

# Smoking as a Risk Factor for CAP



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# Respiratory Effects of Smoking

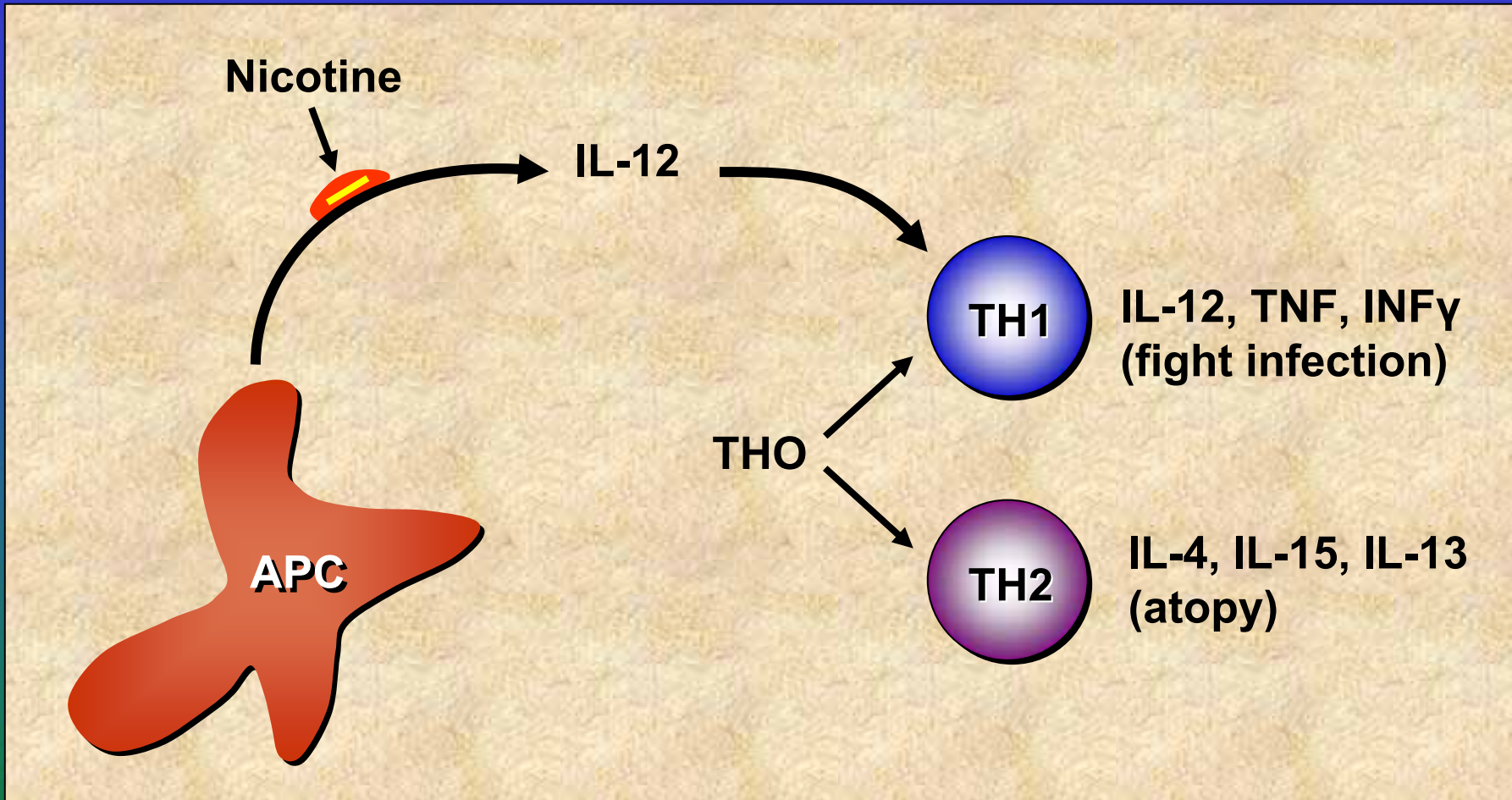
- CAP (including pneumococcus)
- More common colds
- Viral infections (influenza and varicella)
- Tuberculosis
- Fungal infections
- HIV progression
- Opportunistic infections in HIV
- Various other respiratory diseases

# Smoking Weakens Respiratory Defence

- Damage mucociliary function impairing clearance of inhaled substances
- Promote bacterial adherence to airway epithelial cells
- Increase alveolar vascular and epithelial permeability
- Affects the composition, appearance and function of pulmonary inflammatory cells
- Reversibly depress natural killer-cell function

# Mechanisms of Effects of Smoking

- Impaired mechanical defences
  - Mucociliary escalator
  - Bacterial clearance
  - Bacterial adherence
- Impaired innate immunity
  - Macrophages
  - Natural killer cells
  - Suppressed endogenous antibiotic peptide (hBD-2)
- Specific immunological effects
  - Immunoglobulins
  - Cytotoxic T-cells



# Smoking Increases Allergy

- Cultured human bronchial epithelial cell line
- Exposed to cigarette smoke extract and allergen penetration measured
- Three-fold increase in allergen penetration
- Augmented inflammation and activation of various cells

# Effect of Nicotine on Host Response

- Cholinergic nervous system can inhibit systemic inflammation accompanying sepsis by action of acetylcholine on  $\alpha 7$  cholinergic receptors
- Nicotine is an  $\alpha 7$  cholinergic receptor agonist

# Effect of Nicotine on Host Response

- In experimental intraperitoneal mouse model nicotine treatment transiently enhanced pneumococcal growth – higher bacterial loads in lung and blood at 24 hours
- Also enhanced lung inflammation at 24 hours
- Lung and plasma TNF and IFN- $\gamma$  at this time also increased

# Smoking CAP Risk in Elderly

- CAP occurrence in 717 persons  $\geq$  65 years hospitalized between 2002-2005 versus controls
- ORs of risk for CAP measured in relation to environmental and other variables
- Among others, exposure to cigarette smoke in past month was a risk factor (OR = 1,73 [1.04-2.90] for CAP
- Also lifetime history of having smoked > 100 cigarettes

Loeb *et al.* JAGS 2009

# Smoking Increases CAP Risk

- CAP occurrence in young soldiers was studied
- Relationship of nicotine dependence and development of CAP was studied
- Risk of pneumonia was higher in smokers than in non-smokers (OR 2.19 [1.13-4.23])

Children in Vietnam are exposed to substantial levels of tobacco smoke resulting in 44,000 excess hospitalizations for CAP in under 5's

		Cases	Controls	CR	95%CI	<i>P</i>
Age (yrs ± SD)		22.18±1.22	22.18±1.23	-	-	-
Gender M/F		58 / 0	580 / 0	-	-	-
Smoking Status	Non-smokers	12	211	1.00	-	-
	Fagerstrom score ≥3	29	267	1.91	0.95-3.83	0.065
	Fagerstrom score ≥6	17	102	2.93	1.34-6.36	0.005
	Total smokers	46	369	2.19	1.13-4.23	0.017

Tas et al. Inter Med 2008

		Cases	Controls	CR	95%CI	P
Non-smokers		12	211	1.00	-	-
How soon after you wake up do you smoke your first cigarette?	After 60 minutes	11	135	1.43	0.81-3.33	0.403
	31-60 minutes	17	129	2.31	1.07-5.00	0.029
	6-30 minutes	18	96	2.93	1.33-6.43	0.006
	Within 5 minutes	2	9	3.90	0.75-20.12	0.081

Tas et al. Inter Med 2008

# Incidence of CAP

- CAP occurs more commonly in HIV-seropositive patients
- All levels of CD4 count esp  $< 200\text{mm}^3$
- Higher prevalence in IV drug addicts

# Systemic Immune Defects Increasing Susceptibility to Pneumococcus

- CD4 lymphocyte depletion
- Loss of splenic and lymph node architecture
- Decreased RE clearance of opsonised particles
- Decreased dendritic cell function
- Increased activated circulating B cells producing non-specific IgG with altered immunoglobulin repertoire

# Incidence of CAP

- CAP occurs more commonly in HIV-seropositive patients
- All levels of CD4 count esp  $< 200\text{mm}^3$
- Higher prevalence in IV drug addicts
- Risk factors include:
  - neutropenia
  - low albumin ( $<30\text{ g/l}$ )
  - cigarette and drug smoking

<b>Characteristic</b>	<b>No. of episodes</b>	<b>Incidence, no. of episodes per 1 000 py</b>	<b>P value</b>
<b>Antiretroviral therapy</b>			
<b>None</b>	<b>264</b>	<b>9.5</b>	
<b>With 1 drug</b>	<b>208</b>	<b>7.8</b>	<b>&lt;0.01</b>
<b>With 2 drugs</b>	<b>78</b>	<b>7.5</b>	<b>0.05</b>
<b>With 3 drugs</b>	<b>26</b>	<b>5.0</b>	<b>0.01</b>

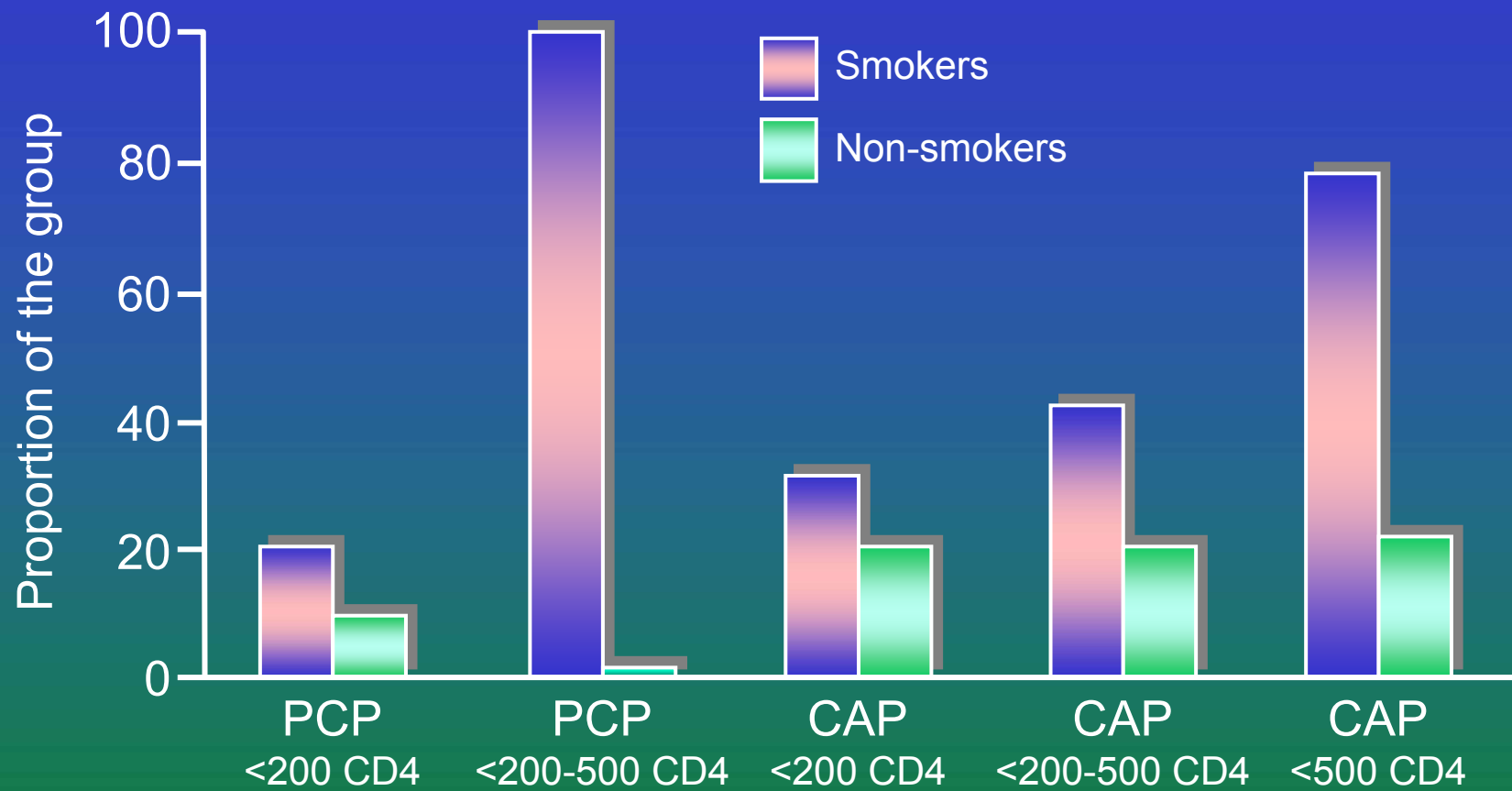
Dworkin *et al.* CID, 2001

# Pulmonary Manifestations in HAART era

- Retrospective chart review of HIV infected patients during two time periods
- PCP was less common
  - HAART was protective against PCP (OR 0.37 [0.61-0.89] in a manner dependent on CD4 count
- Bacterial pneumonia and non-Hodgkins lymphoma were more common
  - OR 2.41 [1.12-5.17] and 15.11 [3.14-28.32] respectively

# Increased Risk of LRTI with Smoking

- Study of 521 HIV-infected patients admitted to Jackson Memorial Hospital in Miami
- 65% were current smokers
- 40% smoking more than one pack per day
- 46% were on HAART and 42% were receiving PCP and/or NTM prophylaxis
- 49% admitted for pulmonary infection of which 52% were bacterial pneumonia and 24% PCP



Miquez-Burbano, *et al.* IJID, 2005

	Wald	Odds Ratio	Significance <i>p</i> -value
<b>Tuberculosis</b>			
Smoking	0.728	1.309	0.394
CD4	3.960	2.377	0.047
<b>PCP</b>			
Smoking	14.159	3.500	0.000
CD4	11.899	6.458	0.001
<b>Pneumonia</b>			
Smoking	12.586	2.278	0.000
CD4	0.206	1.118	0.650

## ***Pneumocystis* Colonisation of HIV-infected Men**

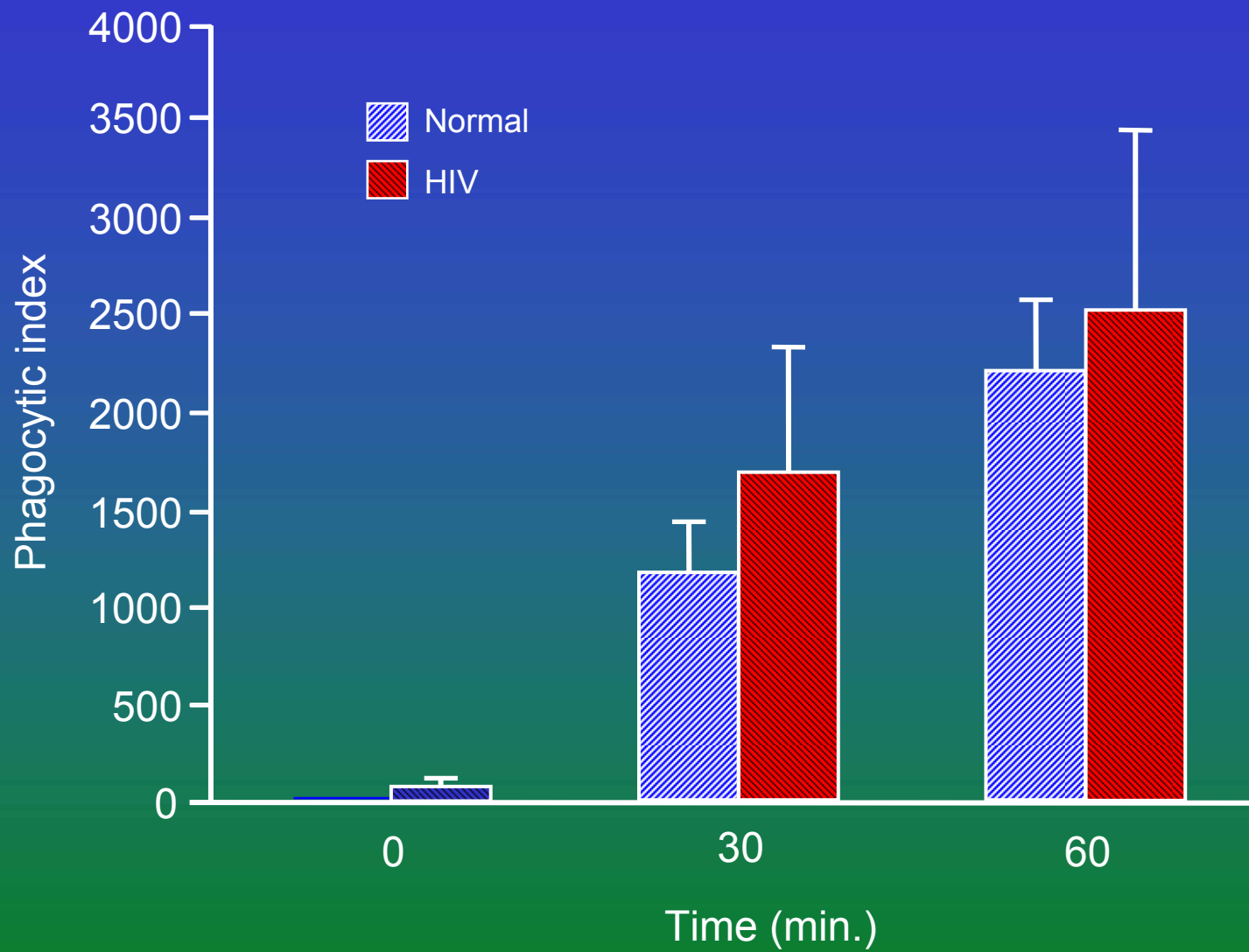
- Study was conducted among HIV-infected patients who died from causes other than pneumonia and agreed to PM
- Nested PCR on extracts of lung tissue to detect *Pneumocystis*
- Clinical data extracted from records
- Analysis undertaken of predictors of colonisation

# ***Pneumocystis* Colonisation of HIV-infected Men**

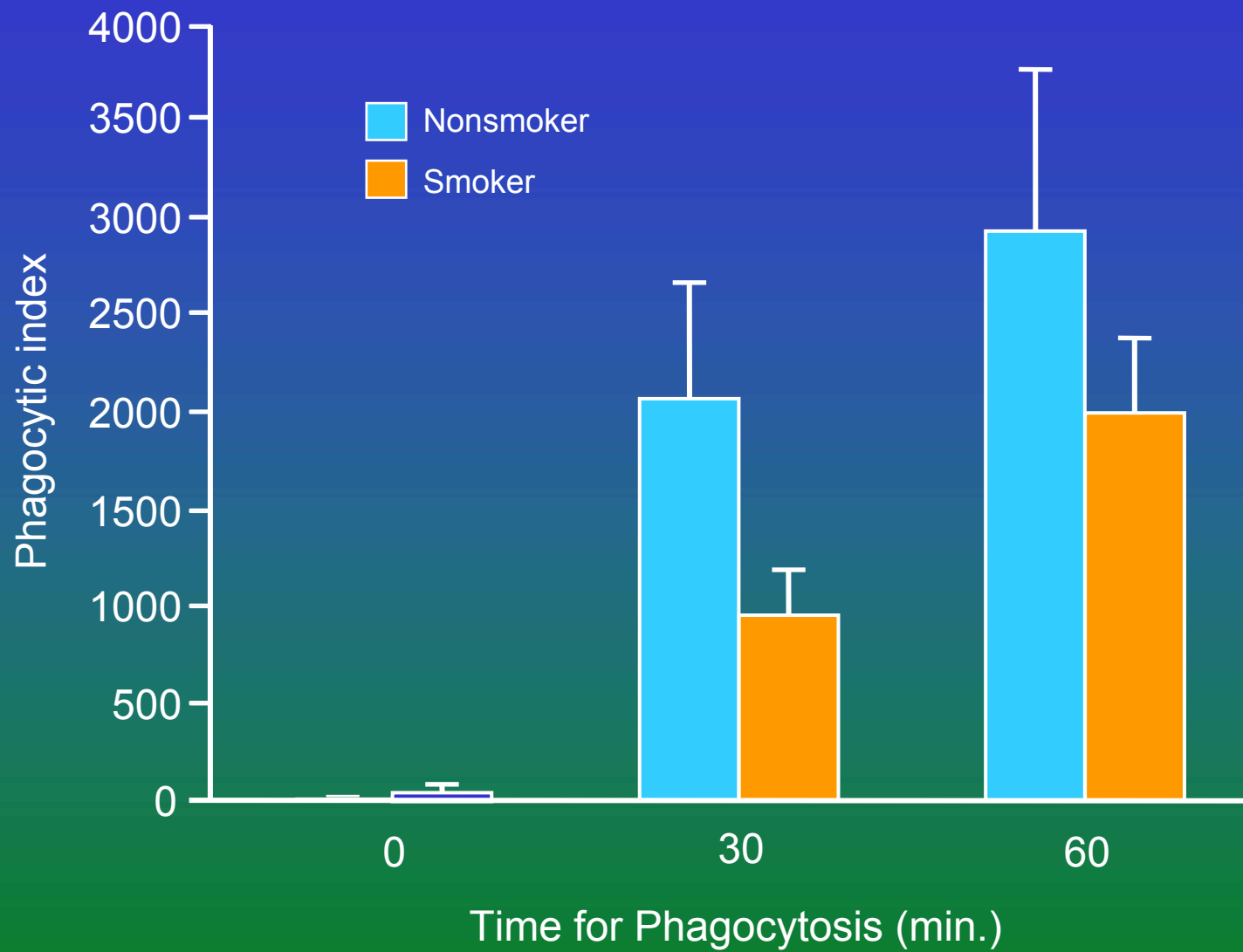
- Predictors of colonisation were
  - Cigarette smoking OR 4.5 [1.27-15.6]
  - City of residence OR 0.12 [0.03-0.45]
- The following did not predict colonisation
  - CD4 count
  - PCP prophylaxis
  - ARV
  - Previous PCP

# Impaired Macrophage Phagocytic Function in HIV-infected Smokers

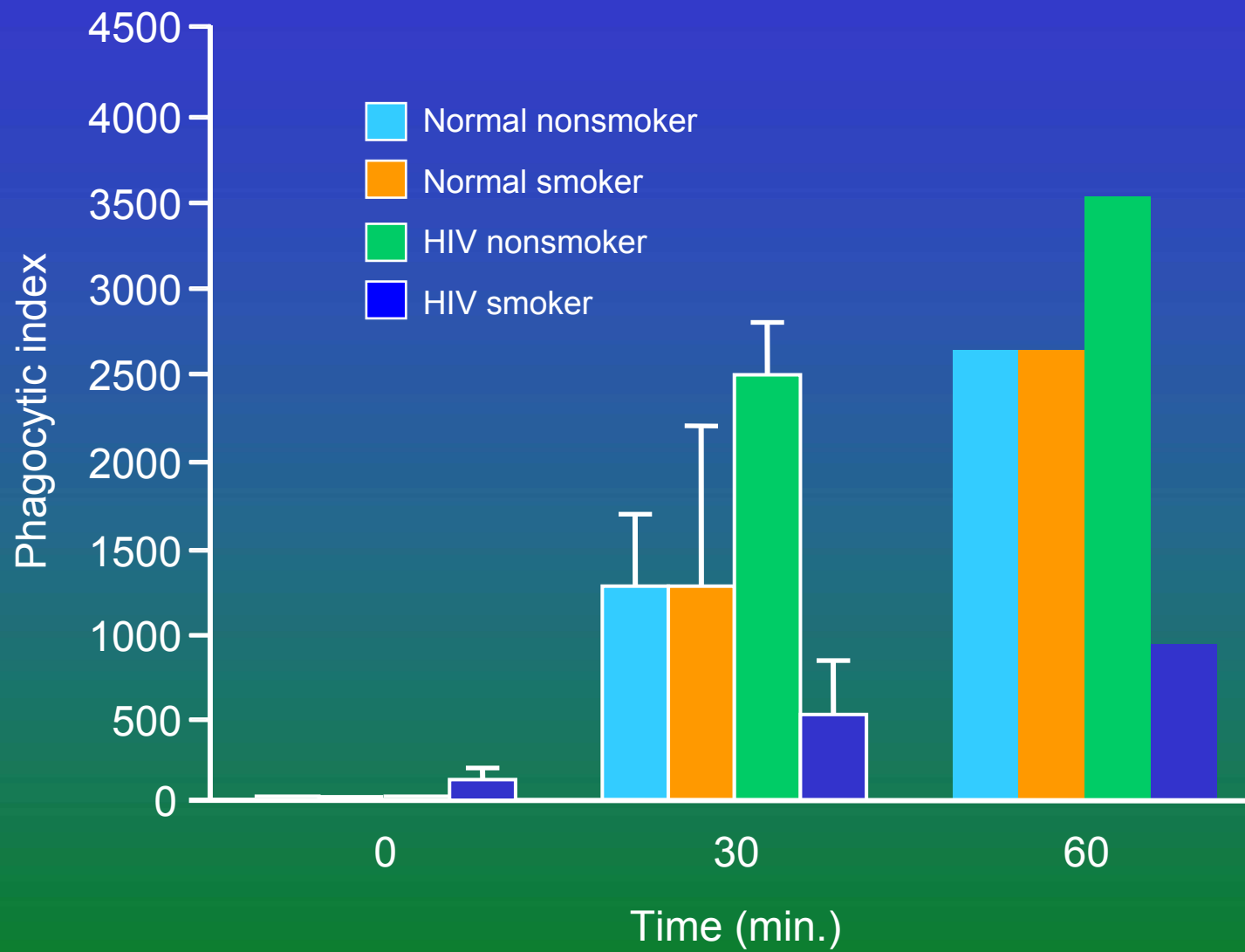
- Macrophage phagocytic activity was compared in asymptomatic HIV-infected patients and healthy seronegative controls
- No significant impairment of phagocytic capacity of HIV-seropositive versus HIV-seronegative cases
- Cigarette smoking depressed phagocytic activity



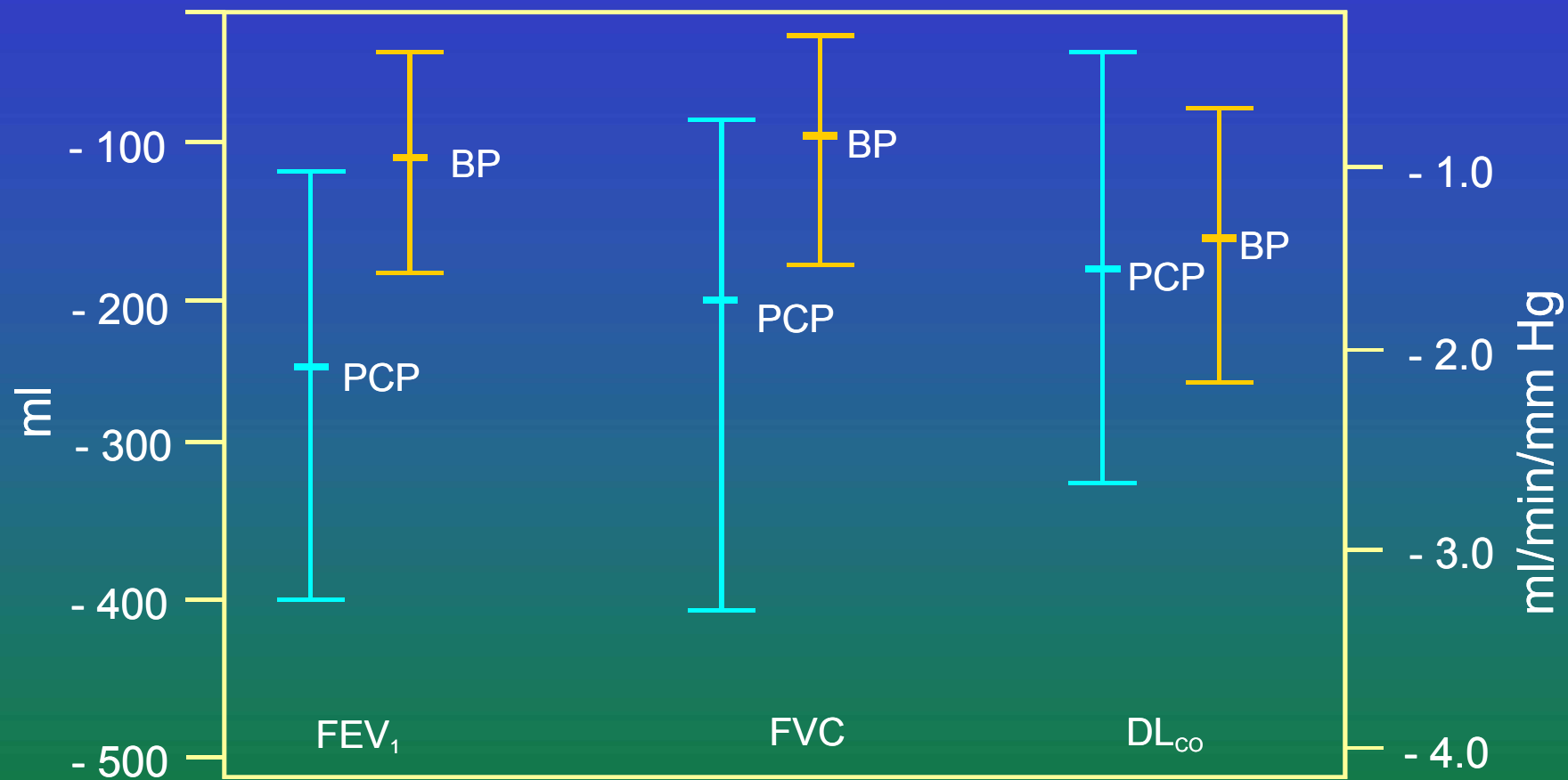
Elssner *et al.* Chest, 2004



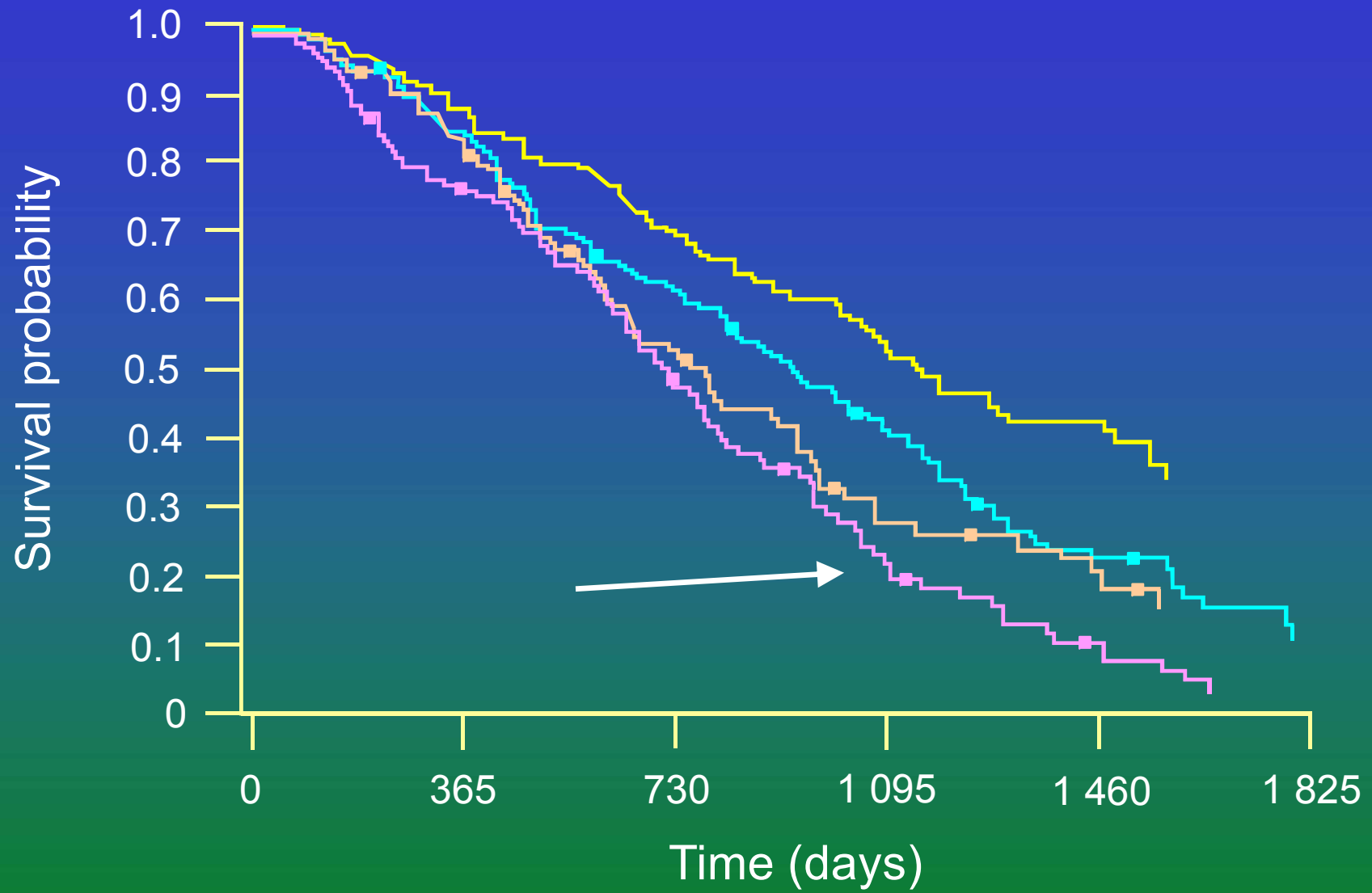
Elssner *et al.* Chest, 2004



Elsner *et al.* Chest, 2004



Morris *et al* Am J Respir Crit. Care Med: 2000



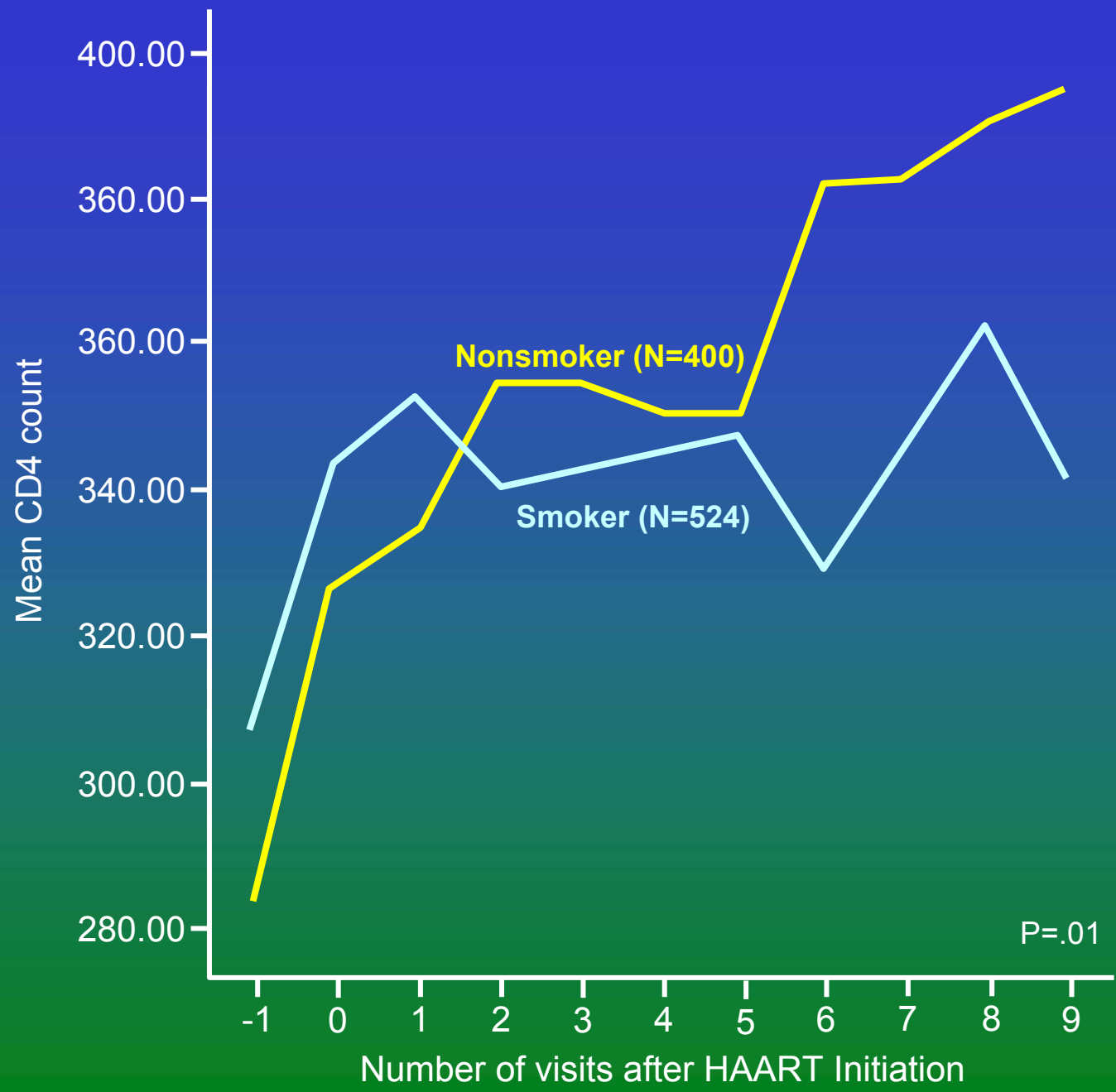
Osmond et al; CID, 1999

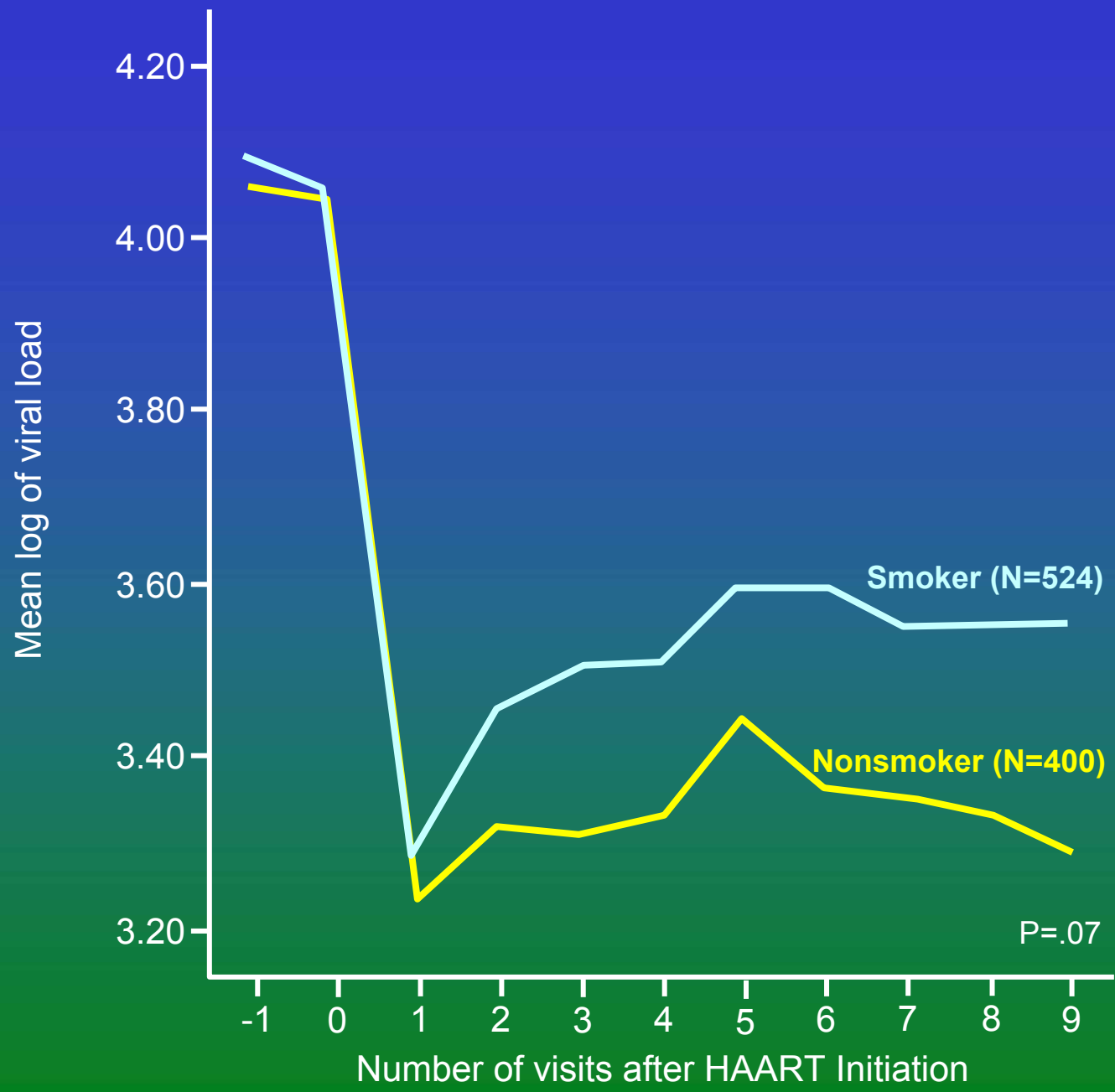
# Effects of Smoking on HAART

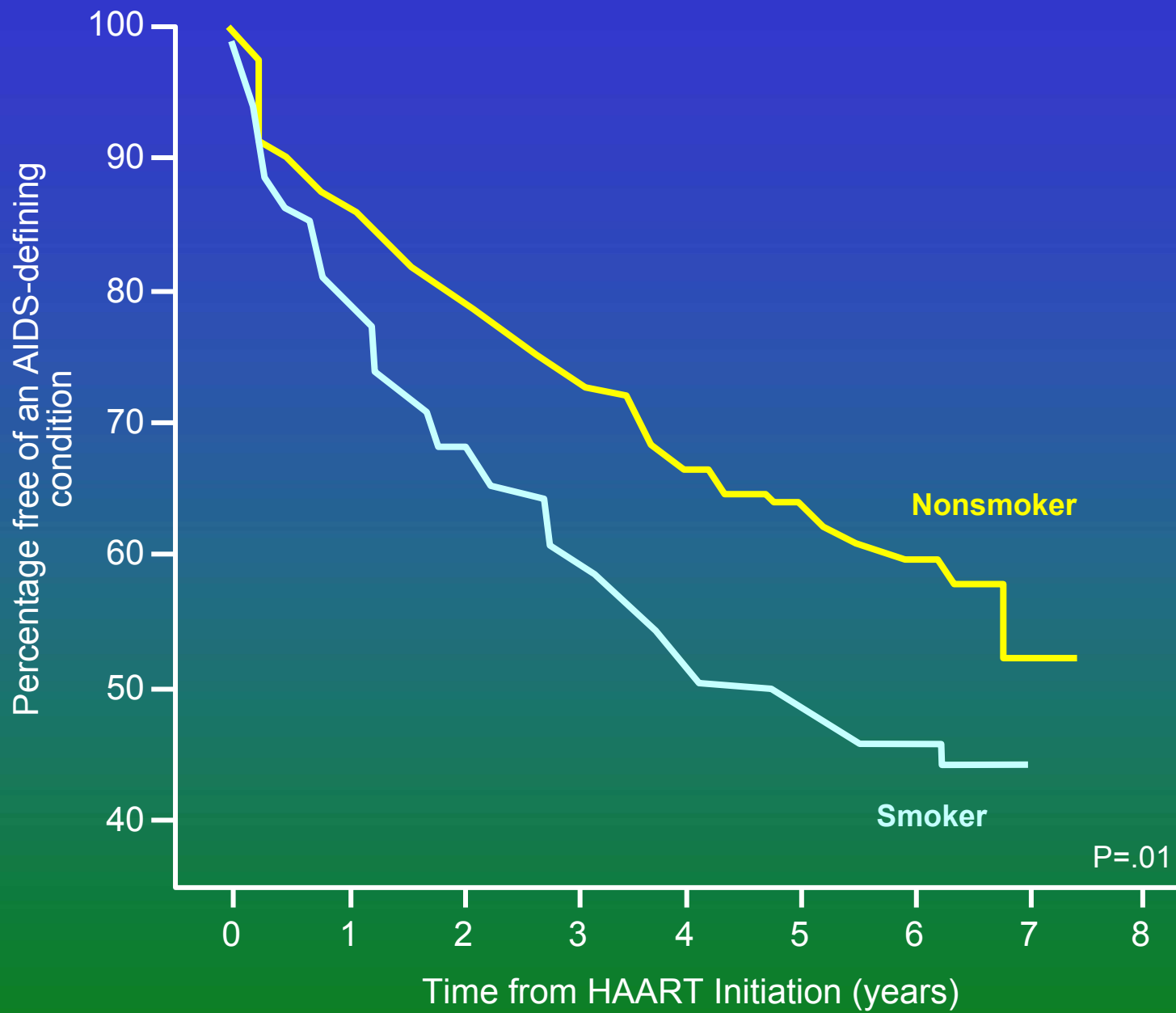
- Analysis of association of cigarette smoking with effectiveness of HAART in WIHS study of 924 women followed for 7.9 years ('95 – '03)
- Of the cases 56% were current smokers and 16% were former smokers
- The average amount smoked was 1 pack per day and the median duration was 12 years

# Effects of Smoking on HAART

- Smokers had
  - Poorer virological response (0.79)
  - Poorer immunological response (0.85)
  - Greater risk of virological rebound (1.39)
  - More frequent immunological failure(1.52)
  - Higher risk of death (1.53)
  - Higher risk of developing AIDS (1.36)







# Smoking as a Risk for HIV Infection

- Systematic review of the evidence for a relationship between smoking tobacco and HIV seroconversion and progression to AIDS
- Six studies had seroconversion as outcome measure and 5 indicated smoking as an independent risk with OR 1.6-3.5
- Ten studies had progression to AIDS as end point and 9 found no relationship
- Tobacco control and smoking cessation important components of HIV/AIDS care

# Local Effects of Smoking in HIV

- Peripheral CD4 counts decrease dramatically in smokers, particularly after initial seroconversion
- BAL fluid from smokers have lower CD4 counts and decreased production of IL-1 $\beta$  and TNF- $\alpha$
- Smoking increases susceptibility of alveolar macrophages to HIV infection and their phagocytic function is markedly impaired

## **Additional Effects of Smoking**

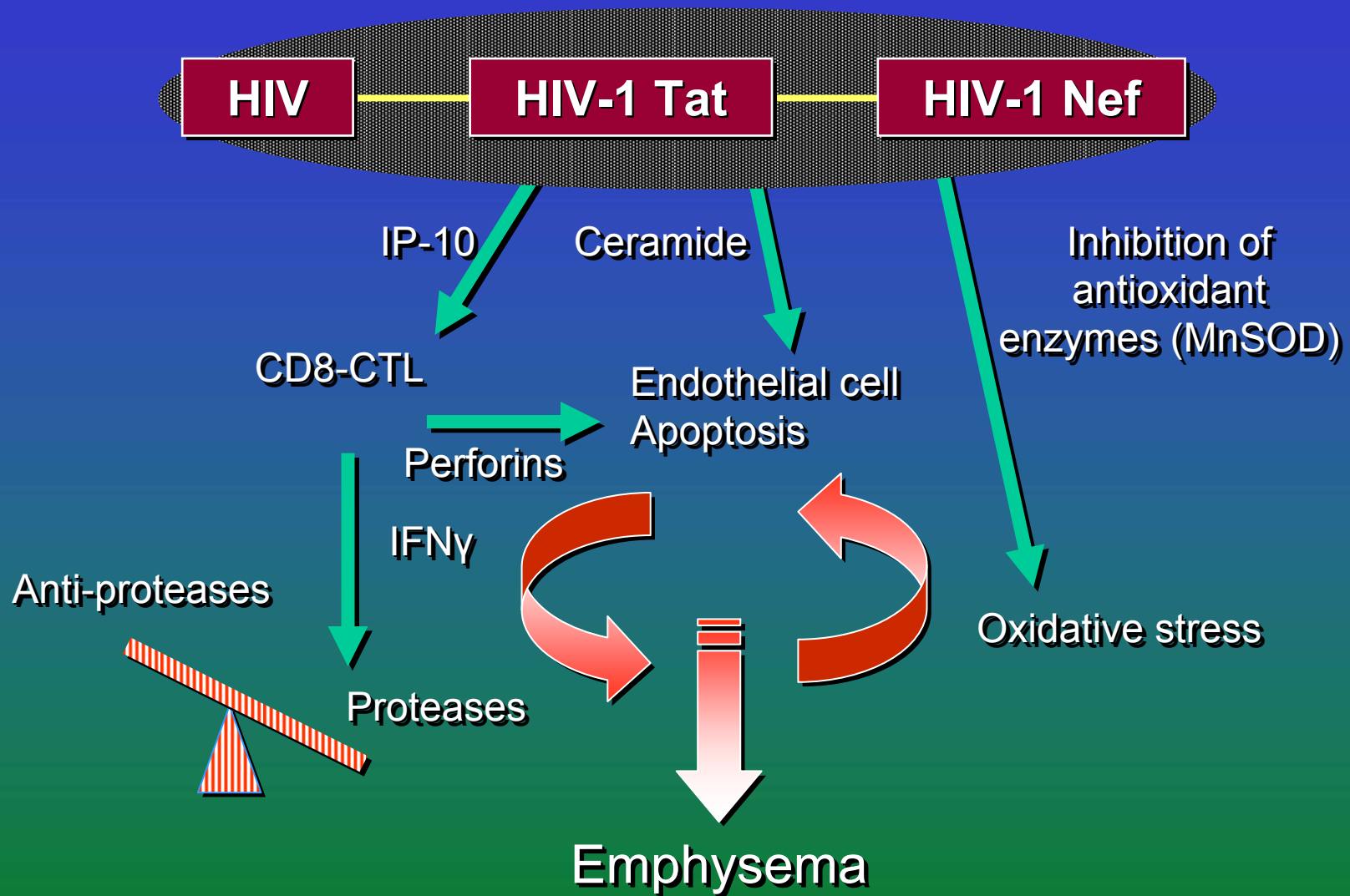
- Increase in respiratory symptoms (cough, sputum, wheeze, dyspnoea) in patients with HIV infection
- Increased bronchial hyperresponsiveness
- Accelerated form of emphysema
- Accelerated form of bronchiectasis especially in pre-HAART era
- Increased risk of mother to child transmission of HIV in pregnant women who smoke (31% versus 22%)

# Additional Effects of Smoking

- Increased risk of cancers
  - Lung cancer, Kaposi's sarcoma, cervical cancer
- Impaired oral health
  - Accelerated periodontal disease, increased oral candidiasis, hairy leukoplakia, oral tumours
- Lower quality of life scores
- Independent risk factor for non-AIDS related mortality even in patients on HAART

# Smoking and Emphysema in HIV

- HIV positive cases have a propensity for developing emphysematous changes in the upper lobes
- Confounding factors
  - *Pneumocystis* colonisation
  - Drug use
  - Malnutrition
- HIV itself is an independent risk factor



# Additional Effects of Smoking

- Smoking-related interstitial lung disease
  - RB-ILD
  - DIP
  - Pulmonary Langerhans cell histiocytosis
  - (UIP)
- Smoking induced acute eosinophilic pneumonia
  - In a “new” smoker, confirmed on challenge testing

Rao *et al.* Annals Diagn Path 2008  
Bok *et al.* J Korean Med Sci 2008

# HIV Infection and Lung Cancer

- Prospective observational cohort study conducted since 1998
- Among 2086 participants, 27 lung cancer deaths were observed, 14 among HIV-infected persons
- Lung cancer risk increased during the HAART era (MRR 4.7 [1.7-16])
- Smoking was the major risk factor
- After adjustments, HIV infection was associated with increased lung cancer risk (HR 3.6 [1.6-7.9])
- Preexisting lung disease (non-infectious disease and asthma) displayed trends for increasing risk

## And TB Makes Ten

- Adult smokers damage their own health
- Adult smokers damage the health of adults around them
- Children exposed to smoke have poorer health
- Smokers are unaware of the risk they pose to themselves and others
- The wealth of a country is damaged by tobacco

## And TB Makes Ten

- Smuggling makes countries poor
- The wealth of families is damaged by tobacco
- Growing tobacco is bad for environment and detrimental to health
- Stopping tobacco production and use is difficult for smokers and farmers
- Smokers in Africa are 3.5 times more likely to be diagnosed with tuberculosis

# Additional Effects of Smoking

- Community survey of children in low income suburbs in Cape Town
- Investigation of infection risk with tuberculosis (TST) in children living in households with and without TB in relationship to passive smoking
- Passive smoking was associated with TB infection risk in patients living in a household with TB (TST positivity)

# Are There More Important Reasons not to Smoke?



Shari Roan

# Are There More Important Reasons not to Smoke?

- Secondhand smoke is as dangerous for pets as it is for humans
- Dog and cats exposed to secondhand smoke have more:
  - Lung cancer
  - Allergies
  - Eye and skin disease
  - Respiratory problems
- More than 25% of smokers said that they would give up if they knew smoking harmed their pets