British HIV Association
BHIVA

HIV and the lung

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Outline

- Epidemiology of chronic lung disease (CLD)
- Spectrum of chronic lung disease (CLD)
- Future research direction

Not talking about

- Acute respiratory disease/ Infections

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Lung disease the ART era

- Substantial mortality declines with ART→ increased life-expectancy

- Drop in absolute incidence of respiratory tract infections: TB, PCP and pneumonia

- Increase in incidence of non-opportunistic lung disease in HIV-infected as a result of increased life-expectancy:
  - 3 × increase in mortality from obstructive airways disease from pre-ART era

--??increase greater than in the background population

---??does ART use reduce the burden of HIV-associated lung disease?

Pallela et al NEJM 1998; Grubb et al AIDS 2006
Louie et al J Infect Dis 2002; Crothers AJRCCM 2011

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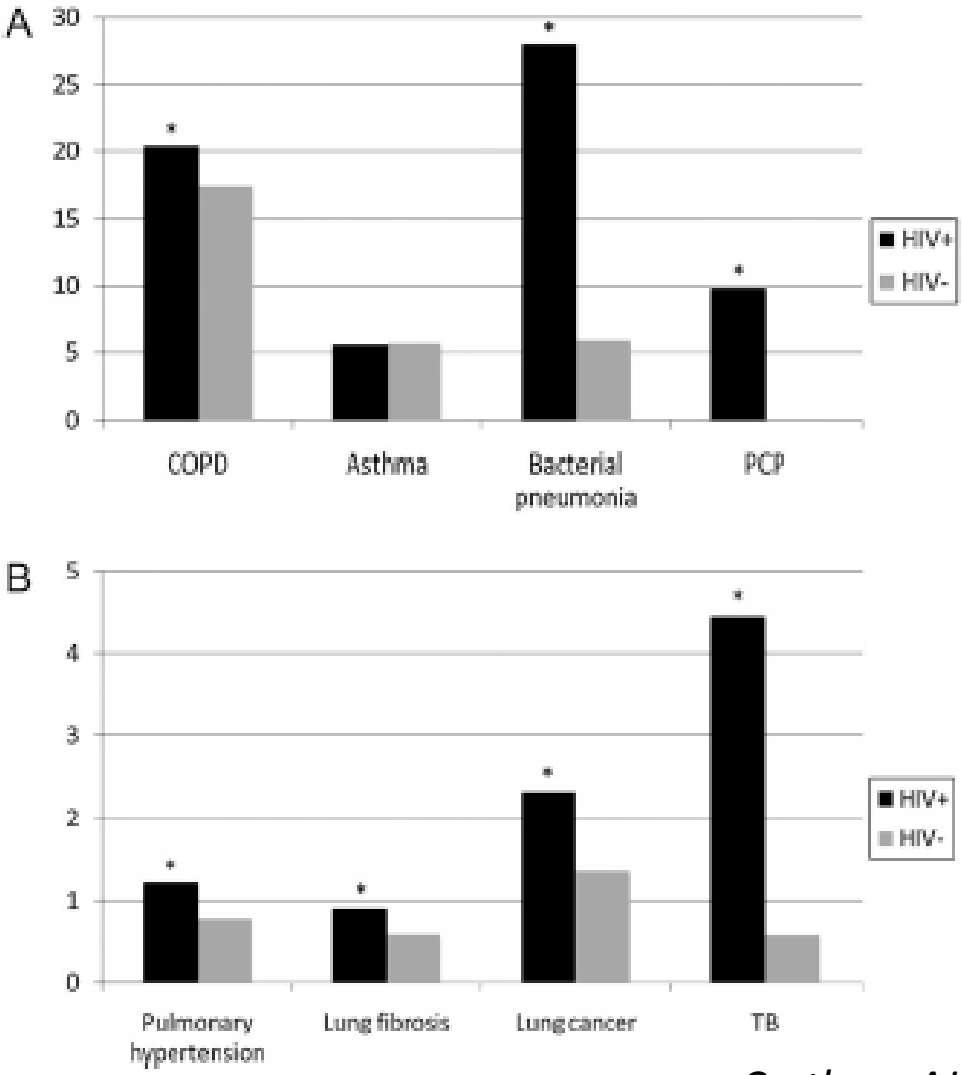
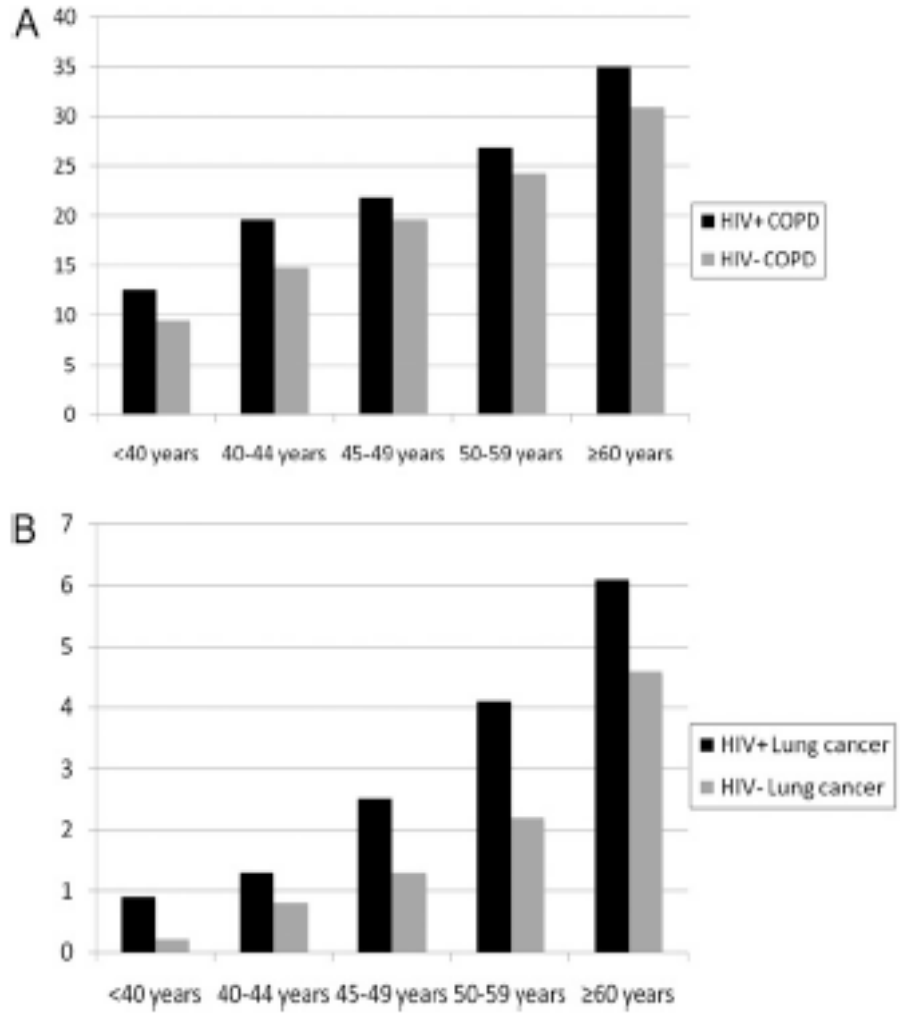
HIV Infection and Risk for Incident Pulmonary Diseases in the Combination Antiretroviral Therapy Era

Kristina Crothers[1,2], Laurence Huang[3], Joseph L. Goulet[2], Matthew Bidwell Goetz[4], Sheldon T. Brown[5], Maria C. Rodriguez-Barradas[6], Krisann K. Oursler[7], David Rimland[8], Cynthia L. Gibert[9], Adeel A. Butt[10], and Amy C. Justice[2,11]





Crothers AJRCCM 2011

Confounders

- Age
- Survival effect
- Smoking status (past and present)
- Recreational drug use
- Exposure to biomass fuels
- Frequency and spectrum of infections: TB, PCP, bacterial pneumonia

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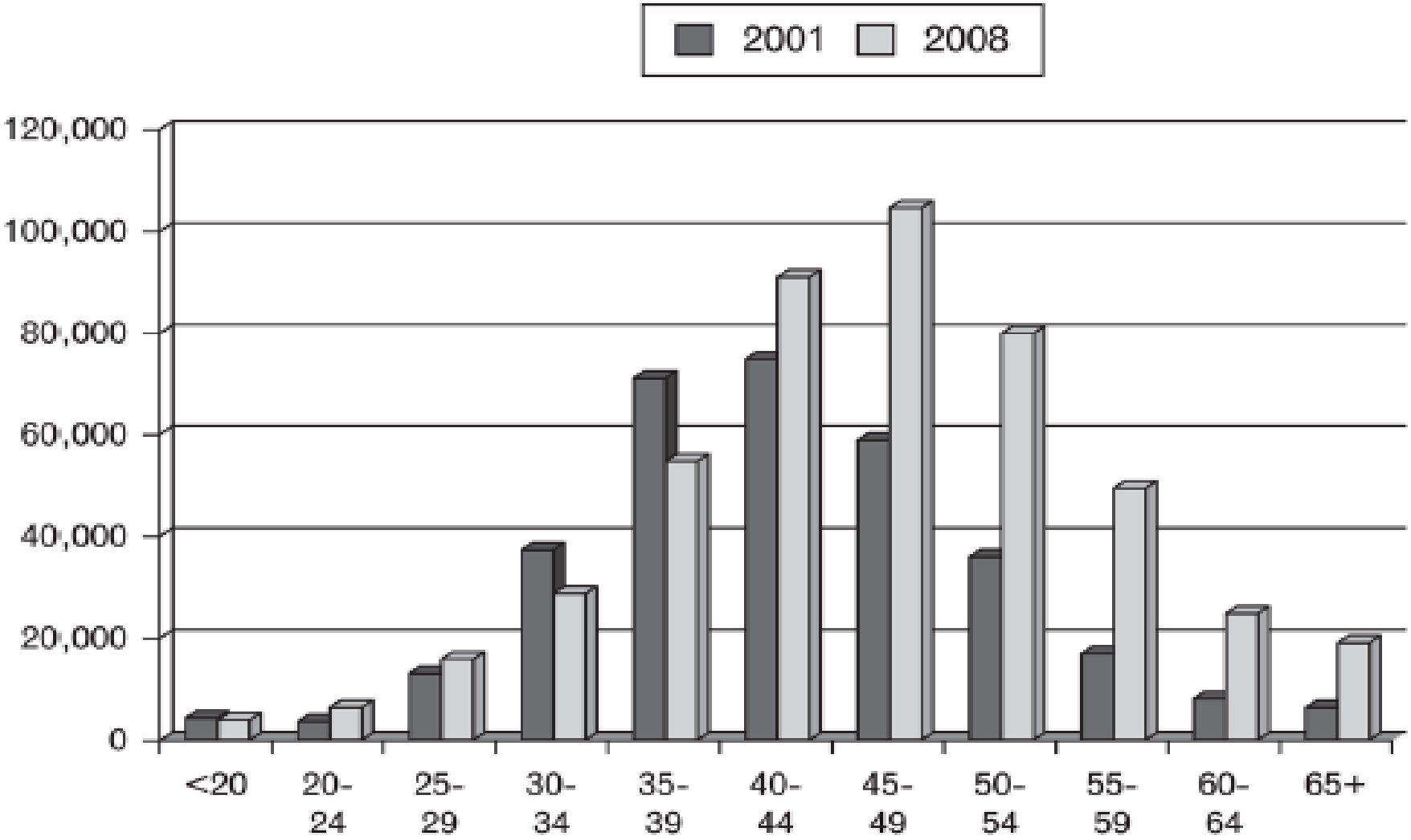
No of people living with AIDS, USA: 2001 vs 2008



Centers for Disease Control HIV Surveillance Report 2011
Adapted from Dubrow et al Curr Opin Oncol 2012

Chronic obstructive pulmonary disease (COPD)

- 3rd leading cause of death ; 5th leading cause of lost DALYS
- "Expiratory airflow limitation PLUS chronic airway inflammation"

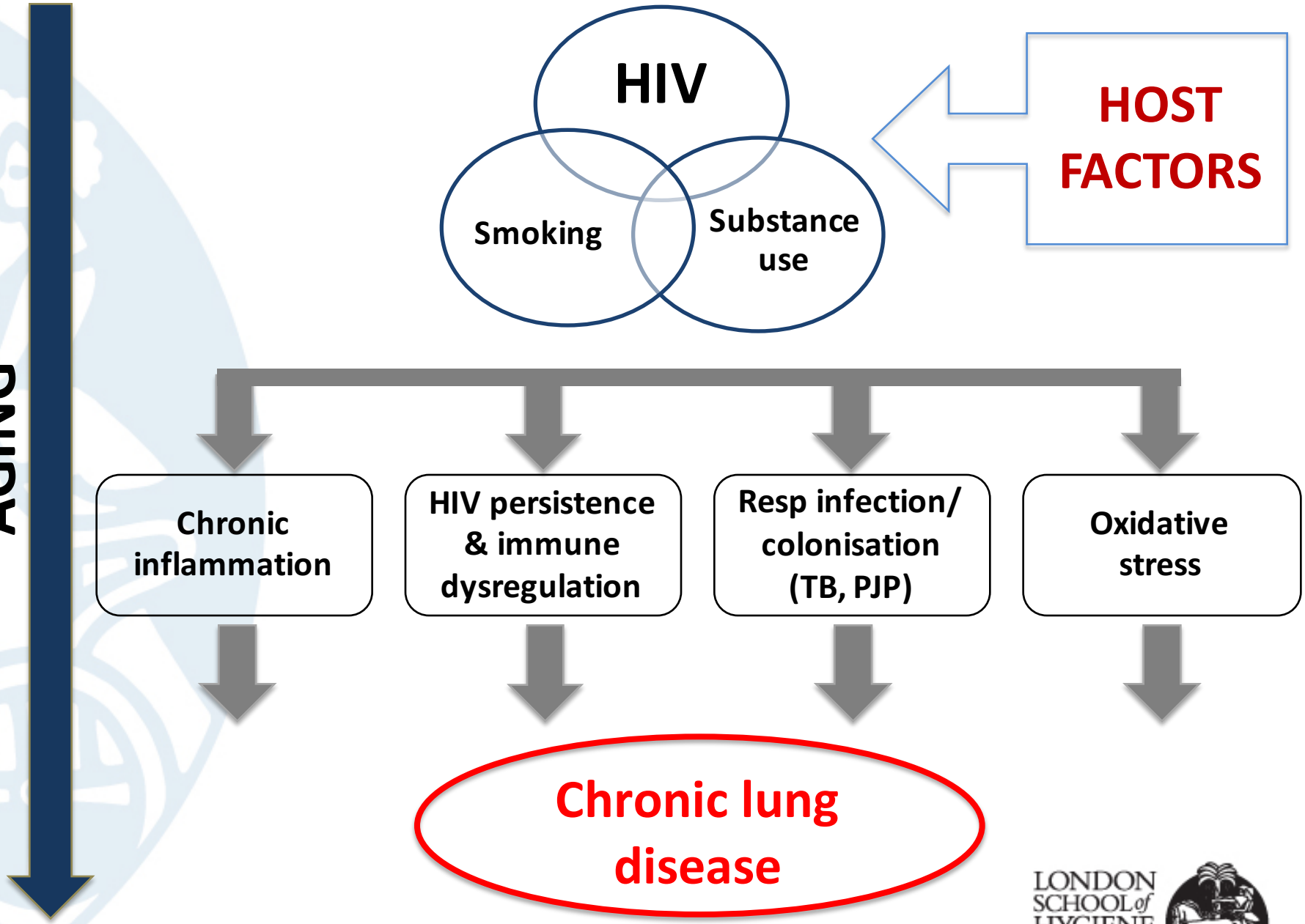
- FEV1 declines with age, smoking, infections

- HIV independently increases the risk of COPD
  - High viral load associated with faster decline rate

- ART and COPD risk:
  - 2 studies suggest no effect or an increased risk with ART[1,2,3]
  - small studies, observational, selection bias, rely on reported symptoms

Drummond Thorax 2012

[1]Crothers AJRCCM 2011; [2]George PloS One 2009 [3]Gingo 2010 AJRCCM



Crothers AJRCCM 2011; Van Zyl Smit Eur Resp Journal 2010

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Pathogenic mechansims

- Colonisation with Pneumocystis *jirovecii*: induce MMP activity and lung tissue destruction
- Altered microbiome
- Abn accumulation of CD8 cells –interact with macrophages to release chemokines, cytokines, Growth factor
- Systemic inflammation
- Oxidative stress—low levels of gluthathione
- Immunesenescence

→correlation with clinical findings and spirometry

Twigg Clin Chest Med 2013; Morris AJRCCM 2000; Almovodar Viral Immunology 2014

Therapeutic considerations

- Ritonavir and inhaled corticosteroid interaction→ hypercortisolism
  - FLUTICASONE > BUDESONIDE > (BECLOMETHASONE)
  - Systemic steroids: levels of PI may be reduced
  - Increased risk of infection

→ Long-acting muscarinic antagonists as first-line inhaled therapy

- PAF risk of death assoc with smoking double in HIV+ : special effort on smoking cessation

- Pulmonary rehabilitation increased importance:
  - synergistic effect of COPD and HIV on physical disability

?role and optimal type of exercise training

Nici et al Am J Resp Crit Care Med 2006

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Lung Cancer & HIV

- Most common non-AIDS defining cancer (NADC): leading source of NADC mortality
- In **most** cohorts: incidence higher in people with HIV compared to HIV-uninfected, **AFTER adjusting for smoking and age**

Sigel AIDS 2012	VACS cohort 37294 HIV+; 75,750 HIV-	**IRR: 1.7 (1.5- 1.9)**
Shiels JAIDS 2010	ALIVE cohort: IVDU 1072 HIV+ ; 1423 HIV-	**HR: 2.3 (1.1-5.1)**
Engels J Clin Onc 2006	JHH cohort 5238 HIV+ (cf gen pop)	**SIR: 2.5 (1.6-3.5)**
Gingo PloS One 2013	MACS cohorts 1706 HIV+; 1774 HIV-	HR: 2.65 (0.29-24.4)

Smoking strata	HIV+ Lung cancer	HIV-ve lung cancer	IRR	P-value
Never smoker	19	30	1.6 (0.9-3.0)	0.08
Former smoker	55	91	1.7 (1.2-2.4)	<0.001
Current smoker	262	370	1.5 (1.3-1.7)	<0.001
Missing data	121	114	2.1 (1.6-2.7)	<0.001

Adjusted for age, sex, race, COPD, prev pneumonia

Sigel et al AIDS 2012

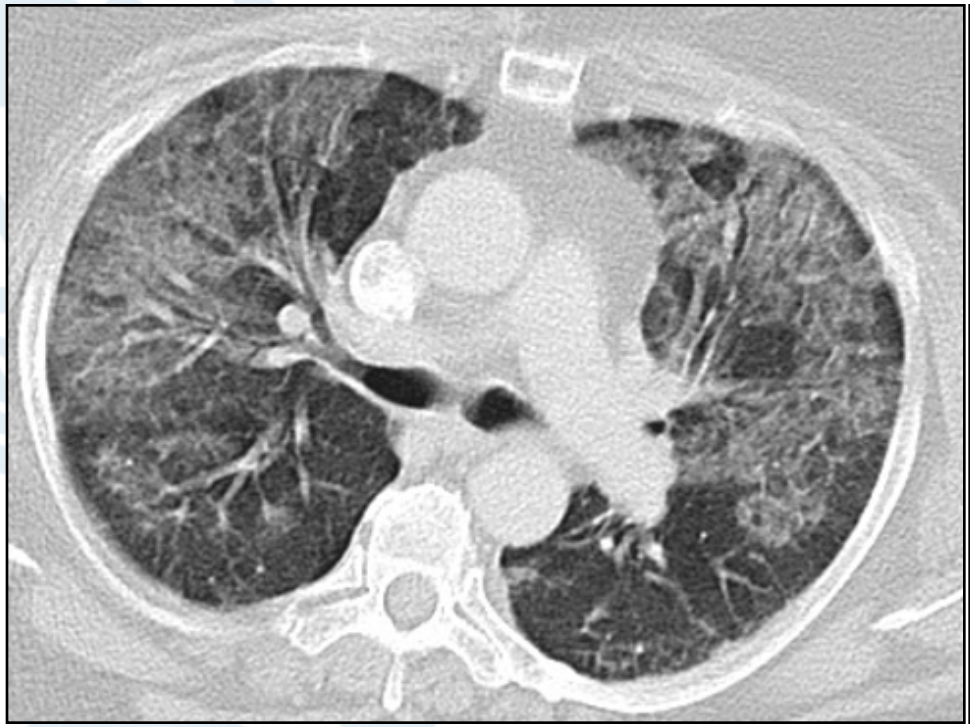
- No association with stage and morphology
- Overall prognosis: 10% at 24 months
- Hypothesised mechansims:
  - Decreased immune surveillance or impaired immune function
  - Enhanced susceptibility to carcinogens
  - Lung injury (2Y infections)
    - **? Screening and early detection in HIV-infected smokers**

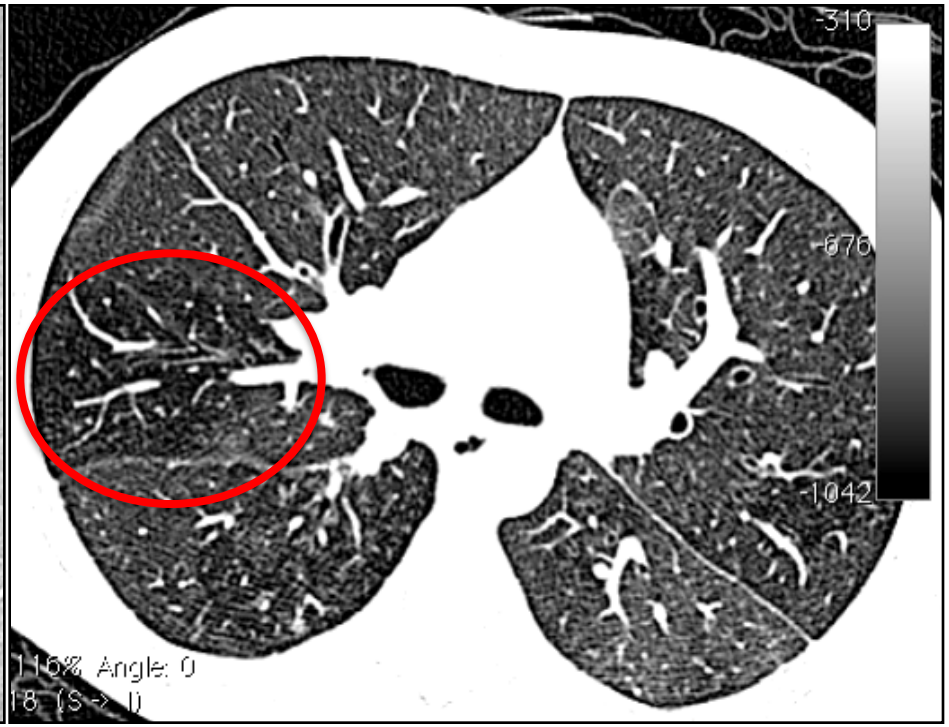
Lung disease: children

McHugh et al JAIDS 2016 In press
McHugh et al IUATLD 2015

	HIV-ve (n=150)	ART naive (n=379)	ART-experienced (n=201)
Median (IQR) Age (y)	11 (9-13)	11 (8-13)	11 (9-13)
Age at diagnosis (y)		11.2 (8-13)	5.2 (IQR 2.9-8.2)
Time on ART (y)		0	5.6 (4.1-7.2)
CD4 count (cells/µl)		375 (215-599)	710 (458-904)
MRC Dyspnoea score >1	0 (0%)	46 (16%)	30 (15%)
Desaturation exercise	5 (6%)	24 (10%)	22 (11%)
FEv1 z-score <-1.64	1 (0.8%)	23 (10%)	7 (4%)
FVC z-score <-1.64	14 (11%)	43 (18%)	36 (20%)
Stunted (HFA z-score <-2)	12 (8%)	91 (23%)	36% (35)

Chronic Lung disease: children





Young children

Lymphoid Intestitial Pneumonitis
Diagnosed easily
Responds to corticosteroids /ART

Older children

Airways disease
Mostly un- or mis-diagnosed
Poor response to steroids/ ART

Ferrand et al Clin Infect Dis 2012

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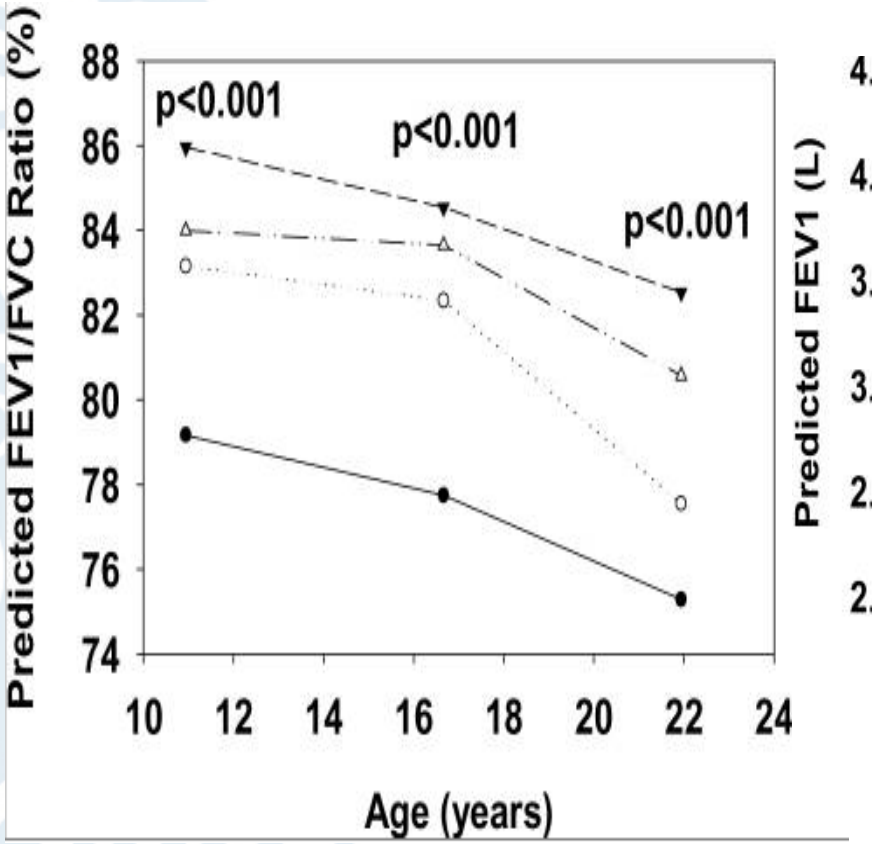
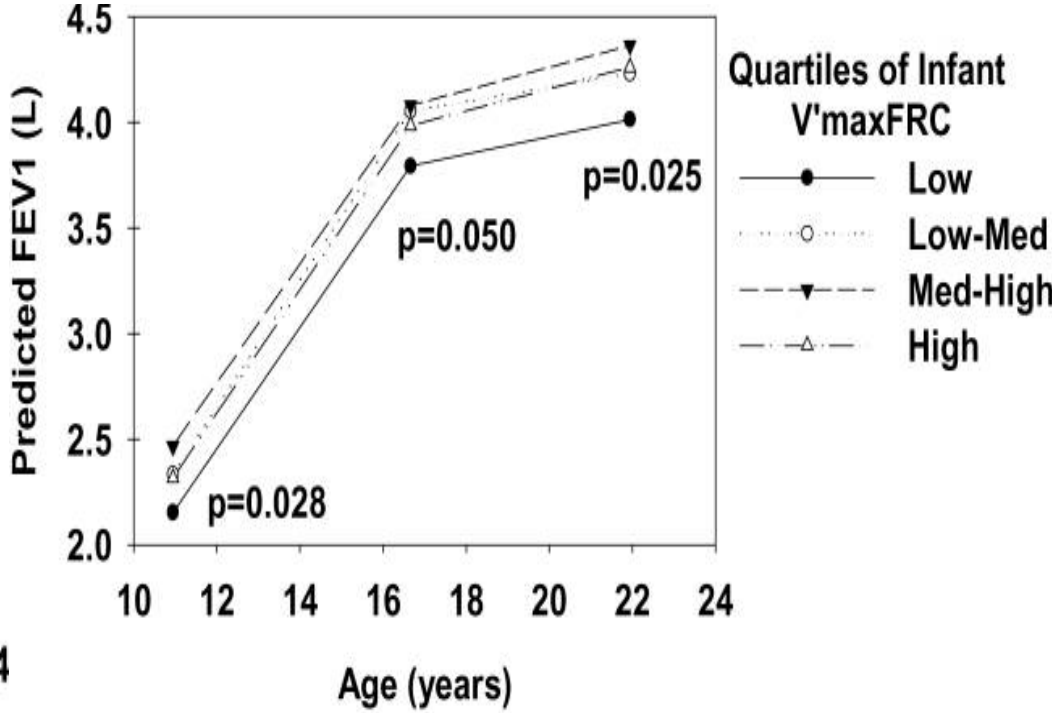
Tracking lung function in children





Predicted FEV_1/FVC ratio and FEV_1 mean values for males at ages 11, 16 and 22 years by length-adjusted infant V'max FRC quartile groups using random effects models. Predicted values were standardized to the mean height and weight for males at 11, 16 and 22 years.

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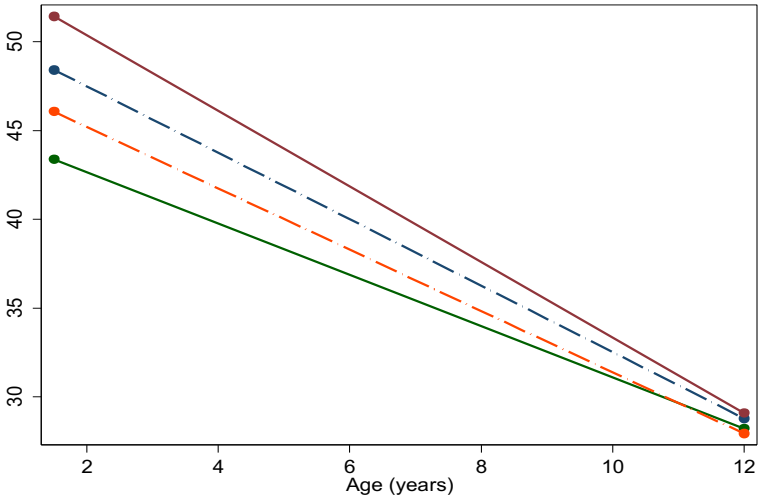
Stern et al Lancet 2007

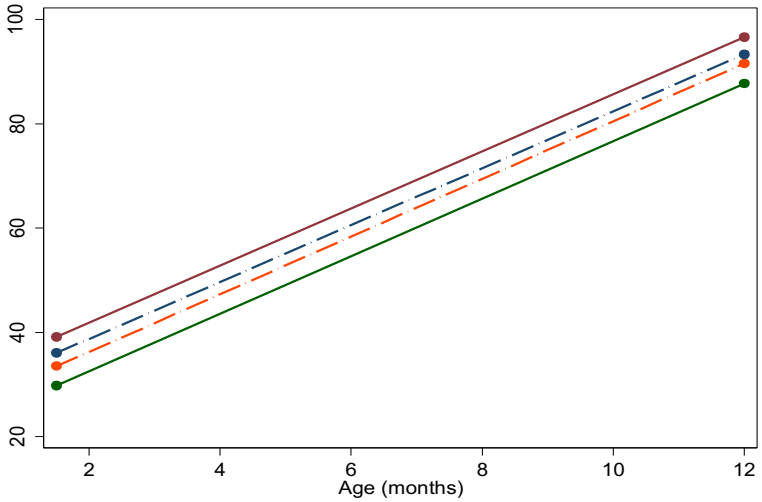
Tracking of lung function 6 weeks to 1 year:

matched unsedated 6 week and 1 year tests; n=279

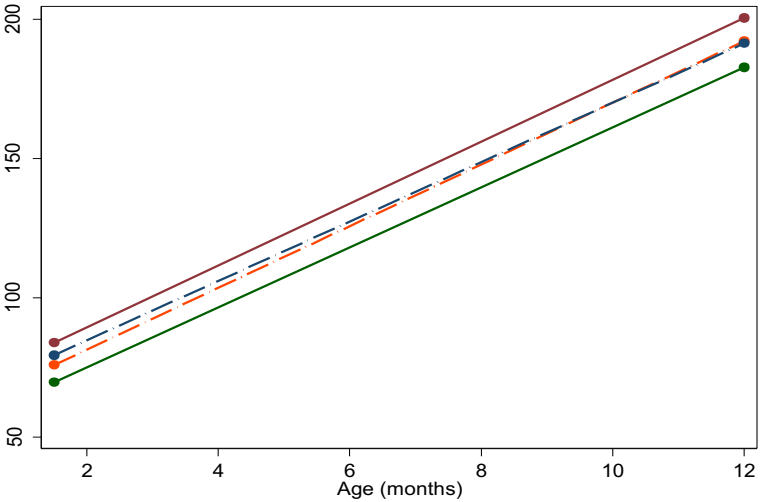
A. Respiratory rate/min



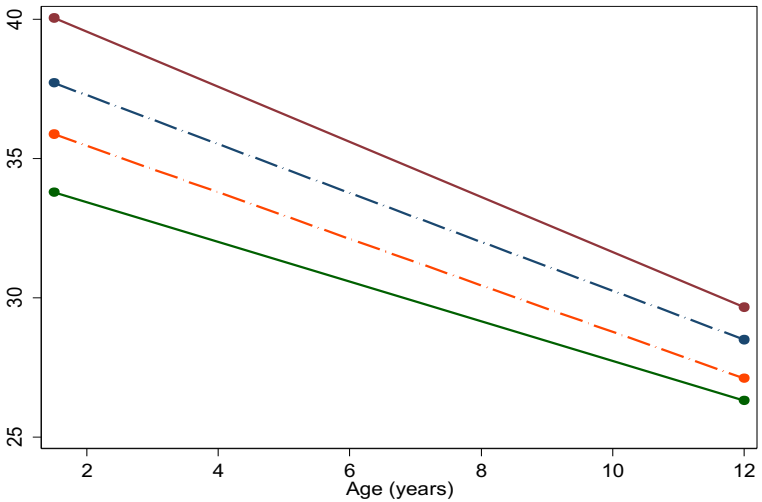
B. Tidal volume



C. Functional residual capacity

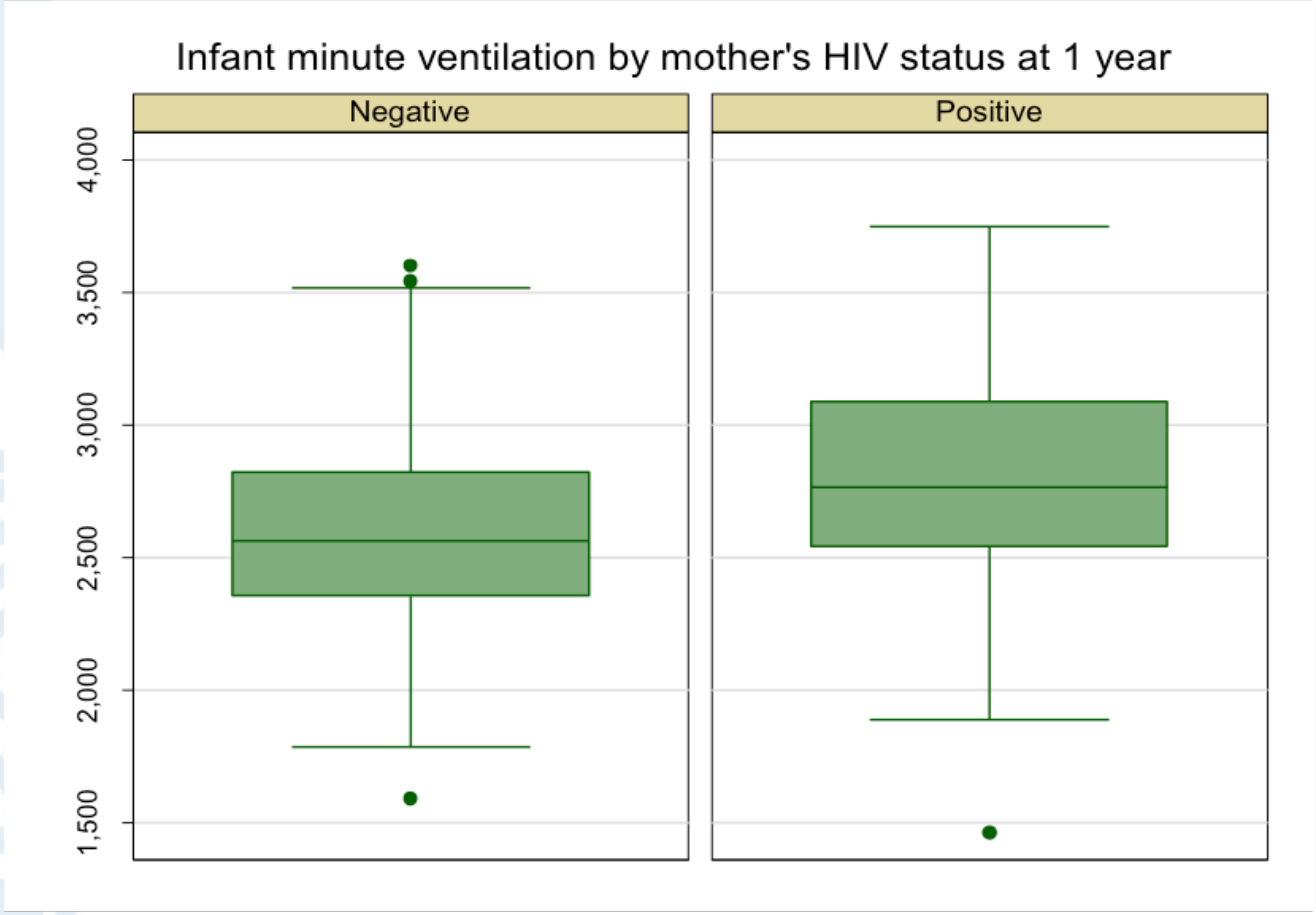


D. Ratio of peak tidal expiratory flow over total expiratory time



Slide: Lauren Willemse

Lung function at 1 yr: effect of maternal HIV infection



Infants of HIV infected mothers had increased minute ventilation compared to unexposed infants: 2.8 $L.min^{-1}$ vs. 2.6 $L.min^{-1}$; $p<0.001$, 95% CI 2.6 to 2.7): **ALL INFANTS HIV-NEGATIVE**

Slide: Lauren Willemse

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Global variation in epidemiology

- Coverage of HIV treatment and prevention

- Early life events
  - Nutritional deprivation
  - Smoke exposure
  - IUGR and pre-term delivery

- Environmental factors
  - Inorganic and organic dusts, metals etc
  - Household air pollution

- Health systems and the wider context
  - Public health approach to treatment
  - Capacity to diagnose and treat chronic conditions
  - Urban development
  - Tobacco control frameworks, political/economic stability

Rylance et al Semin Resp Crit Care Med 2016

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Summary

- Transition from acute to chronic lung disease- adults and children
- HIV a independent risk factor for chronic lung disease-COPD /cancer
- Screening and management strategies need incorporating into management of an increasing cohort of ageing HIV-infected patients
- Future Research:
  - Epidemiological data: impact of ART
  - Pathogenesis of lung disease: respiratory microbiome/immunology
  - Optimal screening and management strategies

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