BPCO e malattia da HIV: una comorbidità emergente

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Disclosure

Dr. Madeddu have received consultancy and/or speakers' fees from Abbott, Bristol Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV.

Many Age-associated Diseases Are More Common in Treated HIV Disease Than In Age-matched Uninfected Persons

- Cardiovascular disease
- Cancer (non-AIDS)
- Bone fractures/osteopenia
- Left ventricular dysfunction
- Liver failure
- Kidney failure
- Cognitive decline
- Frailty
- *Immune system*

Multiple factors likely explain this increased risk, including co-morbid conditions and antiretroviral drug toxicity

From SG Deeks, MD, at Atlanta, GA: March 2, 2010, IAS–USA.

HIV-related chronic pulmonary disease: an emerging issue?

- COPD overview
- COPD and HIV
- COPD and HAART
- Management of COPD

Definition of COPD

- COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.
- Exacerbations and comorbidities contribute to the overall severity in individual patients.

Burden of COPD

- COPD is a leading cause of morbidity and mortality worldwide.
- The burden of COPD is projected to increase in coming decades due to continued exposure to COPD risk factors and the aging of the world's population.
- COPD is associated with significant economic burden.

Mechanisms Underlying Airflow Limitation in COPD

Small Airways Disease

- Airway inflammation
- Airway fibrosis, luminal plugs
- Increased airway resistance

Parenchymal Destruction

- Loss of alveolar attachments
- Decrease of elastic recoil

AIRFLOW LIMITATION

Global Strategy for Diagnosis, Management and Prevention of COPD

Diagnosis of COPD

SYMPTOMS

shortness of breath

chronic cough

sputum

EXPOSURE TO RISK FACTORS

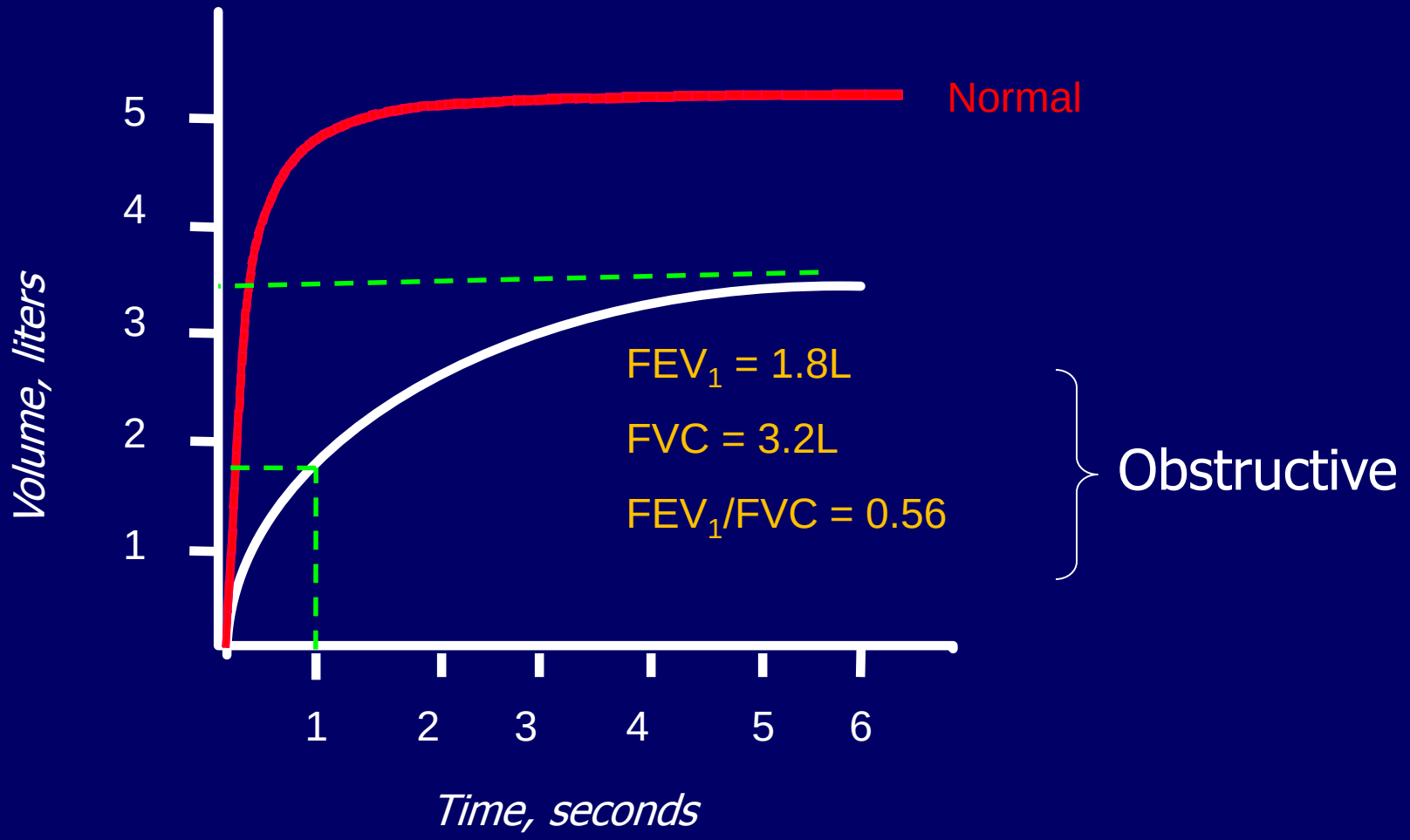
tobacco

occupation

indoor/outdoor pollution

SPIROMETRY: Required to establish diagnosis

Spirometry: Obstructive Disease



Classification of Severity of Airflow Limitation in COPD*

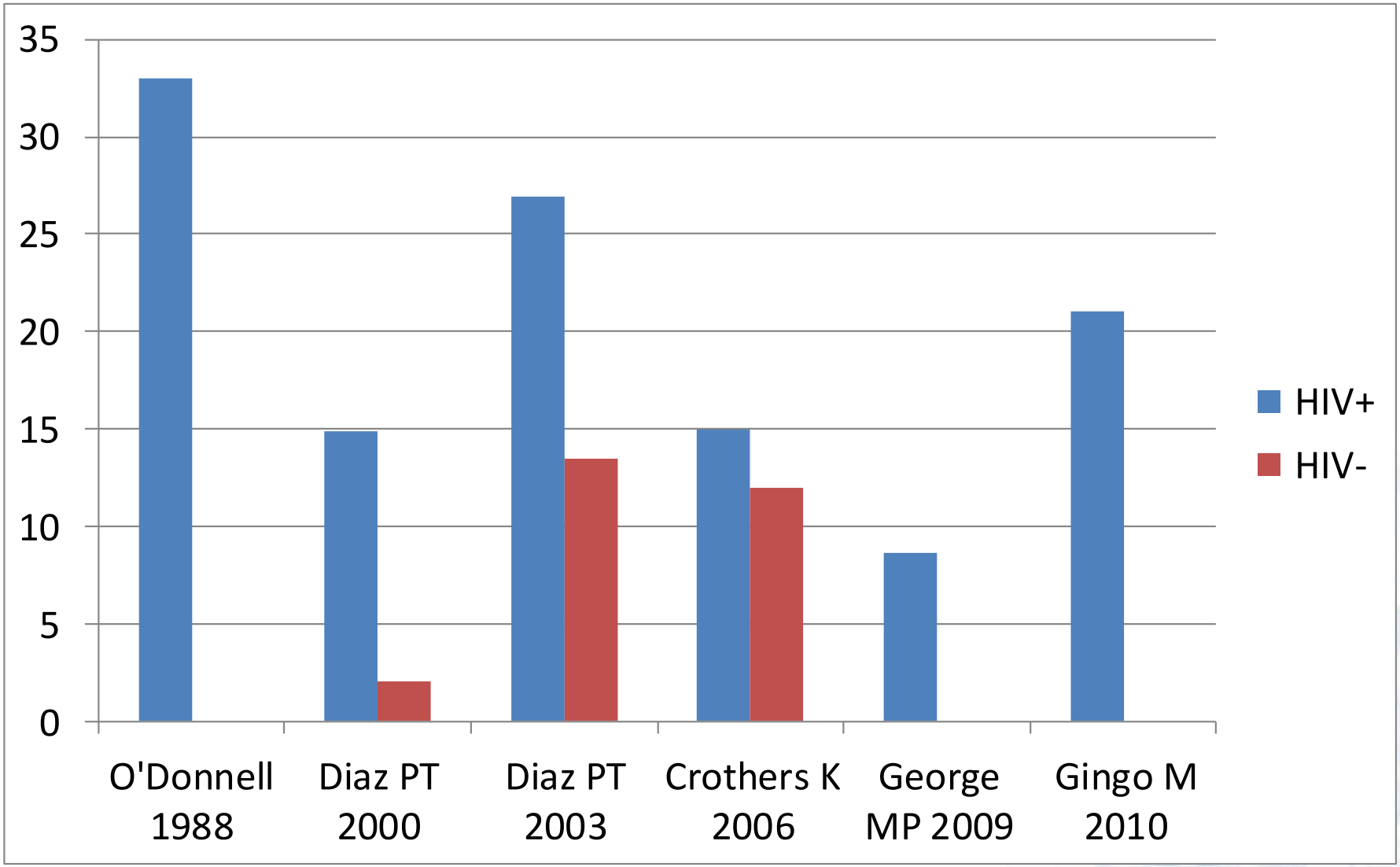
In patients with $FEV_1/FVC < 0.70$:

GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

**Based on Post-Bronchodilator FEV_1*

COPD and HIV

COPD and HIV: prevalence



CHEST Original Research

COPD

Increased COPD Among HIV-Positive Compared to HIV-Negative Veterans*

Kristina Crothers, MD; Adeel A. Butt, MD, MS; Cynthia L. Gibert, MD; Maria C. Rodriguez-Barradas, MD; Stephen Crystal, PhD; and Amy C. Justice, MD, PhD; for the Veterans Aging Cohort 5 Project Team

Table 3—*Predictors of COPD in HIV-Positive and HIV-Negative Subjects

Predictors	COPD Diagnosis	
	ICD-9 Codes	Patient Self-Report
HIV status	1.47 (1.01–2.13)†	1.58 (1.14–2.19)†
Age, per 10 yr	1.57 (1.29–1.87)†	1.17 (1.00–1.37)
Black	0.77 (0.53–1.13)	0.63 (0.46–0.87)†
Hispanic	1.13 (0.67–1.90)	0.80 (0.50–1.27)
Smoking, per 10 pack-yr	1.12 (1.07–1.18)†	1.16 (1.11–1.22)†
IDU	1.44 (0.99–2.12)	1.56 (1.13–2.16)†
Alcohol abuse	2.24 (1.54–3.25)†	1.52 (1.09–2.12)†

*Values are given as the OR (95% CI).
†Significant at $p \leq 0.05$.

(CHEST 2006; 130:1326–1333)

Correlation of HIV-1 Detection and Histology in AIDS-Associated Emphysema

Martha M. Yearsley, Philip T. Diaz, Daren Knoell, and Gerard J. Nuovo

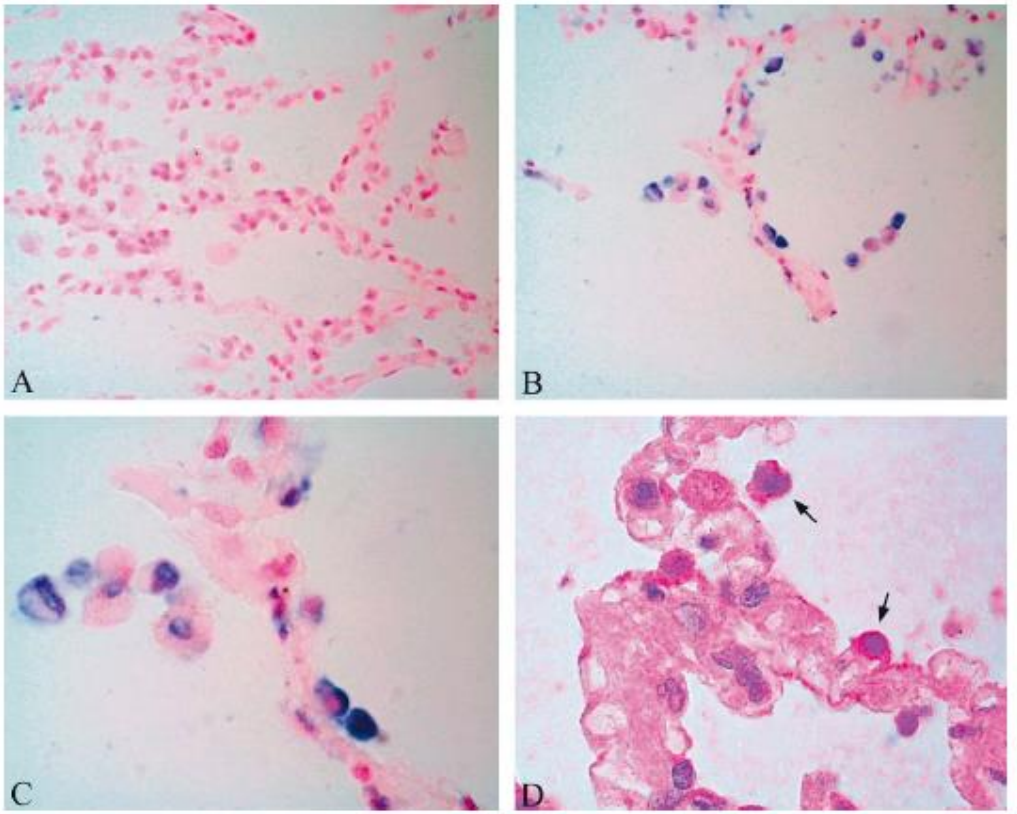


FIGURE 1. Histologic and viral correlates of HIV-1 infection of the lung. Panel A depicts an area of unremarkable lung tissue from an AIDS patient; HIV-1 RNA was not detected after RT in situ PCR. Panel B depicts an adjacent area in the same tissue section where there was marked destruction of the alveolar walls diagnostic of emphysema. Note the many HIV-1–infected cells in this area. Panel C depicts the field in higher magnification; note that infected cells have the cytologic features of macrophages and pneumocytes. Panel D shows the results using immunohistochemistry for the HIV-1 antigen p16; a few positive cells are evident.

Diagn Mol Pathol • Volume 14, Number 1, March 2005

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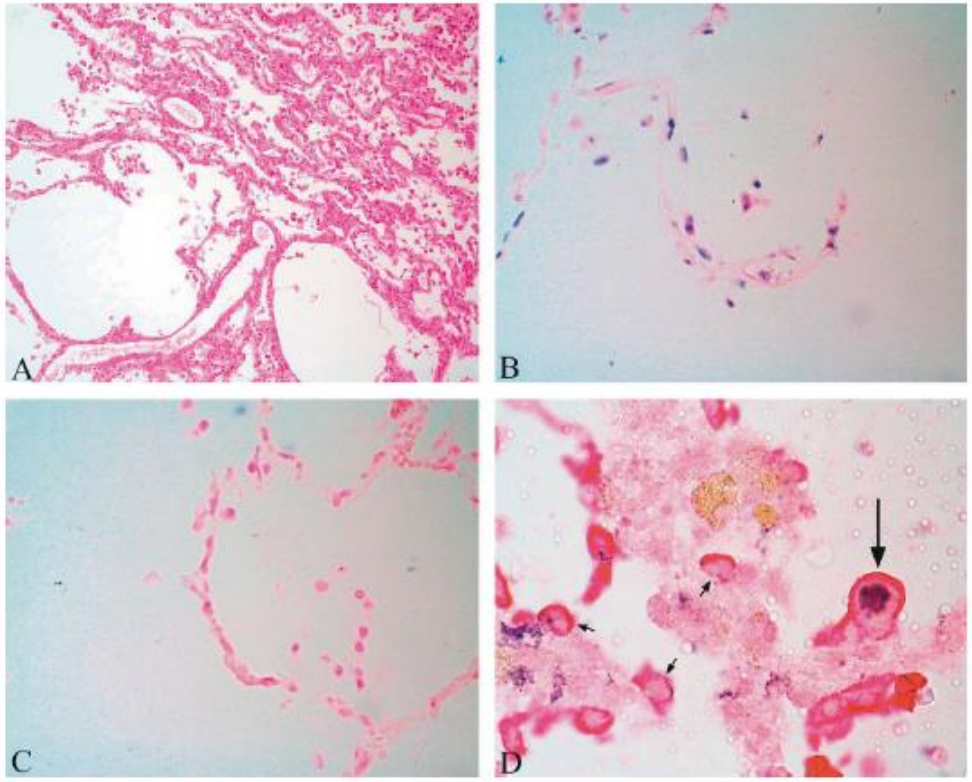


FIGURE 3. Correlation of HIV-1 infection and MMP-9 expression in the lung. Panel A depicts a low magnification view of an area where histologically normal lung is adjacent to emphysematous changes. HIV-1 was noted in the area of emphysema (panel B). The signal was lost in the serial section is either HPV-specific primers were used (not shown) or the reaction was preceded by RNase digestion (panel C). Colabeling experiments with MMP-9 protein and HIV-1 RNA showed rare HIV-1–infected MMP-9 expressing cells (panel D, large arrow); most of the MMP-9-positive cells did not contain HIV-1 RNA but, rather, were directly adjacent to such cells (small arrows, note the cytoplasmic MMP-9 signal).

Diagn Mol Pathol • Volume 14, Number 1, March 2005

Healthy HIV-Infected Individuals Harbor HIV in Alveolar Macrophages

S.K. Cribbs, MD, MSc [1]; D.M. Guidot, MD [1]; A. Caliendo MD, PhD [2]; J. Lennox, MD [3];
[1] Emory University, Division of Pulmonary and Critical Care Medicine; [2] Brown University; [3] Emory University, Division of Infectious Disease

Table 1: Study Population

VARIABLES	(+) Proviral DNA	(-) Proviral DNA	p
N	17	7	
Median Age (IQR)	50 (45-55)	50 (47-53)	0.97
Gender (% male)	47.1	57.1	0.65
Race			0.50
White (n, %)	1 (5.9)	1 (14.3)	
Black (n, %)	16 (94.1)	6 (85.7)	
% HAART	94.1	100	
Median CD4 (IQR)	340 (264-444)	560 (390-730)	0.05
% Undetectable Plasma Viral Load	66.7%	100%	0.08
Median Plasma Viral Load copies/mL (IQR)	0 (0-1506)	0 (0-0)	0.13

Graph 1: HIV Proviral DNA and RNA are Present in Alveolar Macrophages

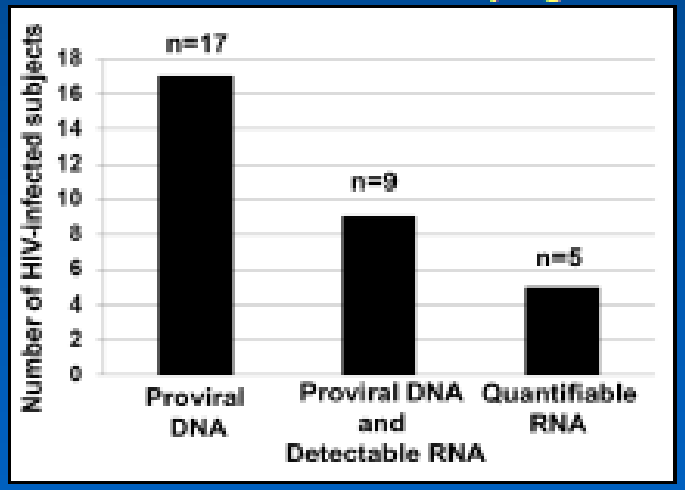
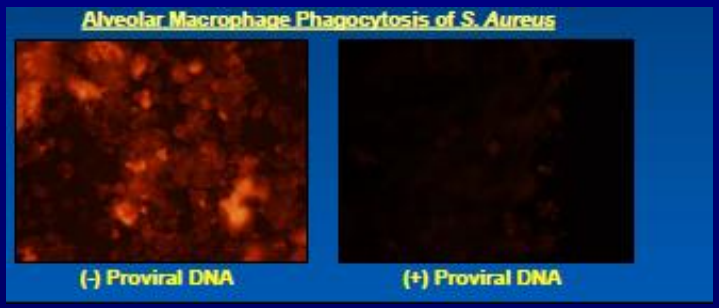


Table 2: Quantifiable HIV RNA in Lung and Plasma

Subjects	Alveolar Macrophage HIV RNA (copies/mL)	Plasma HIV RNA (copies/mL)
1	2305	64,565
2	182	27,542
3	588	undetectable
4	70	undetectable
5	48	undetectable



Conclusions

- Alveolar macrophages harbor HIV even in otherwise healthy individuals with undetectable plasma viral loads, representing a potential reservoir for the virus.
- HIV viral replication within alveolar macrophages may impair phagocytosis and other immune functions, leading to an increased risk for lung infections.

Profound Lung CD4+ T-Cell Depletion in HIV-Associated Chronic Obstructive Pulmonary Disease

- ✓ HIV+COPD+ individuals had profound CD4+ T cell depletion with reduced CD4+:CD8+ T cell ratios and absolute CD4+ numbers in LMNC ($p < 0.002$), not observed in PBMC.
- ✓ In addition, HIV+COPD+ individuals had significantly decreased HIV-specific CD4+IFN-γ+ T cell responses to the antigens Gag ($p<0.05$) and Pol ($p<0.02$) and HIV-specific CD4+ T cell multi-functional responses (IFN-γ, TNF-α, IL-2, MIP-1β and CD107a) compared to HIV+COPD- controls ($p=0.01$), but not in the PBMC ($p=0.6$).
- ✓ Lastly, LMNC, but not PBMC, CD4+:CD8+ ratios were significantly correlated with forced expiratory volumes in one second (FEV1), a physiologic marker of COPD ($p=0.027$, $R=0.48$).
- ✓ Together, our findings reveal profound lung mucosal CD4+ T cell depletion and dysregulation of HIV-specific CD4+ T cell immunity in HIV-associated COPD. Our results also indicate increased BAL HIV-RNA, and activation-induced cell death of lung CD4+ T cells via a Fas-dependent mechanism in HIV-associated COPD. Finally, our data suggests lung mucosal CD4+ T cell depletion plays a role in the pathogenesis of HIV-associated COPD.

Popescu I, CROI 2016

Persistence of HIV-Infected Alveolar Macrophages After Suppressive ART

Table 1: Baseline Characteristics of Study Population

	Viremic (N=2)	Suppressed (N=7)
Age [median(range)]	47 (44,50)	53 (42, 67)
Gender (male)	50%	100%
Race (Caucasian)	100%	29%
(African American)	0%	71%
Current CD4 [median(range)]	226 (138,313)	911 (563, 1198)
Duration of suppression [median years (range)]	N/A	3.61 (2.2, 12.6)
Plasma VL [median (range)]	59,275 (39,778, 78,771)	<50
Smoker (Current smoker)	50%	29%
(Previous smoker)	0%	43%
Diagnosis of COPD	50%	14%
Diagnosis of ILD	0%	0%
Active infection	0%	0%

Figure 2: HIV-1 RNA in Plasma and BAL fluid

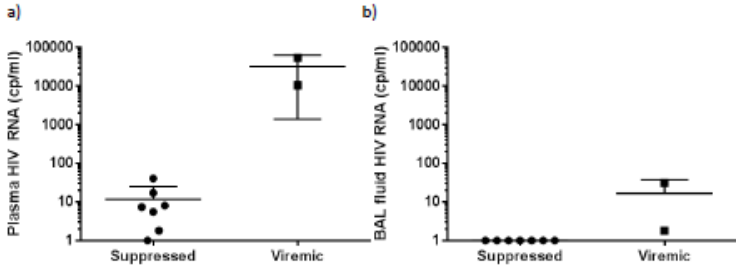


Figure 3: Cell-associated HIV-1 DNA in PBMC and AM

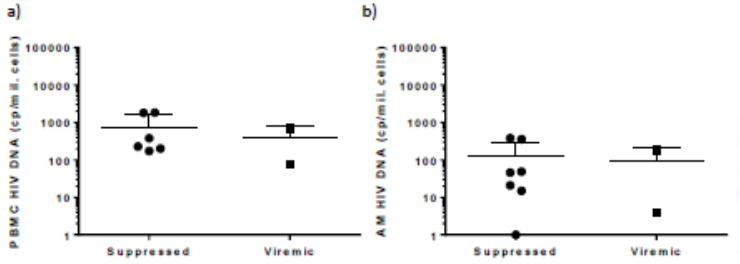
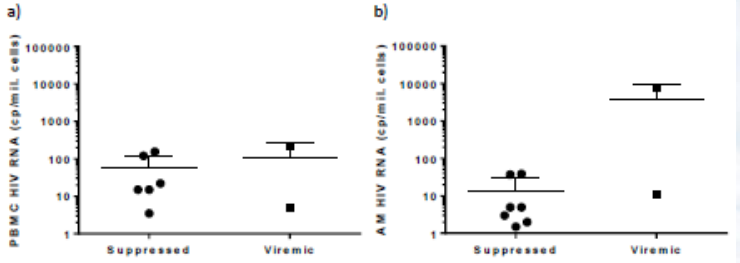


Figure 4: Cell-associated HIV-1 RNA in PBMC and AM



Hong F, P330 CROI 2016

HIV infection and related biomarkers are independent risk factors for radiographic emphysema (Poster 775)

Results

- HIV+ individuals had:
  - Greater emphysema severity
  - Increased lower lung zone and diffuse involvement
- Increased emphysema risk associated with:
  - HIV
  - Nadir CD4 <200 & high sCD14 among those with HIV

Risk factors	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
HIV+ and HIV-		
HIV infection	2.47 [1.25-487]	1.55 [0.71-3.41]
sCD14 >75th %ile	2.63 [1.32-5.21]	2.30 [1.02-5.19]
Pack-years	1.34 [1.13-1.59]	1.39 [1.15-1.68]
HIV+ only		
Nadir CD4 <200	2.39 [1.02-5.62]	2.98 [1.14-7.81]
sCD14 >75th %ile	3.95 [1.20-12.9]	2.55 [1.04-6.22]
Pack-years	1.24 [1.02-1.51]	1.29 [1.05-1.59]

Conclusions

- HIV is an independent risk factor for emphysema, adjusting for smoking
- Emphysema severity is significantly greater among HIV+
- Among HIV+, *nadir CD4 <200* and *elevated soluble CD14* are associated with emphysema

CLINICAL AND EPIDEMIOLOGICAL STUDY

Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the HAART era?

G. Madeddu · A. G. Fois · G. M. Calia · S. Babudieri · V. Soddu · F. Becciu · M. L. Fiori · V. Spada · C. Lovigu · M. Mannazzu · A. Caddeo · B. Piras · P. Pirina · M. S. Mura

Table 1 Comparison of demographic characteristics and lung function parameters in 111 human immunodeficiency virus (HIV)-infected and in 65 HIV-negative subjects

Parameter	HIV-infected ($n = 111$)	HIV-negative ($n = 65$)	p-value
Age (years)	42.3 ± 8.1*	43.8 ± 13.2*	0.349
Male gender	77 (69.4 %)	40 (61.0 %)	0.288
Current smokers	63 (56.7 %)	38 (61.0 %)	0.125
Pack-year history	24.0 ± 14.4*	23.4 ± 14.8*	0.835
Respiratory symptoms	52 (46.8 %)	15 (15.4 %)	0.002
Cough	36 (32.4 %)	9 (13.8 %)	0.006
Dyspnoea	34 (30.6 %)	10 (15.4 %)	0.02
FEV1 (percent predicted)	92.6 ± 11.4*	100.6 ± 9.9*	0.002
FEV1/FVC ratio	81.6 ± 8.2*	84.4 ± 8.1	0.028
TLC (percent predicted)	105.4 ± 14.4*	100.9 ± 6.5*	0.018
COPD	26 (23.4 %)	5 (7.7 %)	0.008

FEV1 forced expiratory volume in one second, *FVC* forced vital capacity, *TLC* total lung capacity, *COPD* chronic obstructive pulmonary disease

* Data are expressed as mean ± standard deviation

Infection. 2013 Apr;41(2):347-53

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Table 4 Predictors of respiratory symptoms and COPD in 111 HIV-infected patients in the multivariate logistic regression analysis

Variable	Respiratory symptoms		COPD	
	AOR (95 % CI)	*p*-value	AOR (95 % CI)	*p*-value
Age: >45 vs. ≤45 (years)	1.89 (0.62–5.56)	0.248	1.45 (0.45–4.73)	0.535
Sex: males vs. females	0.55 (0.18–1.63)	0.281	1.01 (0.32–3.24)	0.981
HIV infection duration: >10 vs. ≥10 (years)	0.76 (0.26–2.27)	0.627	0.34 (0.09–1.21)	0.096
Risk factor: IDU vs. sexual transmission	1.21 (0.46–3.15)	0.700	1.03 (0.37–2.86)	0.961
CDC stage: C vs. A/B	1.97 (0.63–6.17)	0.241	2.09 (0.59–7.41)	0.255
HCV/HBV infection: yes vs. no	1.99 (0.70–5.61)	0.194	1.31 (0.41–4.21)	0.645
Current smoking: yes vs. no	11.18 (3.90–32.12)	<0.001	5.94 (1.77–19.96)	0.004
HAART receipt: yes vs. no	0.44 (0.07–2.90)	0.397	0.59 (0.06–5.93)	0.657
Previous BCAP: yes vs. no	4.41 (1.13–17.14)	0.032	3.28 (0.84–12.75)	0.087
CD4 count: ≤500 vs. >500 (cells/mm^3)	1.31 (0.60–2.87)	0.491	1.28 (0.52–3.18)	0.589
HIV RNA: detectable vs. undetectable	1.76 (0.28–11.03)	0.538	1.26 (0.13–11.88)	0.838

COPD chronic obstructive pulmonary disease, *AOR* adjusted odds ratio, *CI* confidence interval, *IDU* injection drug users, *CDC* Centers for Disease Control and Prevention, *HAART* highly active antiretroviral therapy, *BCAP* bacterial community-acquired pneumonia

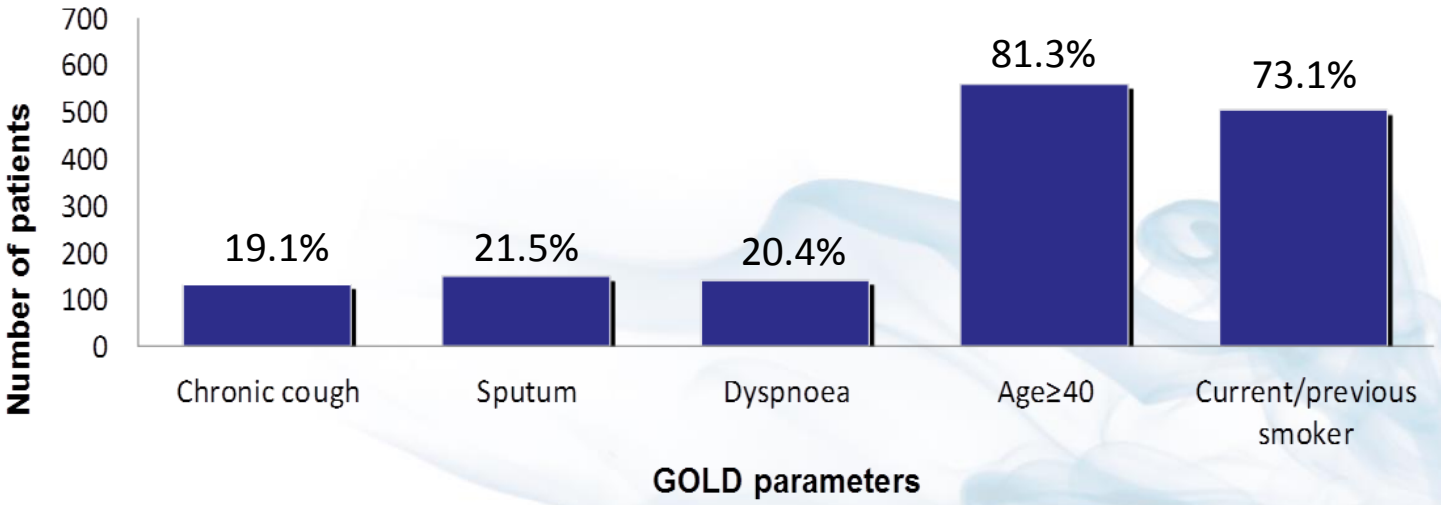
Infection. 2013 Apr;41(2):347-53

Prevalence of respiratory symptoms and screening for Chronic Obstructive Pulmonary Disease: results from an Italian multicenter study

Parameter	cohort (n=687)
Age (years)	47.7 ± 9.9
Male gender	513 (74.7%)
Injection drug users (IDU)	158 (23%)
Heterosexuals	295 (42.9%)
Homosexuals	182 (26.5%)
CDC stage A	244 (35.5%)
CDC stage B	144 (21%)
CDC stage C	159 (23%)
CD4 cell count (cells/μL)	678.9 ± 347.8
Undetectable HIV-RNA	511 (75.9%)
Naïve to antiretrovirals	39 (5.7%)
Chronic hepatitis	191 (28.1%)
Previous pneumonia	168 (24.5%)
Current smokers	328 (47.7%)
Previous smokers	166 (24.2%)
Never smokers	193 (28.1%)

Fois AG et al. EACS 2015

Prevalence of respiratory symptoms and screening for Chronic Obstructive Pulmonary Disease: results from an Italian multicenter study



Fois AG et al. EACS 2015

Prevalence of respiratory symptoms and screening for Chronic Obstructive Pulmonary Disease: results from an Italian multicenter study

Variable	pCOPD		*P*
	No (n=472)	Yes (215)	
Age (years)	46.7 ± 10.6	49.8 ± 7.7	0.0002
Males	343 (72.7%)	170 (79.1%)	0.07
Females	129 (27.3%)	45 (20.9%)	
Caucasian	431 (91.3%)	208 (96.7%)	0.12
IDU	91 (19.8%)	67 (31.2%)	0.0006
CD4 Count (cells/mm^3)	672 ± 331	694.1 ± 383	0.44
CDC stage C	104 (22.0%)	55 (25.6%)	<0.0001
HIV/RNA Undetactable	356 (76.7%)	155 (74.2%)	0.47
HIV/RNA Detectable	108 (23.3%)	54 (25.8%)	
Naive	34 (7.3%)	5 (2.3%)	0.0095
Experienced	432 (92.7%)	210 (97.7%)	
Current/previous smoker	295 (62.5%)	199 (92.6%)	<0.0001
Never smoker	177 (37.5%)	16 (7.4%)	
Previous pneumonia	88 (18.6%)	80 (37.2%)	<0.0001
No pneumonia	384 (81.4%)	135 (62.8%)	
Current/previous alcohol abuse	29 (6.2%)	24 (11.4%)	<0.0001
No alcohol abuse	427 (90.8%)	168 (79.6%)	
Chronic Hepatitis	104 (22.1%)	88 (41.1%)	0.0001
No Chronic Hepatitis	363 (77.2%)	125 (58.4%)	

Fois AG et al. EACS 2015

Prevalence of respiratory symptoms and screening for Chronic Obstructive Pulmonary Disease: results from an Italian multicenter study

	pCOPD	
Variable	Adjusted Odds ratio (95% CI)	*P*
Age (by 5 years)	1.16 (1.05 – 1.28)	0.003
Previous smoking: yes vs no	3.08 (1.62 – 5.87)	
Current smoking yes vs no	10.70 (6.00 – 19.20)	<0.0001
Previous Pulmonary Infection: yes vs no	1.87 (1.22 – 2.88)	0.004
Naïve status: yes vs no	0.32 (0.12 – 0.87)	0.02
Chronic hepatitis: yes vs no	1.52 (1.02 – 2.27)	0.09

Fois AG et al. EACS 2015

COPD and HAART

CHEST Original Research

COPD

Increased COPD Among HIV-Positive Compared to HIV-Negative Veterans*

Kristina Crothers, MD; Adeel A. Butt, MD, MS; Cynthia L. Gibert, MD; Maria C. Rodriguez-Barradas, MD; Stephen Crystal, PhD; and Amy C. Justice, MD, PhD; for the Veterans Aging Cohort 5 Project Team

Table 4—*Predictors of COPD in HIV-Positive Subjects

Predictors	COPD Diagnosis	
	ICD-9 Codes	Patient Self-Report
Age, per 10 yr	1.36 (1.04–1.77)†	1.15 (0.92–1.43)
Black	0.85 (0.51–1.43)	0.75 (0.49–1.15)
Hispanic	1.08 (0.53–2.19)	0.83 (0.45–1.54)
Smoking, per 10 pack-yr	1.11 (1.02–1.21)†	1.19 (1.11–1.29)†
IDU	1.82 (1.15–2.88)†	1.60 (1.07–2.38)†
Alcohol abuse	1.46 (0.89–2.38)	1.06 (0.68–1.64)
Bacterial pneumonia	2.80 (1.70–4.61)†	2.06 (1.29–3.28)†
CD4+ T-cell count, per 50 cells (square root)	0.78 (0.62–1.00)†	0.91 (0.75–1.11)
HAART	0.77 (0.46–1.32)	0.94 (0.58–1.51)

*Values are given as the OR (95% CI).
†Significant at $p \leq 0.05$.

(CHEST 2006; 130:1326–1333)

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PLoS one

Respiratory Symptoms and Airway Obstruction in HIV-Infected Subjects in the HAART Era

M. Patricia George[1], Mouhamed Kannass[2], Laurence Huang[3], Frank C. Sciurba[1], Alison Morris[1,2]*

Table 3. Predictors of airway obstruction in HIV-infected subjects.

Univariate predictors	Coefficient	P
Age	−0.18	<0.001
Hispanic ethnicity (versus non-Hispanic)	2.3	0.01
Smoking history (former/current versus never)	−2.2	0.01
Smoking pack-year history	−0.19	<0.001
Hepatitis C	−3.2	0.02
History of bacteria pneumonia	−3.2	0.001
Use of HAART	−2.8	0.09
Multivariate predictors		
Age	−0.10	0.04
Smoking pack-year history	−0.15	<0.001
History of bacterial pneumonia	−2.8	0.007
Use of HAART	−3.2	0.04

Note: HAART = highly active antiretroviral therapy.
doi:10.1371/journal.pone.0006328.t003

Rationale

Table 2. Studies examining effects of antiretroviral therapy on risk of chronic obstructive pulmonary disease among patients with HIV infection. All studies adjusted for smoking variables

Author	Setting	On ART (*n*)	No ART (*n*)	Design	Conclusions
George [11]	USA, single center (Los Angeles, CA, USA)	195	20	Cross-sectional study	ART use associated with lower FEV_1/FVC ratio in linear regression analysis (β coefficient −3.2; $P=0.04$).
Gingo [12]	USA, single center (Pittsburgh, PA, USA)	134	33	Cross-sectional study	ART use with higher odds COPD (OR 6.22; 95% CI: 1.19–32.43)
Crothers [22▪]	USA, national healthcare system database	~21 700	~11 700	Prospective, administrative data analysis	ART use with lower incident COPD without smoking adjustment (incidence rate ratio [IRR] 0.90; 95% CI: 0.82–0.99). Smoking adjustment resulted in wider CI (IRR 0.93; 95% CI: 0.73–1.18)
Drummond [25▪]	USA, single center (Baltimore, MD, USA)	169	134	Cross-sectional study	ART use not associated with COPD (OR 0.60; 95% CI: 0.29–1.22). However, viral load at least 200 000 copies/ml associated with COPD (OR 3.41; 95% CI: 1.24–9.39)
Drummond [10▪▪]	USA, single center (Baltimore, MD, USA)	172	144	Prospective, observational cohort	ART use not associated with differences in FEV_1 rate of decline. However, viral load at least 75 000 copies/ml associated with faster rate of FEV_1 decline compared with viral load less than 75 000 copies/ml (69 ml/year faster decline; 95% CI: 15.3–123.0 ml/year; $P=0.012$).
Madeddu [14]	Italy, single center (Sassari, IT)	87	24	Cross-sectional study	ART not associated with COPD, but CI very wide (OR 0.59; 95% CI: 0.06–5.93)

From Kunisaki KM. *Curr Opin HIV AIDS* 2014;9(1):27-33.

Lung Function Decline in HIV: Effects of Immediate vs. Deferred ART Treatment on Lung Function Decline in a Multi-site, International, Randomized Controlled Trial

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for the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START Pulmonary Substudy Group

START

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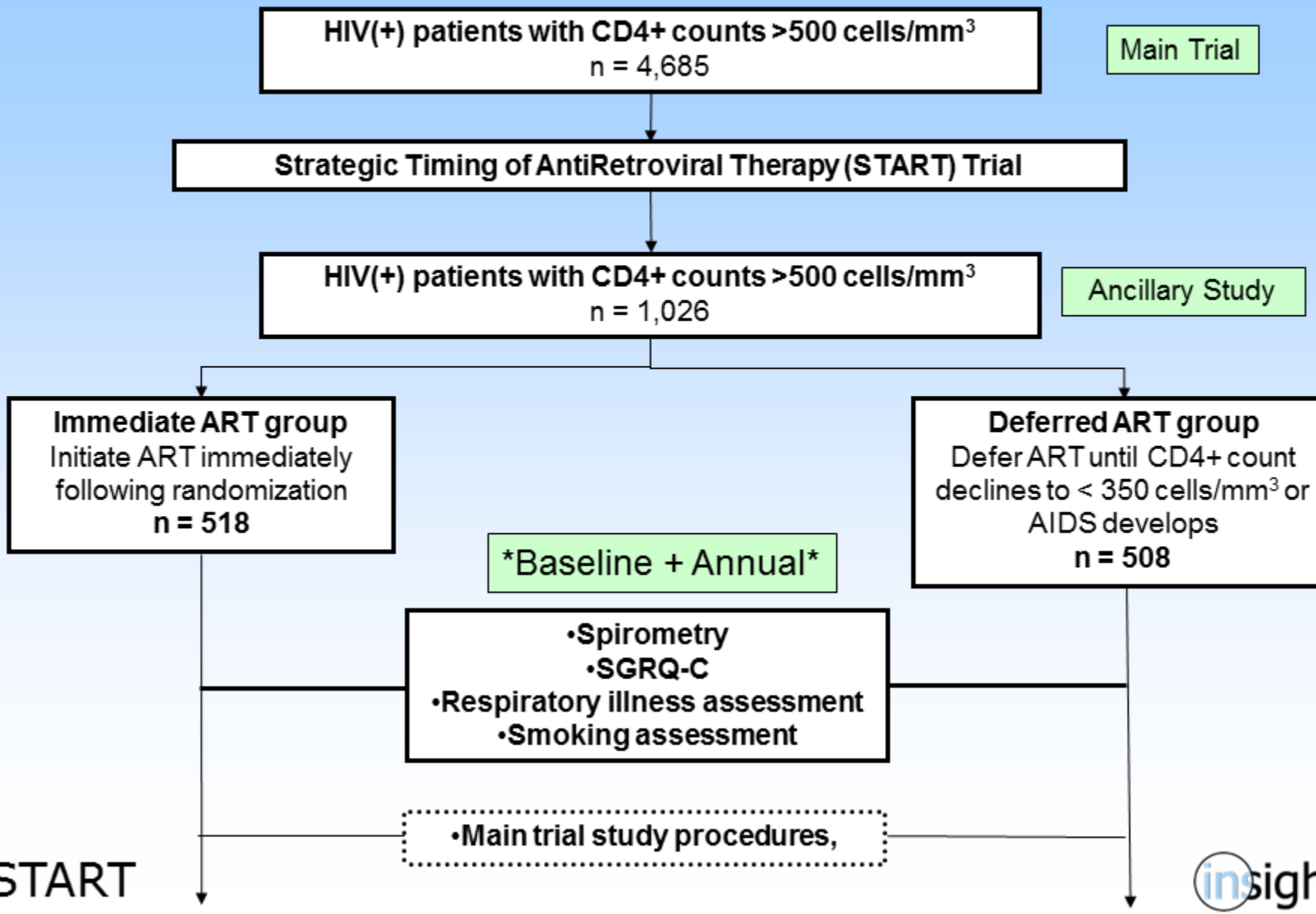
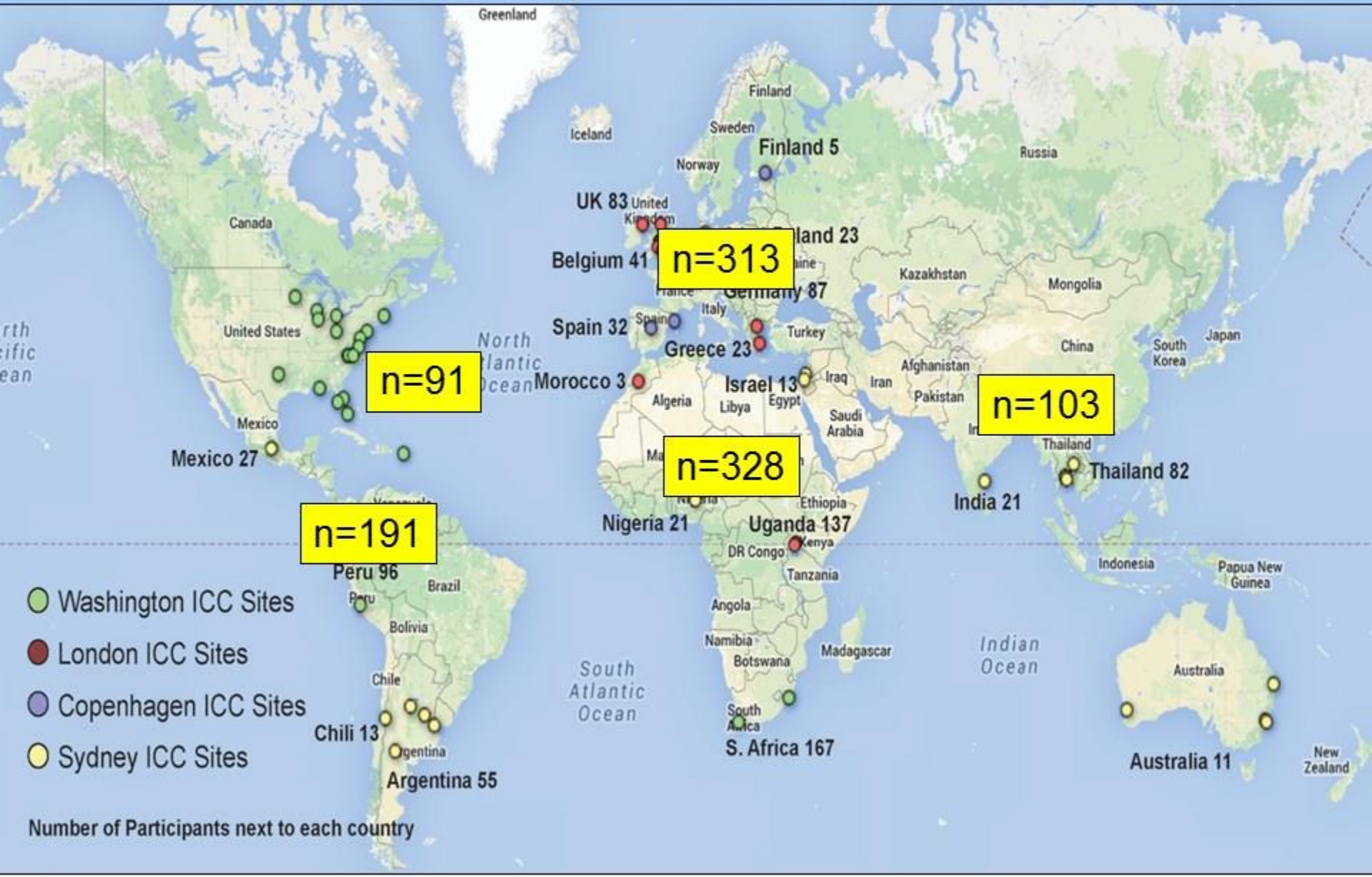
Study Design



START Pulmonary Substudy

- Primary outcome:
  - Rate of FEV_1 decline (FEV_1 slope) between immediate and deferred ART arms
  - Mixed effects model with random slope and intercept terms
- Secondary outcome:
  - Respiratory health status (St. George's Respiratory Questionnaire)



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Results

	Immediate	Deferred	TOTAL
	n=518	n=508	n=1,026
Age, years	37	36	36
Female, %	28%	30%	29%
Known HIV(+), years	1.1	1.2	1.2
CD4, cells/mm^3	650	647	648
HIV-RNA,log_{10} copies/mL	4.2	4.2	4.2
BMI, kg/m^2	24.8	24.8	24.8
Smoking, %			
-Current	26%	30%	28%
-Former	11%	10%	11%
-Never	63%	59%	61%
FEV_1, %predicted	95%	97%	96%

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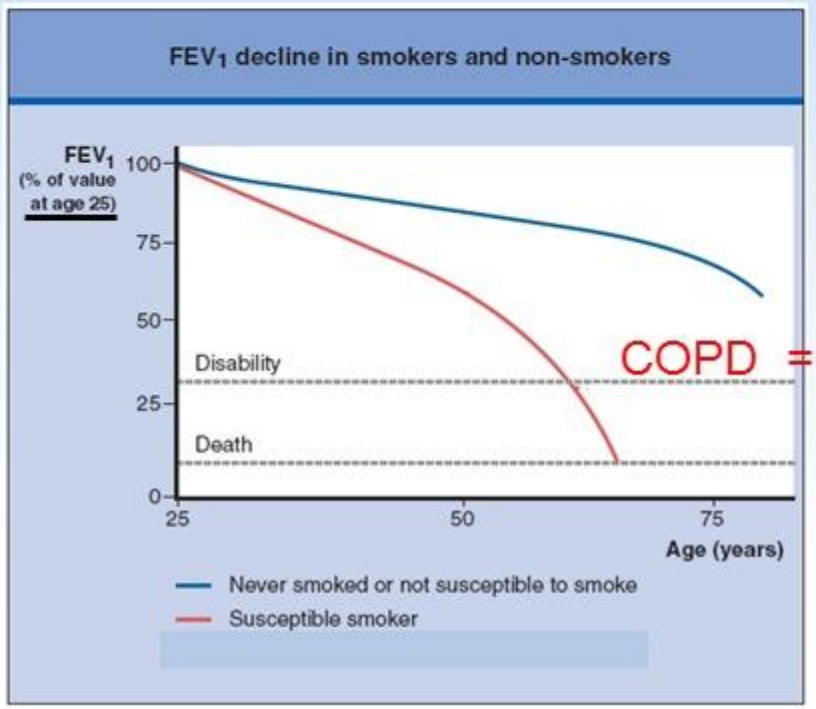
		Immediate ART	Deferred ART	Difference	p-value
Smokers	All spirometry	n=126	n=137		
		-34 mL/yr (-60 to -9)	-31 mL/yr (-55 to -6)	-4 mL/yr (-40 to +32)	0.83
Non-smokers	All spirometry	n=361	n=328		
		-29 mL/yr (-45 to -12)	-22 mL/yr (-39 to -4)	-7 mL/yr (-31 to +17)	0.56
Pooled analysis	All spirometry	n=487	n=465		
		-30 mL/yr (-44 to -16)	-24 mL/yr (-39 to -10)	-6 mL/yr (-26 to +14)	0.56

		Immediate ART	Deferred ART	Difference	p-value
Smokers	All spirometry	n=126	n=137		
		-34 mL/yr (-60 to -9)	-31 mL/yr (-55 to -6)	-4 mL/yr (-40 to +32)	0.83
	Restricted to high-quality spirometry	n=116	n=132		
		-36 mL/yr (-56 to -16)	-34 mL/yr (-53 to -15)	-2 mL/yr (-30 to +26)	0.89
Non-smokers	All spirometry	n=361	n=328		
		-29 mL/yr (-45 to -12)	-22 mL/yr (-39 to -4)	-7 mL/yr (-31 to +17)	0.56
	Restricted to high-quality spirometry	n=353	n=321		
		-18 mL/yr (-29 to -7)	-27 mL/yr (-39 to -15)	+9 mL/yr (-8 to +25)	0.30
Pooled analysis	All spirometry	n=487	n=465		
		-30 mL/yr (-44 to -16)	-24 mL/yr (-39 to -10)	-6 mL/yr (-26 to +14)	0.56
	Restricted to high-quality spirometry	n=469	n=453		
		-23 mL/yr (-33 to -13)	-29 mL/yr (-39 to -19)	+6 mL/yr (-8 to +20)	0.39

Lung Function Decline

FEV_1: Forced expiratory volume in 1 second





Normal:
(-25 to -30 mL/yr)

COPD = **C** hronic
O bstructive
P ulmonary
D isease
(-50 to -60 mL/yr)

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Conclusions

- Immediate vs. Deferred ART has no impact on lung function decline in HIV(+) with CD4>500 cells/mm^3
- Immediate ART can be offered without concern for increasing COPD risk in these patients
- Other non-ART factors should be explored regarding potential effect of HIV on COPD risk

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HIV infection increases the risk of acute exacerbations of COPD

Aims: To determine the factors associated with AECOPD among people with and at risk for HIV infection

Methods: ALIVE cohort: ≥18 years old, inner city Baltimore, history of injecting drugs
- Spirometry and vitamin D measurements within 1 year

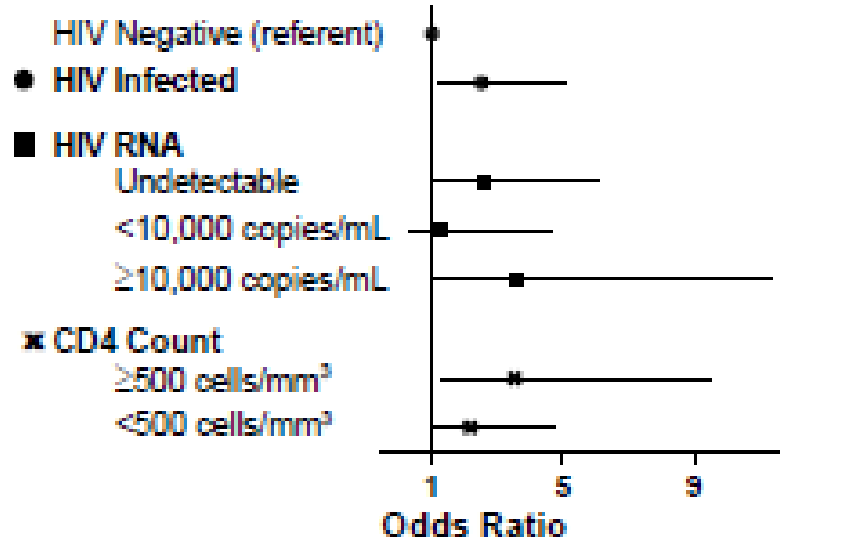
AECOPD Ascertainment: Answering "yes" to: "In the last 6 months, have you had a worsening of your breathing status requiring treatment with antibiotics or steroids.

CHARACTERISTICS ASSOCIATED WITH AECOPD

Covariate	Adjusted OR (95% CI)	p-value
Female	2.67 (1.32, 5.41)	0.006
HIV Infection	2.49 (1.21, 5.10)	0.013
Comorbid Disease*†	2.32 (1.17, 4.63)	0.016
Airflow Obstruction		
Mild (FEV1 ≥ 80% predicted)*	Reference	
Moderate (FEV1 50-79% predicted)*	2.63 (1.13, 6.14)	0.025
Severe (FEV1 < 50% predicted)*	5.86 (2.16, 15.85)	0.001

Odds Ratios mutually adjusted for other covariates in the table.

MULTIVARIABLE MODELS OF AECOPD



3 models presented, all with HIV Negative referent
(adjusted for gender, comorbid disease and COPD severity)

Inclusion of prior AECOPD into our models attenuated HIV effect

Conclusions

- HIV is an independent risk factor for AECOPD
- Healthcare providers should consider a diagnosis of AECOPD in a patient with HIV infection or with frequent respiratory symptoms as this diagnosis is likely under-recognized

Lambert A, CROI 2104, abs 773

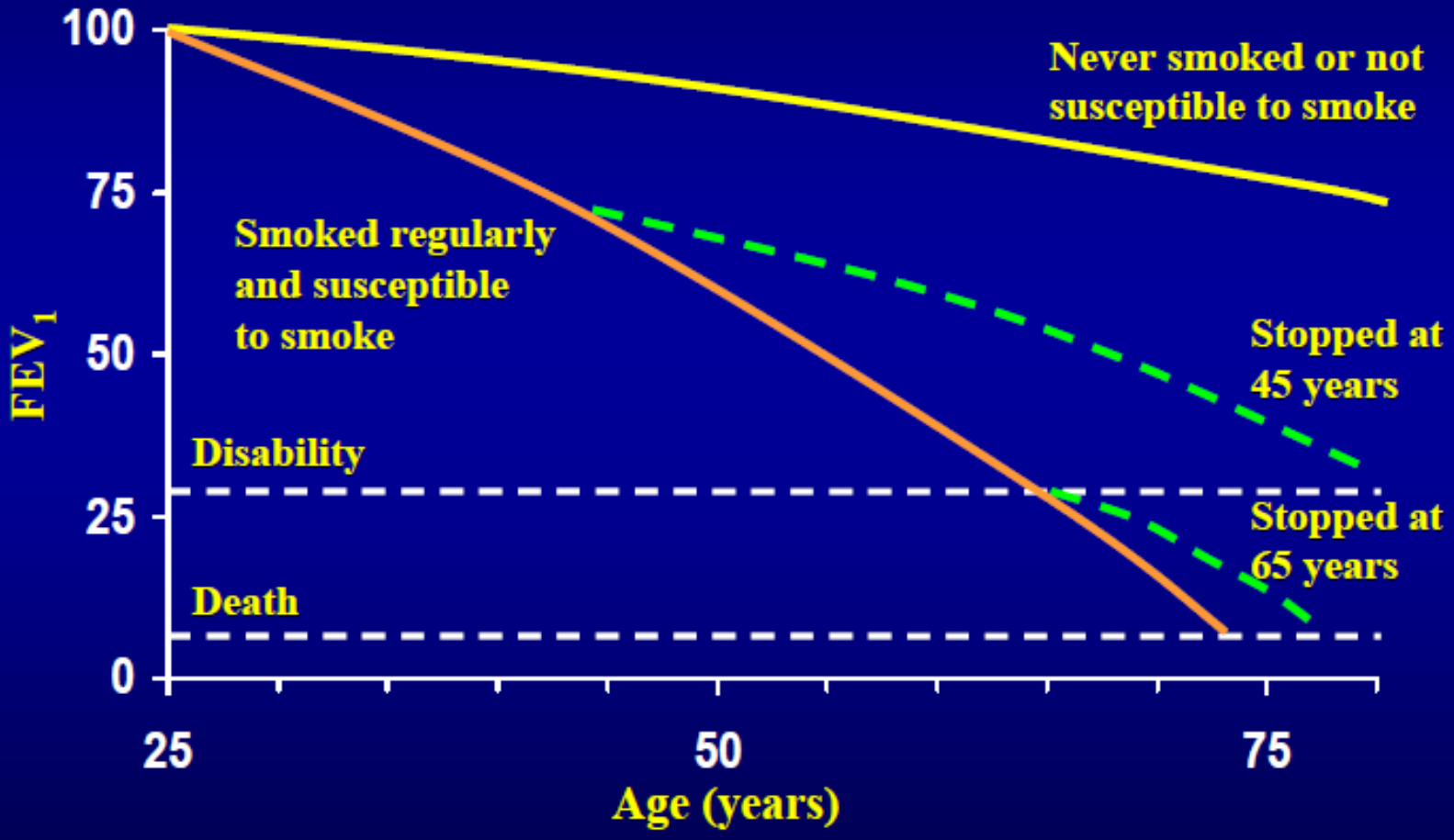
Management of COPD

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: Key Points

- Smoking cessation has the greatest capacity to influence the natural history of COPD. Health care providers should encourage all patients who smoke to quit.
- Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
- All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active.

Smoking and lung function decline



Fletcher et al, BMJ 1977

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: COPD Medications

Beta$_2$-agonists
Short-acting beta$_2$-agonists
Long-acting beta$_2$-agonists
Anticholinergics
Short-acting anticholinergics
Long-acting anticholinergics
Combination short-acting beta$_2$-agonists + anticholinergic in one inhaler
Combination long-acting beta$_2$-agonists + anticholinergic in one inhaler
Methylxanthines
Inhaled corticosteroids
Combination long-acting beta$_2$-agonists + corticosteroids in one inhaler
Systemic corticosteroids
Phosphodiesterase-4 inhibitors

HIV and COPD: Drug interactions

Bronchodilator	Atazanavir	Darunavir	Lopinavir	Ritonavir
Ipratropium bromide	◆	◆	◆	◆
Salbutamol	◆	◆	◆	◆
Salmeterol	■	■	■	■
Theophylline	■	■	■	■

Steroids	Atazanavir	Darunavir	Lopinavir	Ritonavir
Budesonide	■	■	■	■
Fluticasone	■	■	■	■

NNRTI: no significant drug interactions

INI: elvitegravir/cobicistat interactions with fluticasone, budesonide and salmeterol; RAL and DTG no interactions

Maraviroc: no significant drug interactions

www.hiv-druinteractions.org

HIV and COPD
EACS guidelines 2015 v8.0

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment
Pulmonary disease	CXR	+/-		As indicated	Consider CXR if prior history of pulmonary disease
	Spirometry			As indicated	Screen for COPD in at risk persons[xii]

xii A diagnosis of COPD should be considered in persons over the age of 35 who have a risk factor (current or ex-smoker) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze.

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

Individuazione dei fattori di rischio	Alla prima visita raccogliere le informazioni sui fattori di rischio per BCPO, quali: - Familiarità; - Esposizione ad inquinanti: • Fumo di tabacco (attuale o pregresso, con durata nel tempo e numero di sigarette /die). • Polveri organiche ed inorganiche in ambiente di lavoro • Inquinamento domestico legato alla cottura di alimenti e al riscaldamento di ambienti poco ventilati con uso di biocarburanti; • Inquinamento atmosferico. - Alterati sviluppo e crescita dell'apparato respiratorio; - Sesso; - Eta; - Infezioni respiratorie (comprendenti le infezioni opportunistiche e la PCP); - Stato socio-economico; - Asma / Iperreattività bronchiale; - Bronchite cronica.	[AI]	[1-2]
	Alle visite successive raccogliere informazioni relative ai sintomi cronici di BPCO (dispnea, tosse con o senza espettorato,e/o esposizione a fattori di rischio). e sul permanere del tabagismo.	[AI]	[1,3]
Stima del rischio	In tutti i pazienti con sintomi clinici di BPCO e/o esposizione a fattori di rischio è raccomandato un esame spirometrico .	[AI]	[4-5]
	Un VEMS/CVF< 0,70 conferma la presenza di ostruzione bronchiale e quindi conferma la diagnosi di BPCO.	[AI]	[1]

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

PERCORSO DI VALUTAZIONE	RACCOMANDAZIONI/NOTE	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Interventi sugli stili di vita	Astenersi dal fumare modifica la storia naturale della malattia, aumenta la speranza di vita, e i pazienti che ancora fumano devono essere invitati a smettere. La vareniclina è risultata ben tollerata ed efficace nel favorire la sospensione del fumo nei pazienti in terapia antiretrovirale.	[AI] [A1]	[9-12, 21] [22]
Terapia antiretrovirale	cART riduce il rischio di recrudescenze infettive polmonari. La terapia antiretrovirale non risulta quindi rappresentare un fattore di rischio per BPCO.	[AII]	[13-15]
Terapia complementare	Una appropriata terapia farmacologica consente di alleviare i sintomi di BPCO, di ridurre frequenza e gravità delle riacutizzazioni, e di migliorare la qualità della vita e la tolleranza allo sforzo in pazienti con BPCO. Nessun trattamento ad oggi disponibile è in grado di ridurre il declino funzionale respiratorio associato alla BPCO.	[AI]	[1, 16, 17]
	Le vaccinazioni antiinfluenzale e anti-pneumococcica vanno offerte ai pazienti affetti da BPCO in accordo con le indicazioni specifiche per i pazienti HIV+.	[AI]	[18]
	Occorre prestare attenzione al rischio di interazione farmacologica tra farmaci broncodilatatori e alcuni antiretrovirali.	[BII]	[19]

Conclusions

- ✓ The prevalence of COPD is higher in HIV infected patients than in the general population.
- ✓ Cigarette smoking seems to accelerate the development of COPD induced by HIV infection itself with different possible mechanisms.
- ✓ The clinical evaluation of chronic respiratory symptoms and pulmomary function tests are indicated in patients with HIV infection, especially if smokers.
- ✓ Smoking cessation should be considered the first intervention to prevent the development and to slow down the progression of COPD in HIV-infected patients.