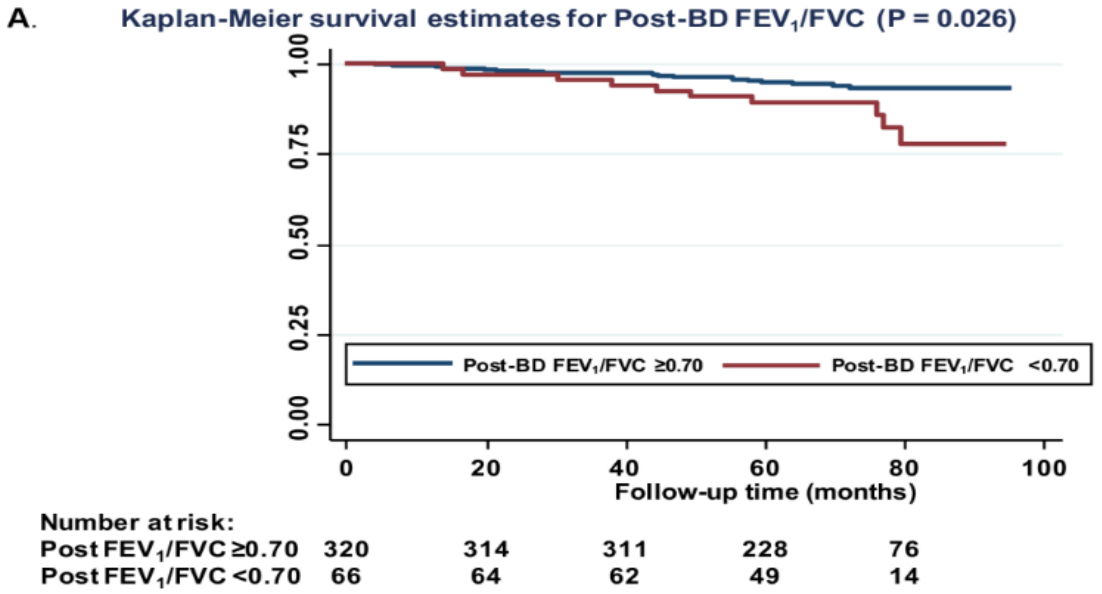
Pulmonary function independently predicts walk distance in HIV

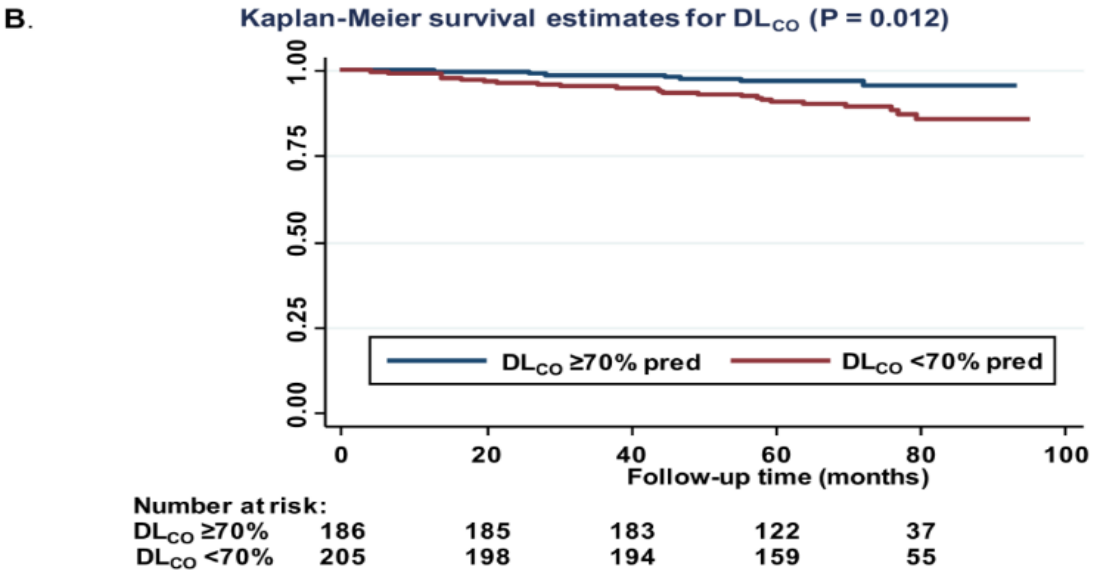
	Beta (95%CI)	P value
Caucasian	28.7 (12.1-45.4)	0.001
Weight kg	-0.9 (-1.4- -0.4)	<0.001
Height cm	1.4 (0.4- 2.3)	0.004
Pack-years	-0.9 (-1.4- -0.4)	0.001
FEV% post-BD	***0.6 (0.01- 1.1)***	***0.047***
DLco %	***0.7 (0.2-1.3)***	***0.006***
SGRQ	***-0.8 (-1.3- -0.3)***	***0.001***
IL-6 (square root)	-22.9 (-42.9- -2.9)	0.025
IL-2 (square root)	14.8 (3.9- 25.6)	0.008
Constant	207.3 (40.6-374.1)	0.012

Robertson T et al, JAIDS, in review

Survival worse in HIV+ COPD

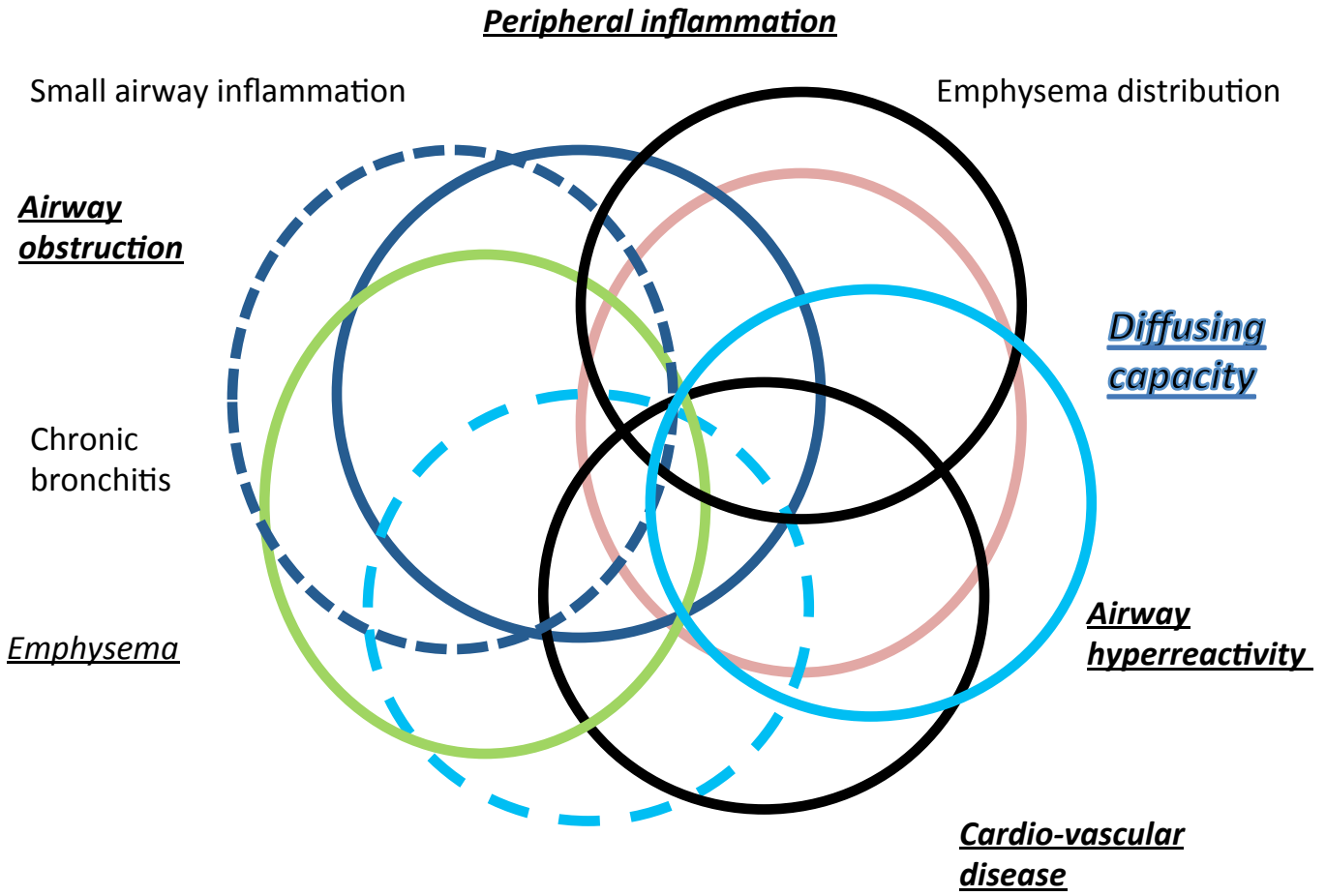
Figure: Kaplan Meier survival estimates for those with and without a post-bronchodilator (BD) forced expiratory volume at 1 second/forced vital capacity (FEV_1/FVC)<0.7 (**A**) and those with and without a single breath diffusing capacity for carbon monoxide (DL_{CO}) <70% predicted (**B**).





Gingo MR el al, Ann Am Thor Soc, 2018

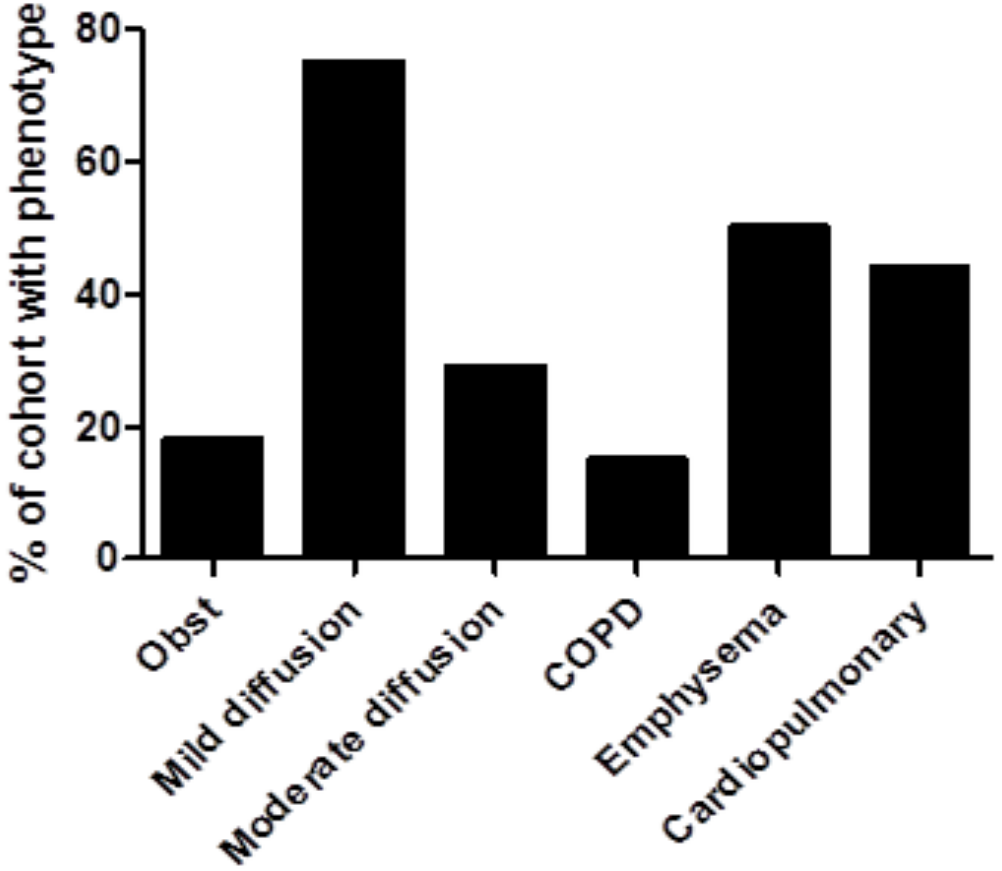
Sub-Phenotypes of COPD



Adapted from F. Sciurba

HIV phenotypes

- Emphysema
- DLco impairment
- Fixed airway obstruction/ COPD
- Asthma
- Pulmonary hypertension
- Cardio-pulmonary

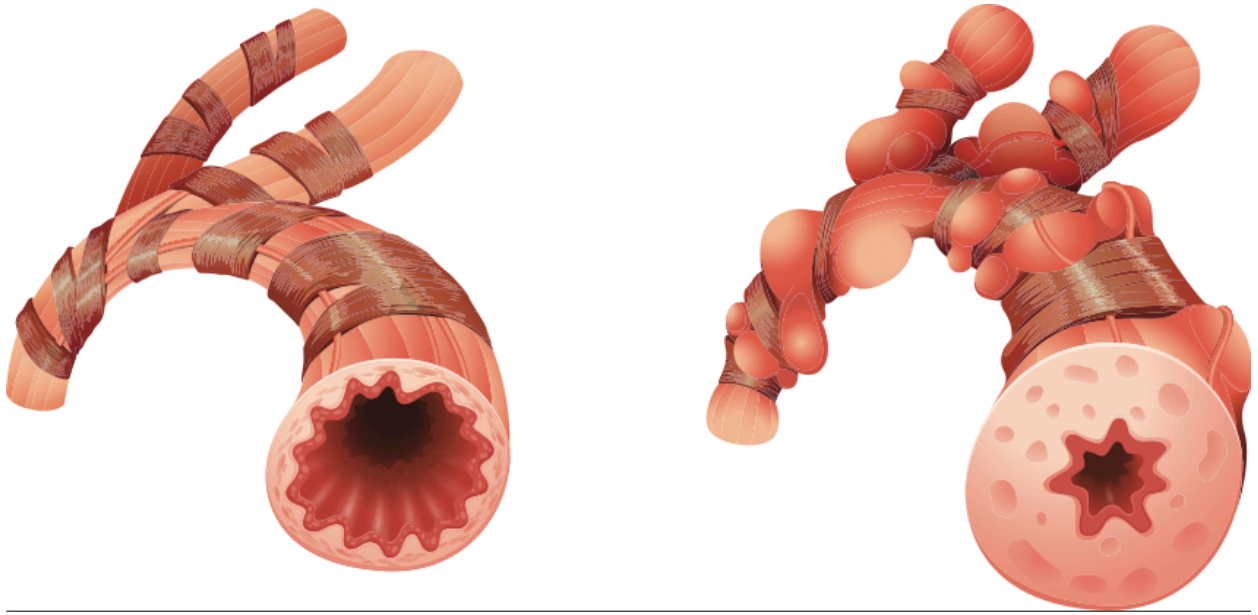


Why are phenotypes important?

- Functional consequences
- Different pathways and biomarkers
- Different response to treatment

Airway obstruction

- Several definitions
- FEV1/FVC<70%, FEV1< 80% predicted
- Below LLN
- Primarily in smokers



Airway obstruction risk factors

- Age
- Pack-year smoking
- Intravenous drug use
- ART
- History of bacterial pneumonia or use of PCP prophylaxis

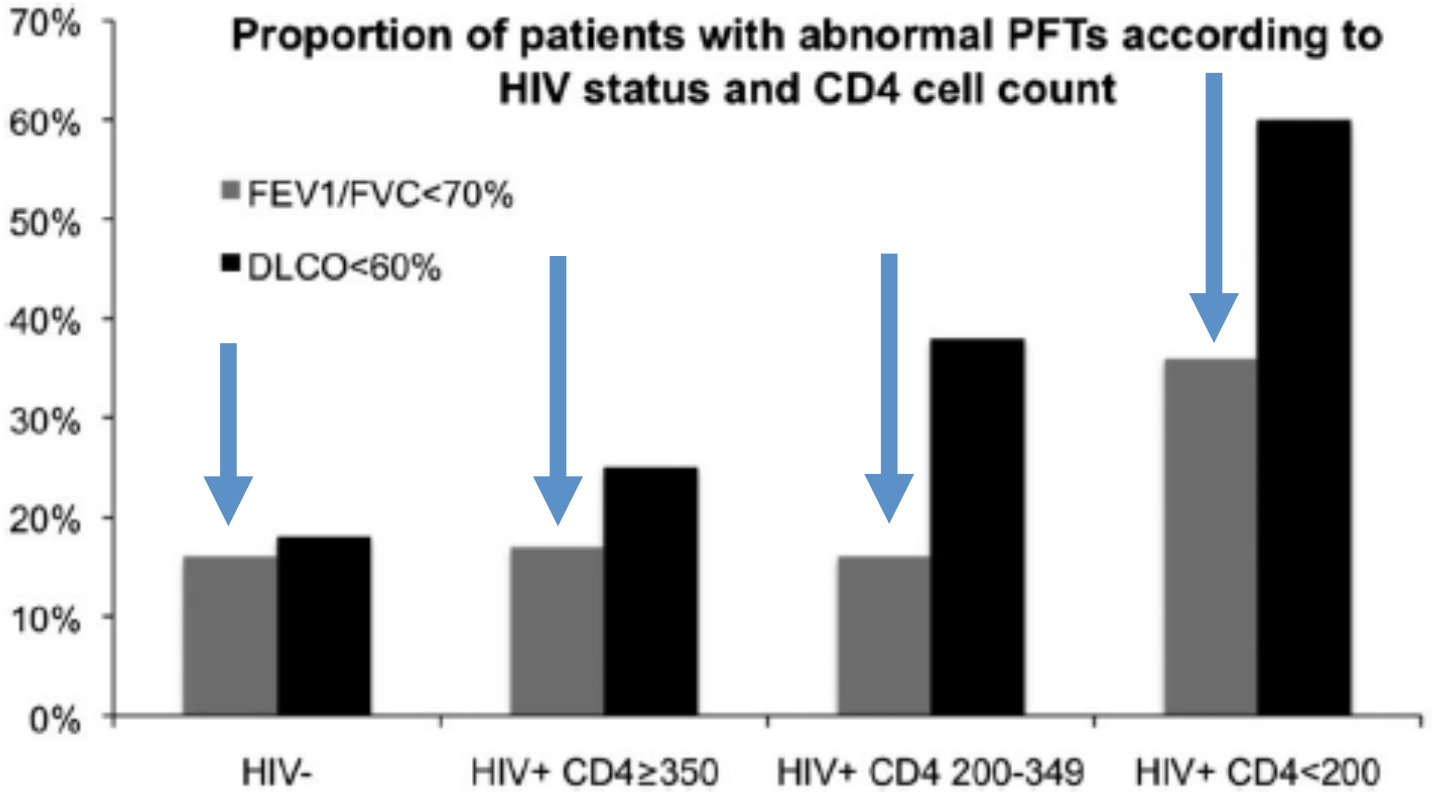
George MP et al, PLoS One, 2009; Gingo et al. AJRCCM 2010

Lung HIV predictors of airway obstruction

- Age: OR 1.75 (p<0.001)
- Current smoking: OR 1.77 (p=0.004)
- >20 pack-years: OR 1.68 (p=0.003)
- History of asthma: OR 1.81 (p=0.005)
- History of *Pneumocystis:* OR 1.97 (p=0.005)

Drummond MB, et al. JAIDS, 2015

Airway obstruction increases by lower CD4 in MACS/VACS

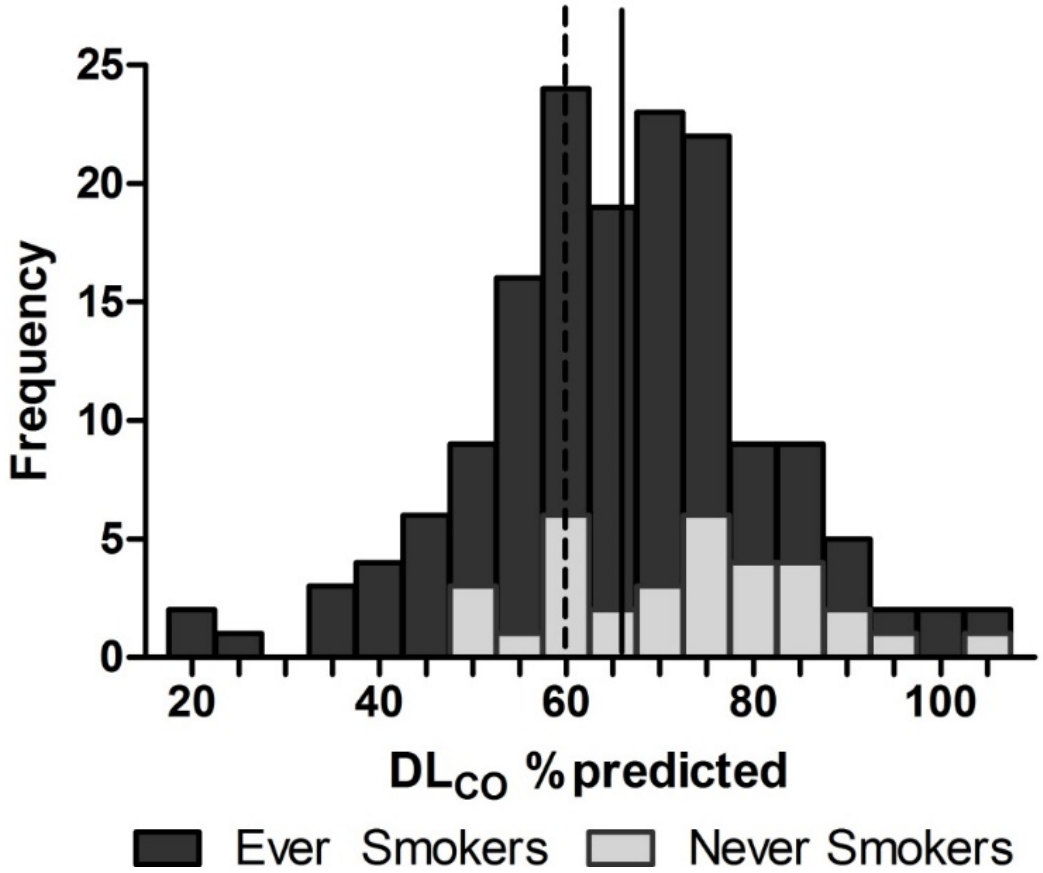


Crothers K et al, *JAIDS*, 2013

Diffusing capacity

- Measures multiple aspects of lung and cardiac function
- Noted to be low in HIV in pre-ART era
- Important phenotype in HIV
- *Persists in ART era*

DLco is abnormal in majority of HIV+ individuals



-85% of cohort have DLco<80% predicted
-35% are below 60% predicted
-24% of never smokers are below 60% predicted

Gingo M et al, *Eur Resp J*, 2014

Different risk factors for DLco in smokers and never smokers

Multivariable regression models showing independent associations for DL_{CO} % predicted in ever smokers and never smokers.

	Ever Smokers*		**Never Smokers**	
	β-coefficient	p-value	β-coefficient	p-value
Post-FEV_1 % predicted	0.3940	<0.001		
Post-BD FVC % predicted			0.3323	0.02
Log Fraction <-950 HU	-0.0423	0.001		
Sputum % Neutrophils			-0.1967	0.03
Sputum % Lymphocyte (square root)			0.9407	0.009

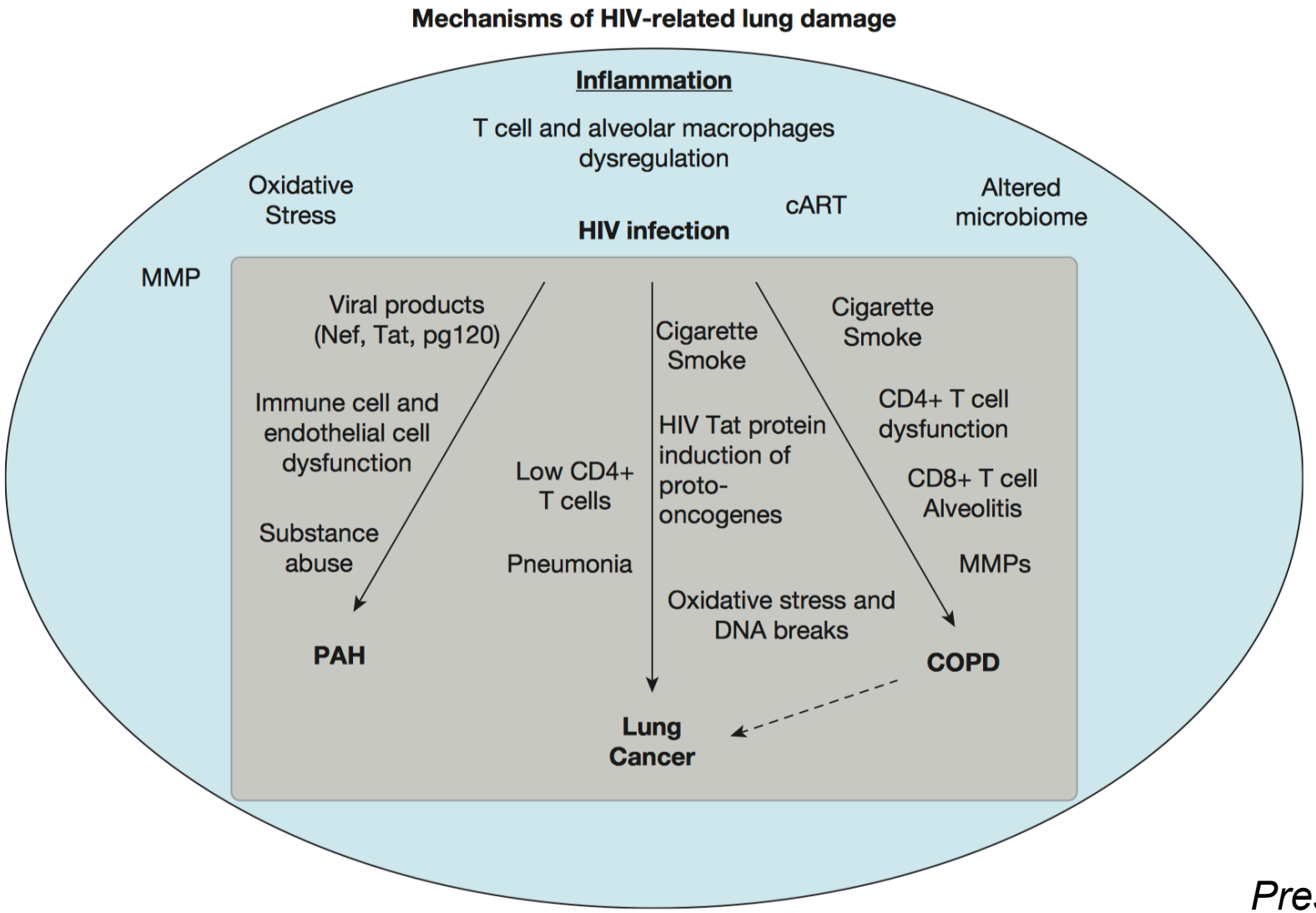
Gingo M et al, *Eur Resp J*, 2014

Clinical risk factors and DLco

- Smoking
- CD4 cell count<200
- HIV viral load >500 copies
- Hepatitis C co-infection

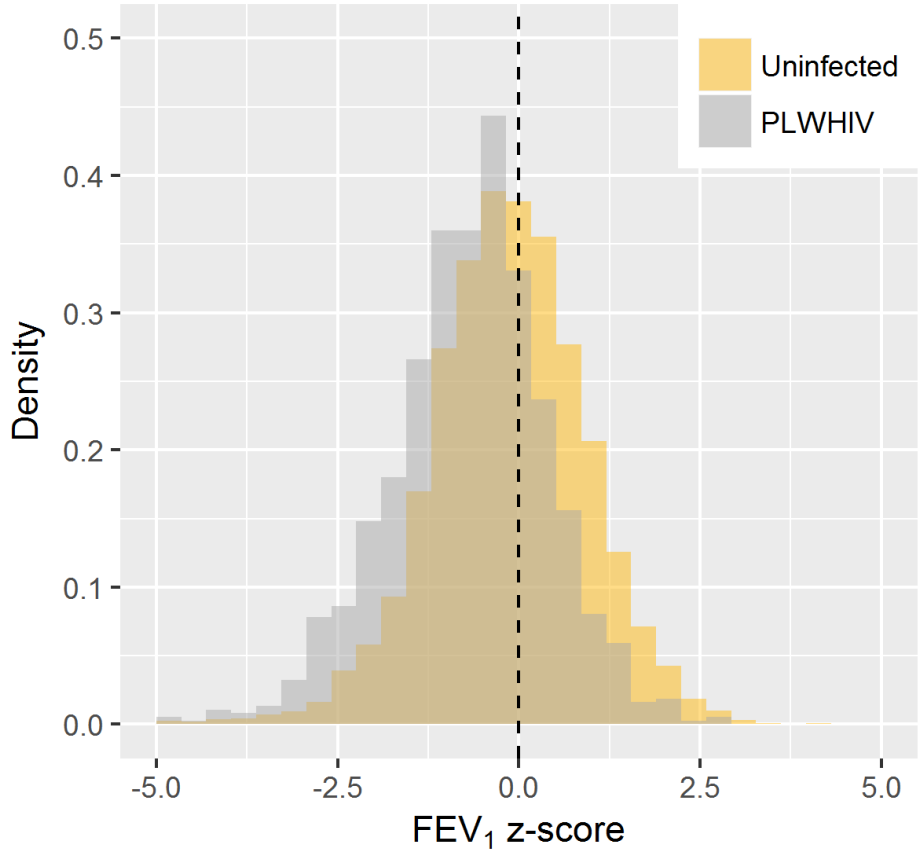
Crothers K et al, *JAIDS*, 2013; Fitzpatrick M, Gingo M et al, *JAIDS*, 2013

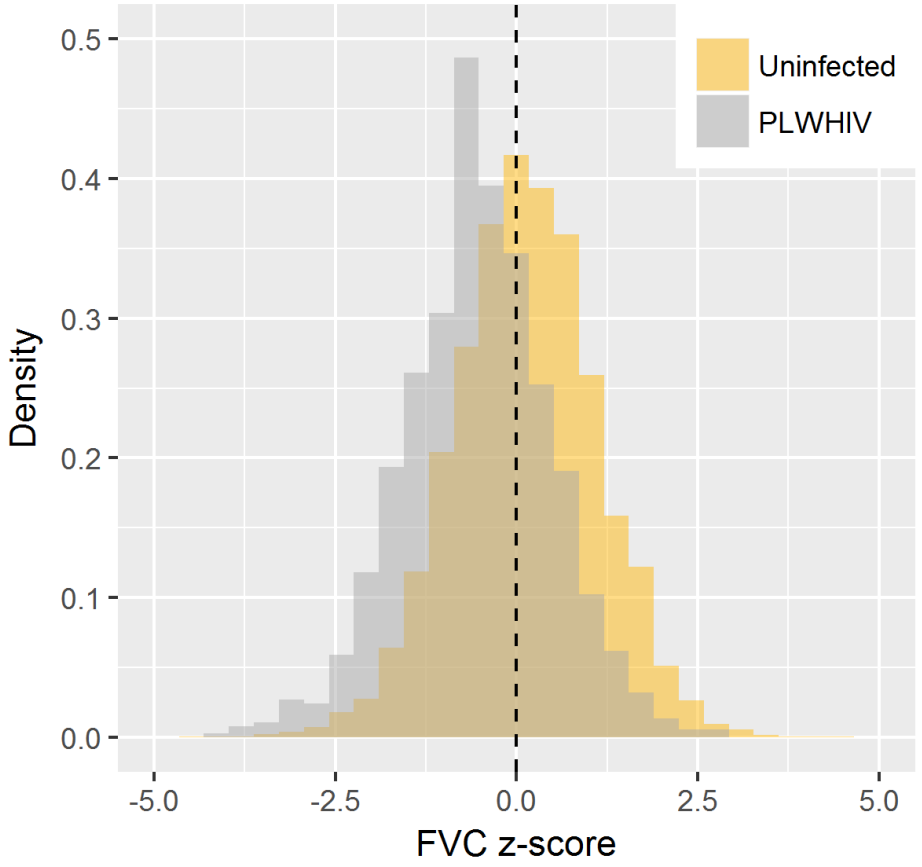
Does HIV contribute to these phenotypes?



Presti RM et al. Chest 2017

HIV associated with lower pre-BD FEV1 although no difference in COPD

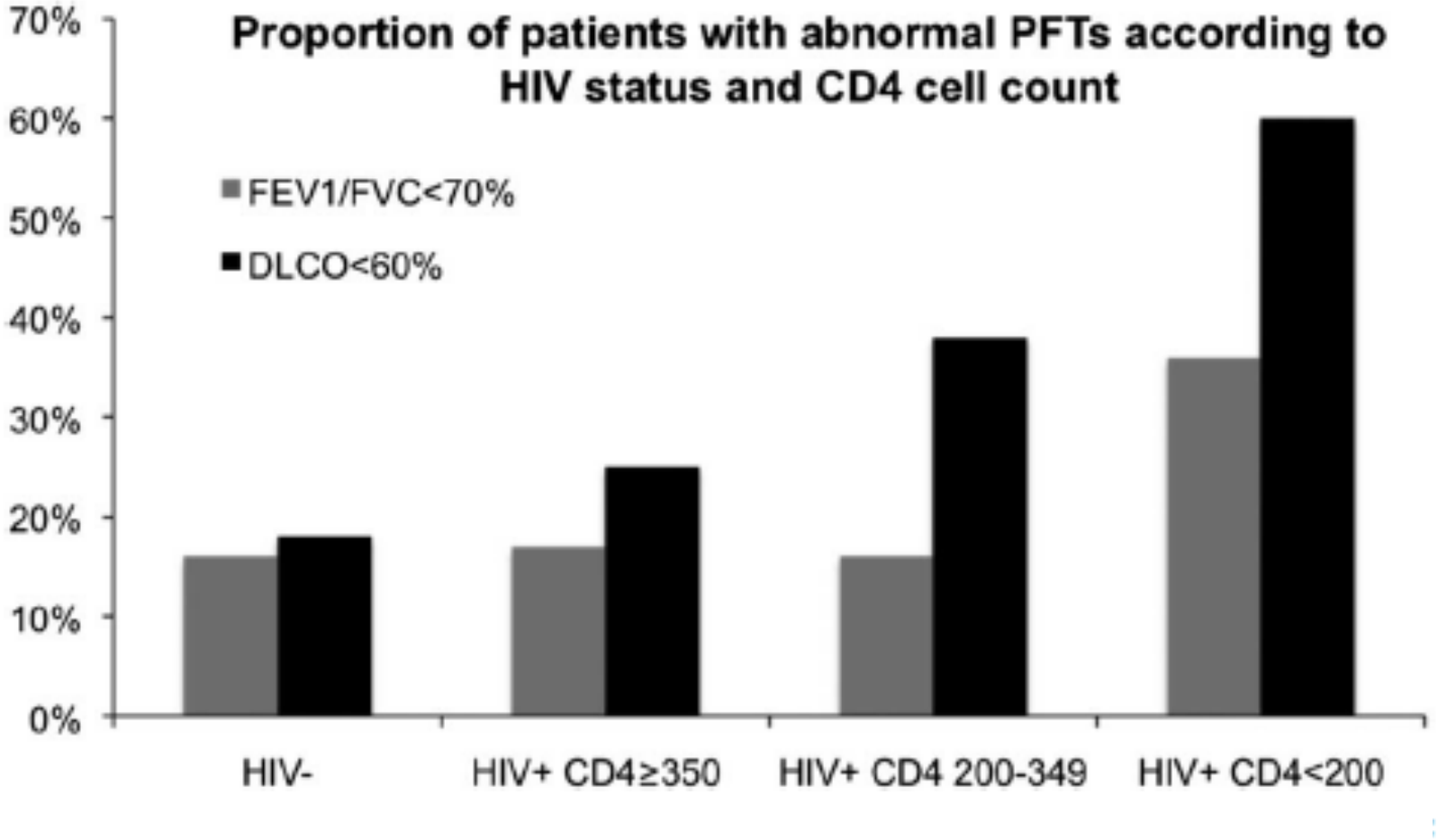




HIV independent predictor of lower FEV1 and FVC in ALIVE cohort

Drummond MB et al, AIDS, 2013; Ronit A et al, Thorax, 2018

No difference in obstruction by HIV status if preserved CD4 count



Crothers K et al, *JAIDS*, 2013

HIV is independent predictor of DLco in MACS/VACS

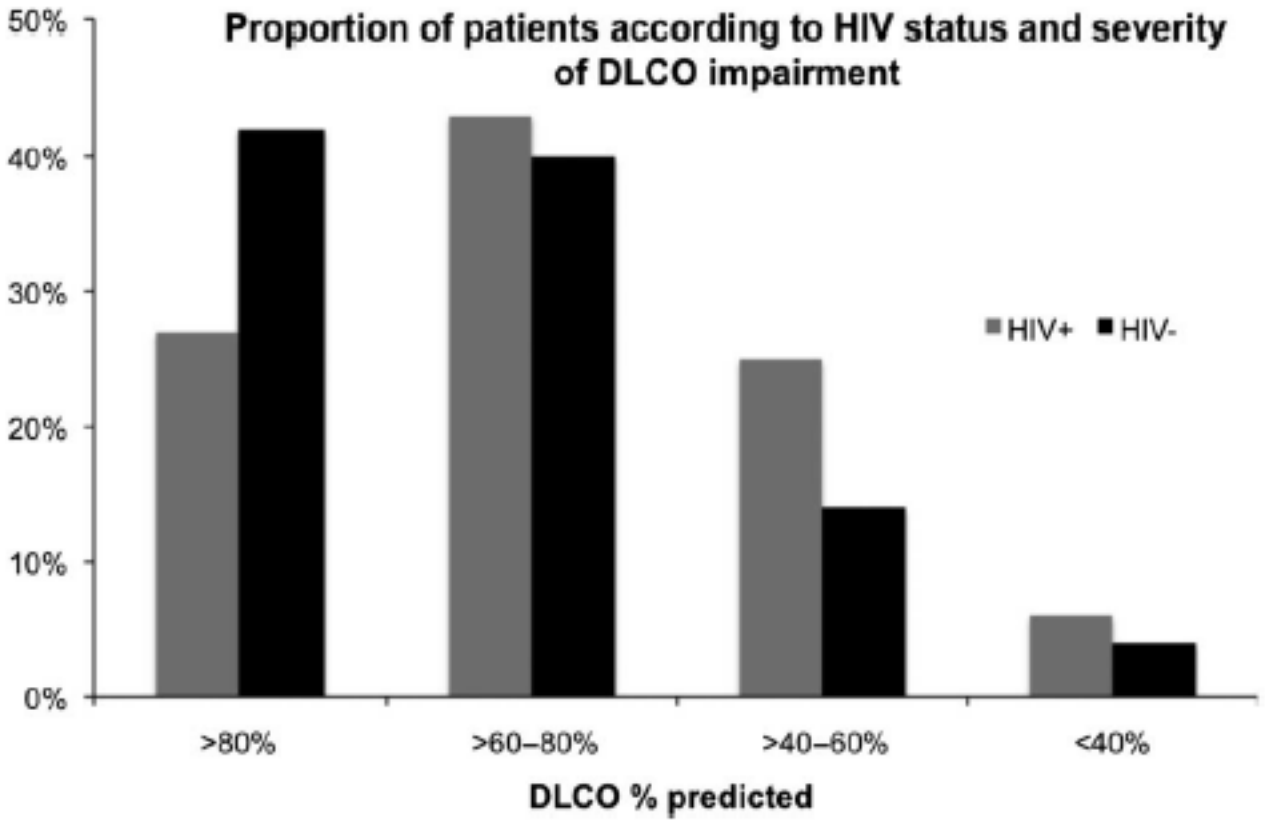
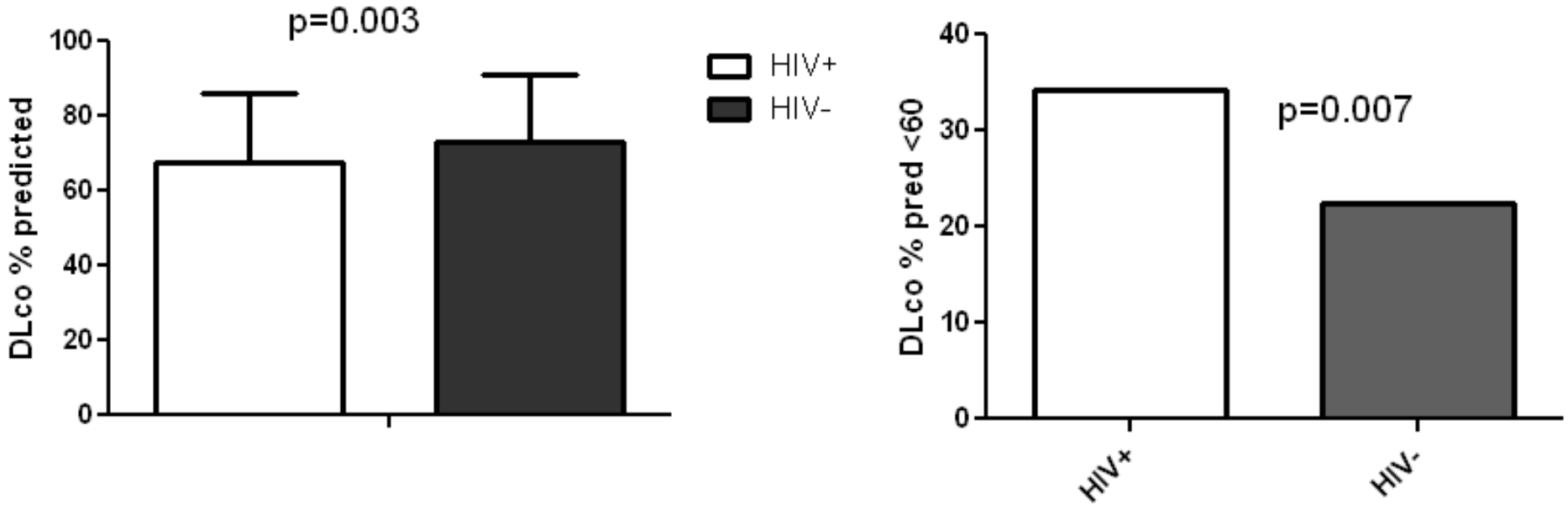


FIGURE 2. Depicts the distribution of severity of DLCO impairment by HIV status.

Effect seen in smokers and non-smokers, high and low CD4 although worse in risk groups

Crothers K et al, *JAIDS*, 2013

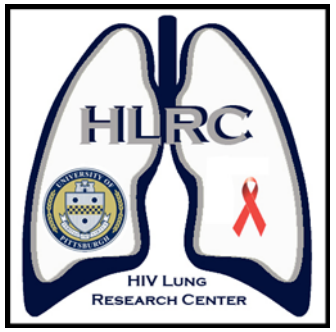
DLco lower in HIV+ women and more have moderately reduced DLco (<60%)



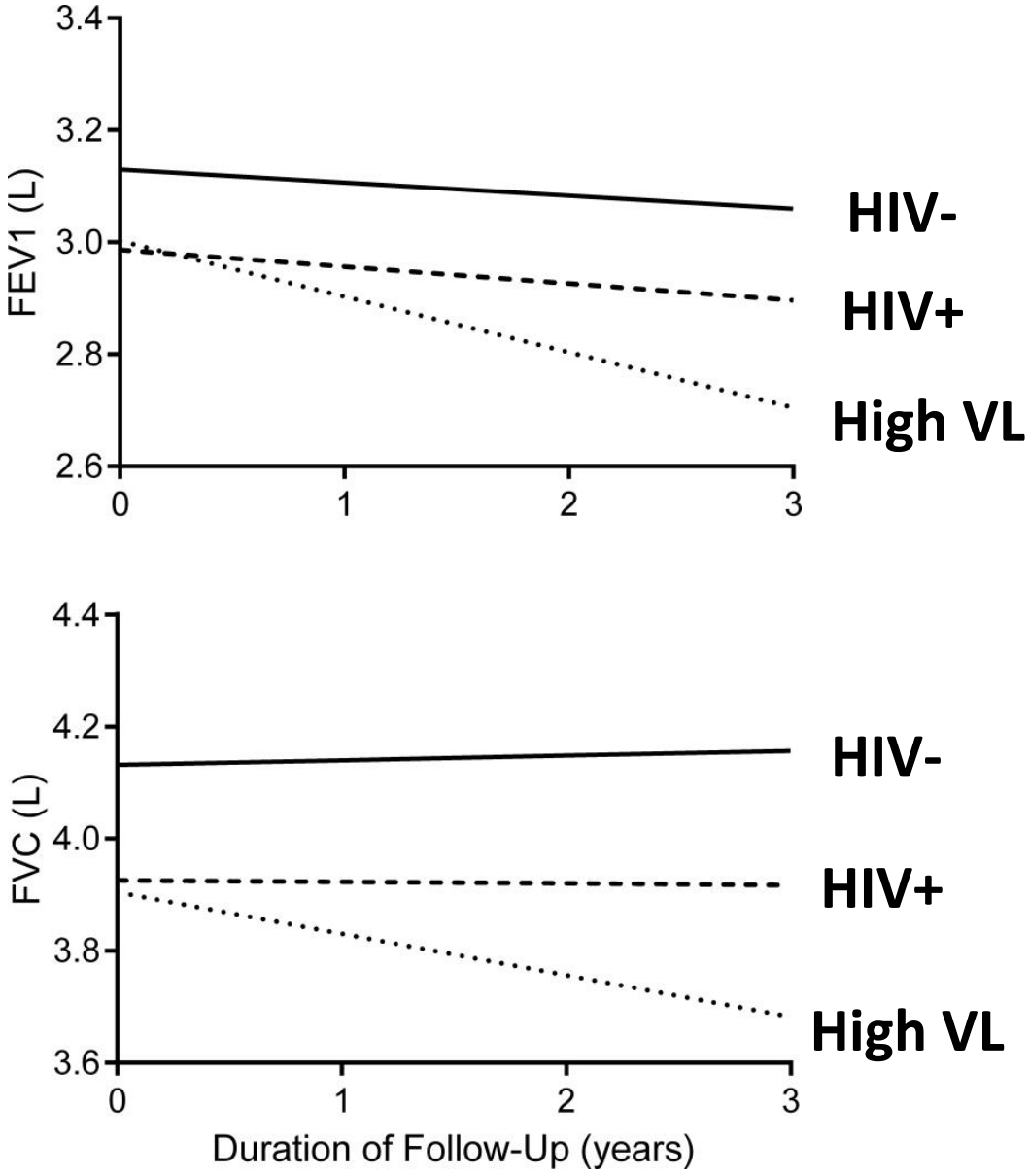
Fitzpatrick M, Gingo M et al, *JAIDS*, 2013

Progression of pulmonary deficits in HIV

- 285 HIV+ individuals
- Median follow-up 6.3 years
- FEV1 declined 1%/62 ml per year
  - Older age, GOLD stage predicted decline
  - Female sex protective
- Rapid FEV1 decline
  - Age, marijuana
  - Female sex protective
- No decline in DLco
  - Smoking, history of pneumonia predicted decline
- No relationship to HIV-associated variables



Li Y et al, JAIDS, in press



HIV not an independent predictor of decline except in those with viral load >75,000

Drummond MB et al, AIDS 2013

Slow progression in HIV in START study

- 1,026 participants
- No impact of early or delayed ART on lung function
- FEV1 -24 to -29 ml per year
- Smokers had faster average FEV1 decline
  - -38.3 mL/yr vs -25.1 mL/yr
  - More likely to be rapid decliners

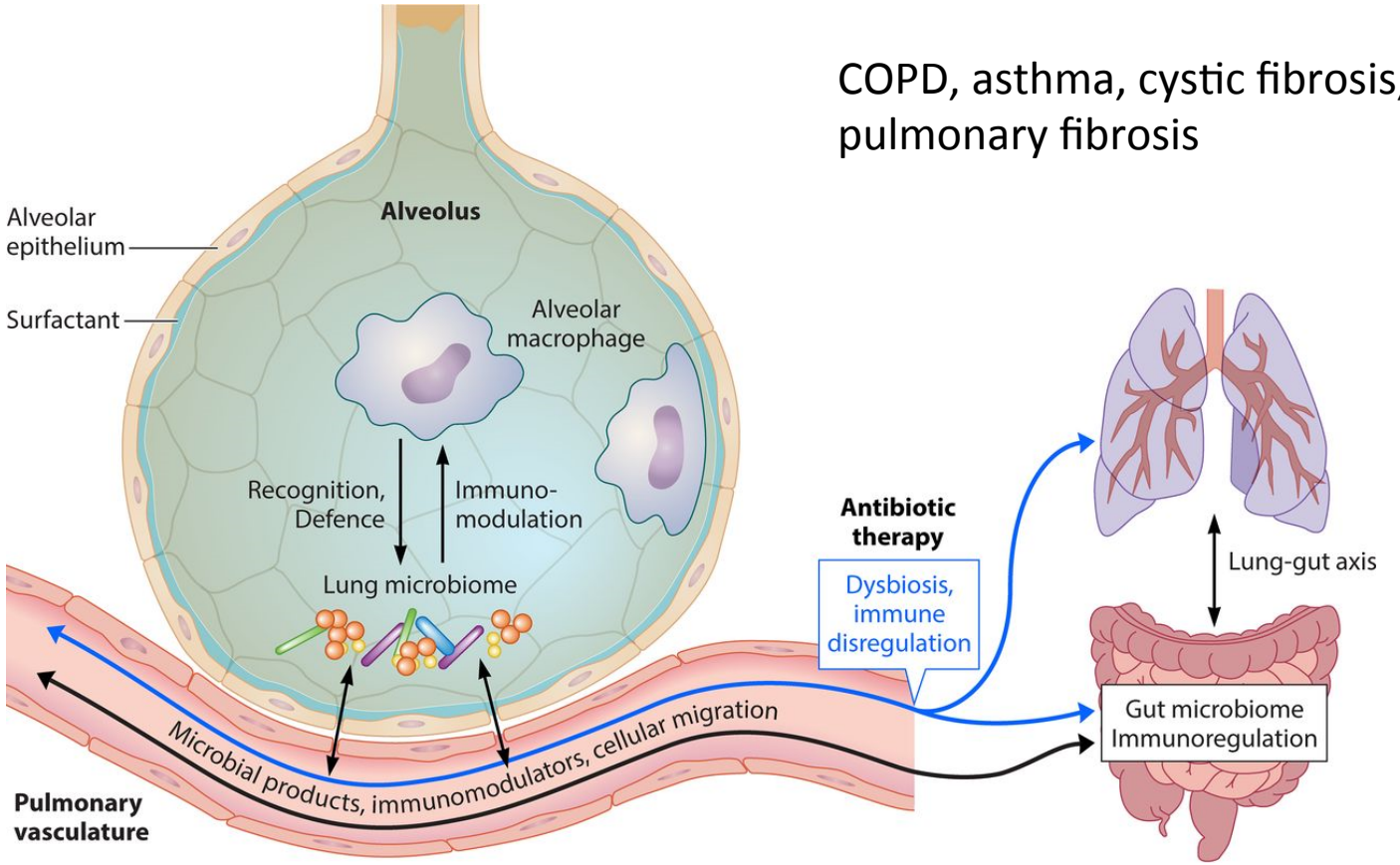
Kunisaki K et al, Lancet Resp Med, 2017;
McDonald DM et al, JAIDS, 2018

Biomarkers suggest potential pathways

Lung measure	Circulating soluble and HIV-related markers
Decreased airflow (low FEV1)	• Inflammation (IL-6, CRP) • Monocyte activation (sCD163) • Endothelial dysfunction (endothelin-1) • Shortened PBMC telomere length
Decreased airflow (low FVC)	• Inflammation (IL-6, CRP) • Monocyte activation (sCD163)
Airflow obstruction (decreased FEV1/FVC)	• Monocyte activation (sCD163)
Impaired gas exchange (low DLCO)	• Inflammation (IL-6, TNFα, CRP) • Monocyte activation (sCD163, sCD14, IL-2 receptor) • Microbial translocation (LPS) • Endothelial activation (endothelin-1)
Emphysema (by CT scan)	• Monocyte activation (sCD14) • Shortened PBMC telomere length

Cribbs S et al, Phys Rev, in press

Lung microbiome has local and systemic effects



COPD, asthma, cystic fibrosis, pulmonary fibrosis

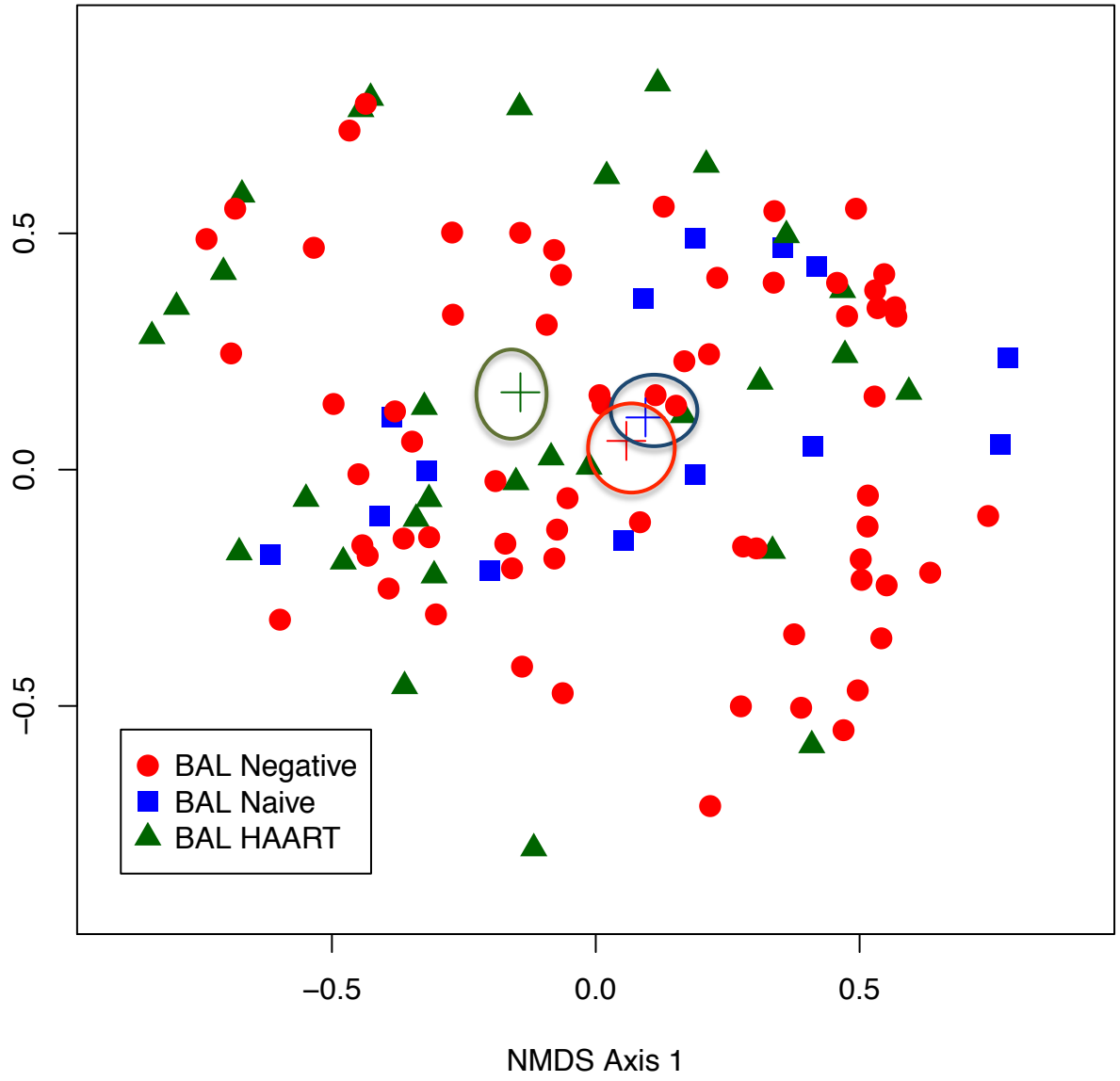
Lung HIV Microbiome Project

- 6 clinical sites and data coordinating center
- Focus on normal lung (non-smokers and smokers) and HIV
- Bronchoscopy with 16S rRNA analyses

National Heart Lung and Blood Institute
People Science Health

Lung HIV Microbiome Project

No significant difference by HIV status in lung bacterial communities

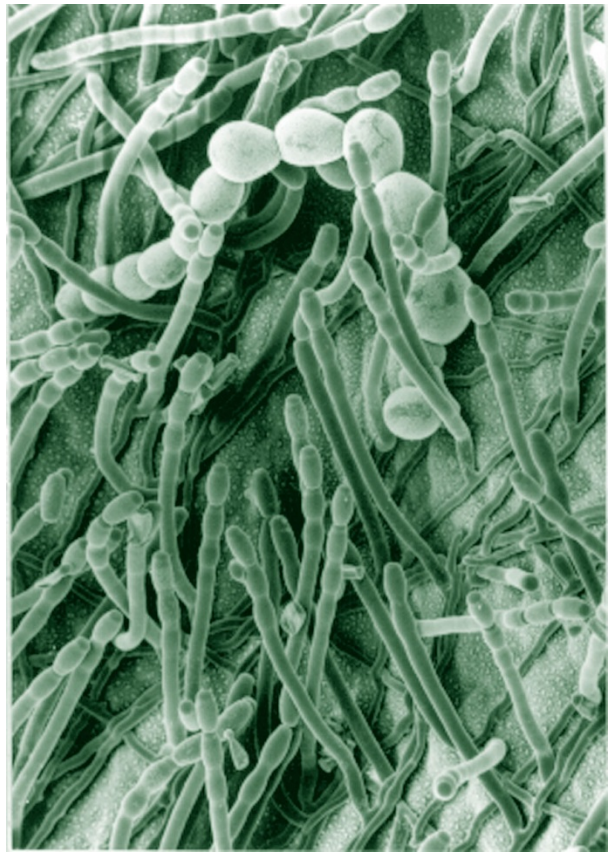


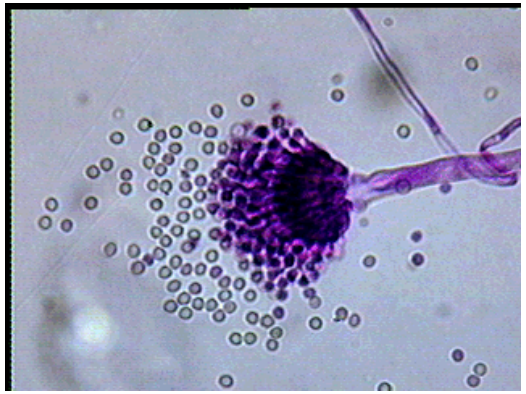
Beck J et al, AJRCCM, 2015

Why do we not see differences?

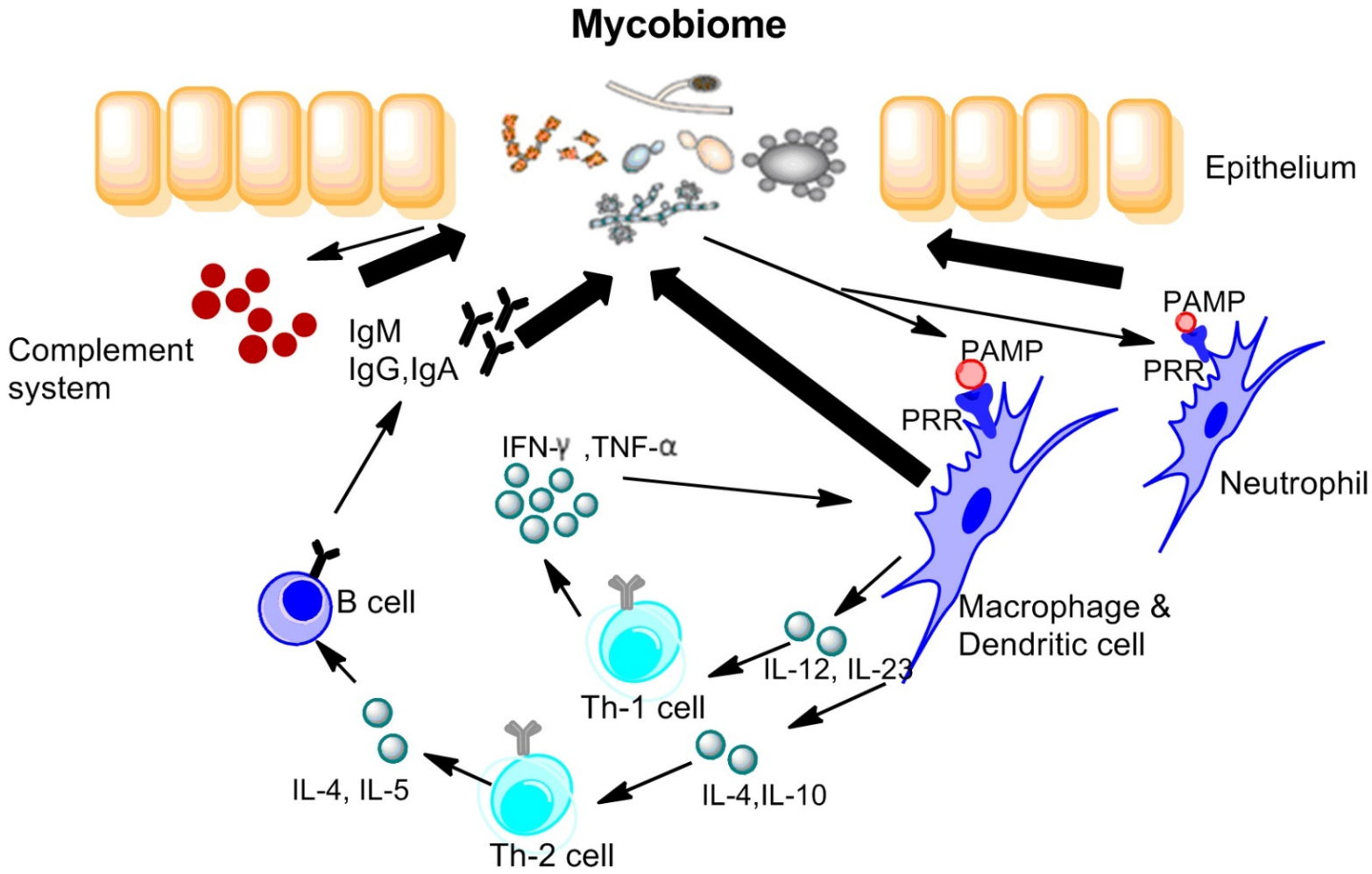
- Wrong populations
- Difficulty with detecting bacteria in BAL
- Longitudinal studies may be needed
- Taxonomy less important: metabolites or gene function
- Other sites may influence lung function
- Need to look at all organisms

What about fungus (mycobiome)?





Mycobiome likely shapes the immune response



-Lung could be affected by local mycobiome, GI tract mycobiome, or translocation of fungus

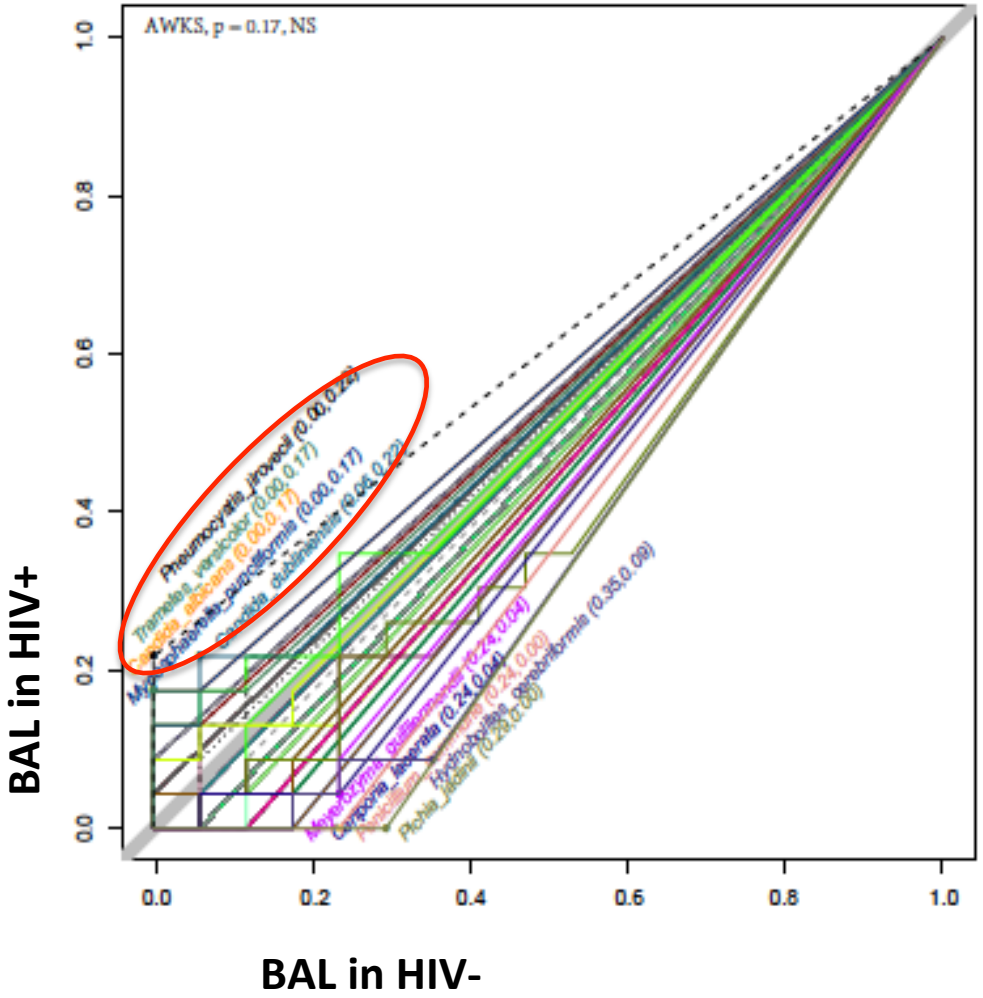
Cui L, et al. Genome Medicine, 2013

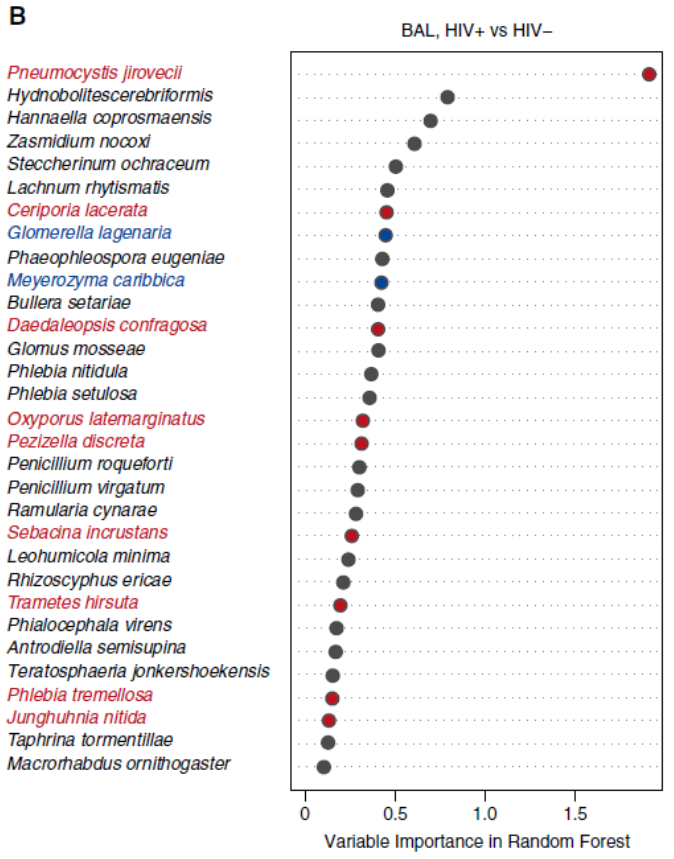
Lung HIV Mycobiome Study

- 56 HIV+ and HIV- individuals from Lung HIV Microbiome Program
- Oral wash (OW), induced sputum (IS) and bronchoalveolar lavage (BAL), environmental controls
- Analyzed by sample type, HIV status, and lung function

Courtesy of L. Cui

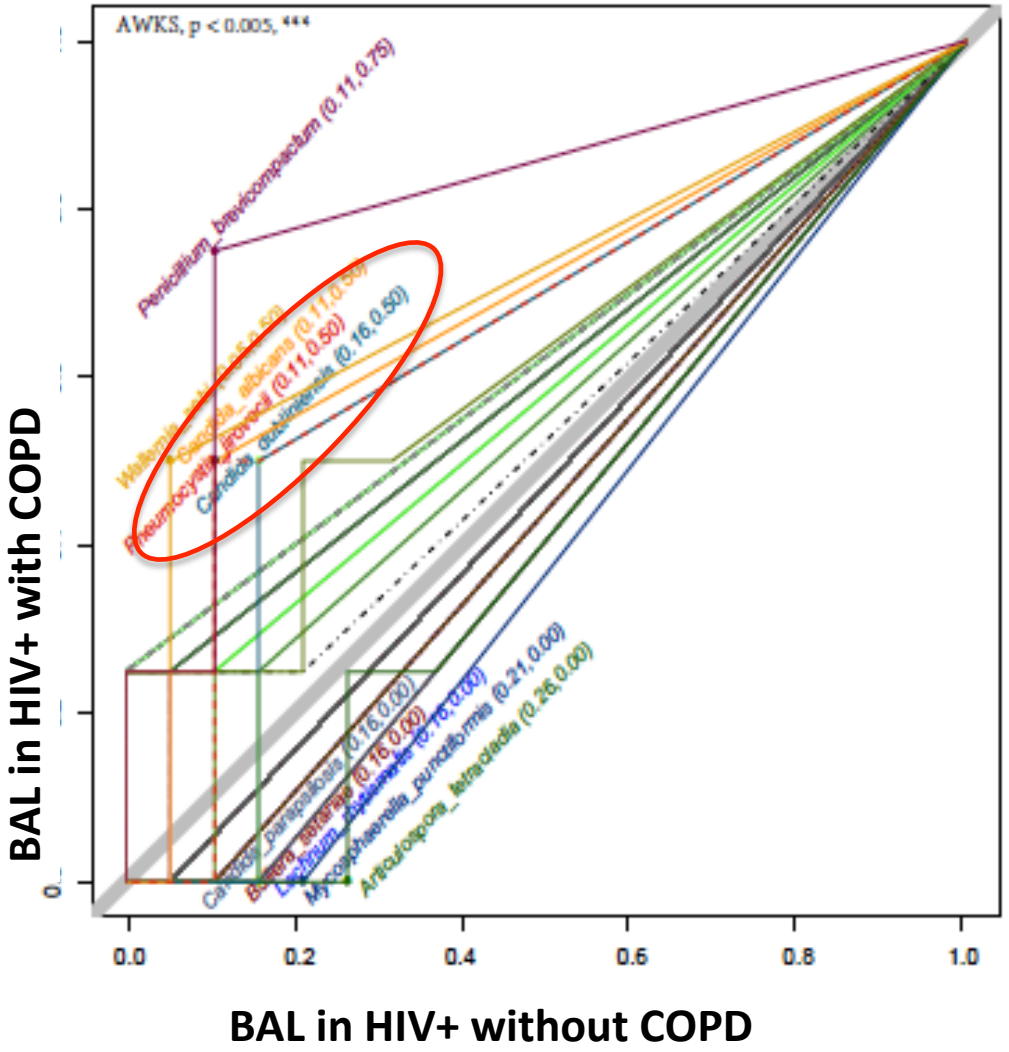
HIV+ and HIV- differ in communities: Primarily *Pneumocystis*

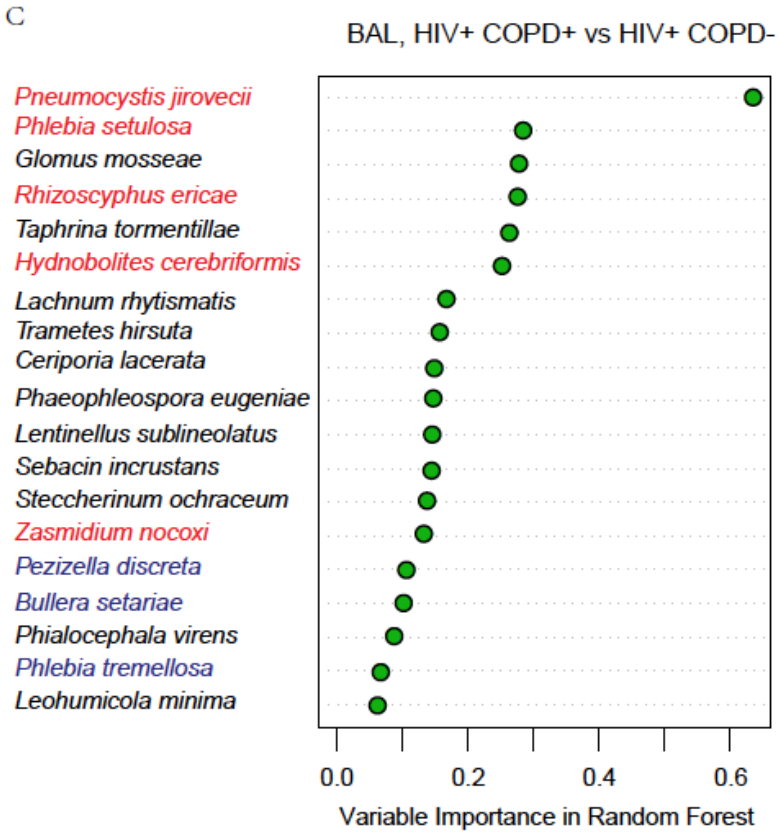




Cui L et al, AJRCCM, 2015

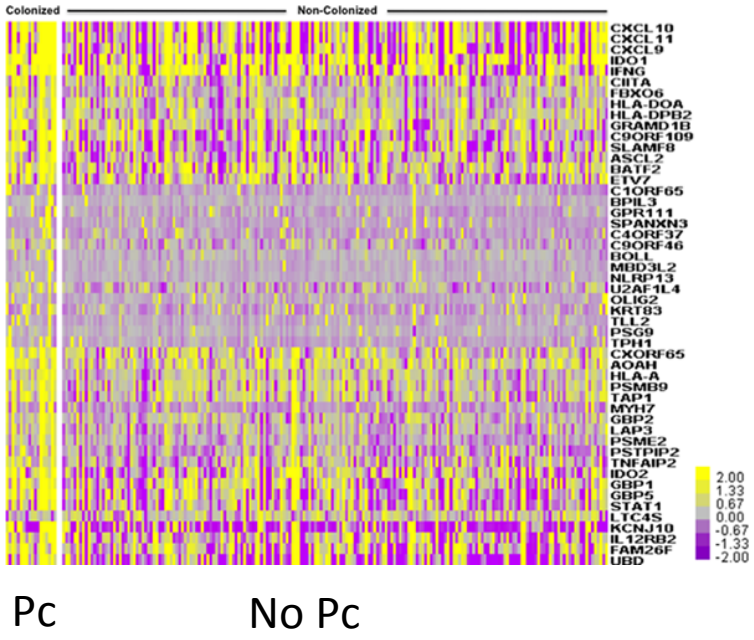
Fungal microbiome in HIV COPD: Primarily *Pneumocystis*

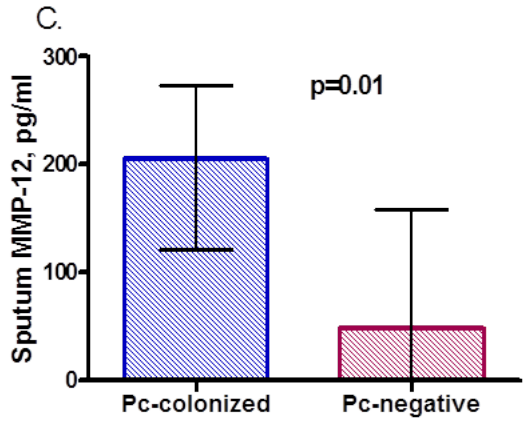




Cui L et al, AJRCCM, 2015

Host response to *Pneumocystis jirovecii* colonization: Th1 inflammatory gene expression, increases in MMP-12, and IL-6





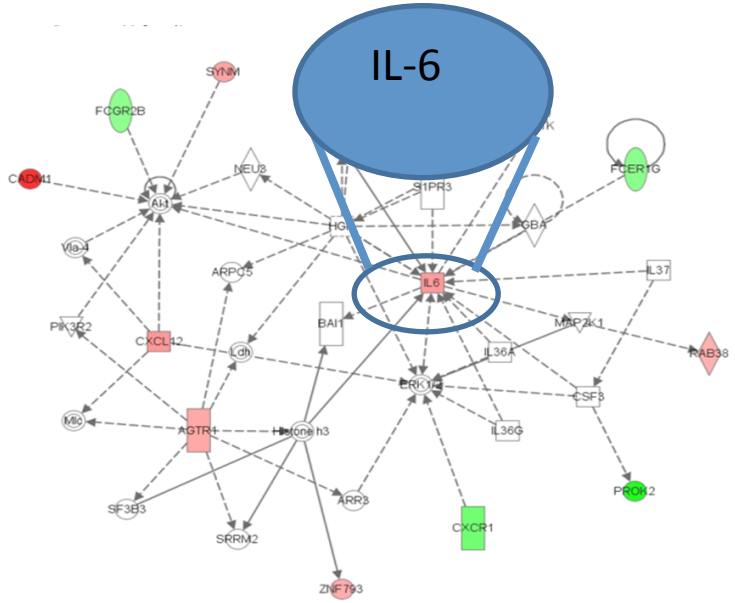
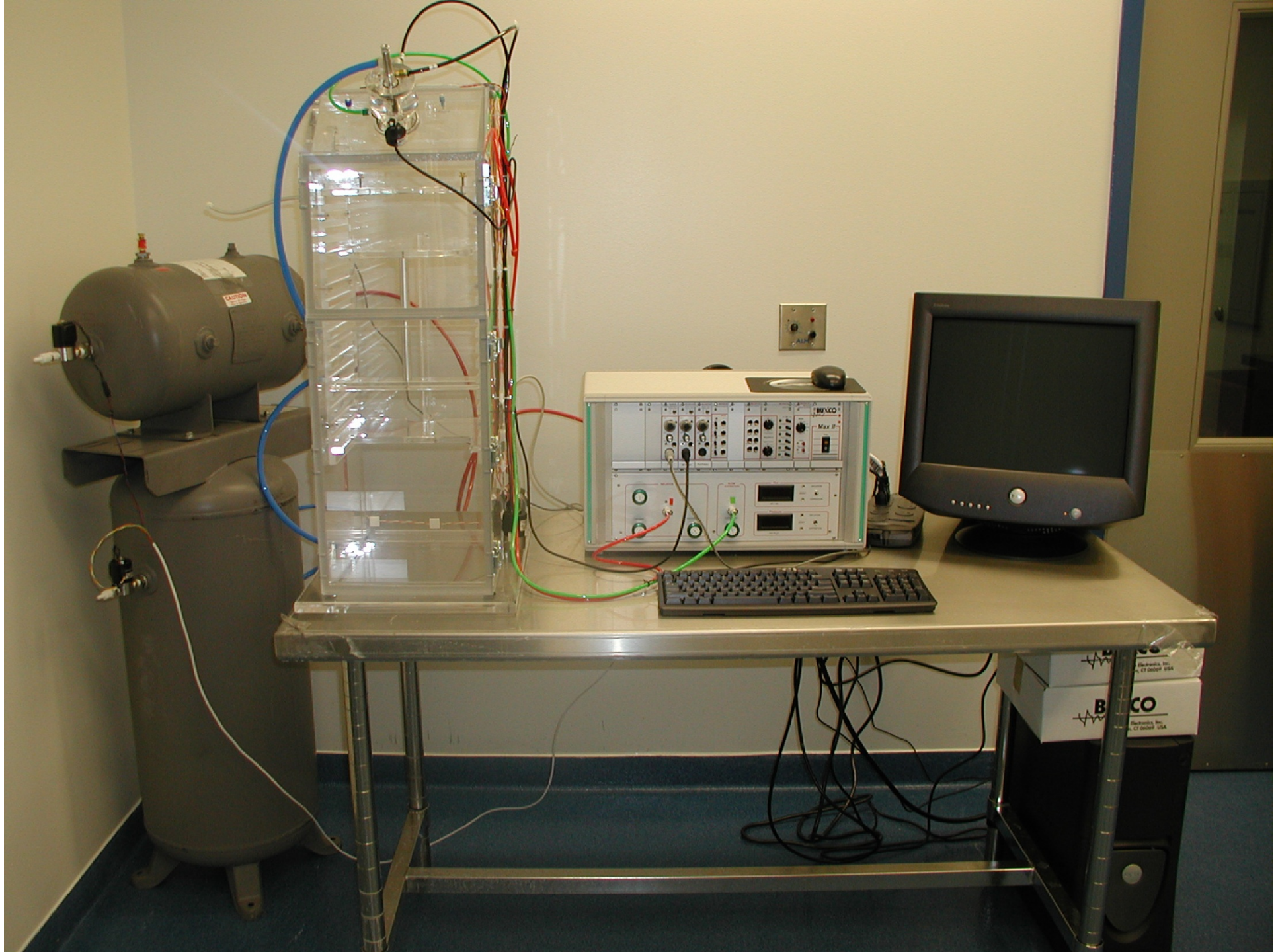


Table 3. Genes differentially expressed between *Pneumocystis*-colonized and non-colonized participants

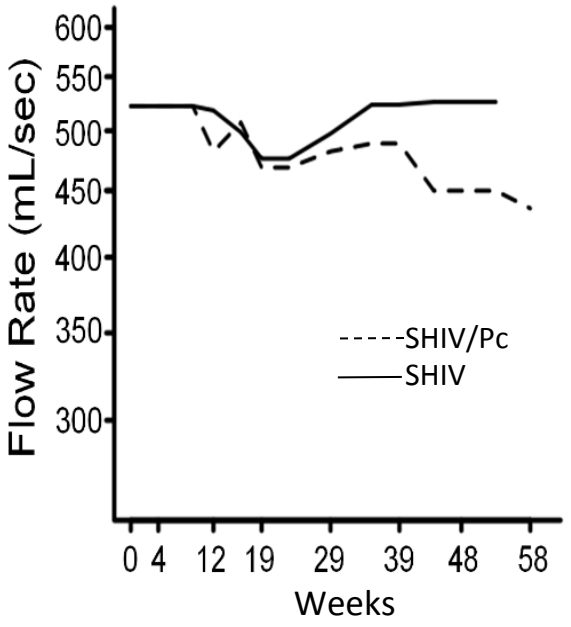
Human gene	Human gene name	FDR	Fold ratio
CXCL9	Chemokine (C-X-C motif) ligand 9	0.00153	3.204959
CXCL10	Chemokine (C-X-C motif) ligand 10	0.00992	3.079771
CXCL11	Chemokine (C-X-C motif) ligand 11	0.0193	2.931513
INF-γ	Gamma interferon	0.0275	2.478151
UBD	Ubiquitin D	0.0487	2.292343
KCNJ10	Potassium inwardly-rectifying channel, subfamily J, Member 10	0.0487	2.257885
IDO1	Indolamine 2,3-dioxygenase 1	0.0487	2.231945
GBP5	Guanylate binding protein 5	0.0487	2.038483
FAM26F	Family with sequence similarity 26, member F	0.0487	1.976551

Genes displayed fell within the criterion of a FDR threshold ≤0.05. Genes are ranked by fold change.

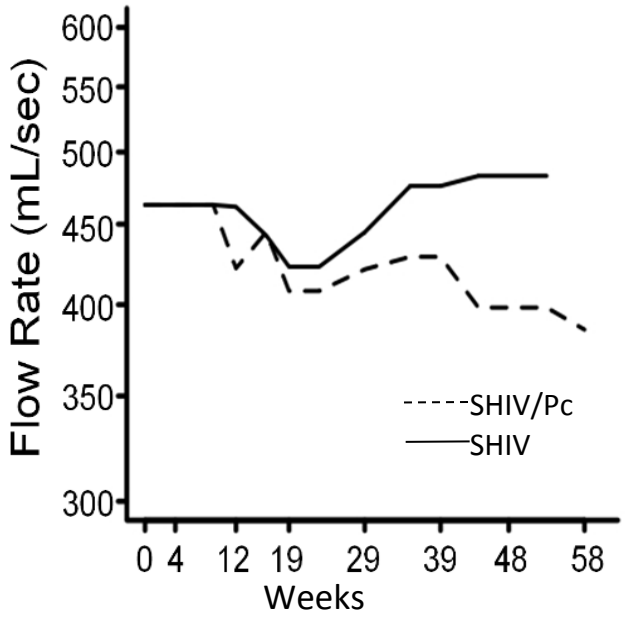
Fitzpatrick M et al, Microbiology and Immunology, 2014; Morris et al., J Clin Micro, 2010


CAUTION
BIOPAC
Max II
BIOPAC

Airway obstruction increases in Pc-colonized monkeys, but not in SHIV infection alone



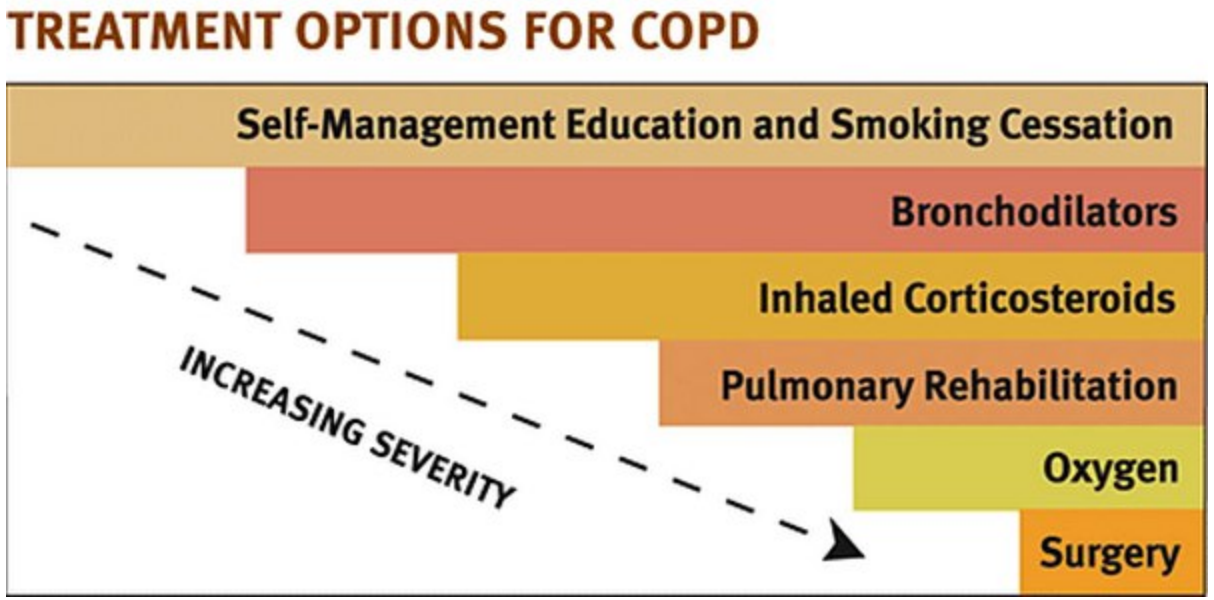
Peak expiratory flow



FEV 0.4

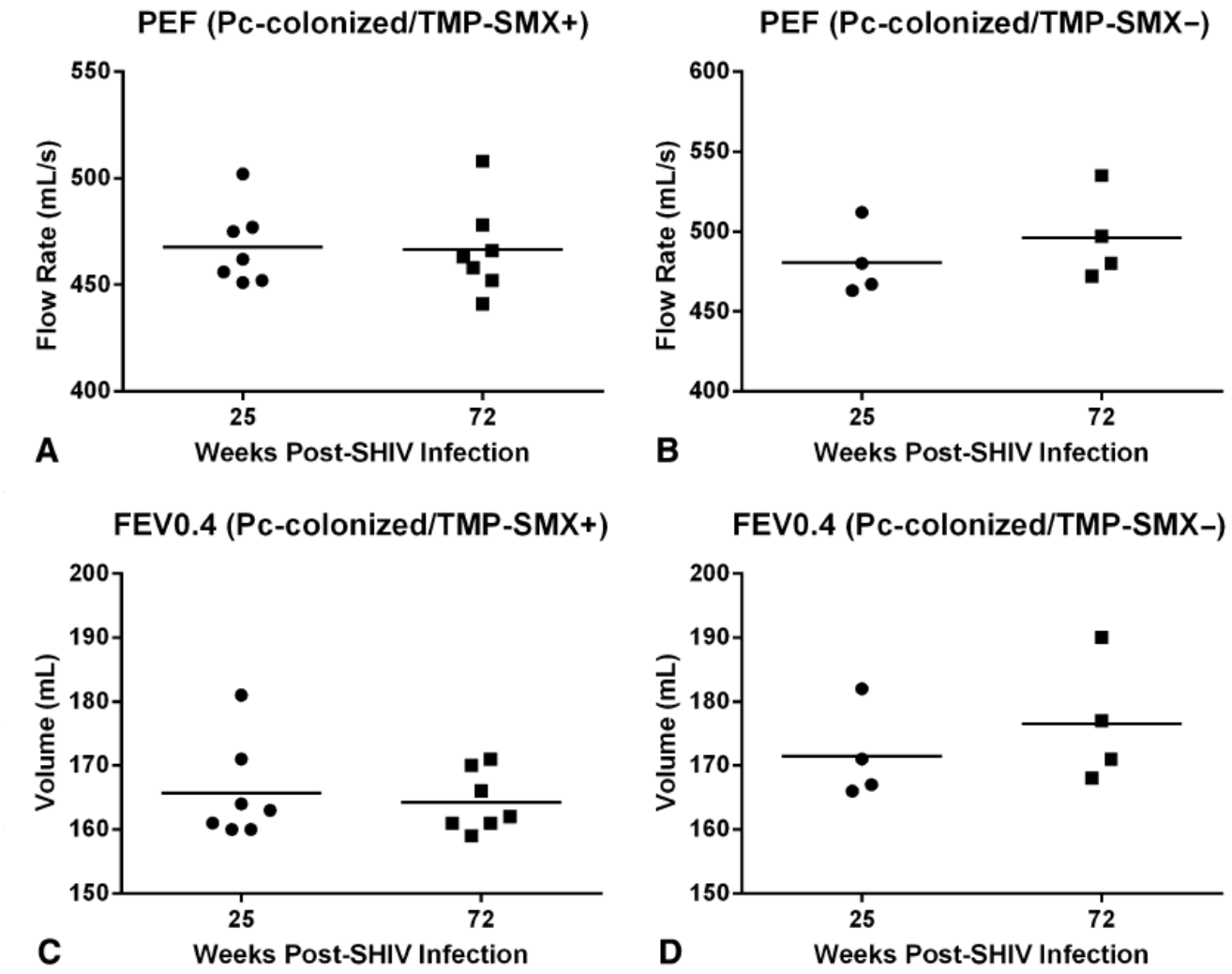
Shipley et al, *JID*, 2010

No therapies tested in HIV

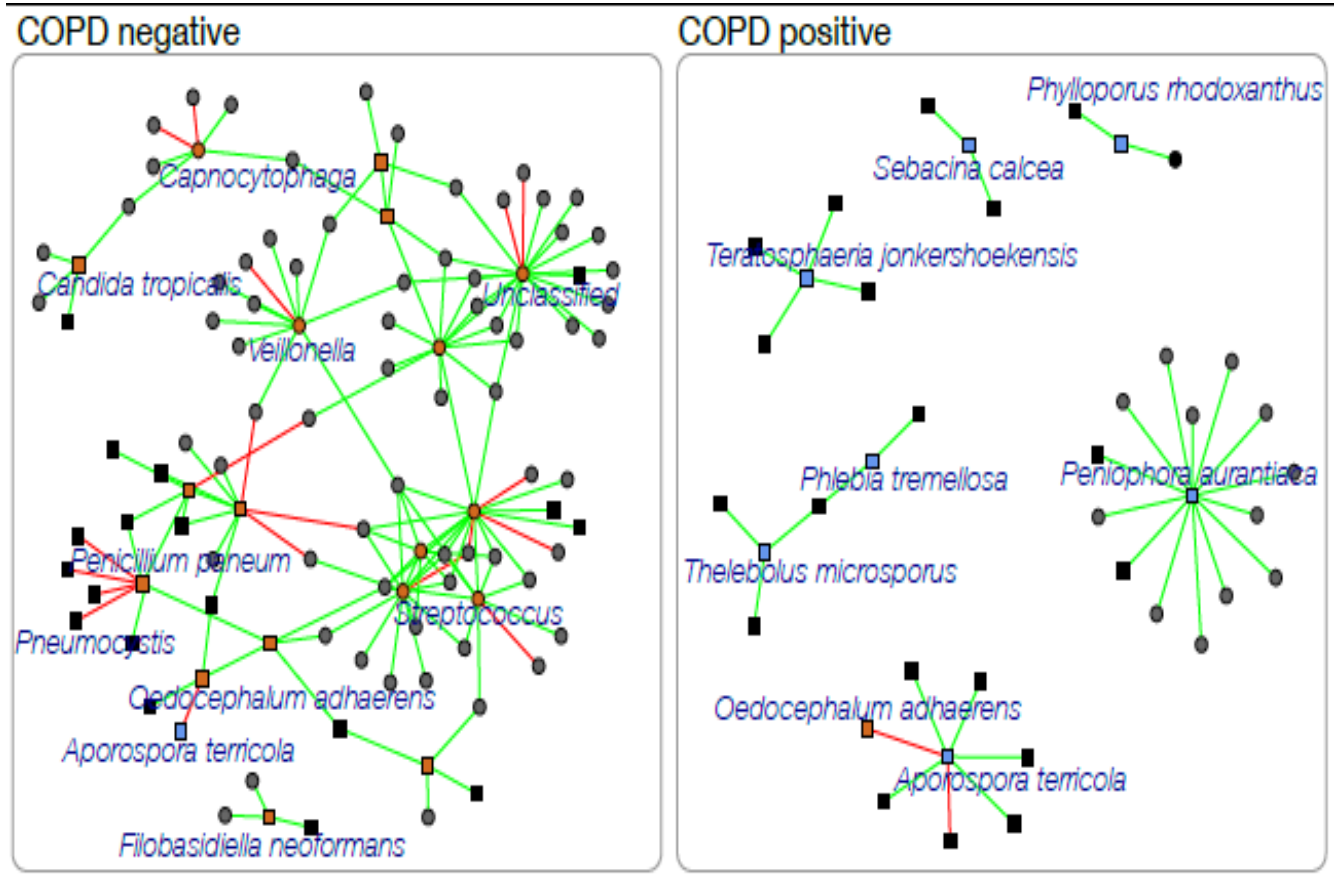


-*Pneumocystis* treatment
-Anti-inflammatories
-Endothelin antagonists

TMP-SMX did not influence lung function in NHP model



Why not?



-Microbial community may be important
-Damage already done
-Perpetuation of inflammation

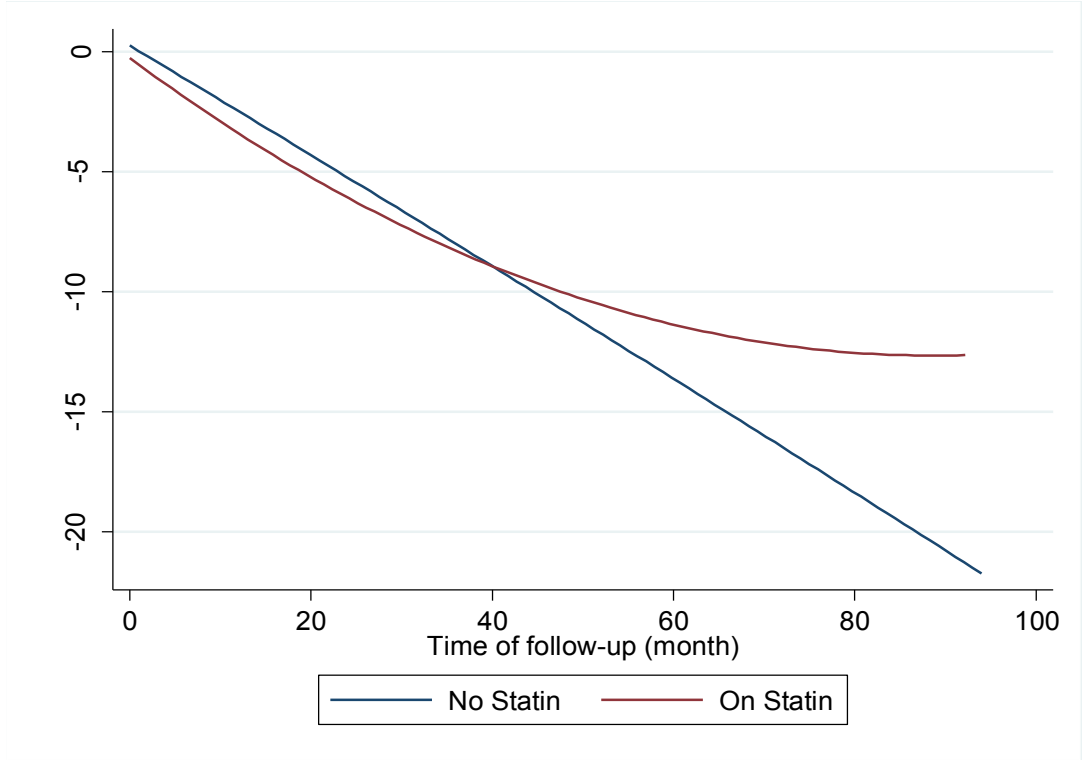
Tipton L et al, 2017

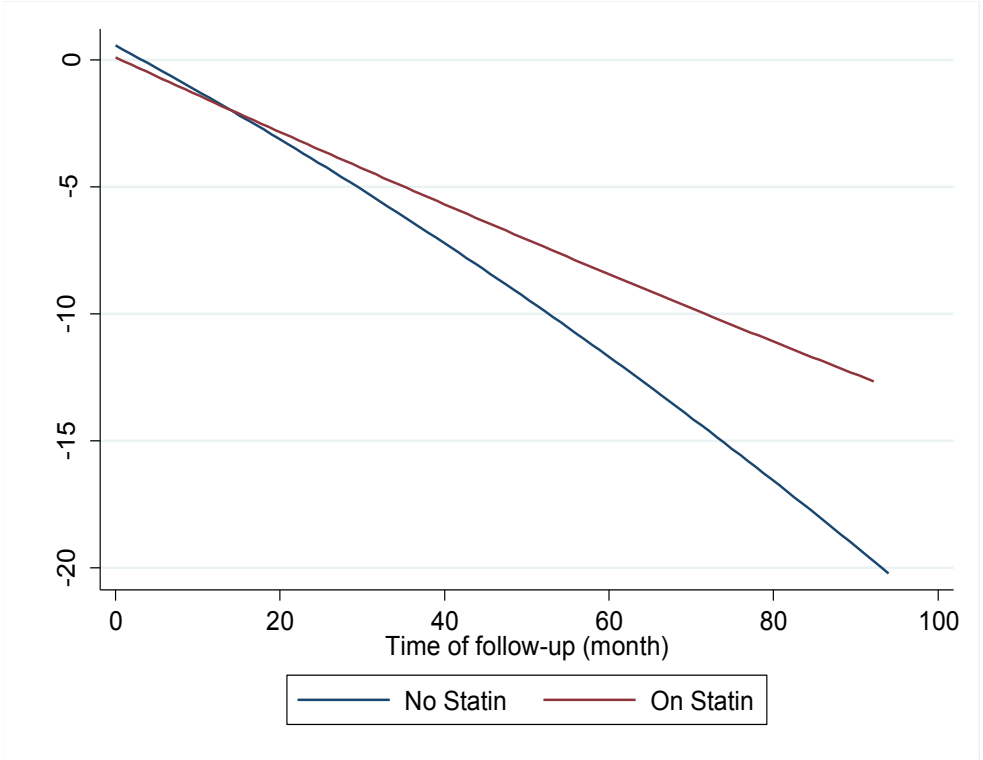
Statins in HIV COPD: Rationale

- Reductions in circulating inflammatory markers (IL-6, CRP, and MMPs) pertinent to HIV COPD
- General population COPD statin RCT disappointing, but trend to improvement in decline in lung function (FEV_1 % predicted) over time
- COPD in chronic HIV, with enhanced immune activation, may be more likely to derive benefit

Kinlay et al *Circ* 2003 (108); Balk et al *Ann Int Med* 2003 (189); Bellosta et al *Arterioscler Thromb Vasc Biol* 1998 (18); Criner et al; *NEJM* 2014 (370)

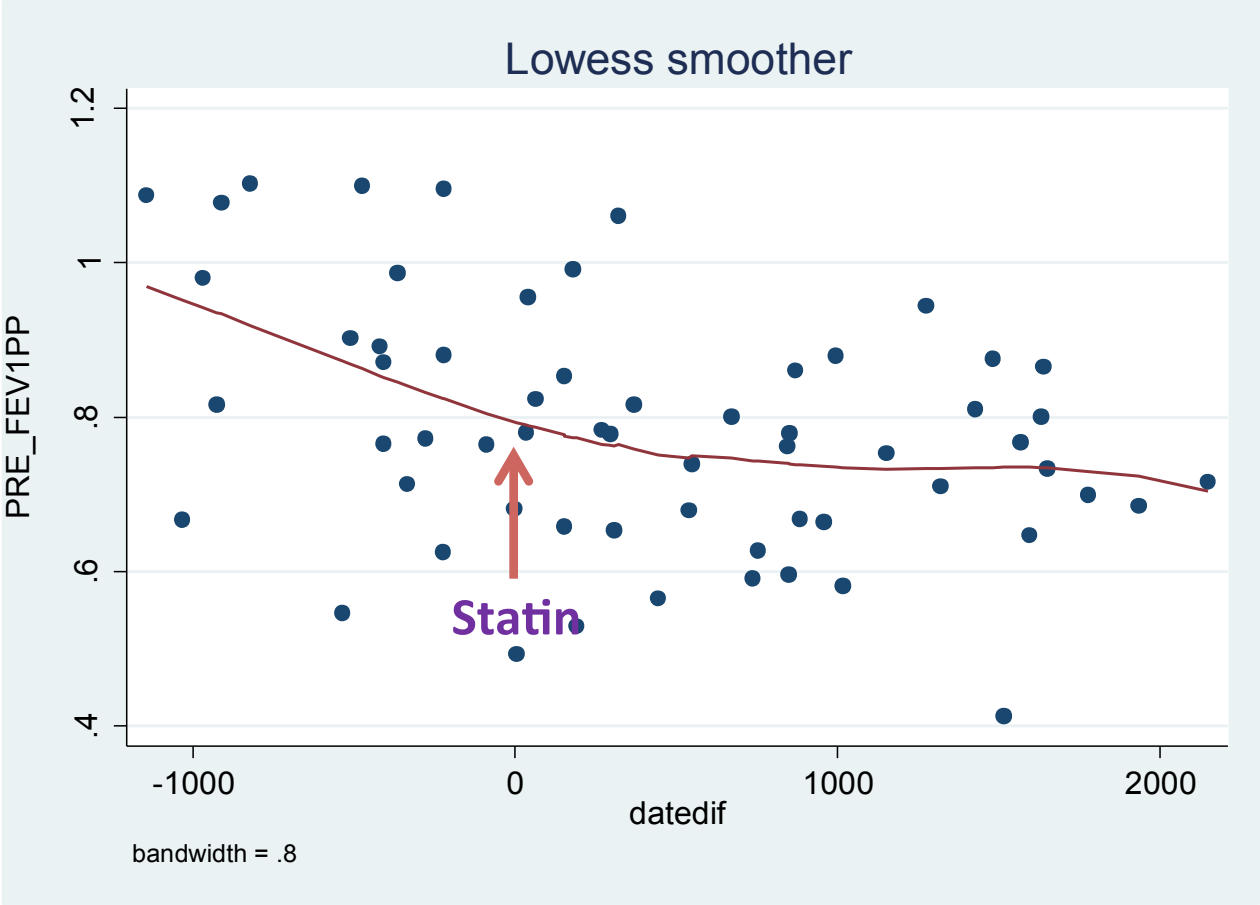
Trend for effect on rate of decline in HIV+ statin users





McLaughlin M et al, ATS, 2015

Statin initiation slowed decline in FEV_1



-Pre-statin rate of decline -1.2% /100 days (p=0.002)

-Post-statin rate of decline -0.2% (p=0.3)

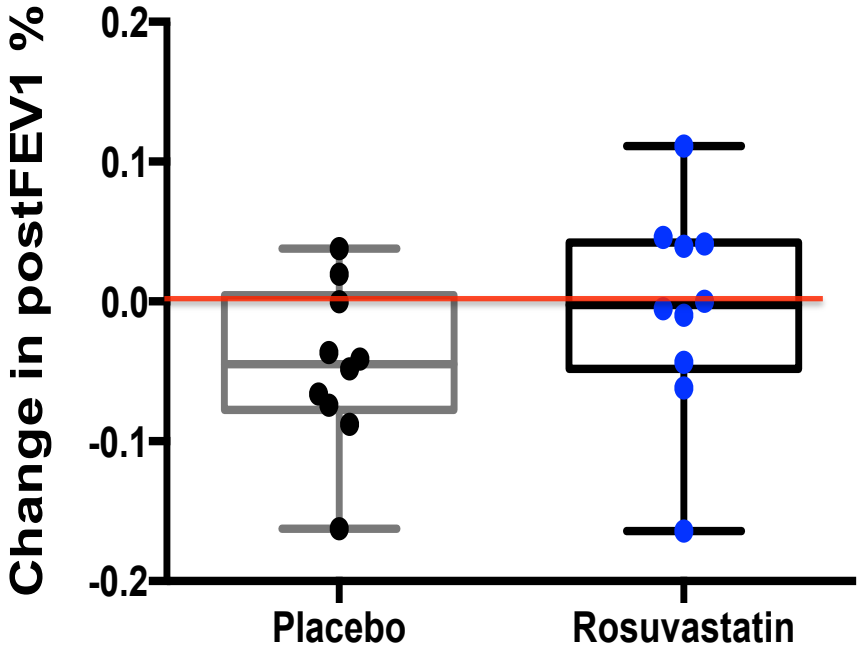
-p=0.002 for comparison

McLaughlin M et al, ATS, 2015

Statins for Pulmonary Complications of Chronic HIV (SPARC Trial)

- HIV+ participants from 2 sites (Pitt, UCSF)
- Inclusion: $FEV_1/FVC<0.7$ or $DL_{CO} < 0.8$
- Exclusion: Pre-existing indication for statin, contraindication to study drug, plans to change ART or smoking status
- Adaptive randomization to placebo vs. rosuvastatin, double-blinded
- PFTs and biomarkers collected at 0, 12, and 24 weeks
- Comparisons performed using paired t-tests and Wilcoxon rank-sum

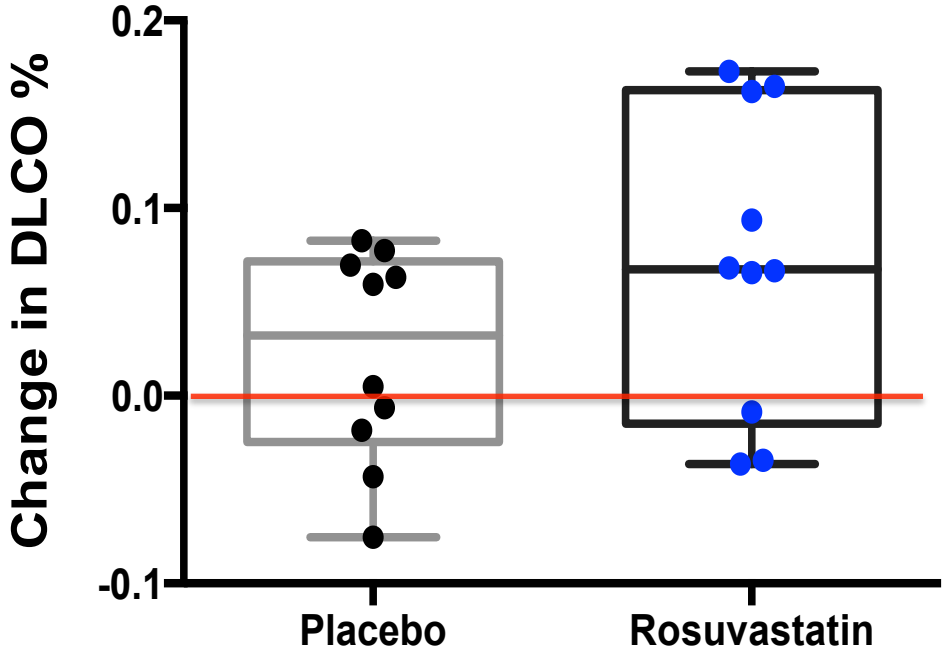
FEV_1 % predicted declined significantly in placebo group, stable in those receiving rosuvastatin



- Median decline in absolute FEV_1 70 mL over 6 months

Morris A et al, AIDS, 2017

DLco % predicted unchanged in placebo, but increased in those receiving rosuvastatin



Morris A et al, AIDS, 2017

Decreases in IL-6 and endothelin-1 in rosuvastatin group

	Placebo (n = 11)			Rosuvastatin (n = 10)			
	Median	**(Q1, Q3)**	**p***	**Median**	**(Q1, Q3)**	**p***	**p****
hs-CRP	-0.02	(-0.14, 0.08)	0.65	-0.05	(-0.43, 0.08)	0.43	0.79
IL-6	***-0.01***	***(-0.12, 0.08)***	***0.52***	***-0.12***	***(-0.21, -0.09)***	***0.02***	***0.11***
ET-1	***-0.16***	***(-0.44, 0.10)***	***0.08***	***-0.32***	***(-0.39, 0.04)***	***0.005***	***0.003***

*Signed Rank Test to determine if the median differs from zero
**Wilcoxon test to determine if the change in the placebo group equals the change in the statin group

Statins for lung disease?

- Need bigger trial, absolute difference not significant between groups
- Indications?
  - FEV_1 decline prevented even in those without airway obstruction
  - Non-smokers
  - DLco abnormalities

Summary

- COPD is a common problem in HIV
- Associated with morbidity and mortality
- Different phenotypes of lung disease
- Potential role of the microbiome
- Optimal therapy undefined

Acknowledgments

Meghan Fitzpatrick
Adam Fitch
Cathy Kessinger
Heather Michael
Seyed Nouraie
John Ries
Vicki Petraglia
Shulin Qin
Barbara Methe
Kelvin Li
Libing Yang
Danny Dunlap
Georgios Kitsios
Carl Koch
Tim Hand

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University of California, Los Angeles
- Eric Kleerup

University of Washington
- Kristina Crothers

New York University
- Elodie Ghedin

National Heart Lung and Blood Institute
People Science Health

LUNG HIV
An NHLBI sponsored cooperative project

Lung HIV Microbiome Project