Opportunistic Infections – Community Acquired Pneumonia

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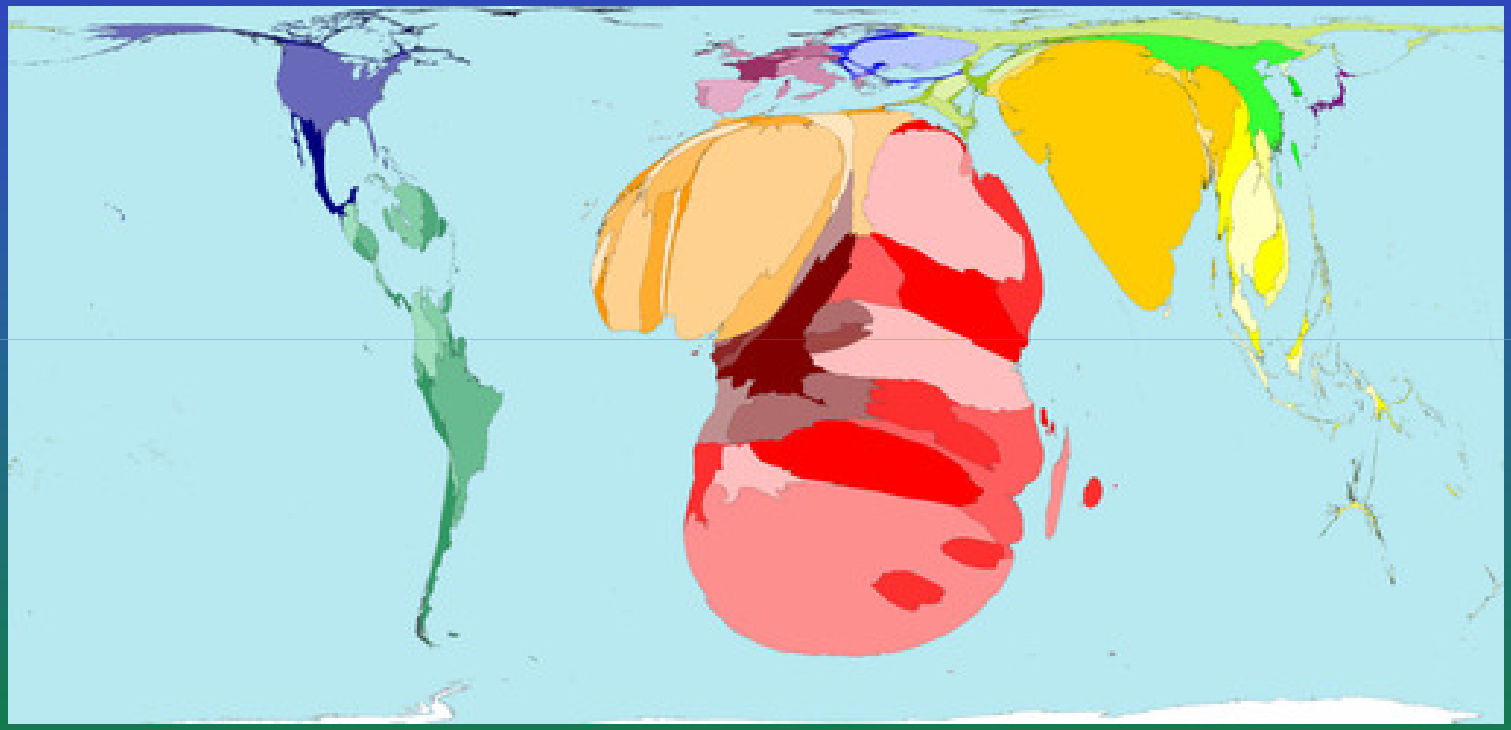
Introduction to the Talk

- Aetiology of community-acquired pneumonia
- Smoking as a major risk factor
- Clinical features of CAP and mortality
- Evolution and interpretation of the CD4 cell count
- Impact of CAP on long-term prognosis
- Prevention of infection - vaccination

The World-wide HIV Prevalence



www.worldmapper.org

Spectrum of HIV-associated Pulmonary Disease

Opportunistic Infections

Bacteria

- *Streptococcus pneumoniae*
- *Haemophilus* species
- *Pseudomonas aeruginosa*
- Other bacteria

Mycobacteria

- *Mycobacterium tuberculosis*
- *Mycobacterium avium* complex
- *Mycobacterium kansasii*
- Other mycobacteria

Fungi

- *Pneumocystic jirovecii*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Coccidiodes immitis*
- *Penicillium marneffei*
- *Aspergillus* species *(*most often *A. fumigatus)*
- Other fungi

Viruses

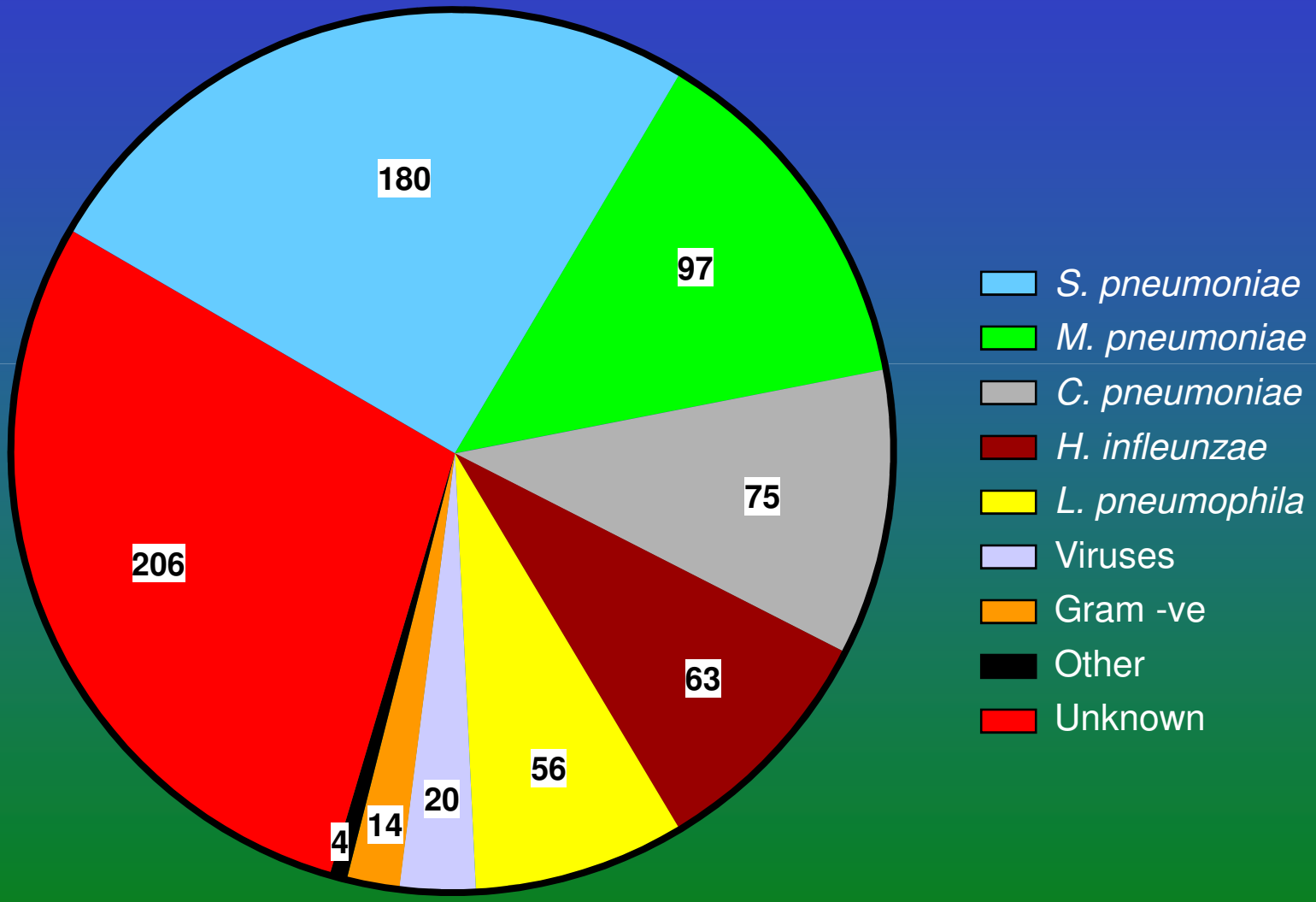
- Cytomegalovirus
- Other virsus

Parasites

- *Toxoplasma gondii*
- Other parasites

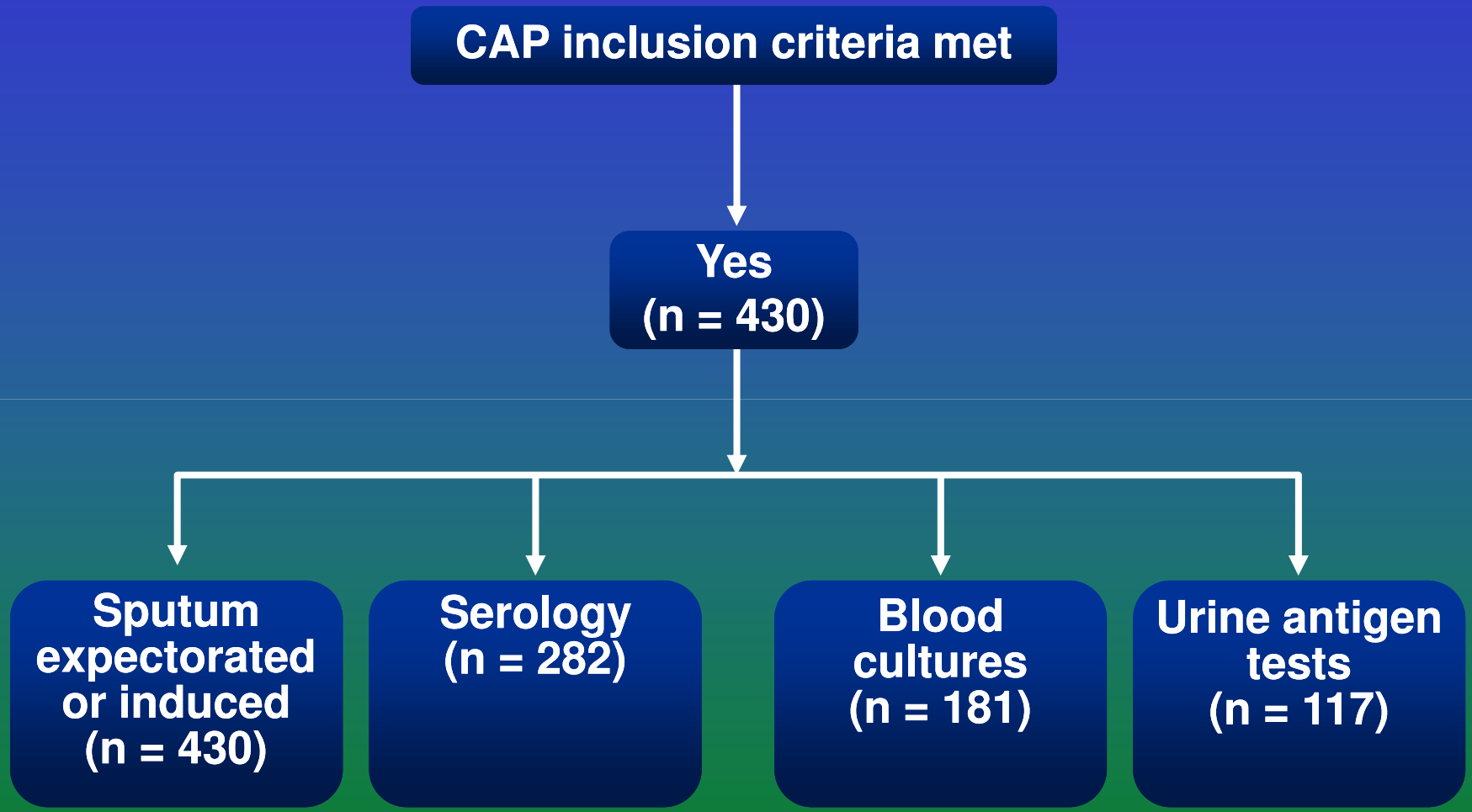
Huang L et al. Respirology 2009; 14: 474-485

Aetiology of CAP in Selected Studies of >100 Immunocompetent Hospitalised Patients with CAP



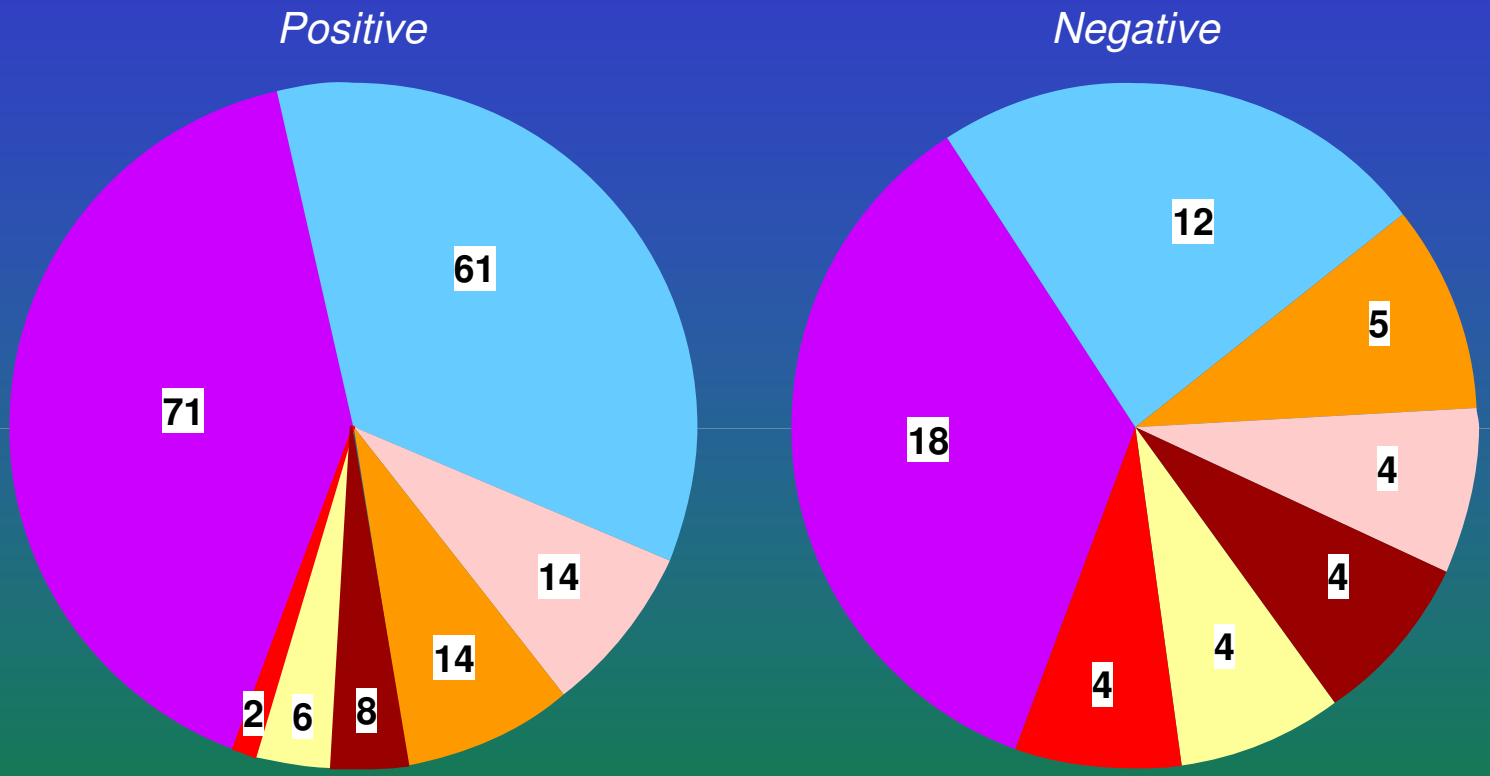
Nyamande K. PhD Thesis UKZN 2007

South African Study of Aetiology of CAP



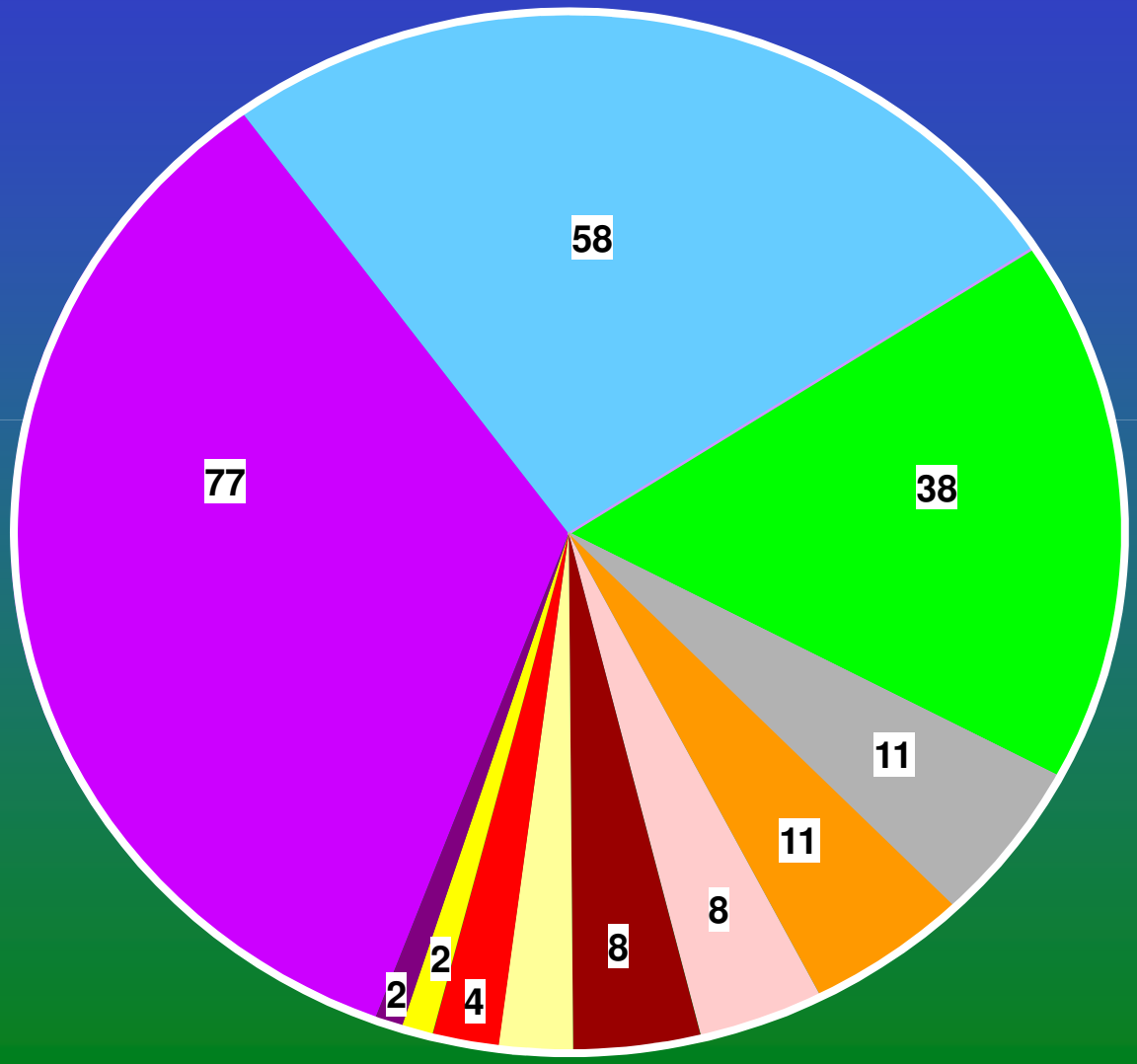
Nyamande K et al. Int J Tuberc Lung Dis 2007; 11: 1308-1313

Aetiology of CAP in 430 HIV-infected and HIV-non-infected Subjects



Nyamande K et al. Int J Tuberc Lung Dis 2007; 11: 1308-1313

Aetiology of CAP in 282 Patients who had Serology for Atypical Organisms



- *M. tuberculosis*
- *S. pneumoniae*
- *M. pneumoniae*
- *C. pneumoniae*
- Other Gram -ve
- *S. aureus*
- *H. influenzae*
- Other
- *P. aeruginosa*
- *L. pneumophila*
- Chicken pox

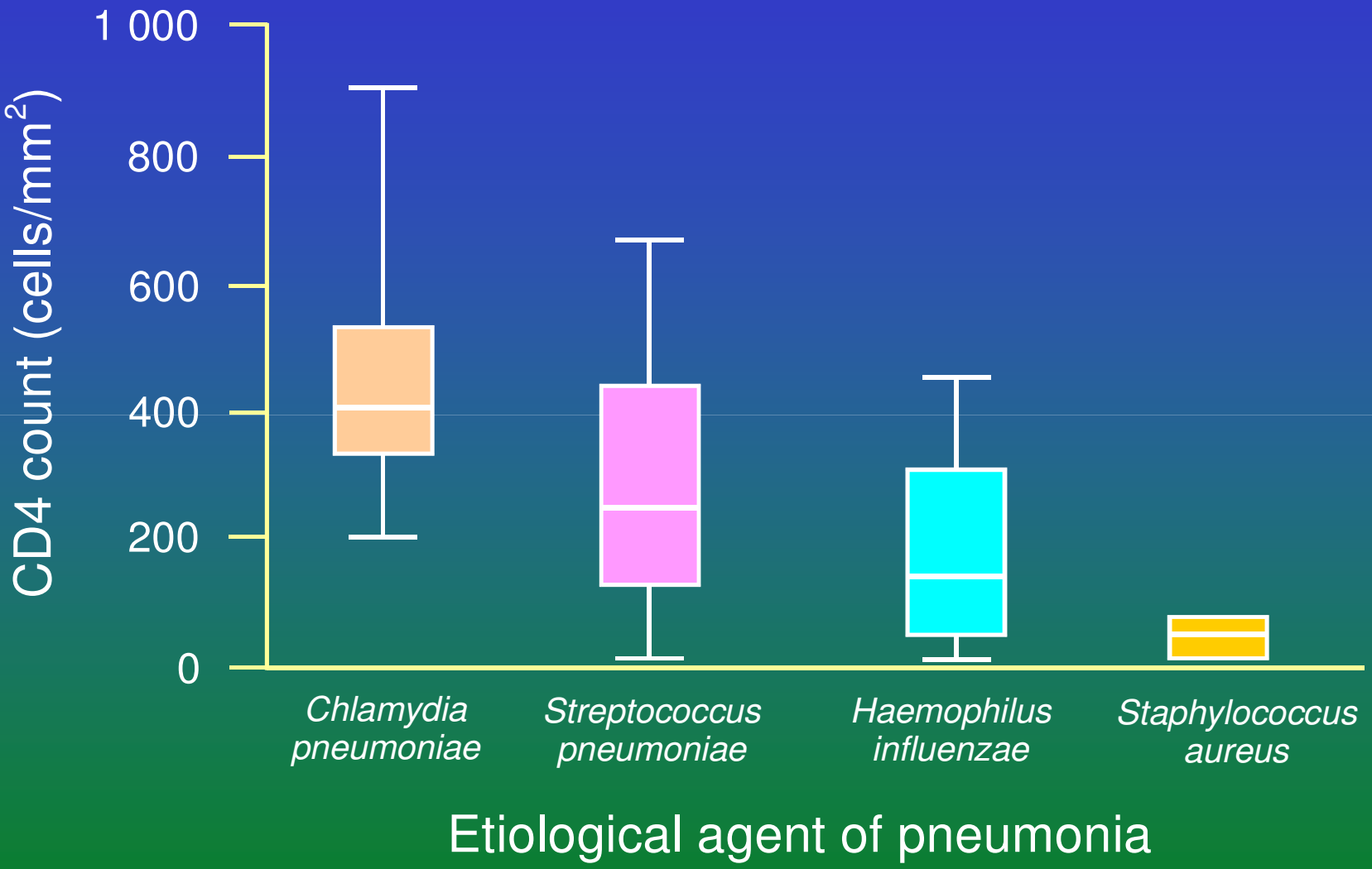
Nyamande K et al. Int J Tuberc Lung Dis 2007; 11: 1308-1313

Mortality in HIV-negative and HIV-positive Patients in Relation to Pathogen

	HIV + (*n* = 50) *n* (%)	HIV - (*n* = 18) *n* (%)
TB	13 (26)	2 (11)
S. pneumoniae	9 (18)	4 (22)
Atypical	8 (16)	
S. aureus	1 (2)	4 (22)
Other	4 (8)	3 (17)

Nyamande K. Int J Tuberc Lung Dis 2007; 11: 1308-1313

Bacterial Pathogens Causing CAP



Boschini et al; CID, 1996

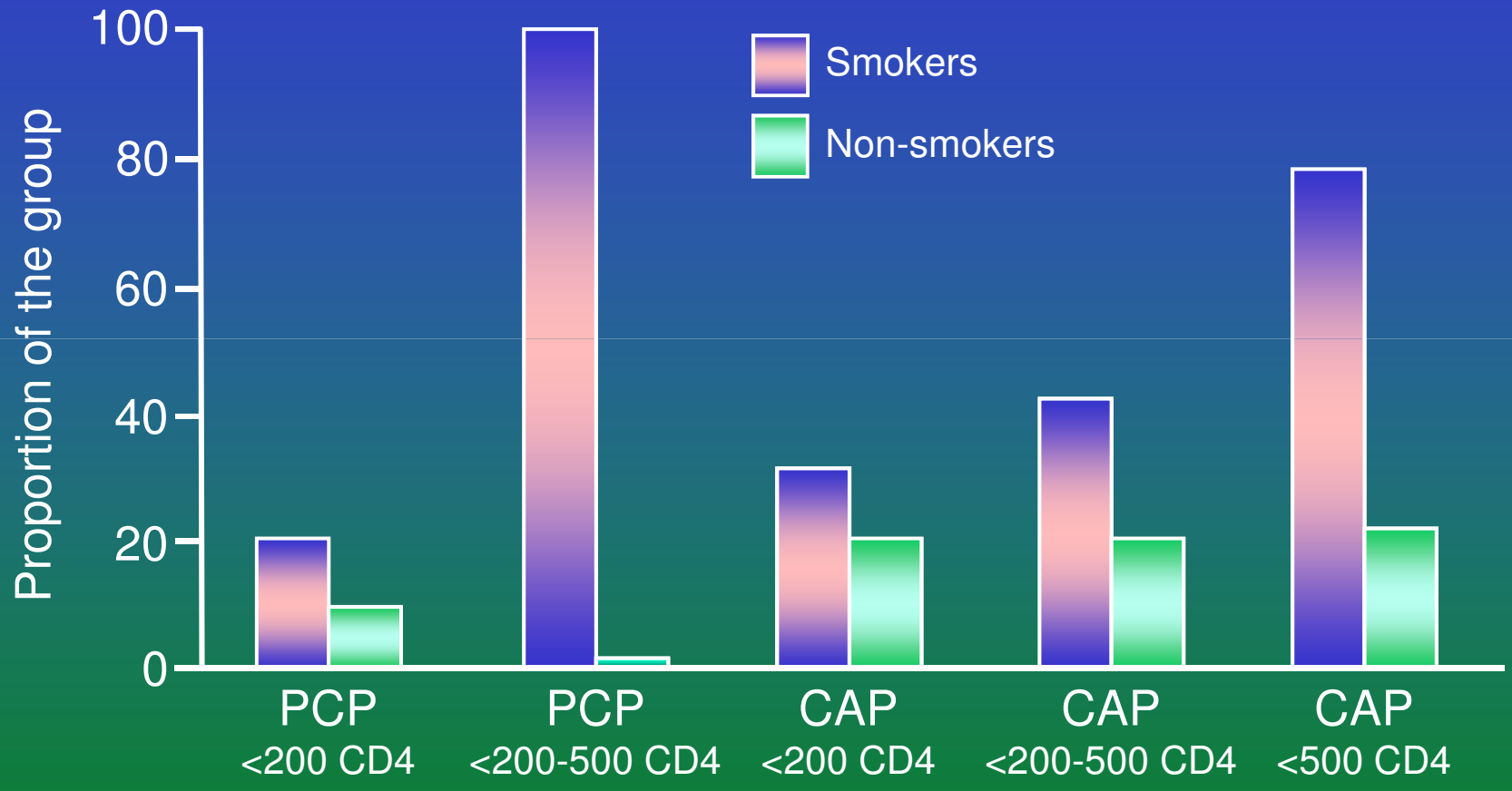
Boschini A et al. Clin Infect Dis 1996; 23: 107-113

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 MJ et al. Int J Infect Dis 2005; 9: 208-217

Increased Risk of LRTI with Smoking



Miquez-Burbano MJ et al. Int J Infect Dis 2005; 9: 208-217

Effects of Smoking on HAART

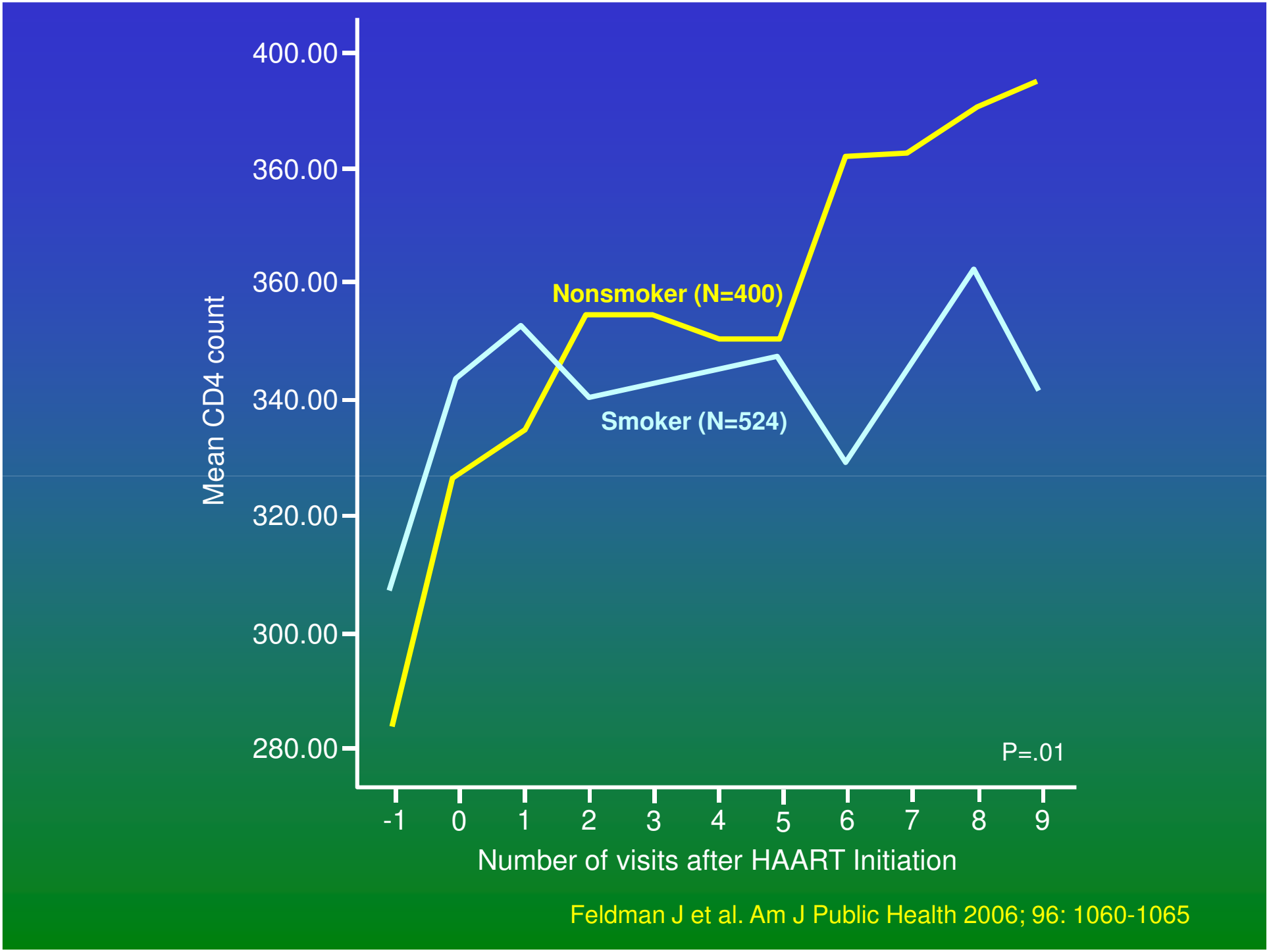
- Analysis of association of cigarette smoking with effectiveness of HAART in WIHS study of 924 women followed for 7.9 years (’95 – ’03)
- Of the cases 56% were current smokers and 16% were former smokers
- The average amount smoked was 1 pack per day and the median duration was 12 years

Feldman J et al. Am J Public Health 2006; 96: 1060-1065

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)

Feldman J et al. Am J Public Health 2006; 96: 1060-1065



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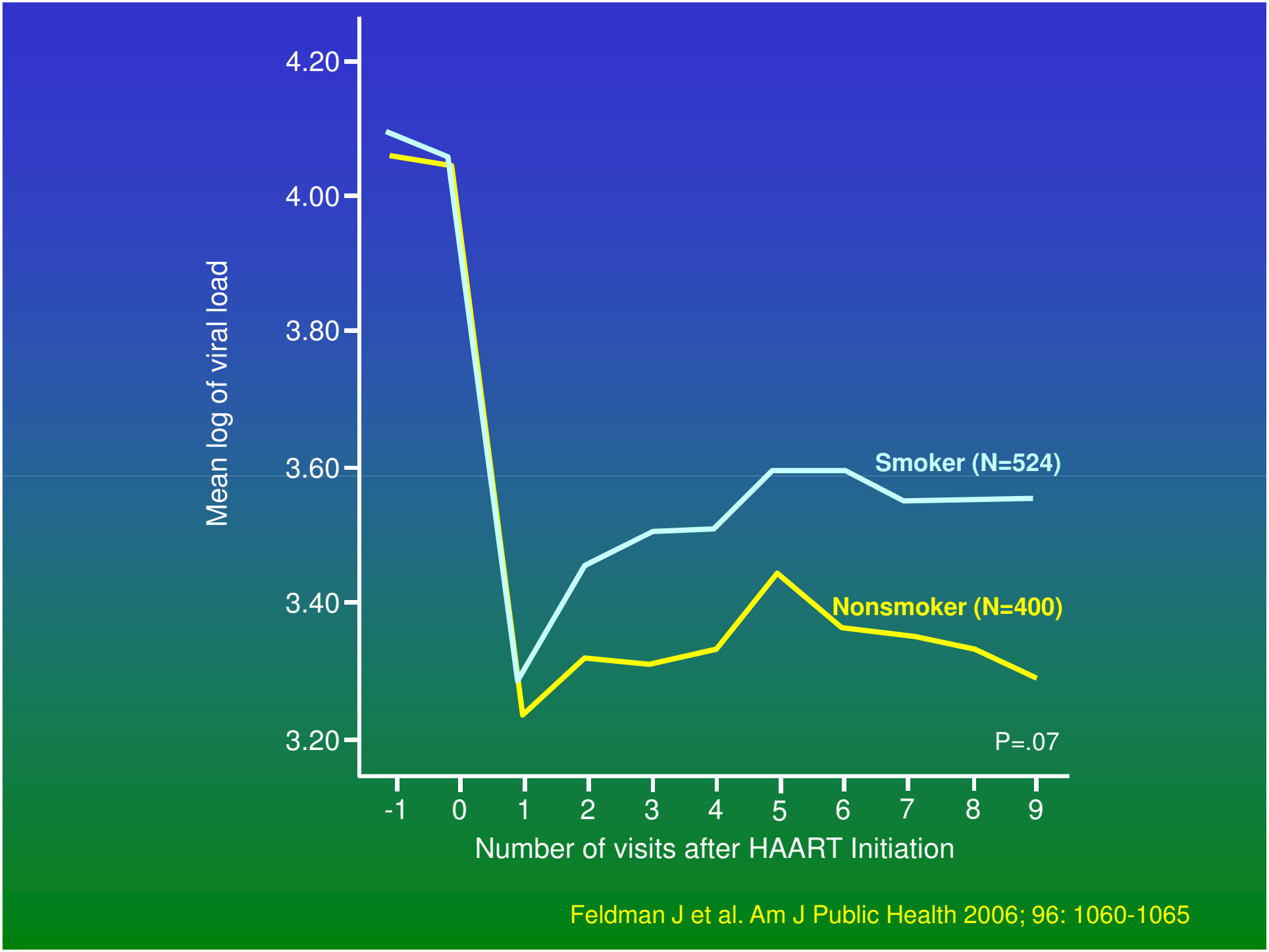

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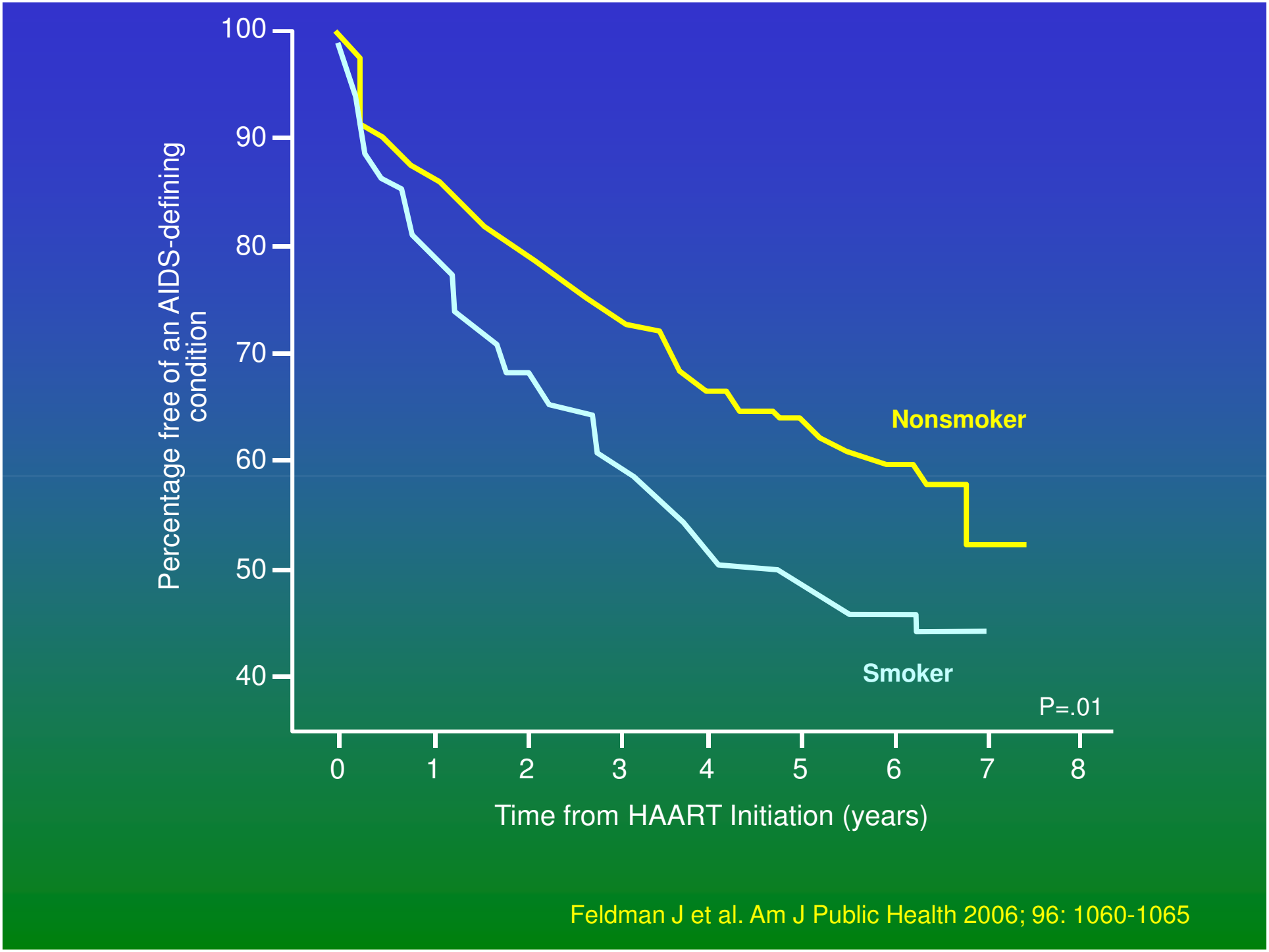

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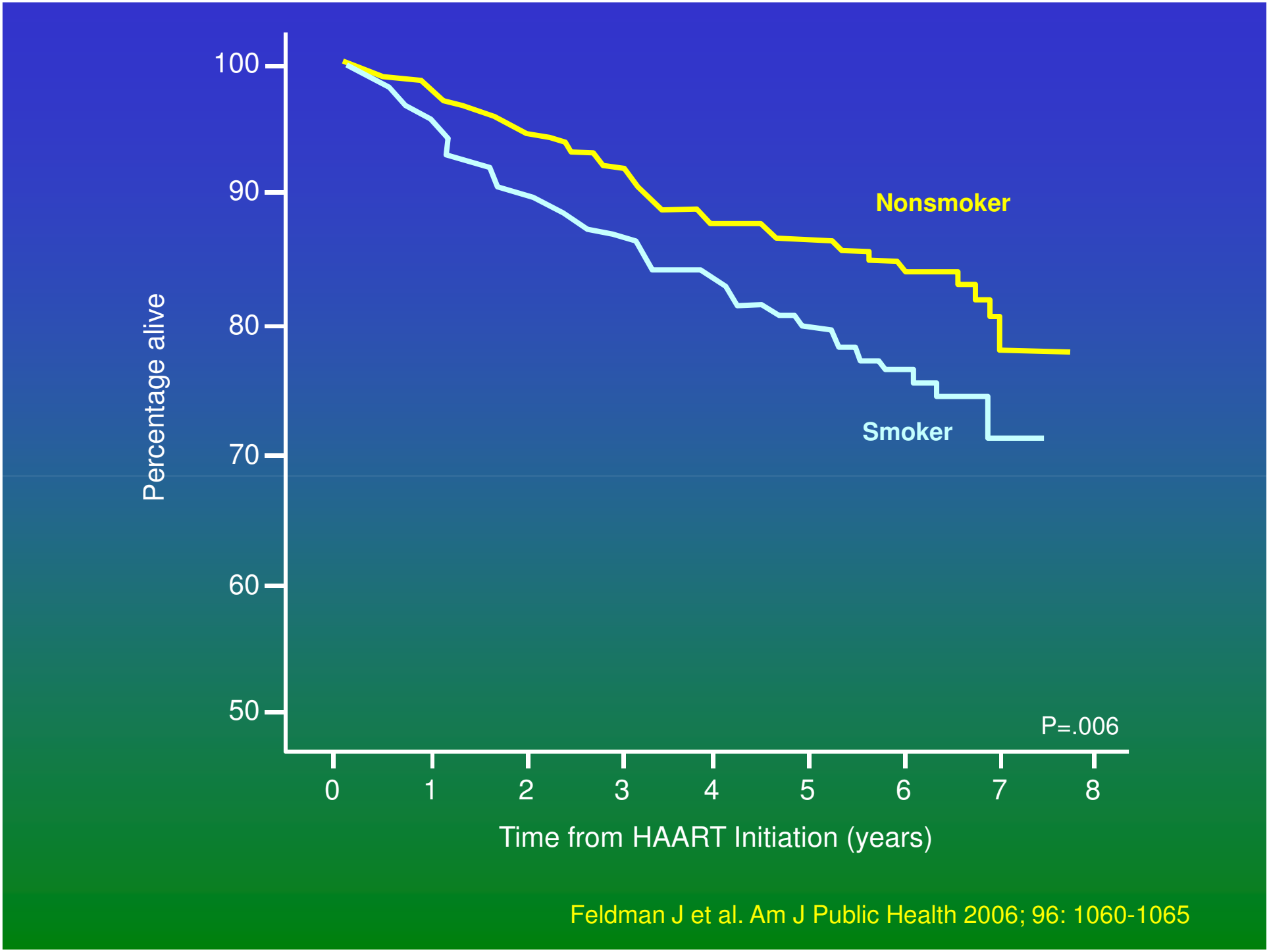


Feldman J et al. Am J Public Health 2006; 96: 1060-1065

Lymphocyte Subsets During CAP

- Studies have measured T-lymphocyte subsets during various infections, but only in the acute phase of infection
- Levels measured in CAP patients within 72 hours of admission
  - Acute phase lymphocyte counts decreased
  - Percentage CD4 cell count remained unchanged
  - Changes not affected by age, HIV status or aetiology
  - In HIV-seronegative cases CD4 cell counts $<200/mm^3$ were associated with underlying disease, TB, and age $\geq$ 60 years

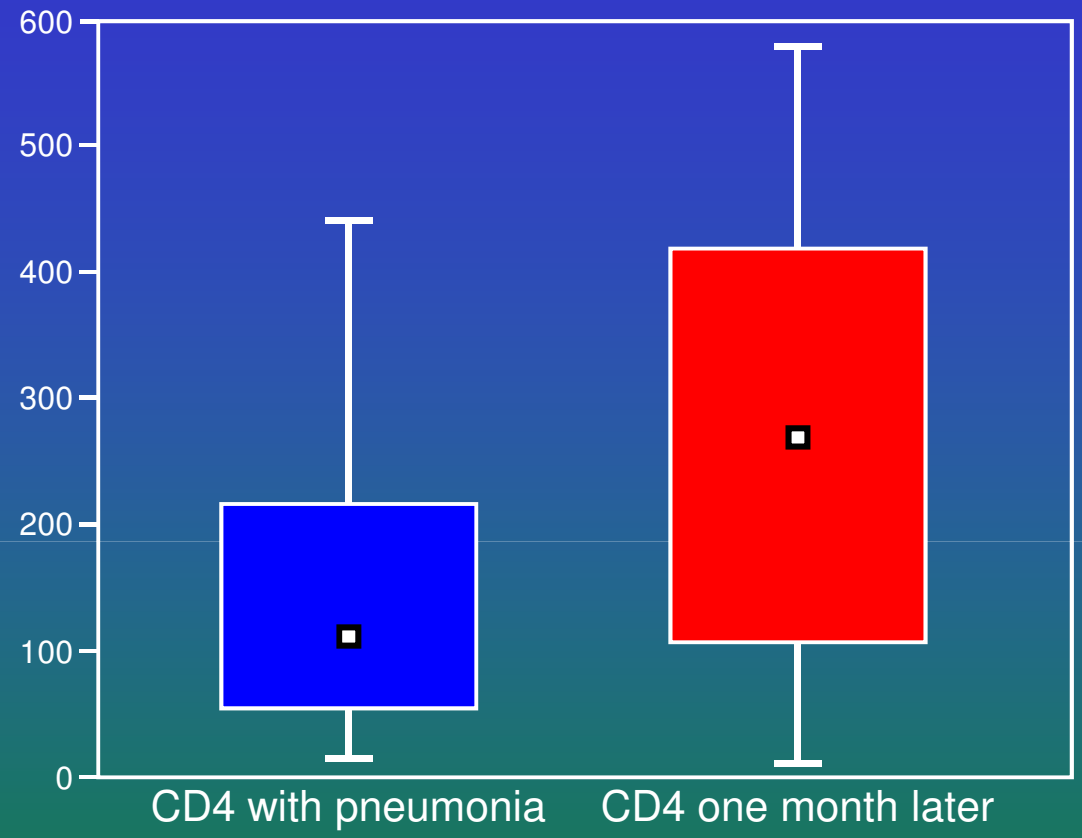
Fantin B et al. Clin Infect Dis 1996; 22: 1096-1098

Lymphocyte Subsets During CAP

- Study of 30 ARV naïve HIV-infected patients with pneumococcal CAP
- Total Lymphocyte and CD4 cell counts were measured upon hospital admission and one month after resolution of CAP
- CAP diagnosis based on compatible clinical features with new infiltrate on chest X-ray
- Pneumococcal diagnosis based on blood or sputum culture or positive urine antigen test

Schleicher G, et al. Eur J Clin Micro Infect Dis 2004; 10: 574-592

CD4 T-lymphocyte Counts (x 10^6 cells/L)

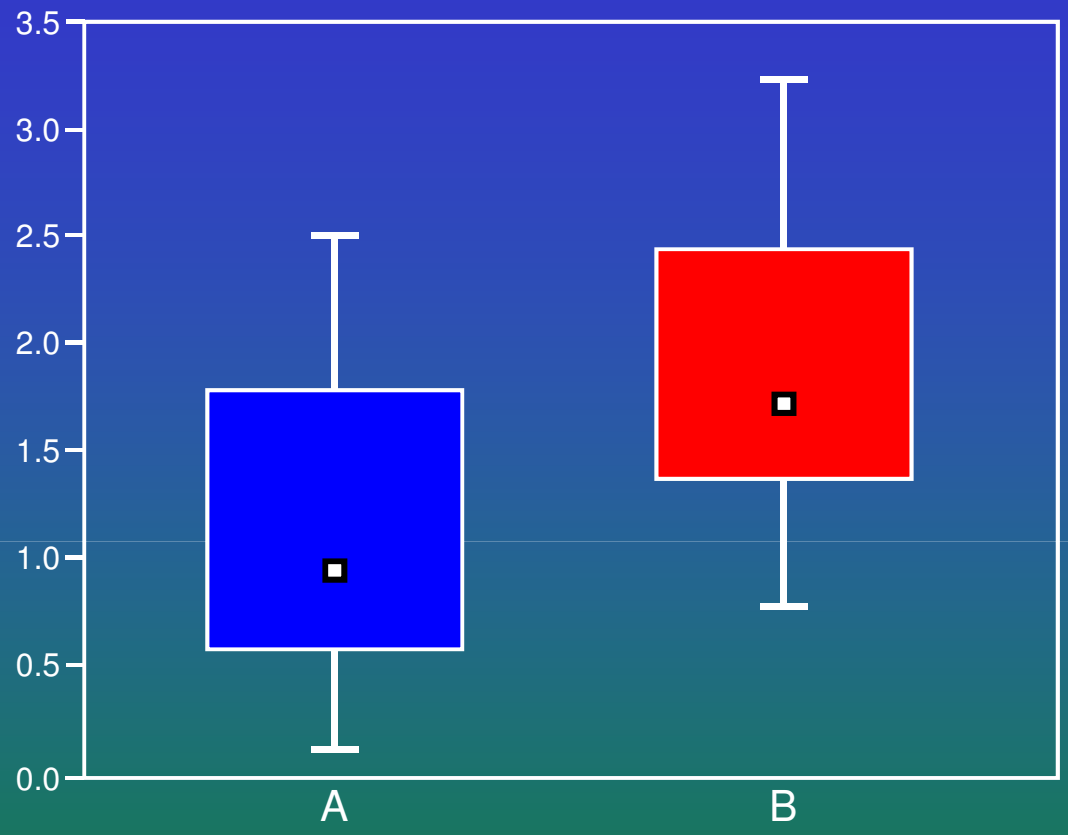


Wilcoxon matchdd pairs test (p 0.000009)

	Min	Max	25%	75%	Median
On admission	14.00	439.00	54.00	212.00	112.00
One month later	7.00	578.00	107.00	419.00	270.00

Schleicher G, et al. Eur J Clin Micro Infect Dis 2004; 10: 574-592

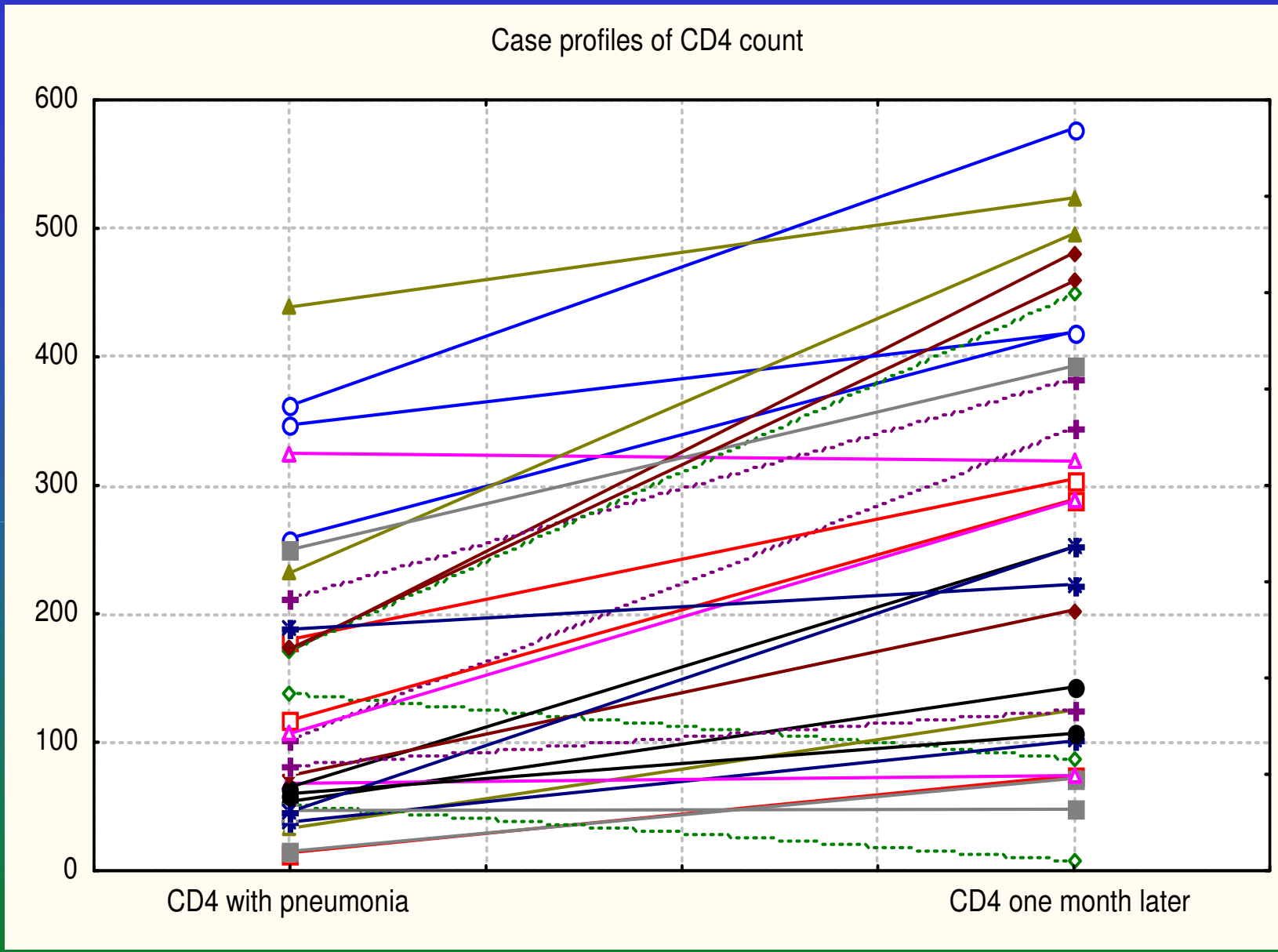
Total Lymphocyte Counts (x 10^6 cells/L)



Wilcoxon matchdd pairs test (p 0.000009)

	Min	Max	25%	75%	Median
On admission	0.15	02.29	0.60	1.80	0.99
One month later	0.82	3.16	1.39	2.24	1.73

Schleicher G, et al. Eur J Clin Micro Infect Dis 2004; 10: 574-592



Schleicher G, et al. Eur J Clin Micro Infect Dis 2004; 10: 574-592

Clinical Features and Management of Pneumococcal Pneumonia

	HIV-infected patients	HIV noninfected patients
Clinical features	Often atypical frequently bacteremia in low death risk patients according to PSI. Bilateral inflates common,	Typical in the young and possible atypical in the elderly and in other clinical conditions/
Simple collection for etiologic diagnosis	Sputum Gram stain and culture, blood for culture and urine for pneumococcal UAT in all patients.	Sputum for Gram stain and culture, blood for culture and urine for pneumococcal UAT depending on severity of pneumonia and patient's risk factors.
Empiric therapy	Combination antibiotic therapy (β-lactam plus a macrolide or a respiratory fluorquinolone alone).	Monotherapy or combination antibiotic therapy according to outpatient or inpatient management, patient's comorbidities and local prevalence of antibiotic resistance.
Prevention	Lifestyle modification, HAART, pneumococcal vaccine.	Lifestyle modification, pneumococcal vaccine.

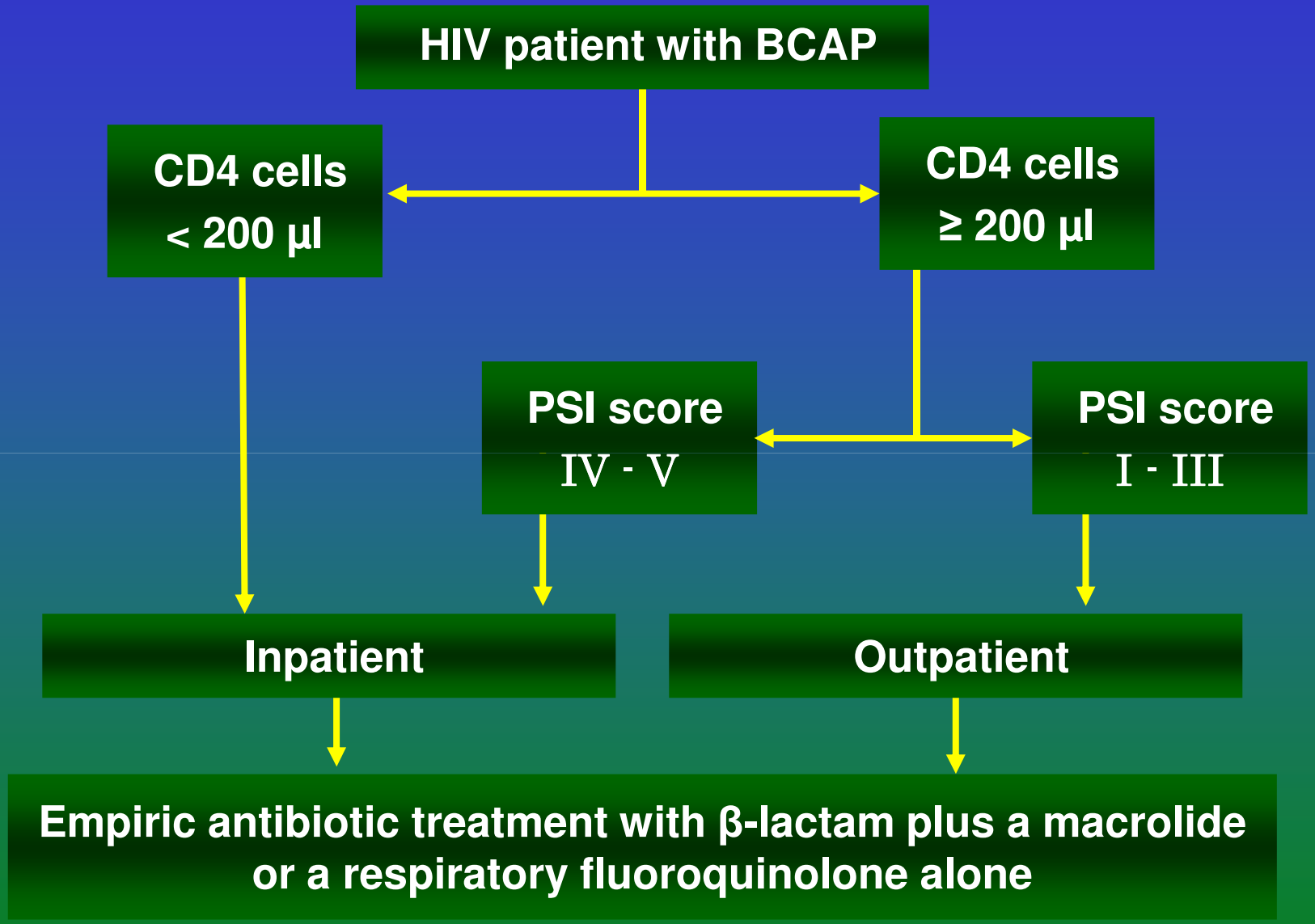
Madeddu G et al. Curr Opin Pulmon Med 2009; 15: 236-242

Mortality of CAP in HIV infected Patients

- Prospective, international, multicentre, observational study
- 700 cases with bacteraemic pneumococcal pneumonia
- Univariate analysis – no difference in 14-day mortality in HIV + versus HIV – cases
- Multivariate analysis – stratified by age and severity of illness – higher mortality in HIV +
  - Mortality higher in the sicker cases and stratified according to the CD4 cell count

Feldman C et al. J Infect 2007; 55: 125-135

Management of HIV-infected Patients with Bacterial CAP



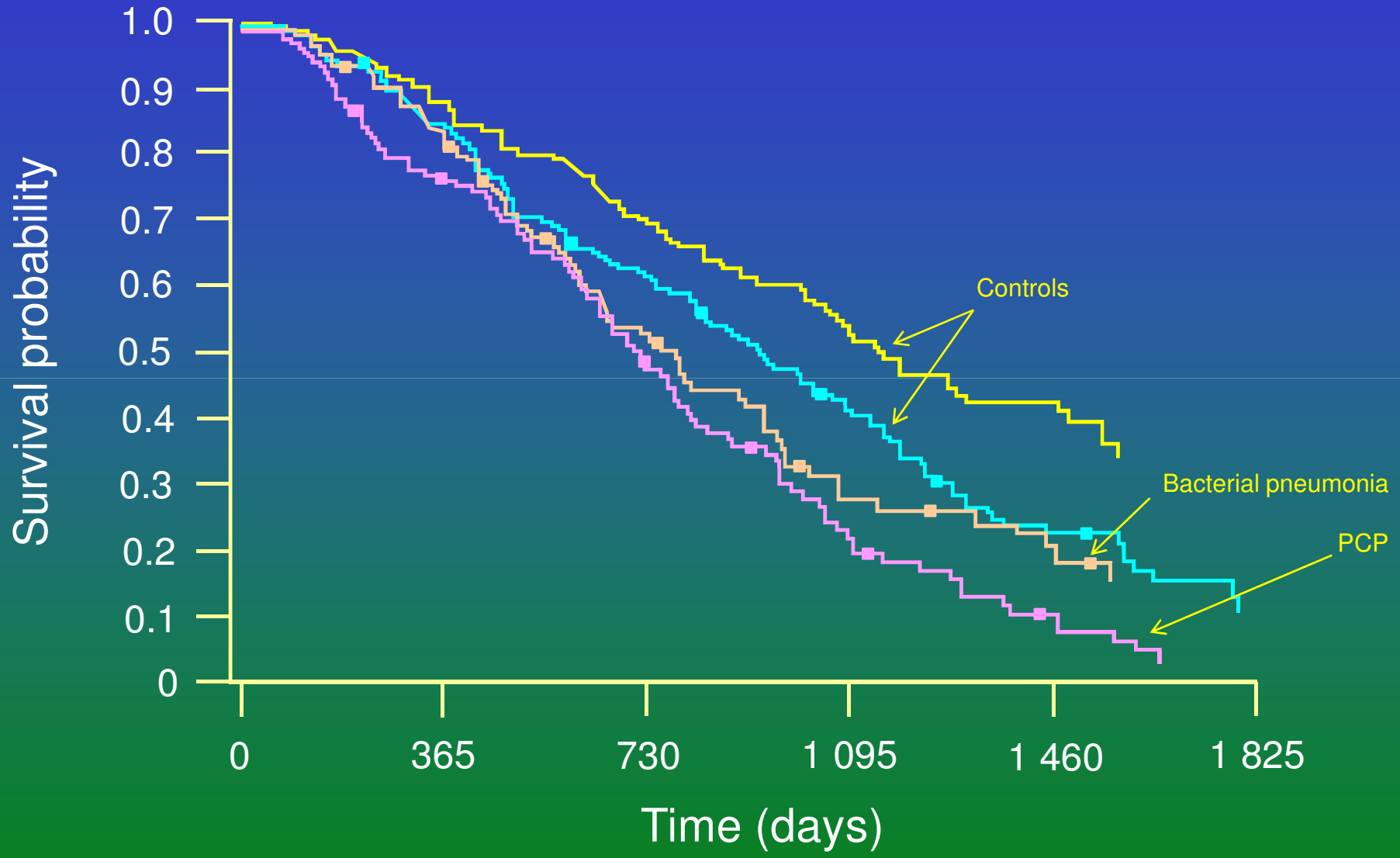
Madeddu G et al. Curr Opin Pulmon Med 2010; 16: 201-207

CAP and PCP Accelerate Progression of HIV

- Patients with bacterial pneumonia and PCP had shorter median survival time than controls
- Associations persisted when controlled for other predictors of survival in multivariate analysis i.e. CD4 count or history of AIDS-defining OI
- Neither of the associations due to acute mortality
- ? Associated with decreased long-term survival
- Prevention of infection is important

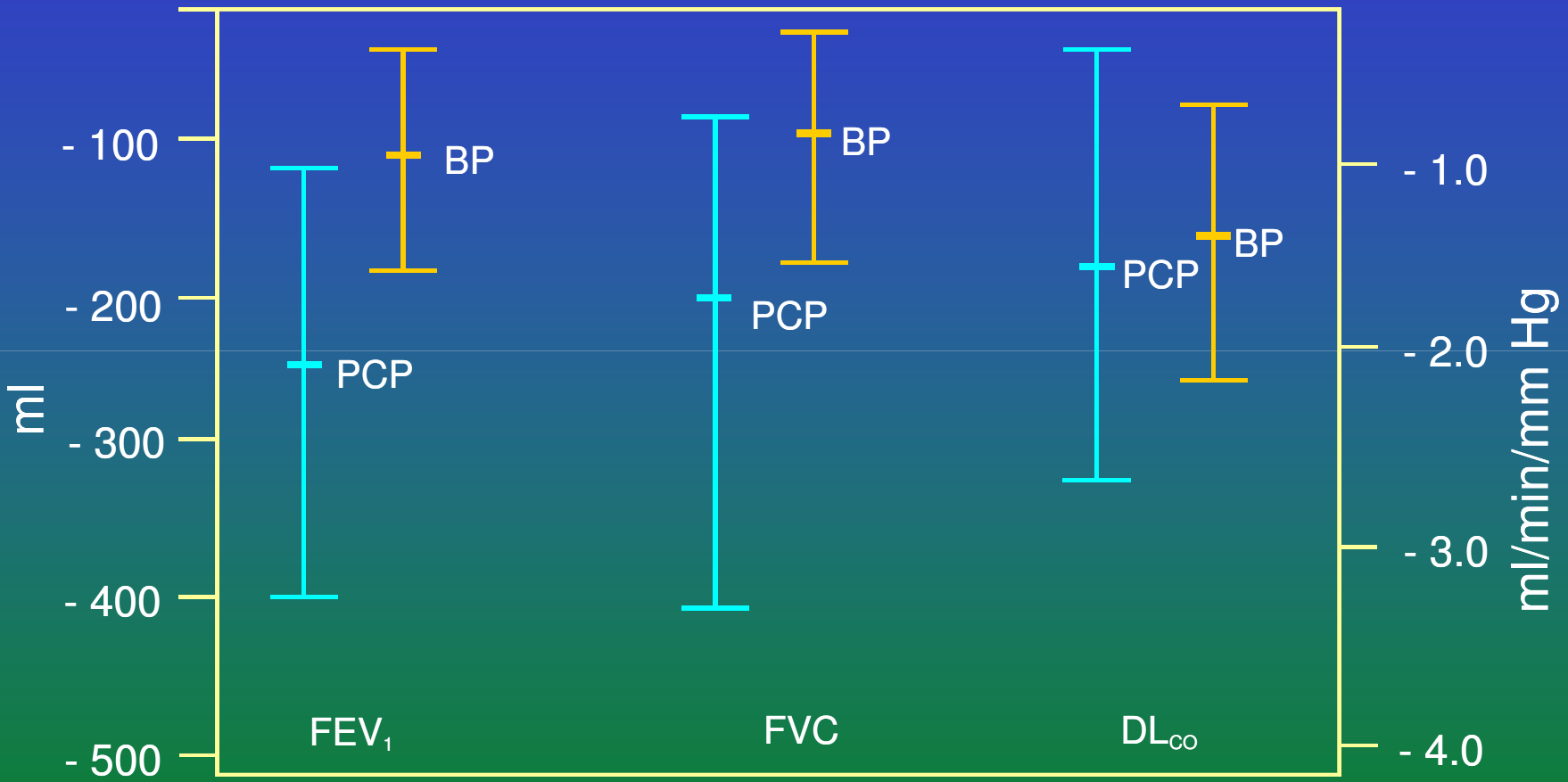
Osmond DH et al. Clin Infect Dis 1999; 29: 536-543

CAP and PCP Accelerate Progression of HIV



Osmond et al; CID, 1999

Permanent Decline in Lung Function



Morris AM et al. Am J Respir Crit Care Med 2000; 162: 621-616

Prevention of CAP in HIV-infected Persons

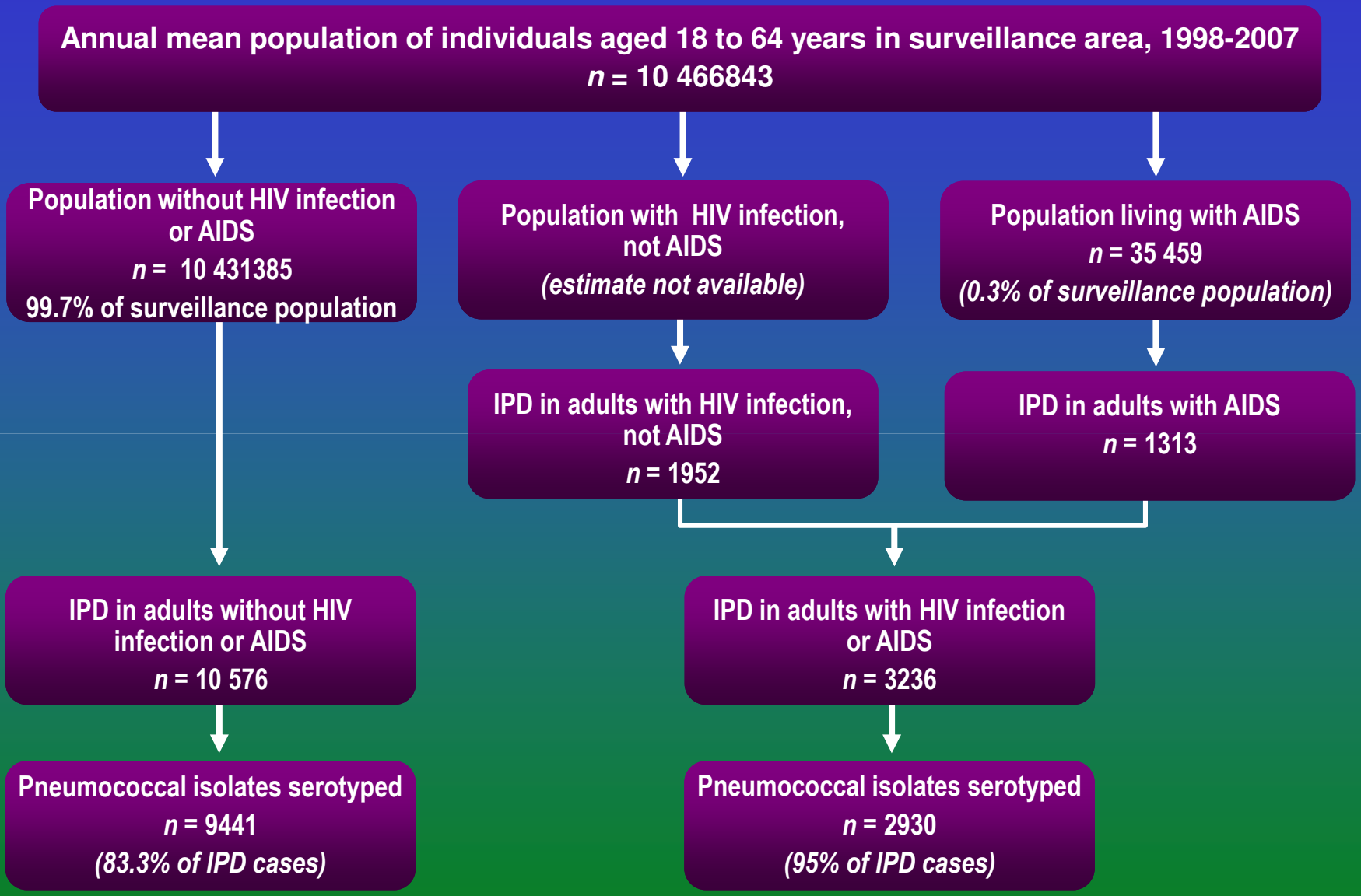
- Lifestyle modification - smoking cessation
- Anti-pneumocystis prophylaxis
- HAART
- Pneumococcal vaccine
  - 23 valent polysaccharide
  - Protein conjugate
  - ? *Haemophilus* cover

IPD According to Prior Vaccination Status (PPV)

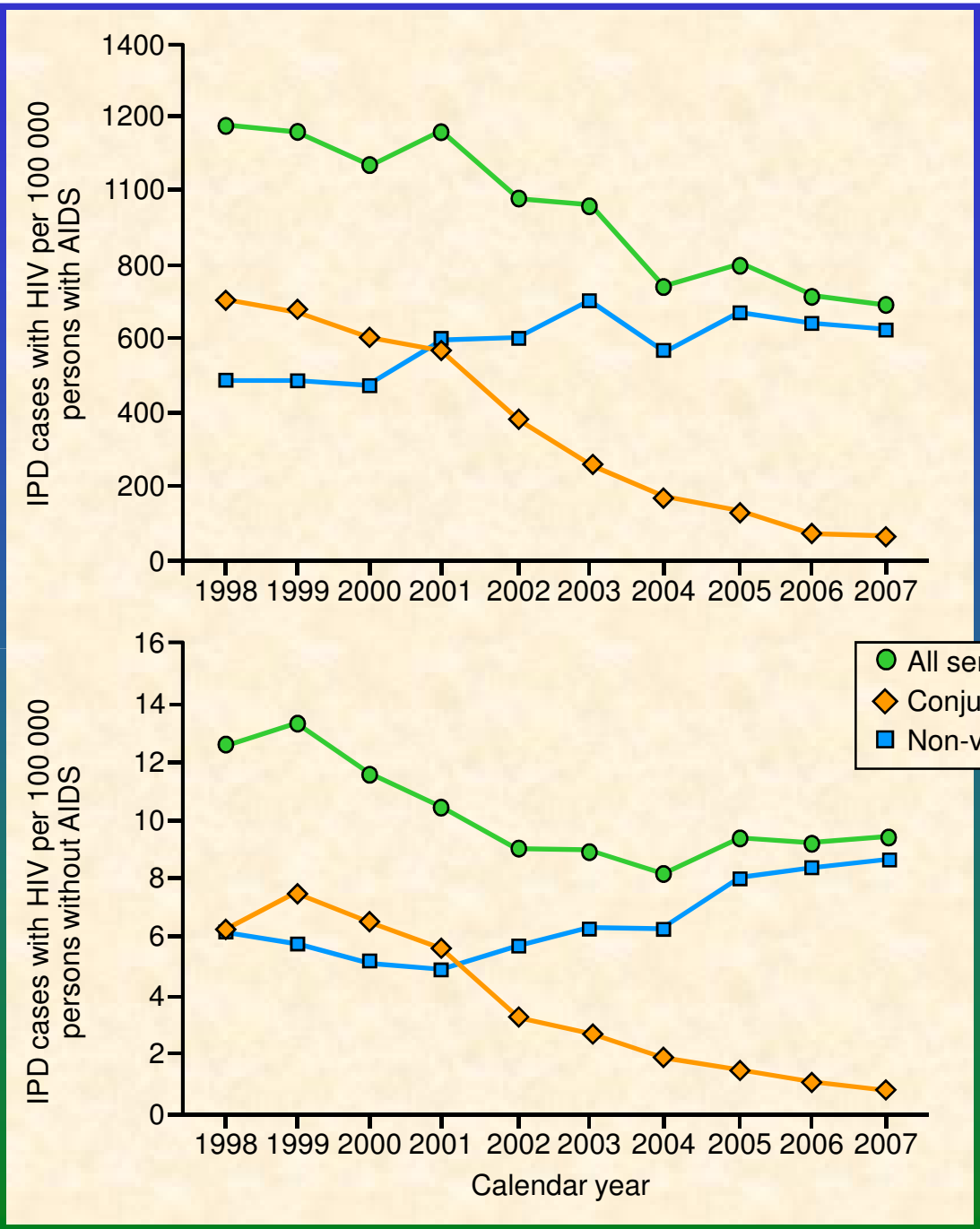
	All patients (n = 162)	All patients included			Patients with chronic liver disease excluded		
		Vaccinated (n = 23)	Unvaccinated (n = 139)	*P*	Vaccinated (n = 22)	Unvaccinated (n = 22)	*P*
Death and/or ICU admission	34/162 (21)	0/23	34/139 (24.5)	0.004	0/22	25/112 (22.3)	0.013
In-hospital mortality	25/162 (15.4)	0/23	25/139 (18)	0.026	0/22	16/112 (14.3)	0.073
ICU admission	21/162 (13)	0/23	21/139 (15.1)	0.046	0/22	19/112 (17)	0.042
Orotracheal intubation	15/162 (9.3)	0/23	15/129 (10.8)	0.132	0/22	13/112 (11.6)	0.126
Shock	17/135 (12.6)	1.21 (4.8)	16/114 (14)	0.471	1/20 (5)	14/96 (14.6)	0.463
Empyema	10/129 (7.8)	0/21	10/108 (9.3)	0.365	0/20	10/95 (10.5)	0.206
PSI high risk classes	43/125 (34.4)	3/18 (16.7)	40/107 (37.4)	0.111	2/17 (11.8)	29/95 (30.5)	0.146
Days of hospital stay (mean SD)	12.62 (13.87)	8.48 (6.14)	13.27 (14.62)	0.011	8.5 (6.29)	14.29 (15.88)	0.007
Days to defervescence (mean SD)	3.11 (4.09)	2.55 (2.72)	3.21 (4.28)	0.484	2.62 (2/76)	3.17 (3.52)	0.497

Imaz A et al. HIV Medicine 2009; 10: 356-363

IPD in Adults 18 – 64 years of Age with and without HIV Infection or AIDS

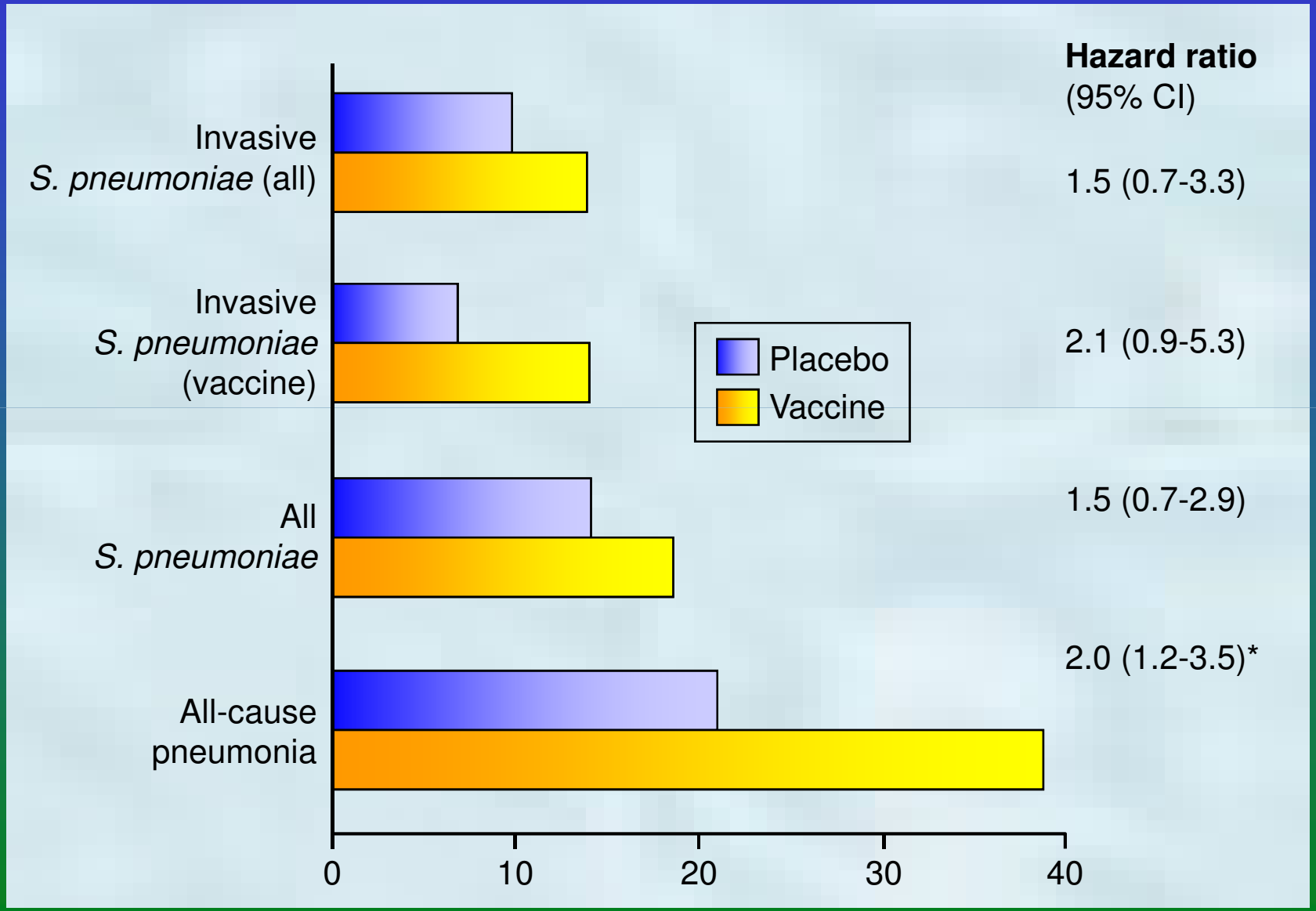


Cohen AL, et al. AIDS 2010; 24: 2253-2262



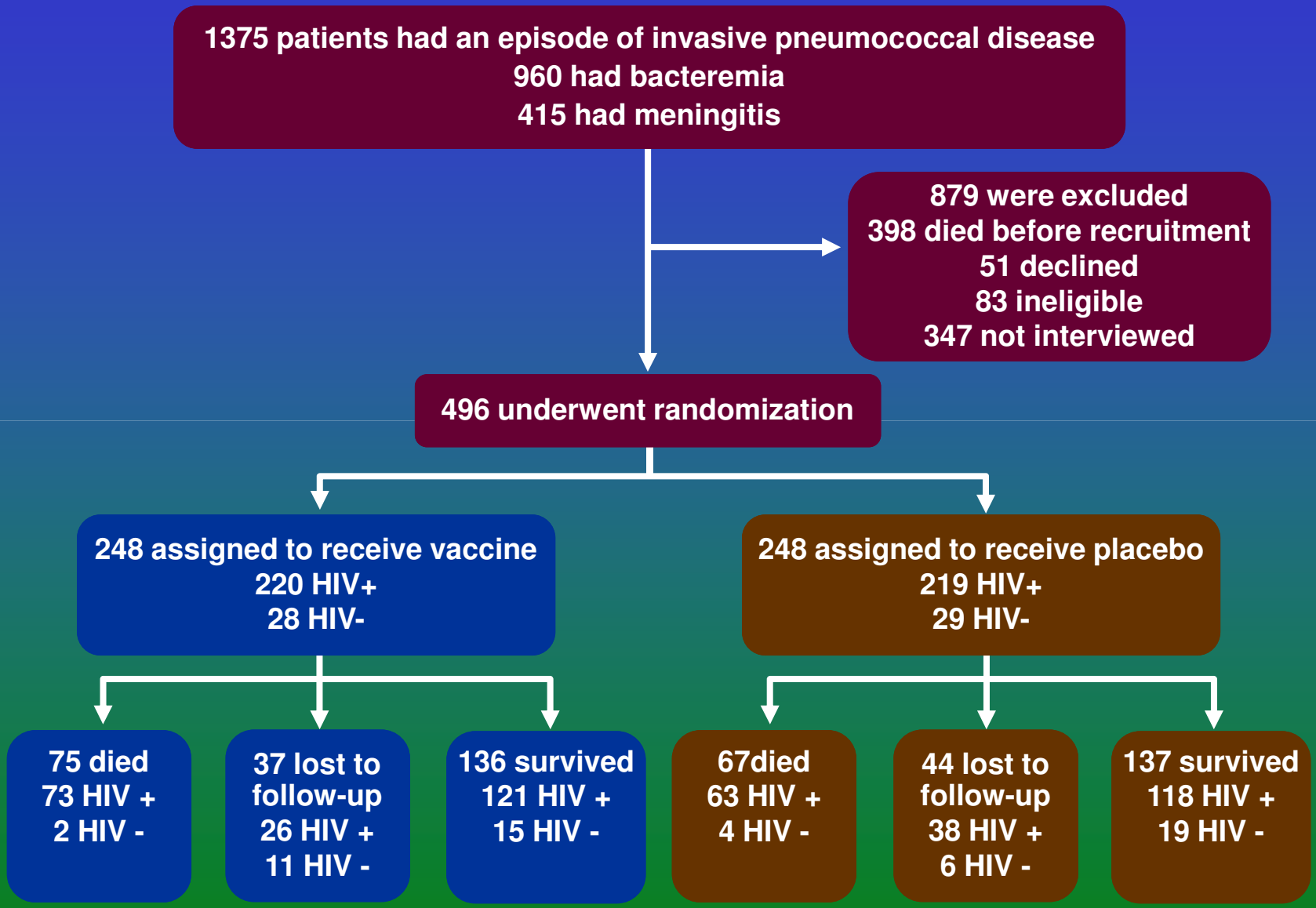
Cohen AL, et al. AIDS 2010; 24: 2253-2262

Effect of the 23-valent Pneumococcal Polysaccharide Vaccine: Uganda 1985-1998



Feikin DR et al. Lancet Infect Dis 2004; 4: 445-455

Study of 7-valent PCV in HIV-infected Adults



French N et al. New Engl J Med 2010; 362: 812-822

Effectiveness of PCV7 in 437 Patients with HIV infection

	VACCINE		PLACEBO		Hazard ratio for First Event (95%)		Hazard ratio for Recurrent Events (95%)	
	No. of patients	No. of events	No. of patients	No. of events	Unadjusted	Adjusted	Unadjusted	Adjusted
PRIMARY ENDPOINT								
Vaccine serotype or serotype 6A (intention-to-treat analysis)	5	5	19	19	0.26 (0.10-0.70)	0.31 (0.11-0.84)		
Vaccine serotype or serotype 6A (per-protocol analysis)	4	4	18	18	0.22 (0.08-0.66)	0.25 (0.08-0.78)		
SECONDARY ENDPOINT								
Vaccine serogroup	7	7	19	20	0.37 (0.15-0.87)	0.42 (0.18-1.02)	0.19 (0.06-0.66)	0.30 (0.09-1.02)
Any invasive pneumococcal disease	22	29	30	38	0.72 (0.02-1.25)	0.80 (0.45-1.44)	0.35 (0.12-1.01)	0.34 (0.11-1.02)
Any type of pneumonia	32	44	41	58	0.77 (0.47-1.19)	0.71 (0.43-1.17)	0.54 (0.26-1.17)	0.49 (0.20-1.21)
DEATH								
Any cause	73		63		1.18 (0.84-1.66)	1.24 (0.88-1.75)		
Definite, probable or association with IPD	35		35		1.02 (0.64-1.63)	1.14 (0.71-1.85)		
Loss to follow-up	26		38					

French N et al. New Engl J Med 2010; 362: 812-822

Summary and Conclusions

- Incidence of pulmonary opportunistic infections has declined with HAART
- Bacterial pneumonia and influenza infection are commonly seen and vaccination strategies in HIV infected adults needs to be better evaluated
- Episodes of bacterial pneumonia provide an important opportunity for HIV testing
- TB/HIV remains frequent and difficult to diagnose and simple clinical algorithms appear to be helpful
- New TB diagnostic test, such as Xpert MTB/RIF are showing exciting results but even cheaper and simpler tests would be welcome
- Lifestyle modification is important

Adapted from Raju R et al. Curr Opin Pulmon Med 2012; 18: 253-258