Double Trouble
HIV & TB
Coinfection

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HIV & TB

Epidemiology

Pathogenesis and Immunology

Clinical presentation

Management

- ... Infection Control
- ... TB Diagnosis
- ... TB treatment
- ... HIV treatment

Immune reconstitution syndrome

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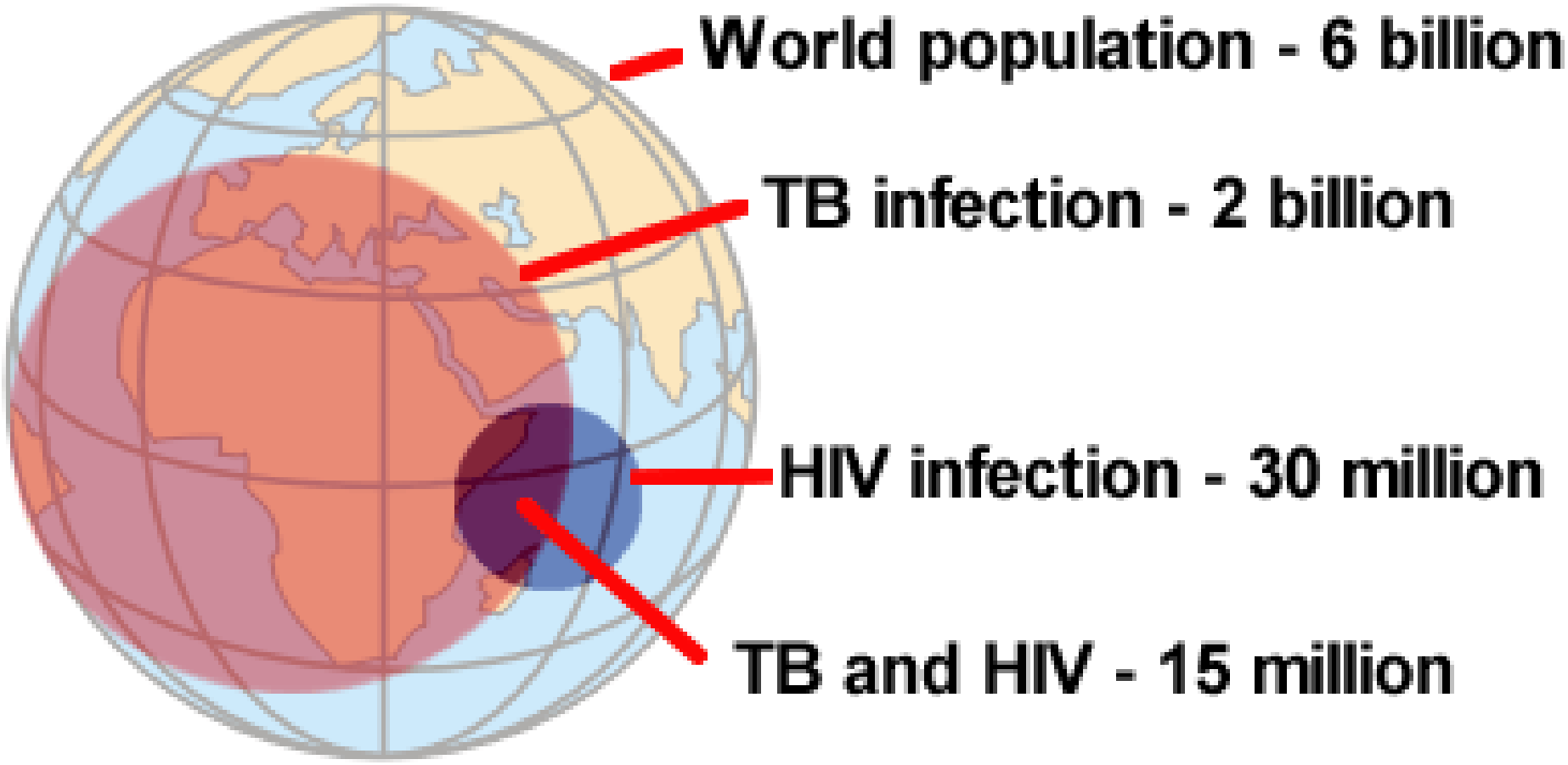
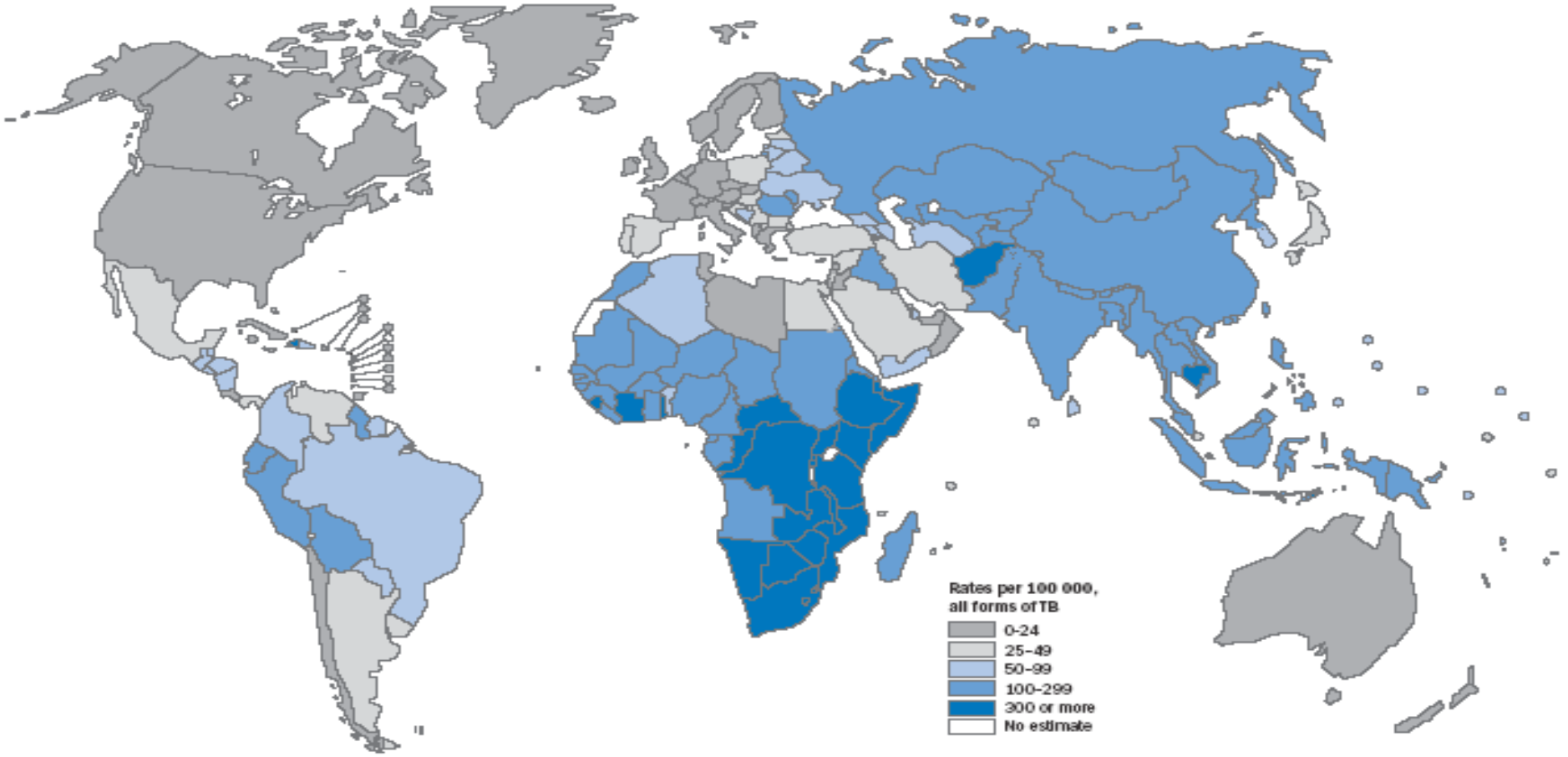
TB and HIV – Double Trouble



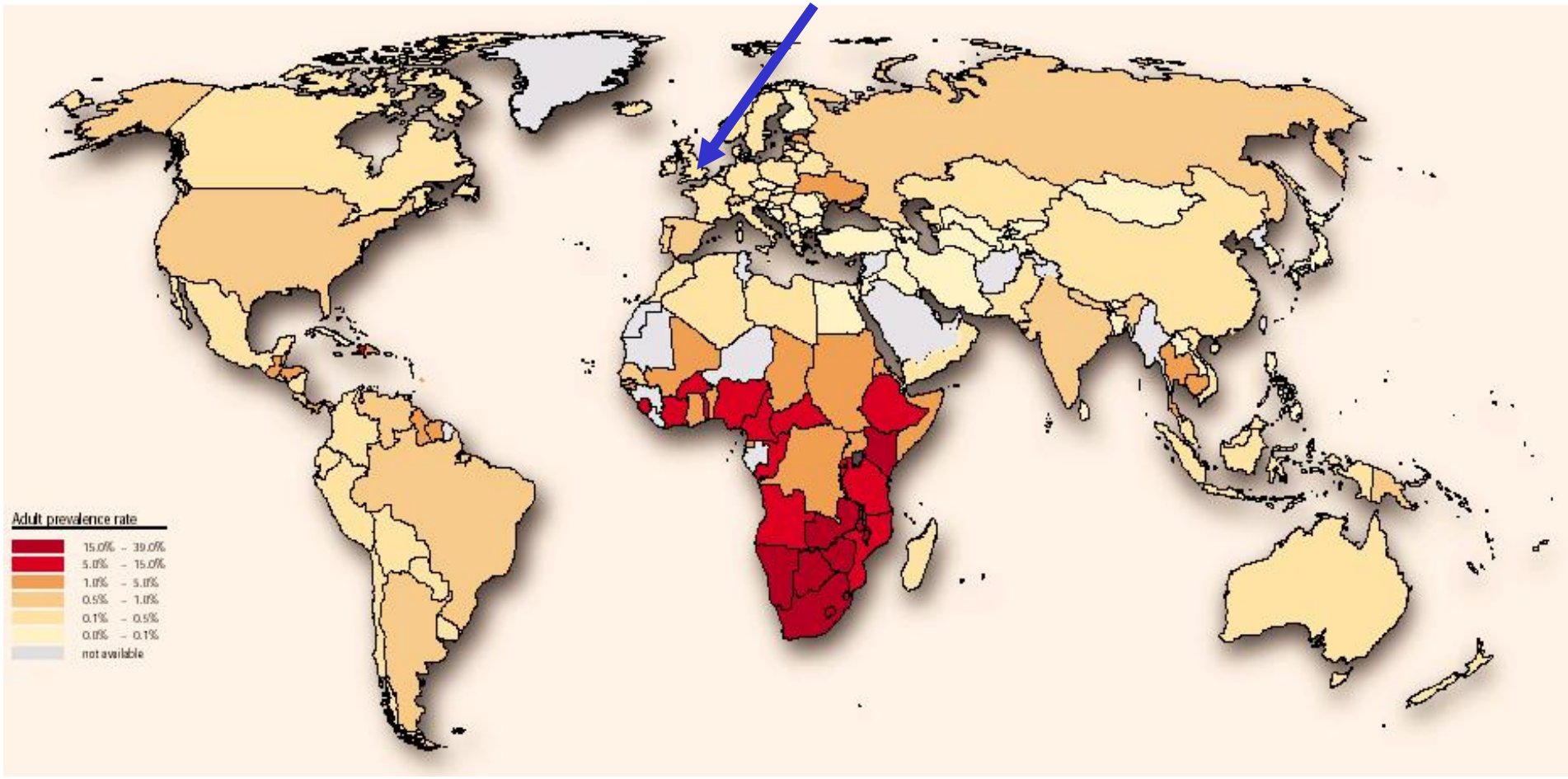
Geography of Tuberculosis



WHO TB Report 2005

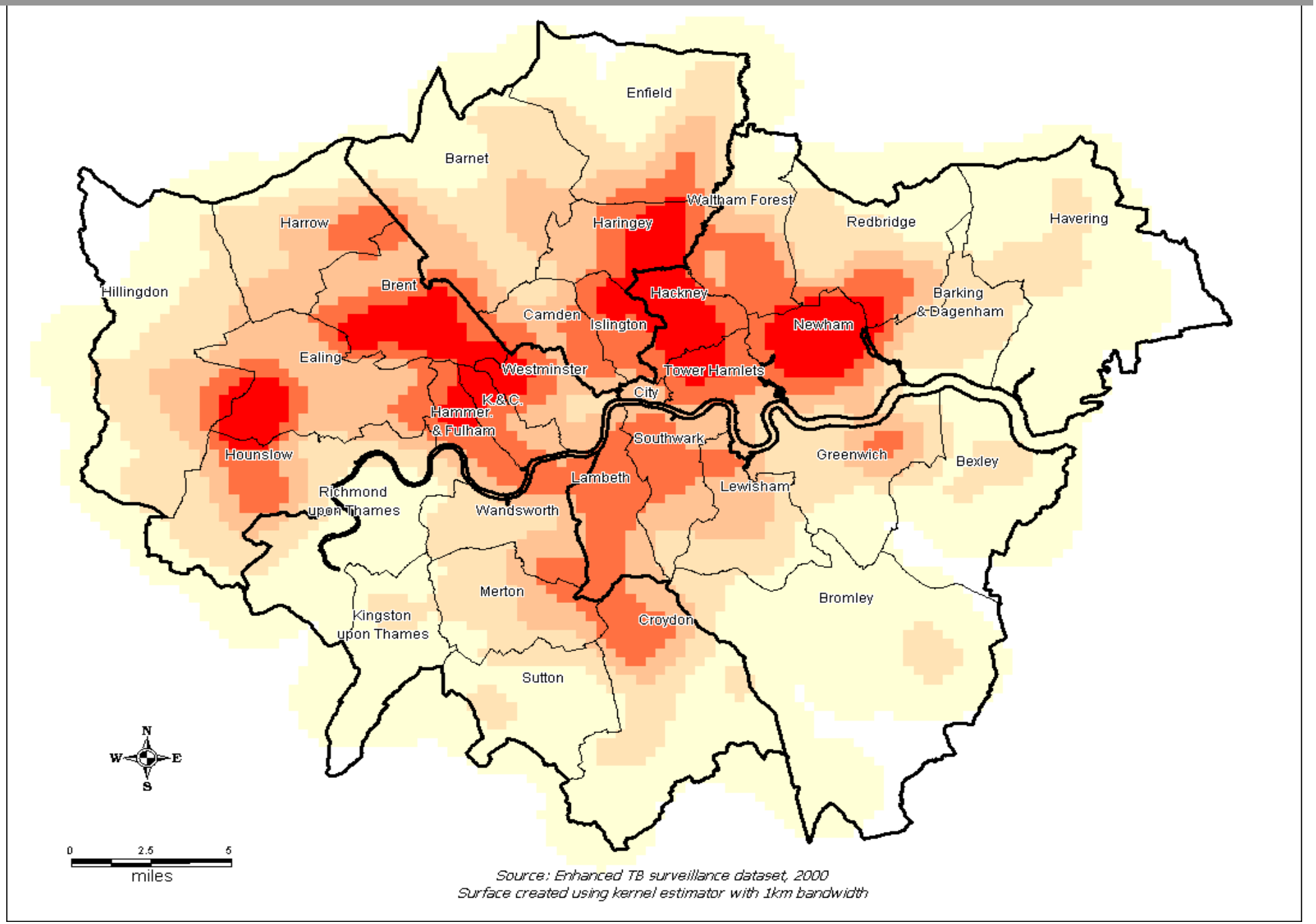
Geography of HIV

North Middlesex Hospital, London

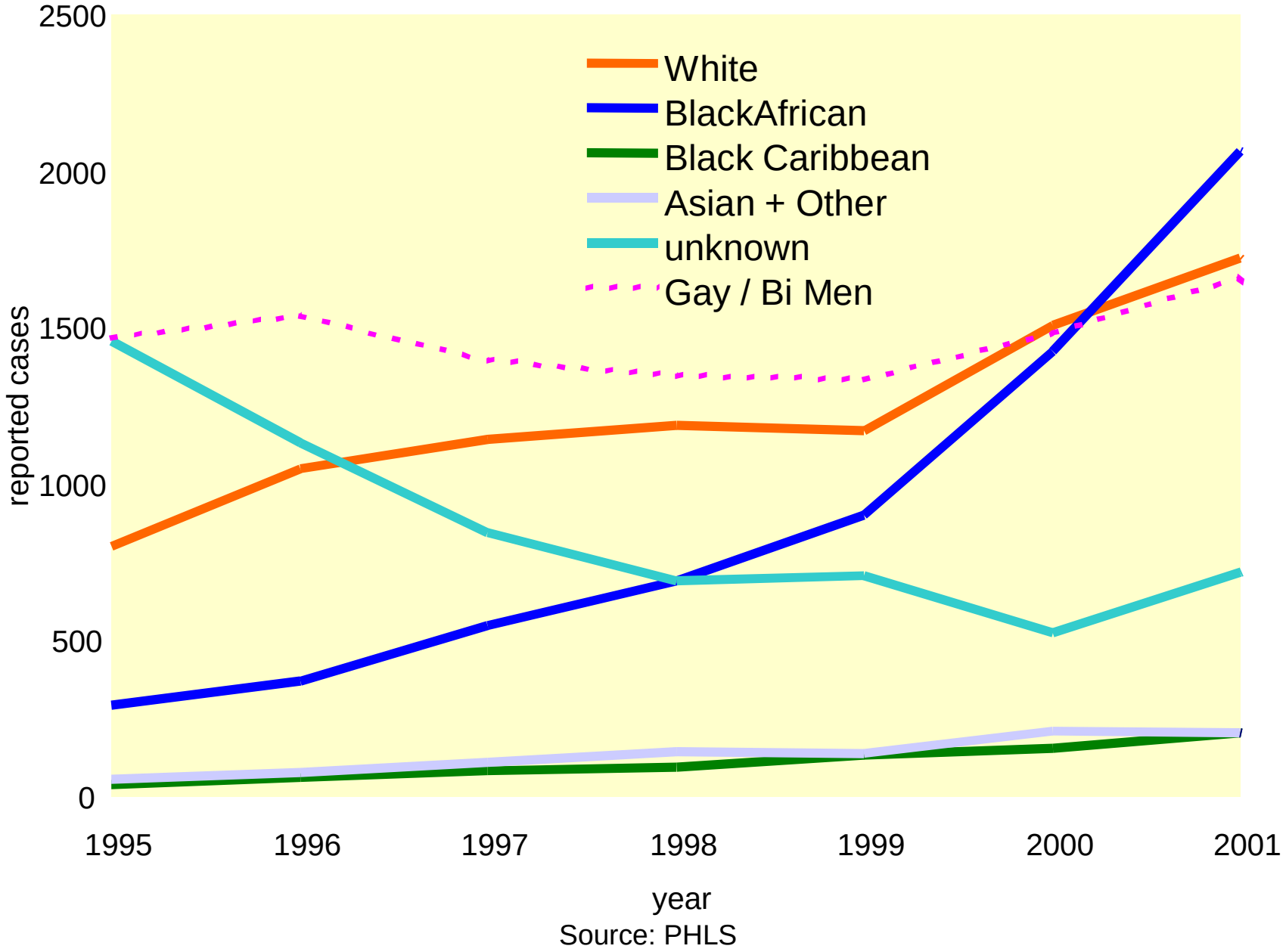


UNAIDS December 2003

TB case rates in London 2000

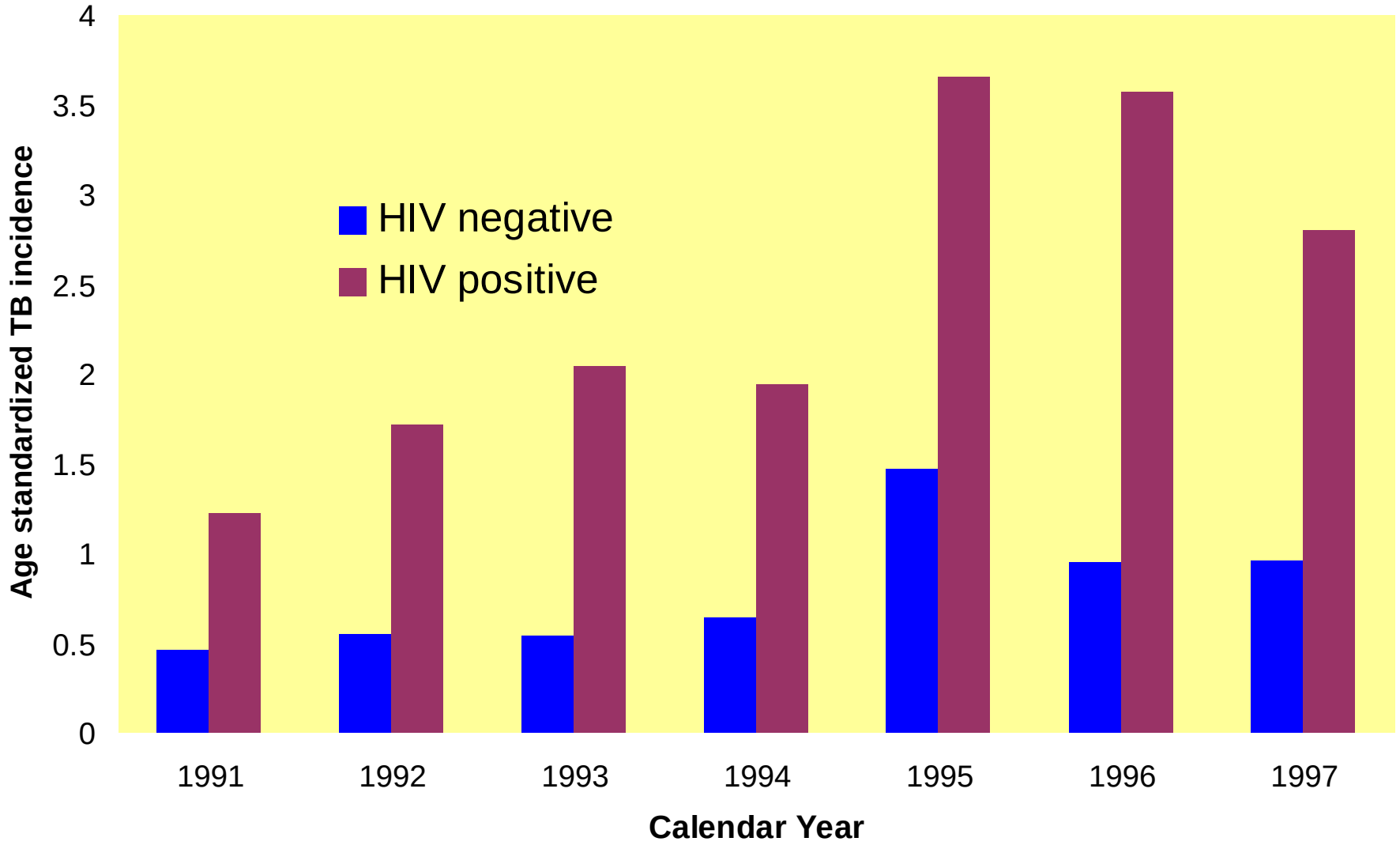


Ethnicity and HIV cases in England & Wales



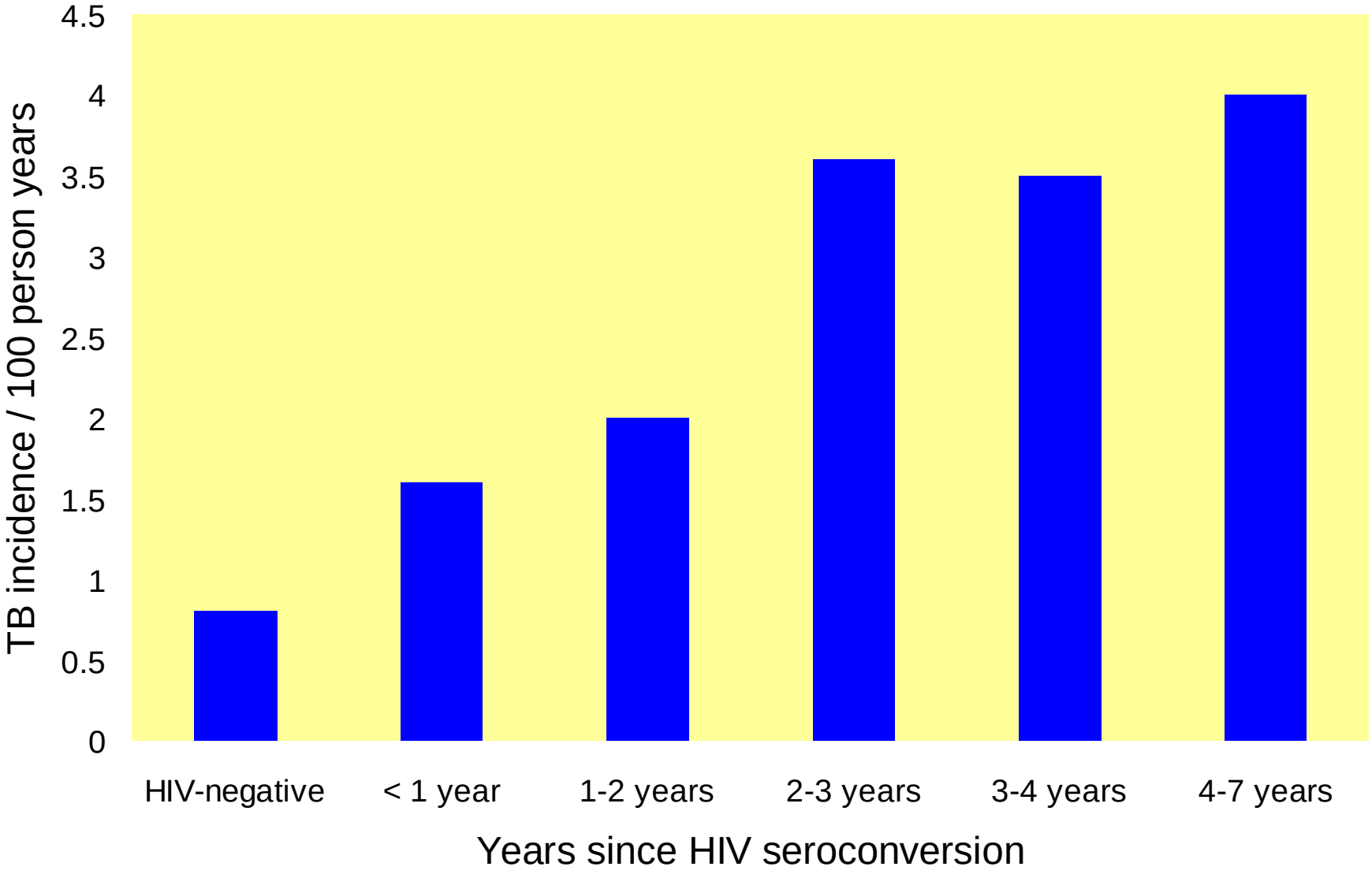
Source: PHLS

HIV Epidemic and TB Rates among South African Miners



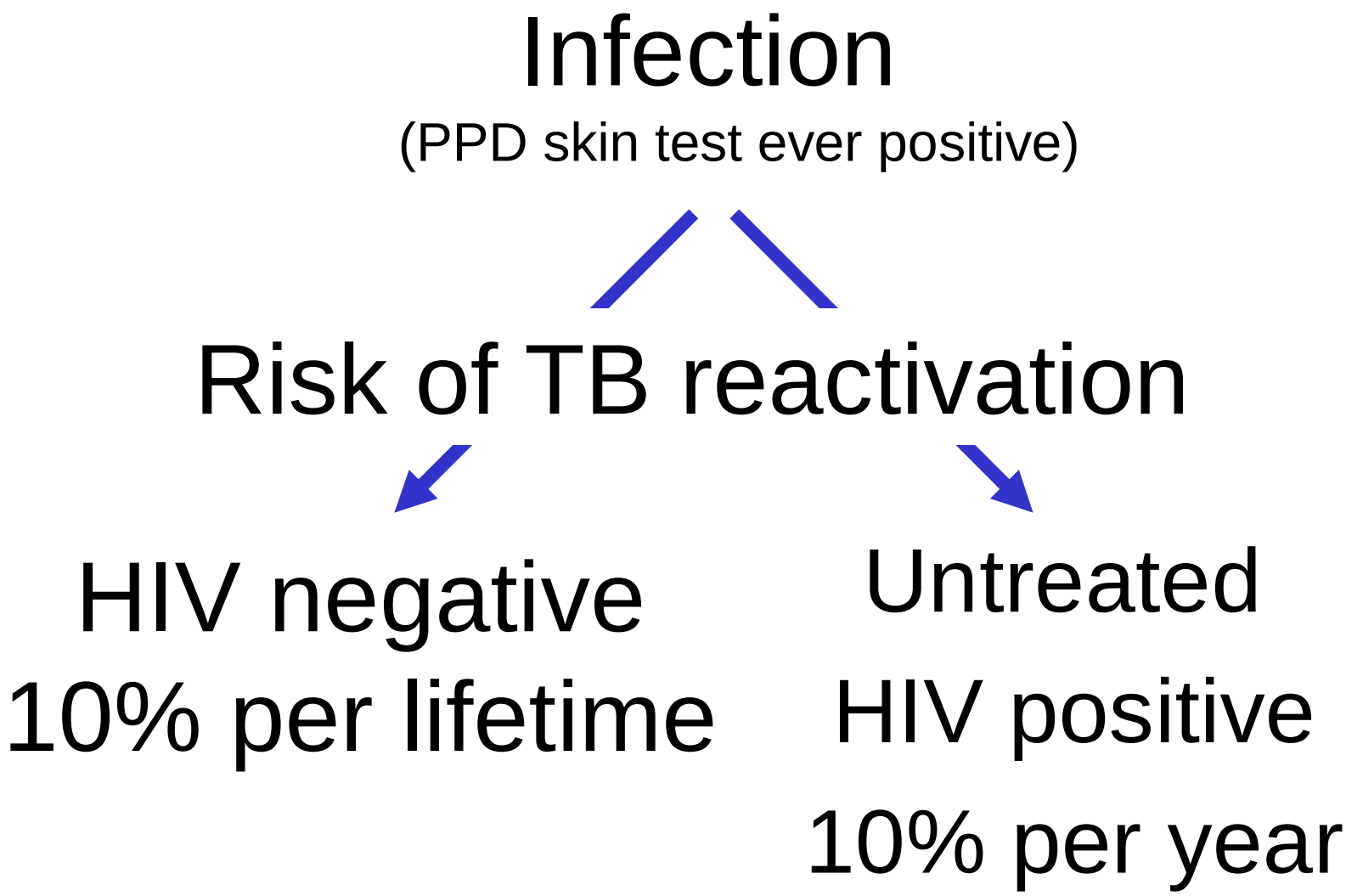
Gold miners in South Africa
Sonnenberg et al, AIDS 2004, 18:657–662

Tuberculosis Risk Increases Soon After HIV Seroconversion



Gold miners in South Africa
Sonnenberg et al, J Infect Dis. 2005;191:150-158

Impact of HIV infection on Tuberculosis



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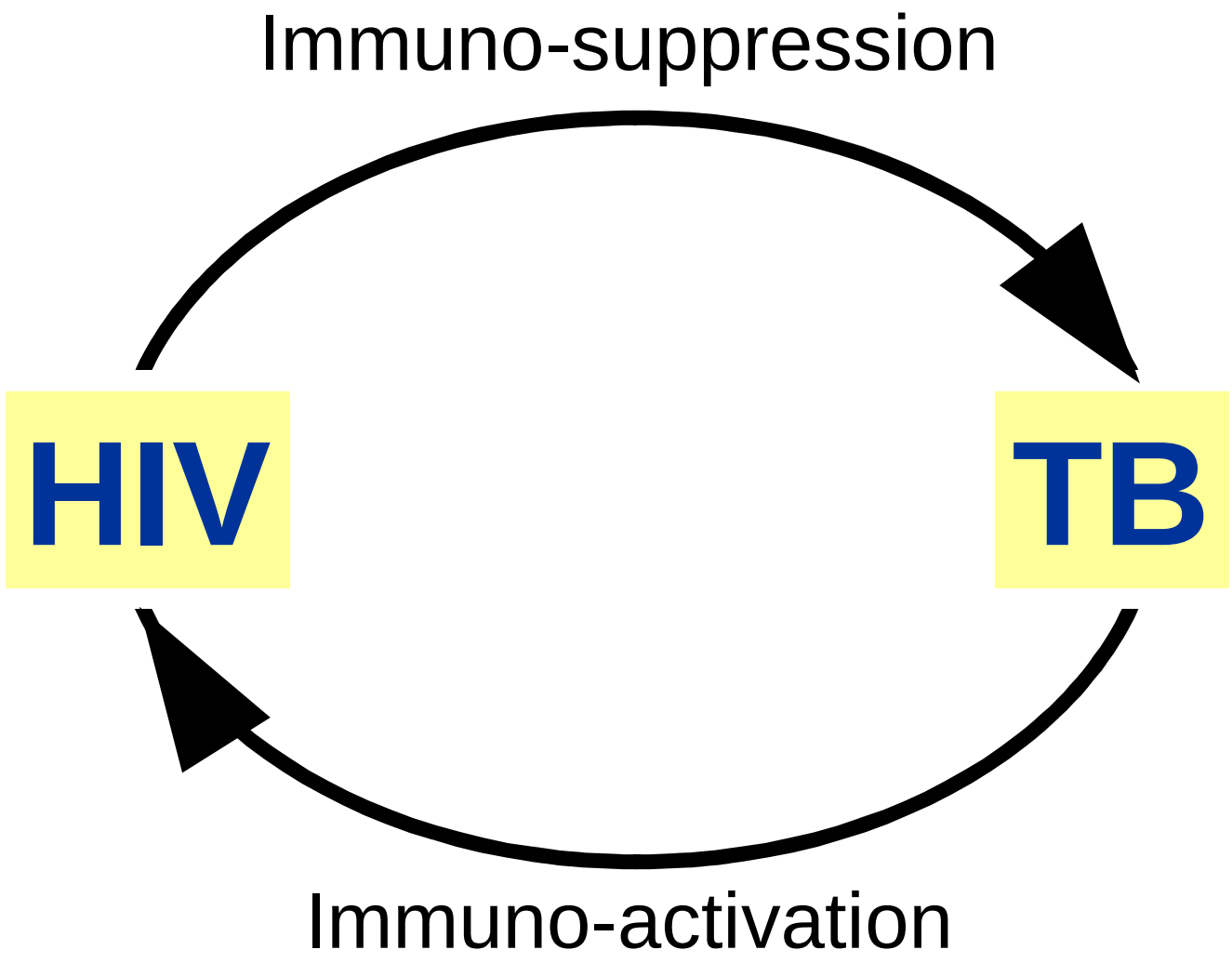
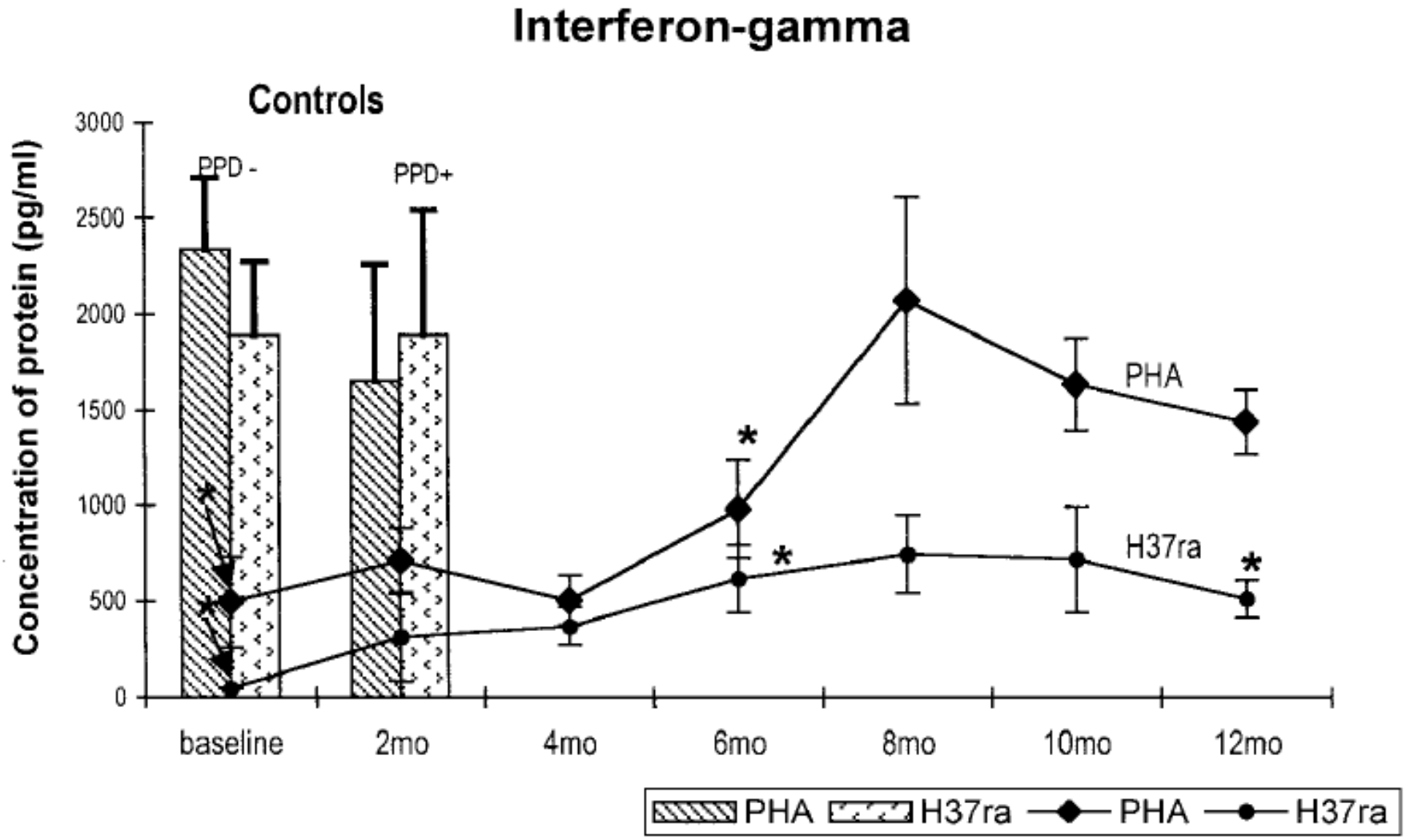
HIV and TB – Double Trouble



Immune Response to Tuberculosis

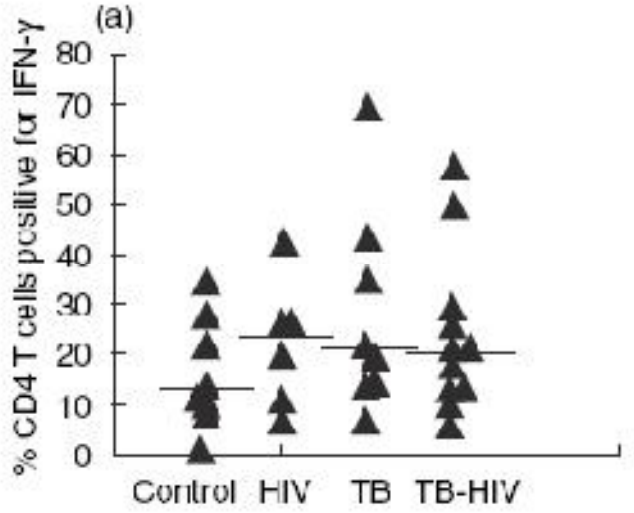
Changing over time	Innate immunity
	T-cell dependent
	Granuloma formation
Macrophages as target	Pathogen induced anergy
Immune compartments	Lung
	Lymph node
	Peripheral blood
Symptoms ≠ Severity	tissue destruction
	immune mediated damage

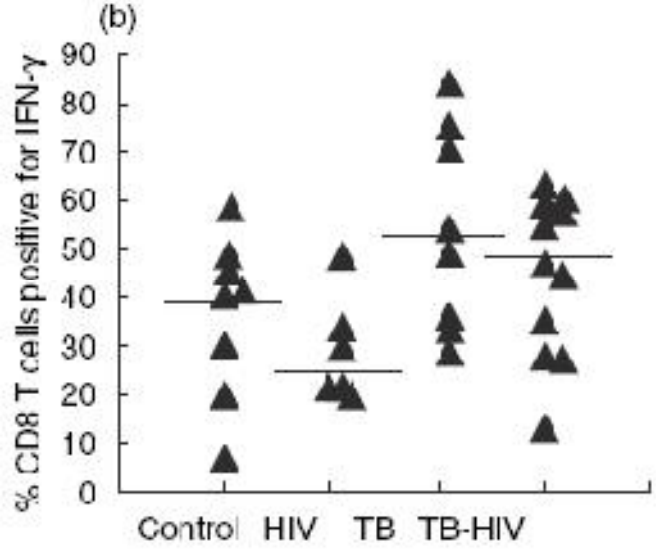
Interferon-γ response to TB antigen during HAART



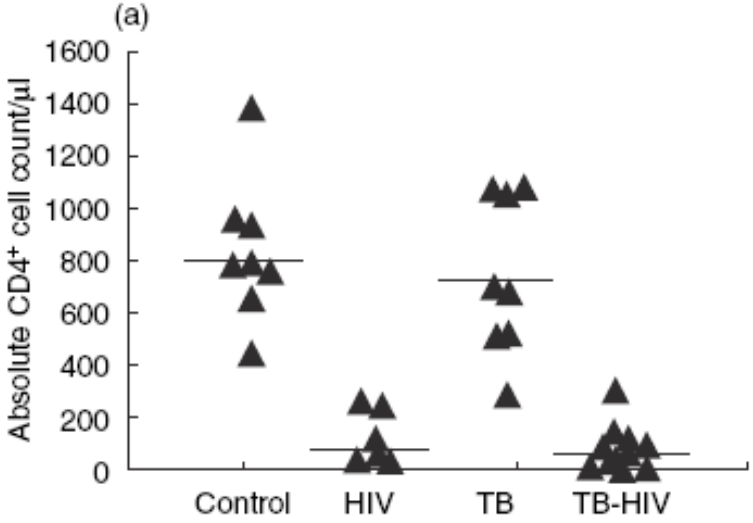
10 HIV+ patients starting HAART (8 latent, 2 clinical TB)
Schluger Chest 2002; 122:597–602

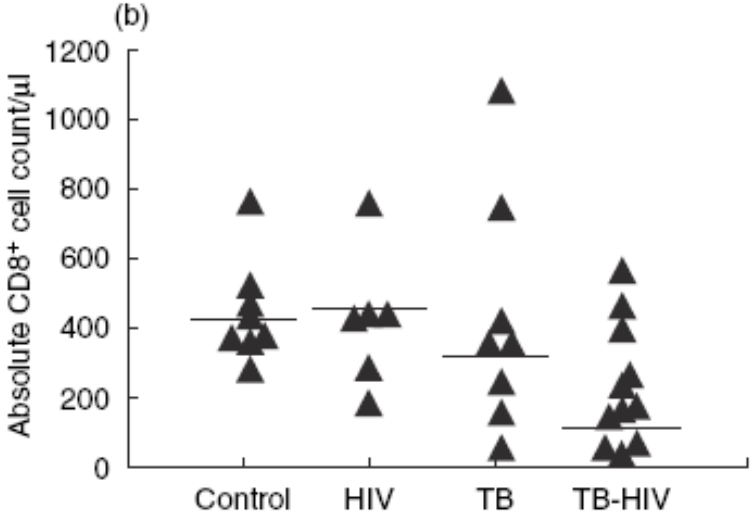
T cell numbers and function in HIV & TB





IFNγ production by blood T cells

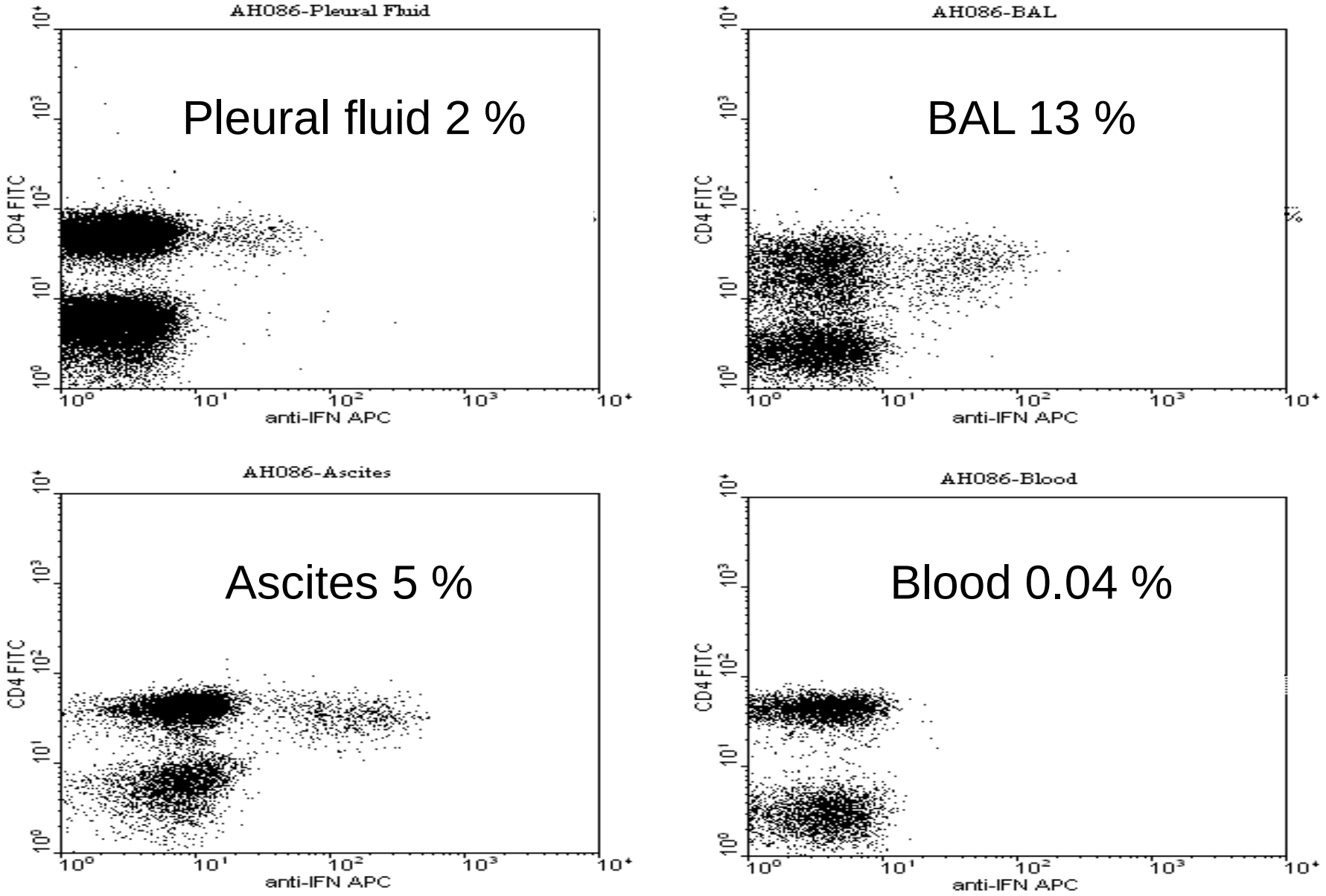




Blood T cells counts

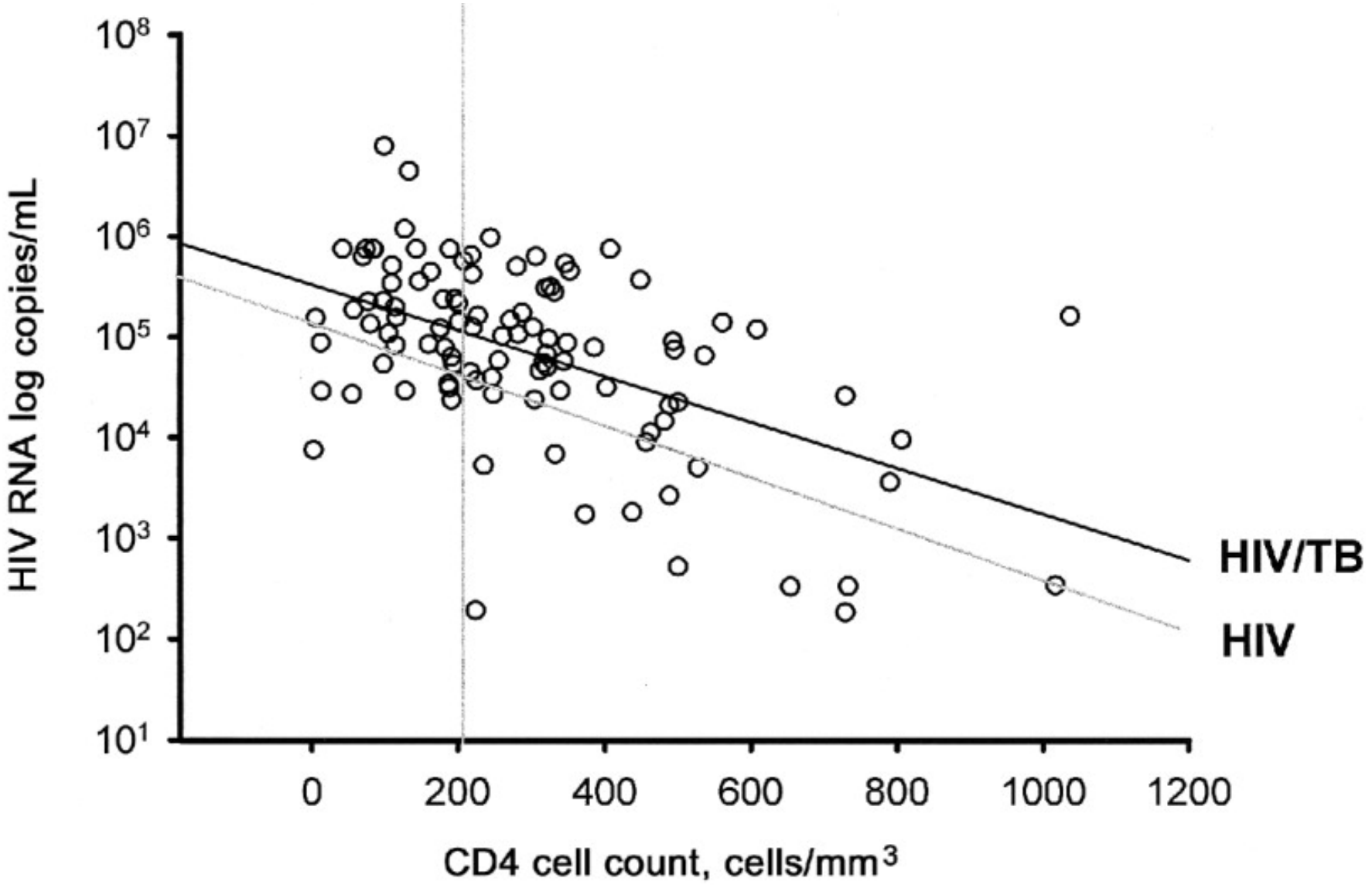
De Castro Cunha et al (Brazil) Clin Exp Immunol 2005

IFN Responses to TB Antigen in a TB&HIV Patient



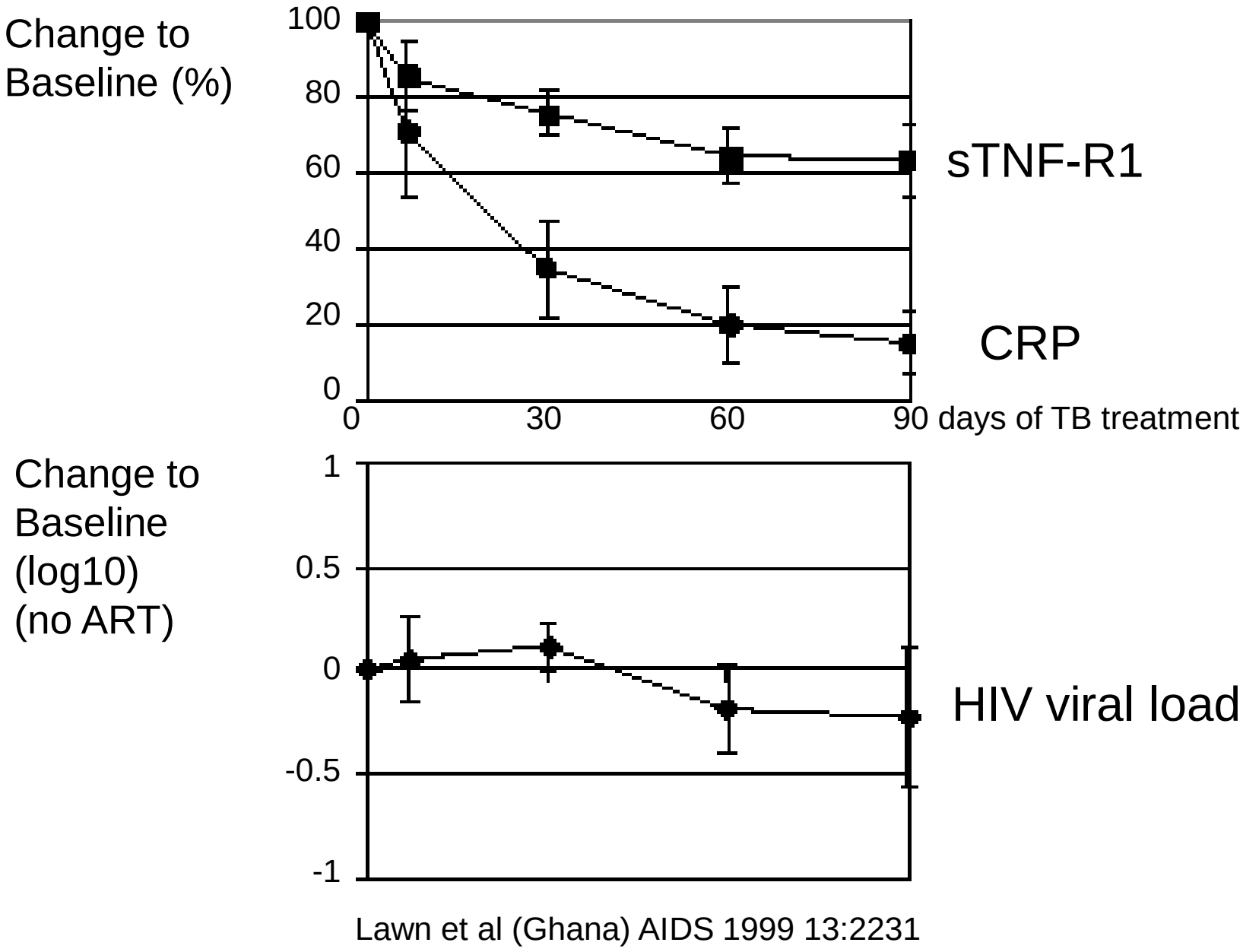
Barry S et al (London) J Inf Dis 2003; 87:243–50 (and Lipman M personal communication)

HIV Viral Load increased by Tuberculosis



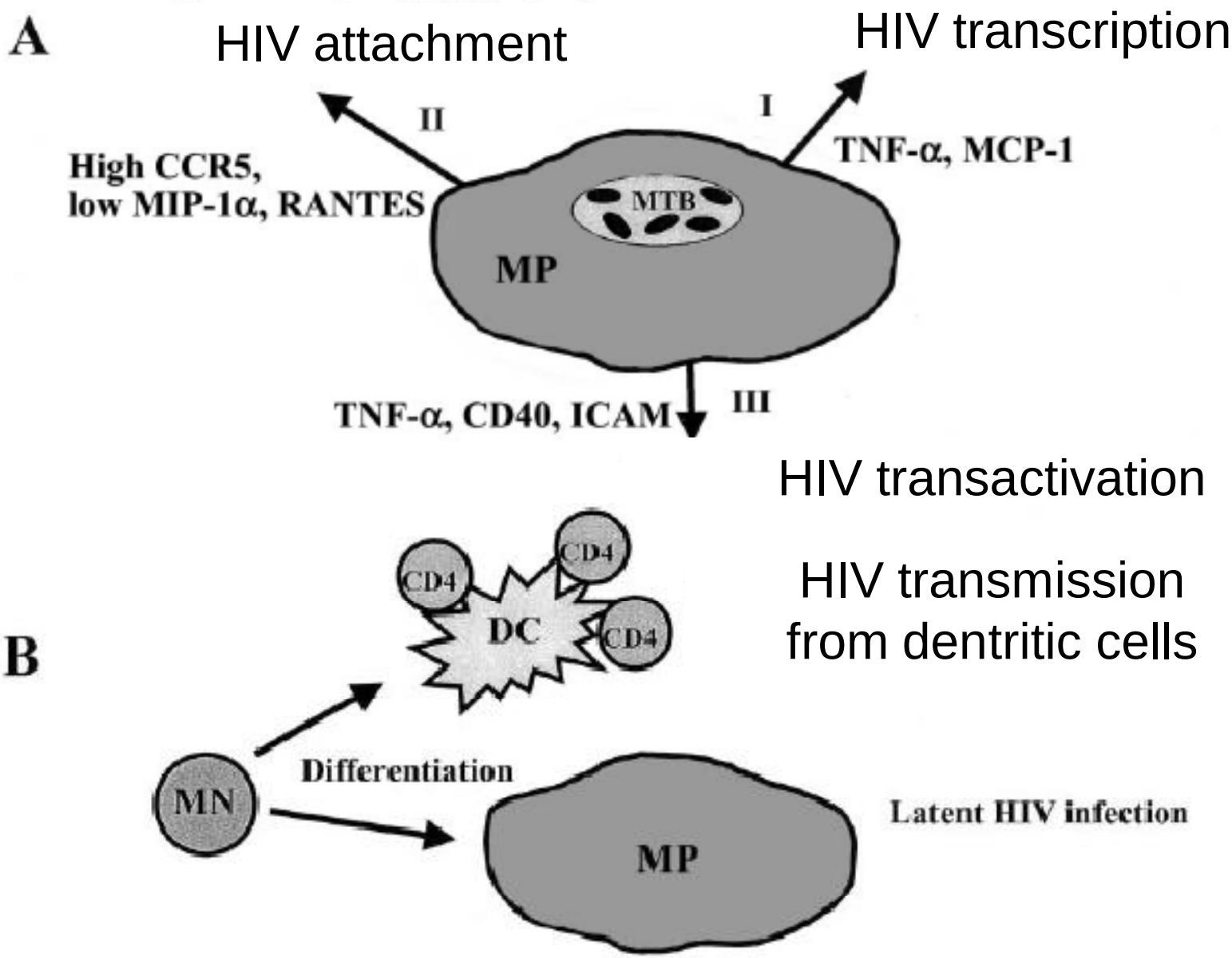
Toossi J Inf Dis 2003; 188:1146–55

TB treatment does not decrease HIV viral load



Lawn et al (Ghana) AIDS 1999 13:2231

HIV propagation by M tuberculosis



[MP=Macrophage, MN= mononuclear cell, CD=dendritic cell]

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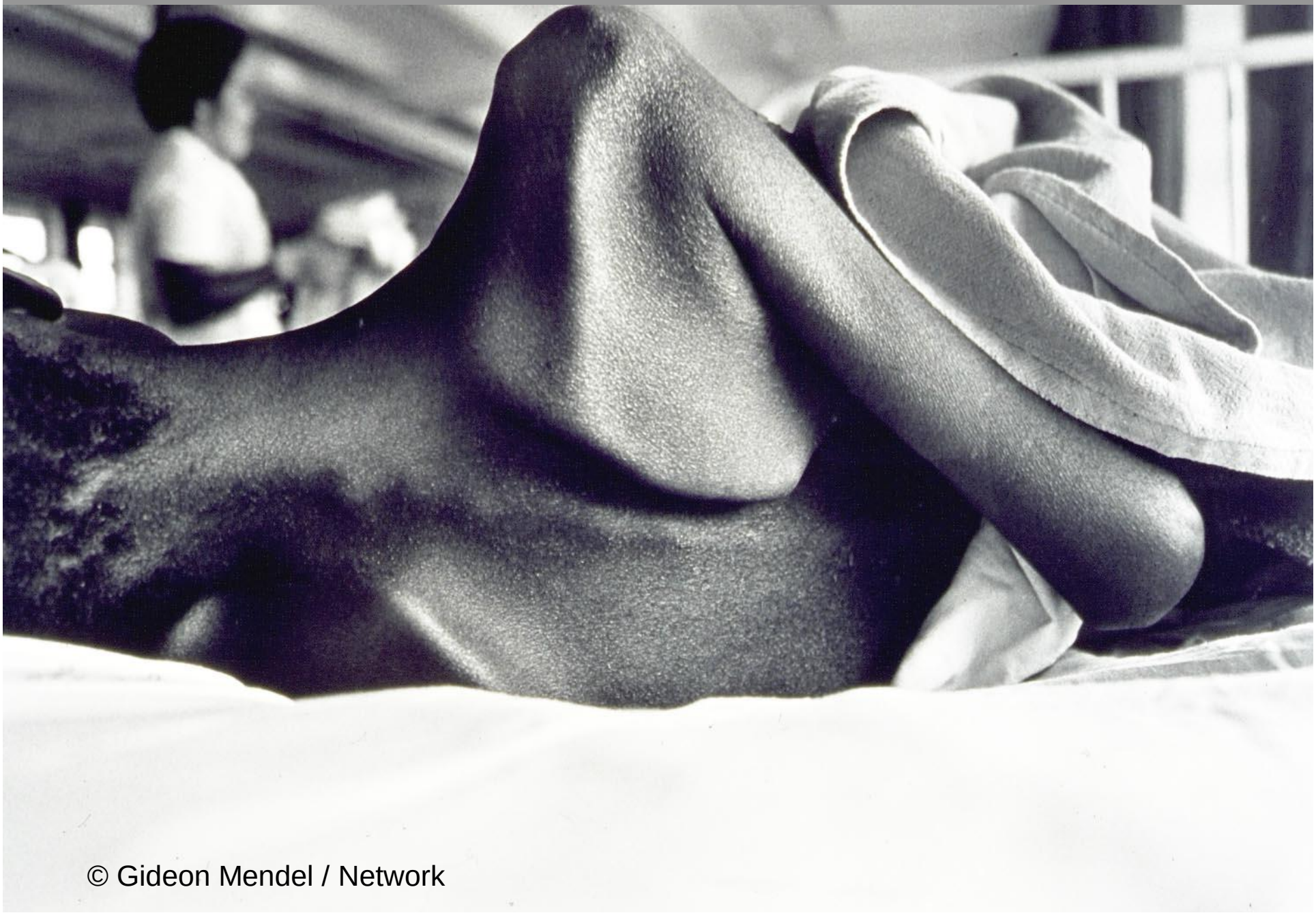
Wasting Syndrome



Impact of HIV on TB presentation

Pulmonary

- cavitation and infiltrate (more with good immunity)
- lower lobe infiltrate
- multiple lobes
- mediastinal lymph nodes
- Normal chest X ray with sputum culture positive (8-20%)
- Pleural effusion (progressive primary pTB)

Extrapulmonary (53% to 63%)

- abdominal and other lymph nodes
- extranodal disease
- cerebral tuberculoma

Disseminated

- miliary lesions (with few symptoms)
- fever of unknown origin
- wasting syndrome (weight loss)

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Infection Control

Nosocomial outbreak of TB on HIV ward

12 of 32 (**37%**) exposed patients developed TB

contact to disease 106 days

Daley New Engl J Med **1992**

Nosocomial outbreak of MDR-TB in Buenos Aires

1992 to 1995

101 patients MDR-TB (resistant against ≥5 drugs)

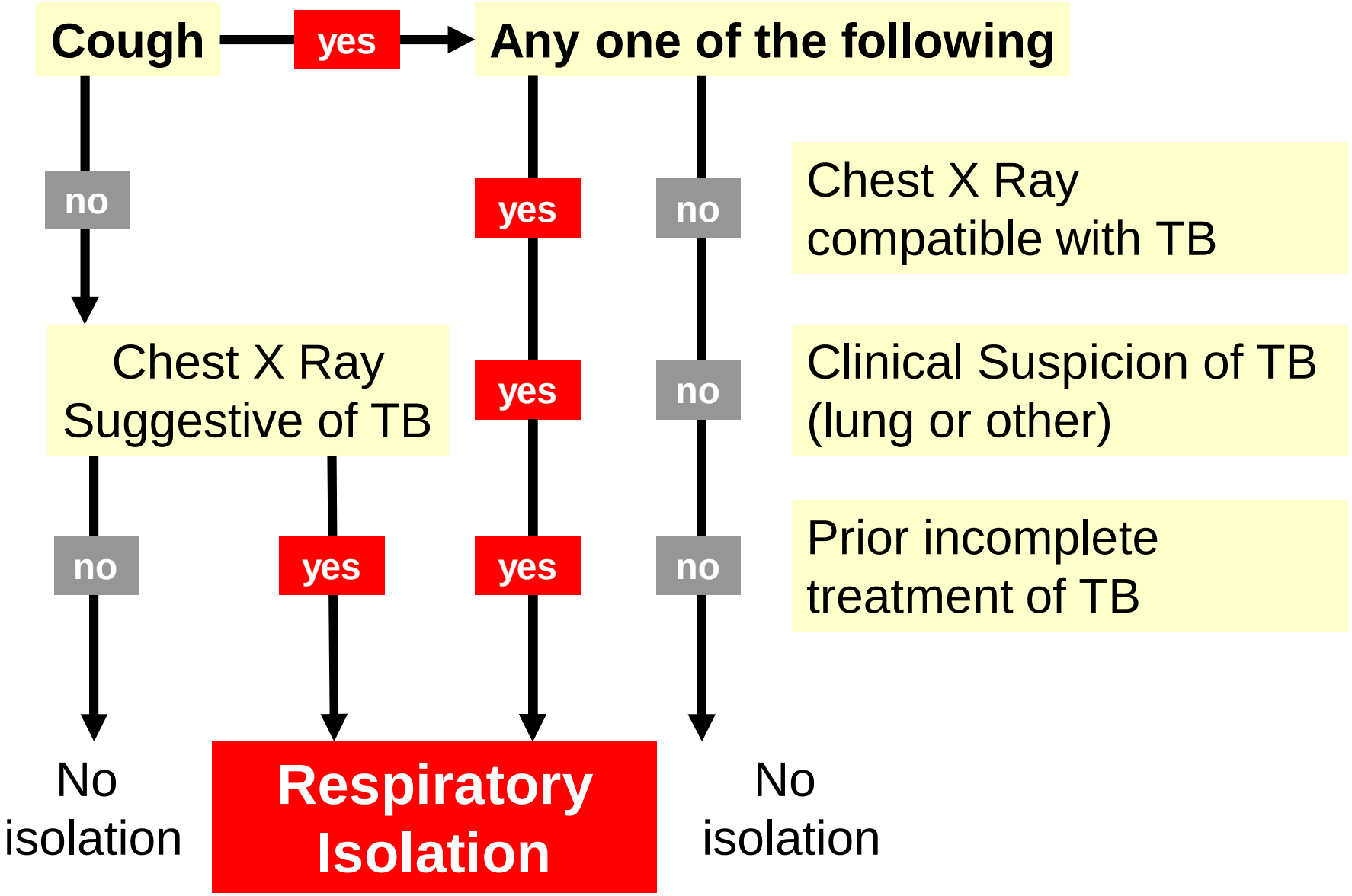
68/77 patients single strain (RFLP)

Ritacco J Infect Dis. **1997**

MDR = Multi-drug resistant

RFLP = Restriction fragment length polymorphism

Respiratory Isolation Policy



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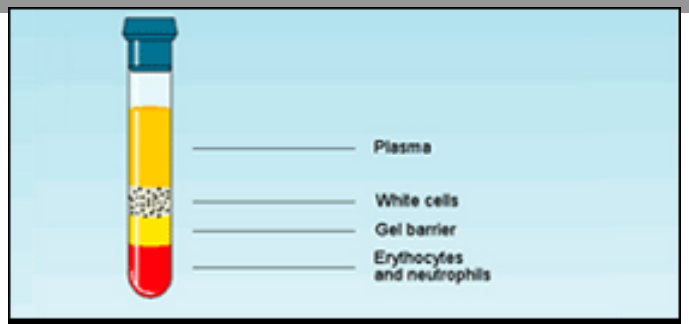
Impact of HIV on TB diagnosis

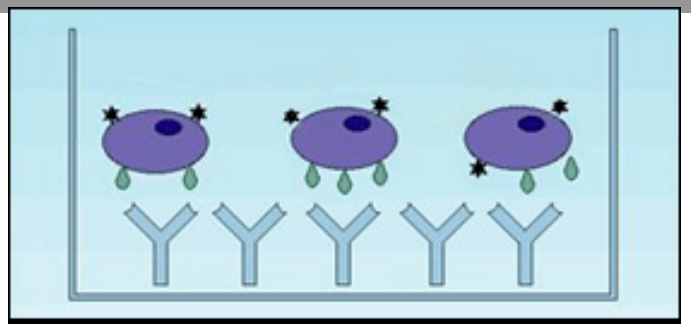
Skin test negative	30% with CD4<200 /µl
	50% with CD4 >200/µl
Sputum AFB positive	30 to 60% in HIV+
	57% in HIV -
Normal chest X ray &	
sputum culture positive	8 to 20%
Granulomata on biopsy	60 to 100%
Blood culture positive	0 to 42%
Diagnosis via BAL	70%

Aaron CMI 2004

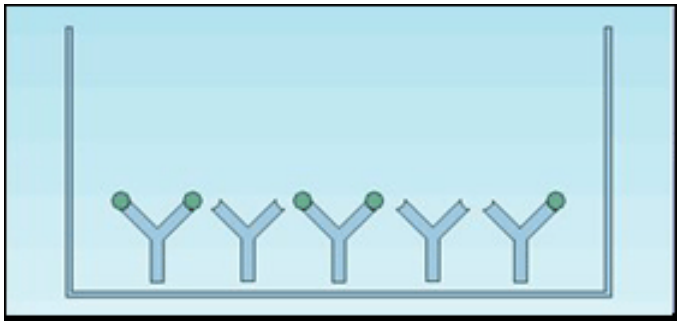
Elispot for Diagnosis of Tuberculosis



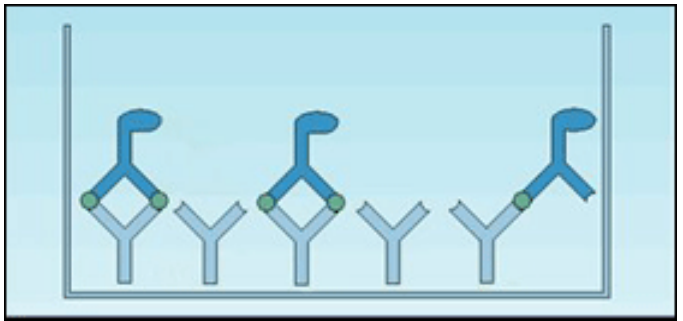
White cells separated from other blood components using ficol gradient or simply collect blood in BD CPT Vacutainer™ tubes and place in centrifuge.



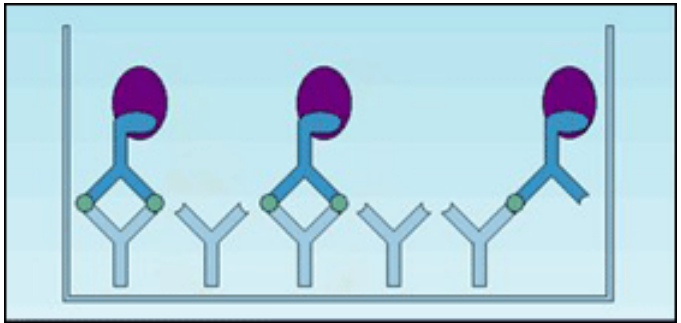
Add white cells and TB antigens to microtite plate wells. TB activated T cells will release gamma interferon.



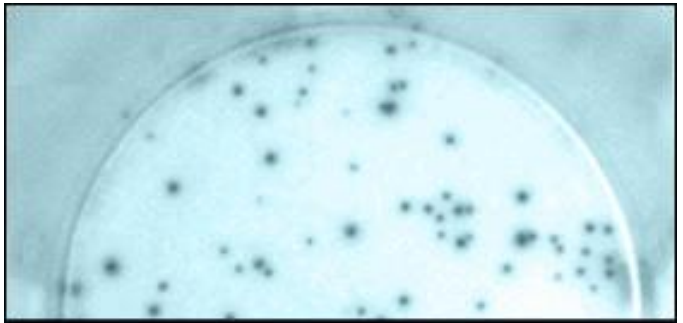
Gamma interferon is captured by antibodies on floor of the microtiter plate



Add conjugated second antibody to gamma interferon. Incubate and wash wells.



Add substrate to develop colour and count spots manually or in reader.



Each spot in the microtiter plate well corresponds to an individual T cell that has released interferon gamma due to challenge by TB antigens.

TB-spot (Elispot) in African Children

	ELISPOT positive/ total tested by ELISPOT	Sensitivity of ELISPOT* (95% CI)	TST positive/total tested by TST	Sensitivity of TST* (95% CI)
Age				
>36 months	64/79	81% (71 to 89)	46/63	73% (60 to 83)
<36 months	46/54	85% (73 to 93)	27/53	51% (37 to 65)
p†		0·53		0·01
HIV				
Negative or not tested	88/103	85% (77 to 92)	64/91	70% (60 to 80)
Positive	22/30	73% (54 to 88)	9/25	36 % (18 to 58)
p†		0·12		0·002
Z score				
>−2	61/71	86% (76 to 93)	48/63	76% (64 to 86)
<−2	46/59	78% (65 to 88)	22/50	44 % (30 to 59)
p†		0·24		0·0003

Liebeschuetz et al Lancet 2004; 364:2196-2203

BAL response to PPD antigen

PPD-specific CD4+ interferon-γ response in bronchoalveolar lavage mononuclear cells

	Tuberculosis	**TB not diagnosed**
HIV Negative	**21.8%** (0.1 – 79.3%) n=73	**0.5%** (0.0 – 27.1%) n=61
HIV Positive	**7.1%** (0.0 to 67.1%) n=16	**0.0%** (0.0 – 16.1%) n=18

Barry S et al (London) J Inf Dis 2003; 87:243–50 (and Lipman M, personal communication 2005)

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Treatment Duration (BHIVA 2005 / BTS 1998)

Fully sensitive TB, no intolerance

Pulmonary	Bone	Disseminated
Lymph node	CNS	Miliary (no meningitis)

Lack of CD4 increase >100/μL

H Isoniazid
R Rifampicin
Z Pyrazinamide
E Ethambutol

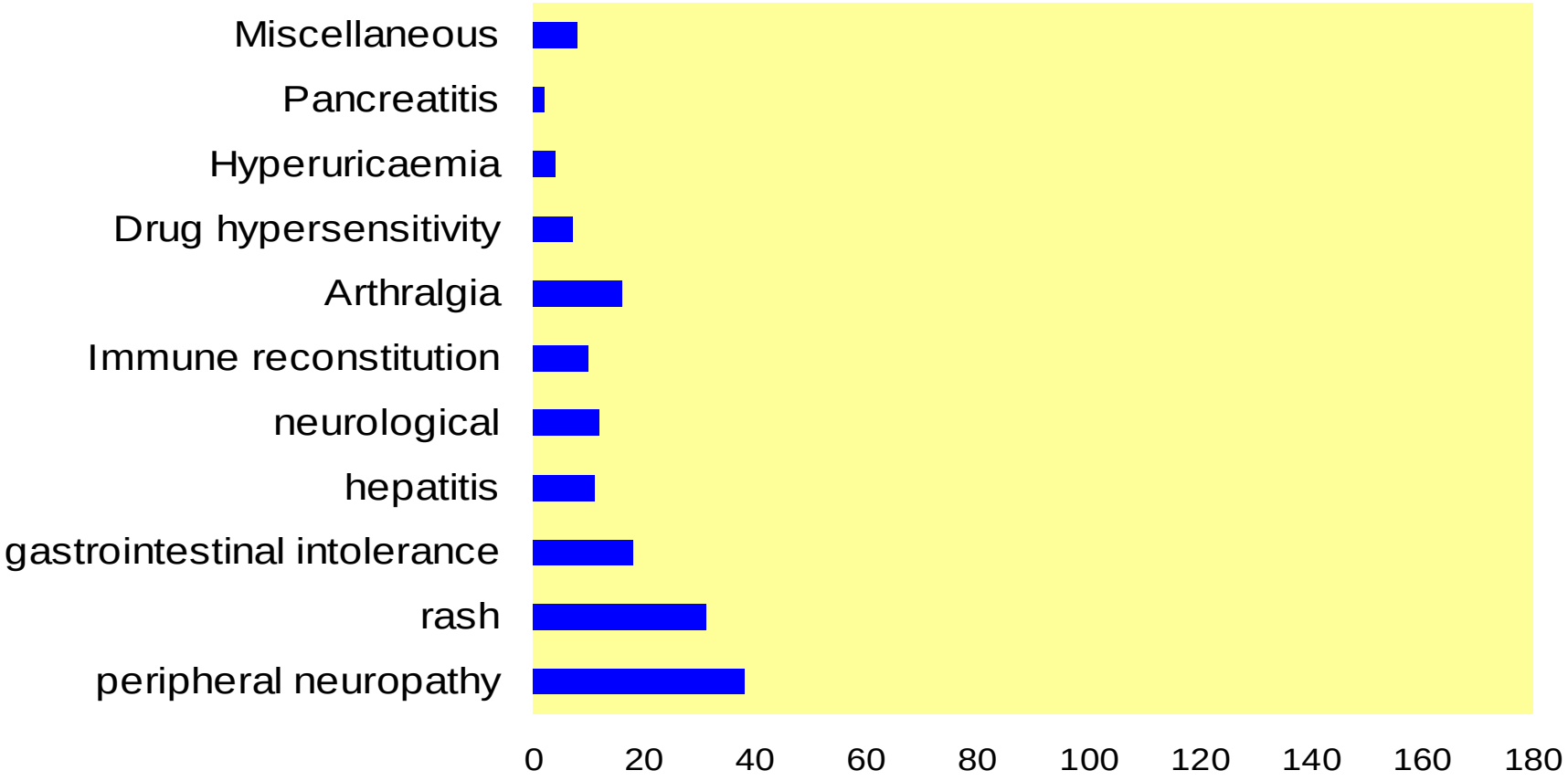
North Middlesex Hospital policy

Adverse reactions to TB treatment in HIV+

167 adverse events in 99/183 (54%) patients

Stop TB or HIV therapy in 63 (34%)

mostly first 2 months



Dean et al AIDS 2002, 16:75-83

Adverse Reactions to TB Treatment + Differential Diagnosis

Fever	immune reconstitution
	progressive TB
	other infection
Rash	Non-nucleosides, Abacavir
Liver disease	Non-nucleosides
	progressive TB
	Hepatitis B/C
Polyneuropathy	nucleoside analogues, HIV

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The case for

…immediate treatment	… delayed treatment
Early AIDS progression	Attributable adverse reactions
Immunosuppressive effect of TB	Adherence to treatment
	immune reconstitution syndrome ↓

Progression to AIDS or Death during TB Treatment

Time from start of TB treatment without HIV treatment	**CD4 count at baseline**	
	>100	**<100**
	n = 61	n = 35
0 to <2 months	41.3 (4)	**248.6 (11)**
2 months to <1 year	26.3 (11)	54.9 (8)
1 to 6 years	8.3 (12)	10.3 (3)
Total	**13.8 (27)**	**45.6 (22)**

Events / 100 person years

Dheda et al J Infect Dis 2004; 190:1670

Drug interactions

Efavirenz 800 mg od (if weight >60kg)

Antibacterials	Amprenavir	Atazanavir	Indinavir	Lopinavir	Nelfinavir	Ritonavir	Saquinavir	Efavirenz	Nevirapine
Ciprofloxacin	◇	◇	◇	◇	◇	◇	◇	◇	◇
Ethambutol	◇	◇	◇	◇	◇	◇	◇	◇	◇
Isoniazid	◇	◇	◇	◇	◇	◇	◇	◇	◇
Pyrazinamide	◇	◇	◇	◇	◇	◇	◇	◇	◇
Rifabutin	□	□	X	□	X	□	●	□	?
Rifampicin	●	●	●	●	●	□	●	□	X
Rifapentine	□	□	□	□	□	□	□	□	□
Streptomycin	◇	◇	◇	◇	◇	◇	◇	◇	◇

+ Therapeutic Drug Monitoring

+ low-dose Ritonavir
Rifabutin 150 mg 3* weekly

www.hiv-druginteractions.org
University of Liverpool

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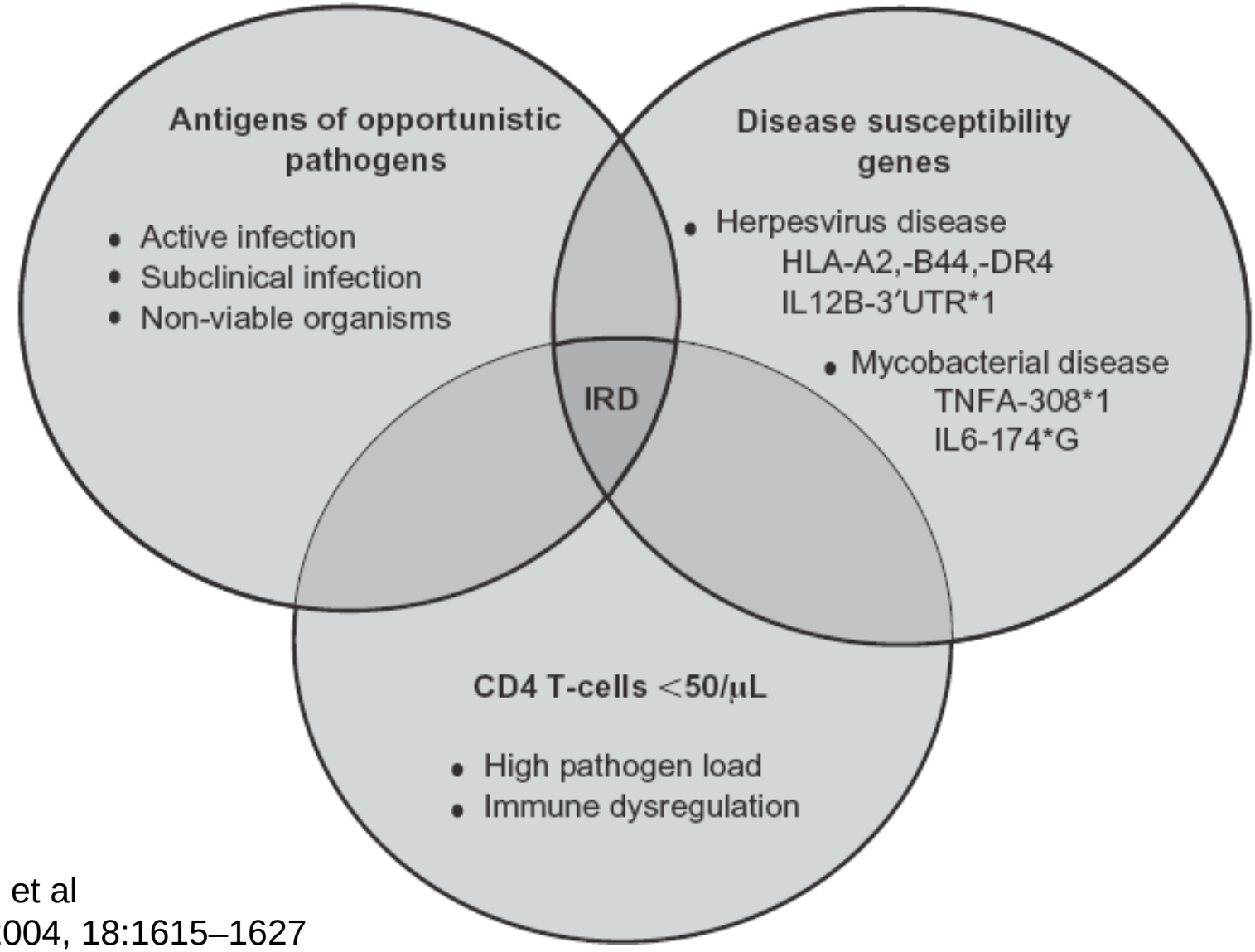
Immune Reconstitution Inflammatory Syndrome (IRIS)

Fever	high without malaise
Lymph node abscess	inflamed skin, fistula
New infiltrates	Lung, Brain, Psoas abscess
Onset	Median 2 weeks after starting HIV treatment
Duration	up to 2 years
Risk ↑ with	low CD4 at baseline?
	increase CD4?
	early start of HIV treatment

Pathogenesis of IRIS in HIV



French et al
AIDS 2004, 18:1615–1627

Paradoxical Reactions (IRIS)

	HIV+ve (n = 50)	HIV −ve (n = 50)
PR	14 (28%)	5 (10%)
Disseminated TB and PR	9 (65%)	4 (80%)
Median (range) time from starting TB medication to onset of PR (days)	33 (3–173)	87 (23–157)
Median (range) time from starting HAART to onset of PR (days)	11 (8–18)	NA
PR treated with corticosteroids	8	1
Manifestations of PR		
Fever	4	2
Ascites	1	0
Lymph nodes	7	2
CNS	2	0
Respiratory	2	0
Pleural effusion	1	1
Ocular	0	1
Joint swelling	0	1
>1 manifestation of PR	4	2

Breen R et al (London), Thorax 2004;59;704-707

IRIS and HAART in HIV+TB

	No (%) with PR	p value*
CD4 count at starting HAART		
>50 cells/mm^3	4/17 (24%)	0.7
<50 cells/mm^3	4/11 (36%)	
Viral load at starting HAART		
<5.5 log copies/ml	3/14 (21%)	0.7
>5.5 log copies/ml	5/14 (36%)	
Disseminated TB		
No	2/15 (13%)	0.09
Yes	6/13 (46%)	
CD4 cell response to HAART		
>100 cells/mm^3 increase	6/18 (33%)	0.7
<100 cells/mm^3 increase	2/10 (20%)	
Viral load (VL) response to HAART		
Achieved VL <400 copies/ml	8/24 (33%)	0.3
Did not achieve VL <400 copies/ml	0/4 (0%)	
Ethnicity		
Black African	5/16 (31%)	1.0
Other	3/12 (25%)	
Time from TB treatment to HAART		
<6 weeks	7/13 (54%)	0.03
6 weeks–6 months	1/11 (9%)	
>6 months	0/4 (0%)	

Breen R et al (London), Thorax 2004;59;704-707

Treatment of Immune Reconstitution Syndrome

Prednisolone

- 1 – 1.5 mg/kg for 1 – 2 weeks
- if no response stop
- if response taper down
- efficacy ½ by rifampicin after 2 wks

Recurrent aspiration

Immunomodulatory therapy?

- no data

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