TB/HIV

BSc Infection and Immunity

25th November 2011

Imperial College London

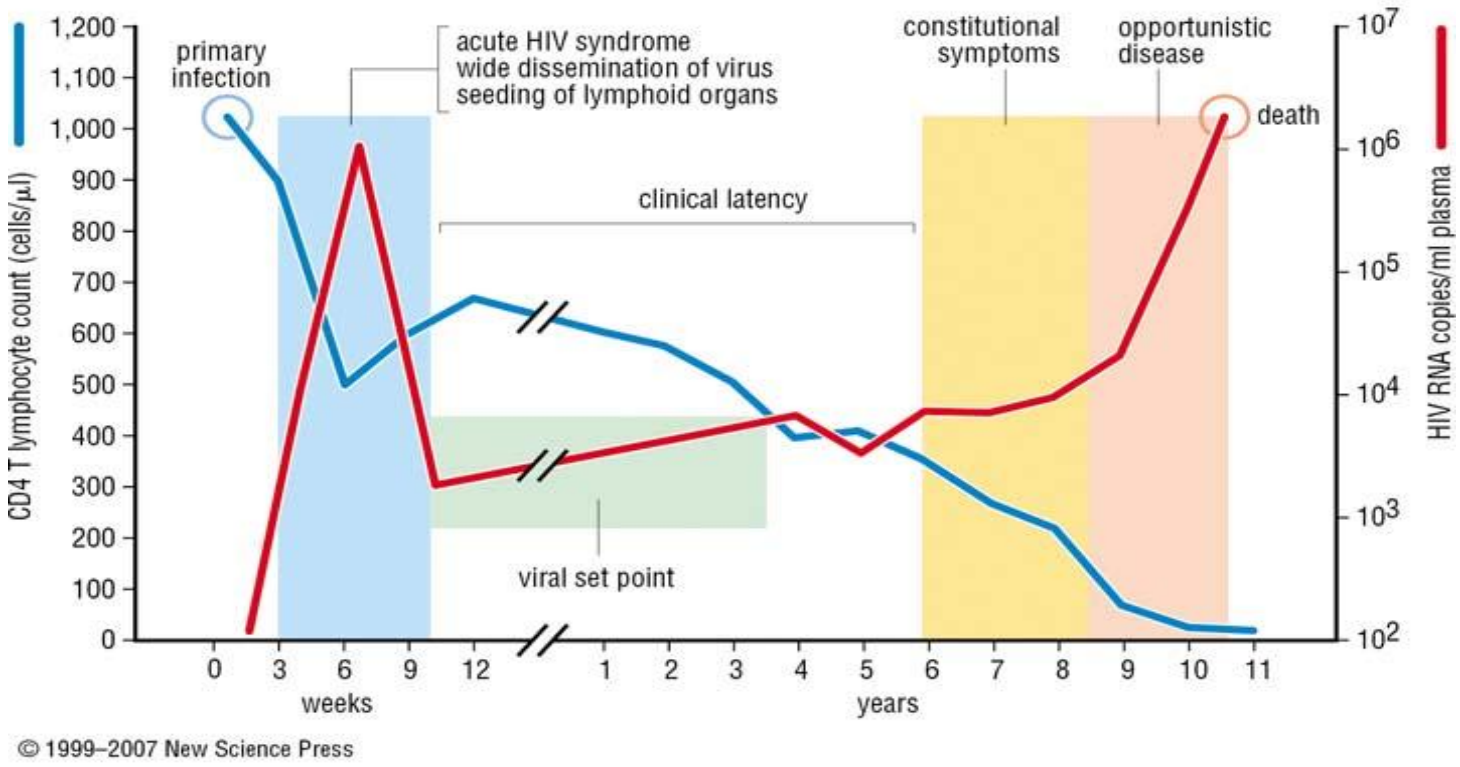
Talk outline

- Some basics of HIV and TB
- Recent advances in Diagnostics
- TB prevention in PLHW
- The timing of HAART in patients with TB
- MDR/XDR and TMC207

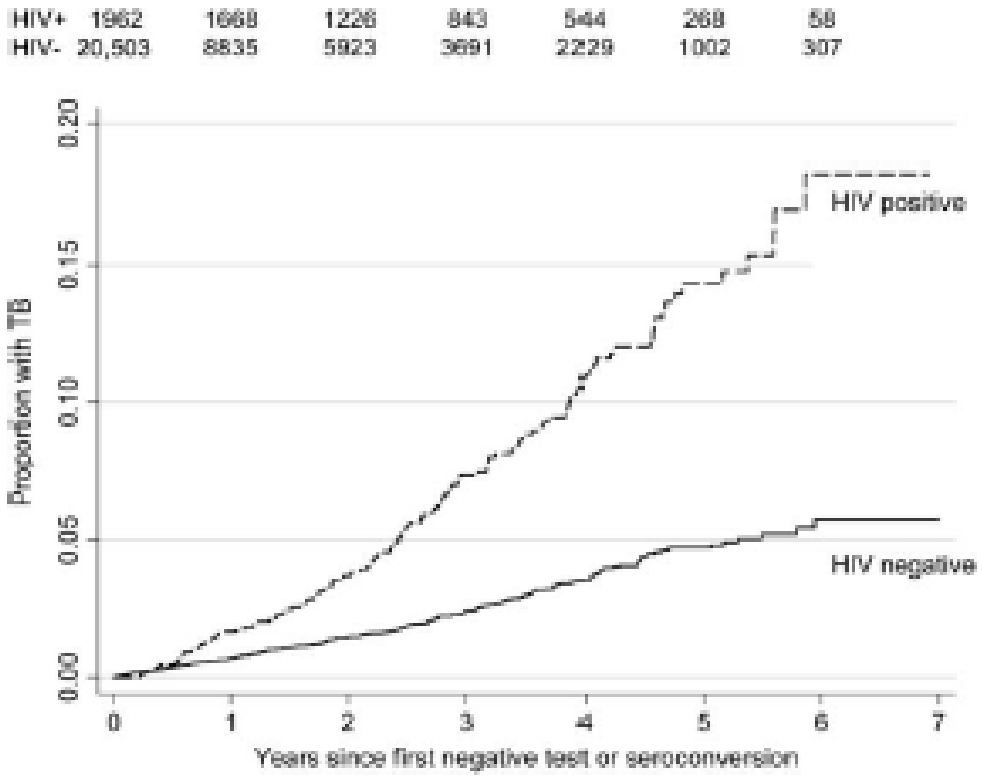
HIV and TB

HIV

From **Immunity: The Immune Response in Infectious and Inflammatory Disease**
by DeFranco, Locksley and Robertson



Risk of TB increases from time of HIV infection



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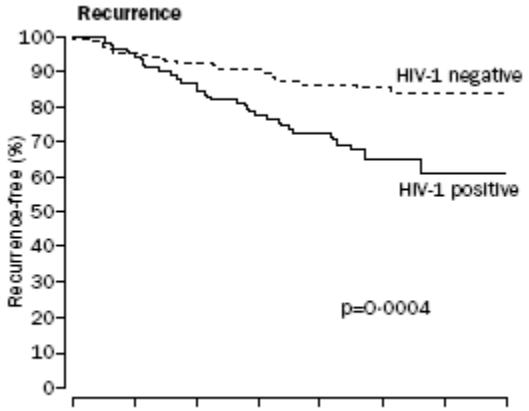
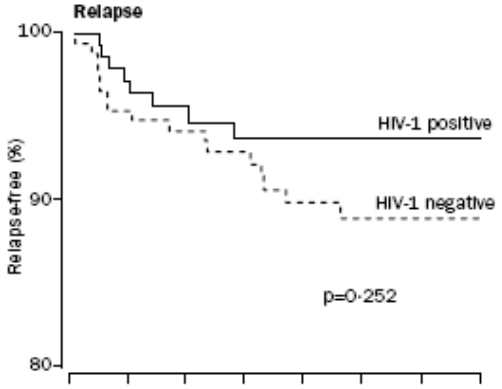
Sonnenberg , 2005

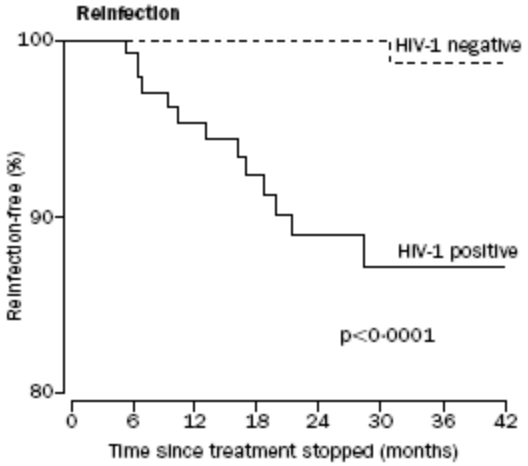
HIV increases risk of recurrence, particularly reinfection



Recurrence



Relapse



Reinfection

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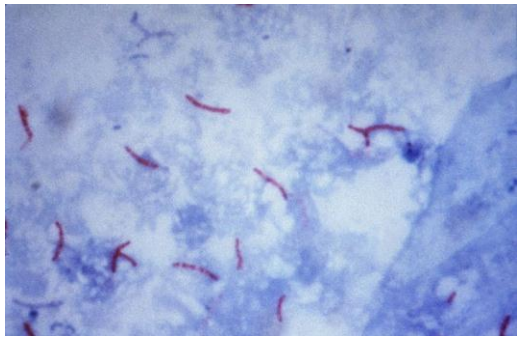
Sonnenberg , 2001

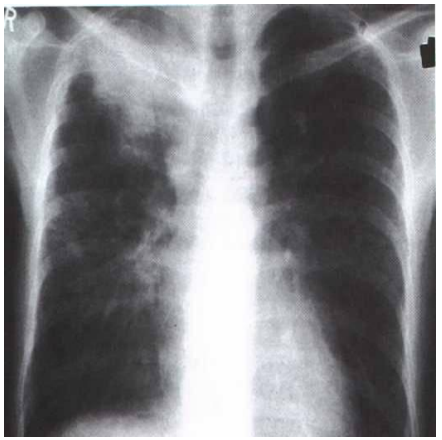
Just a reminder on TB…..

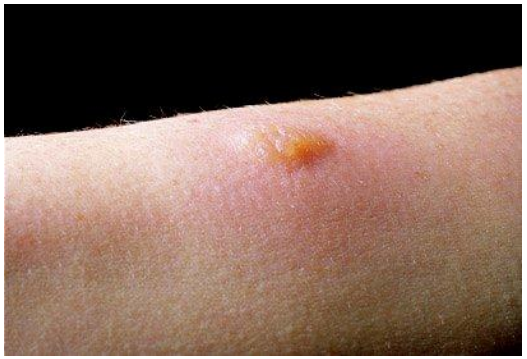
Tuberculosis: discrete states?

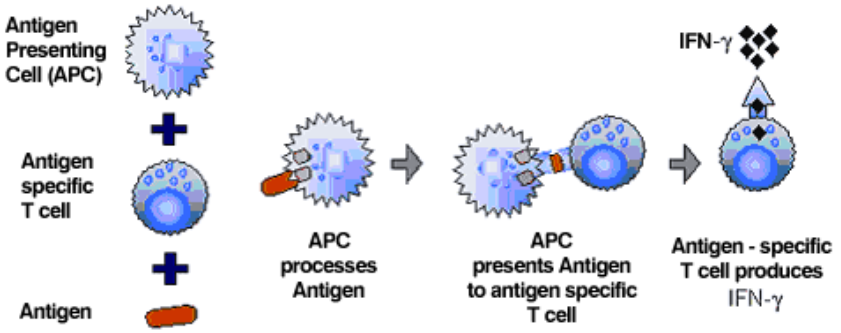
The organism: MTB



The disease

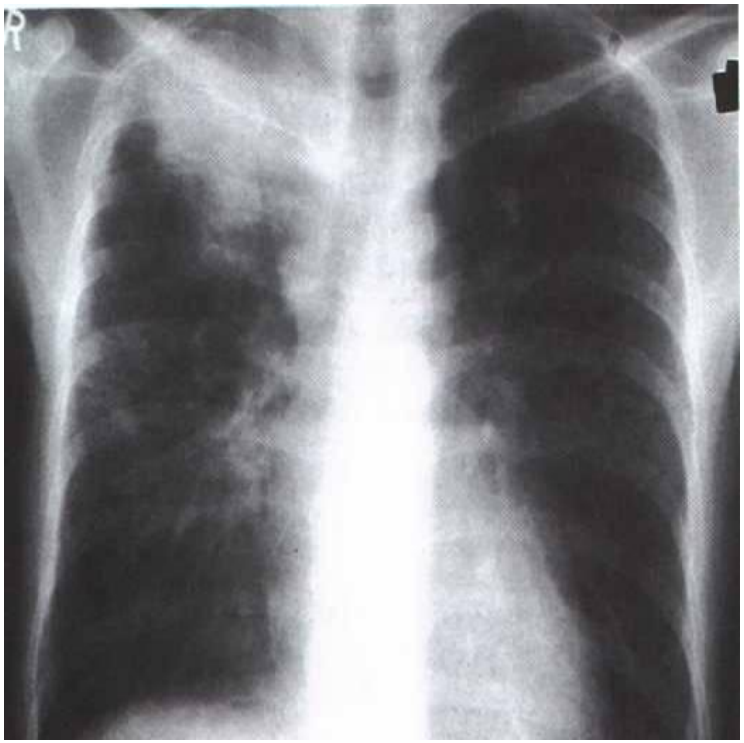


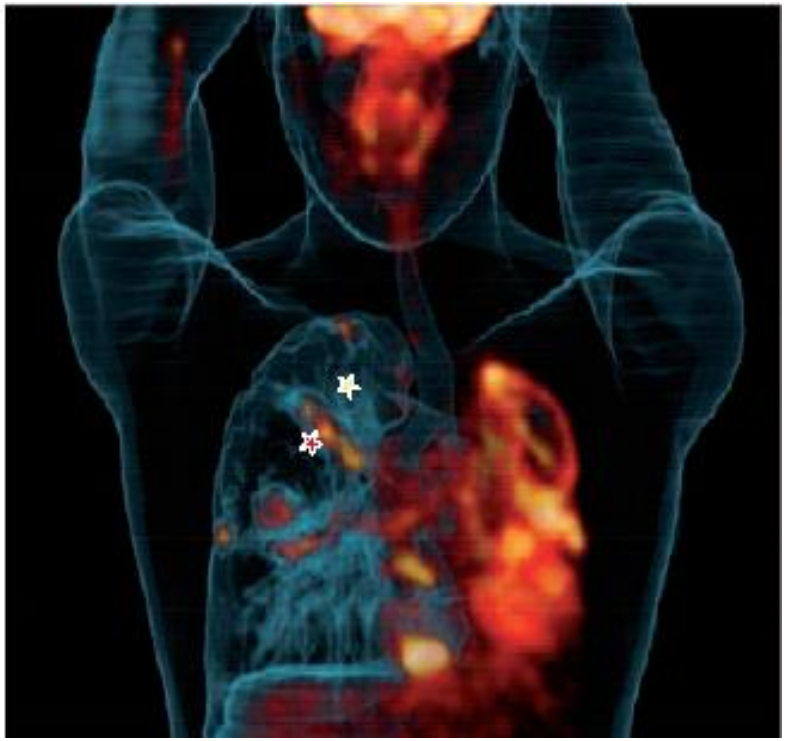




Latent TB Infection

TB: a spectrum of disease





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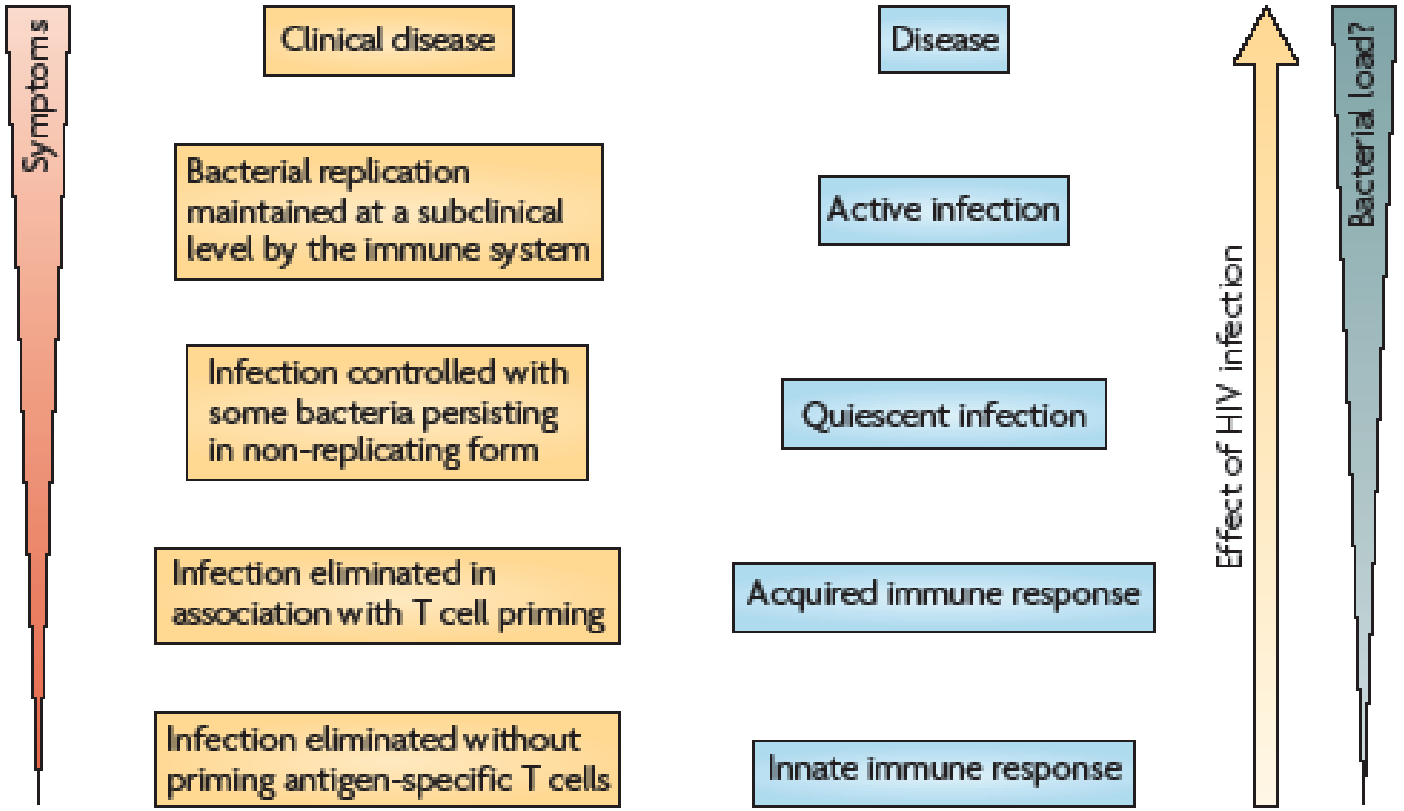
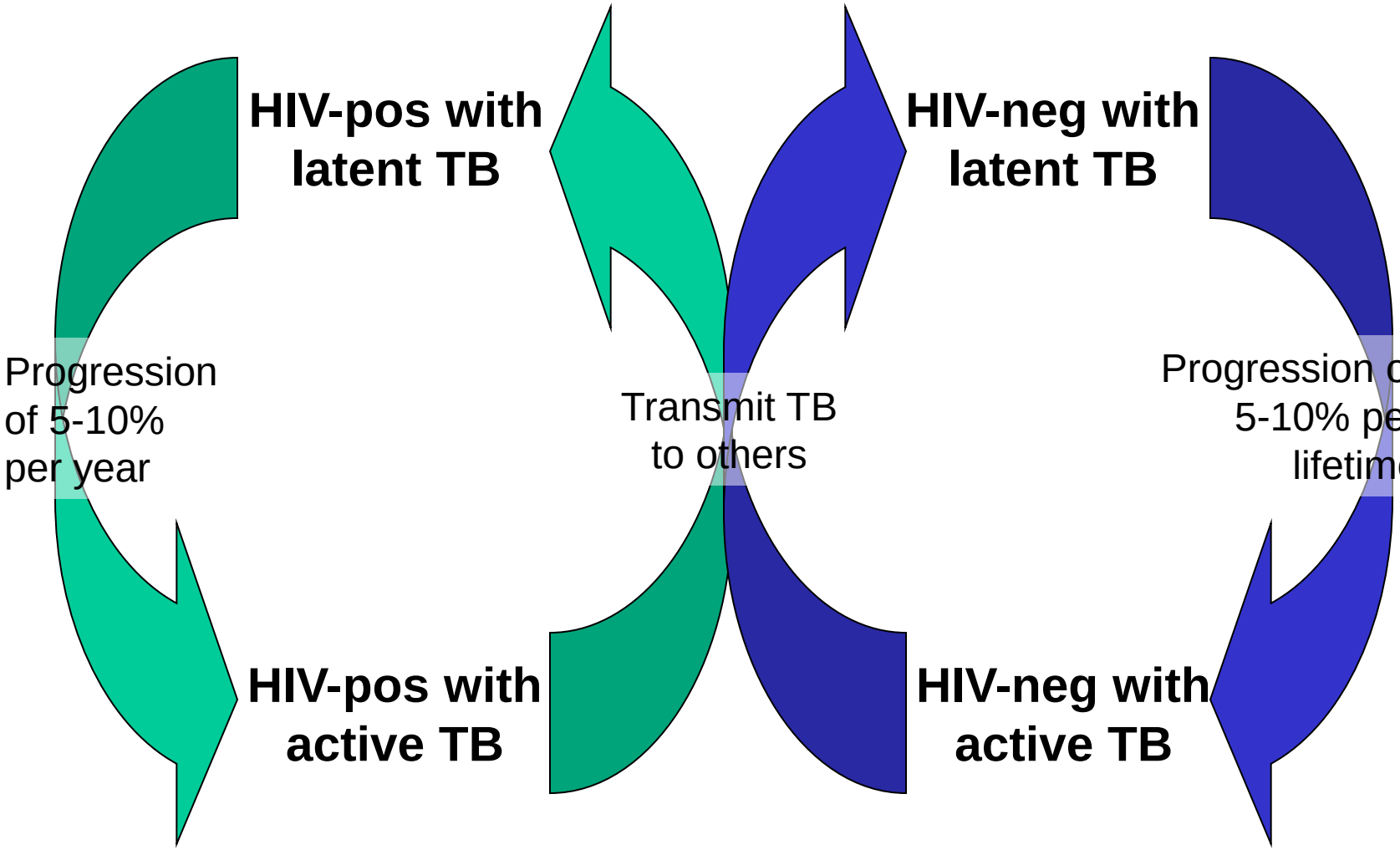
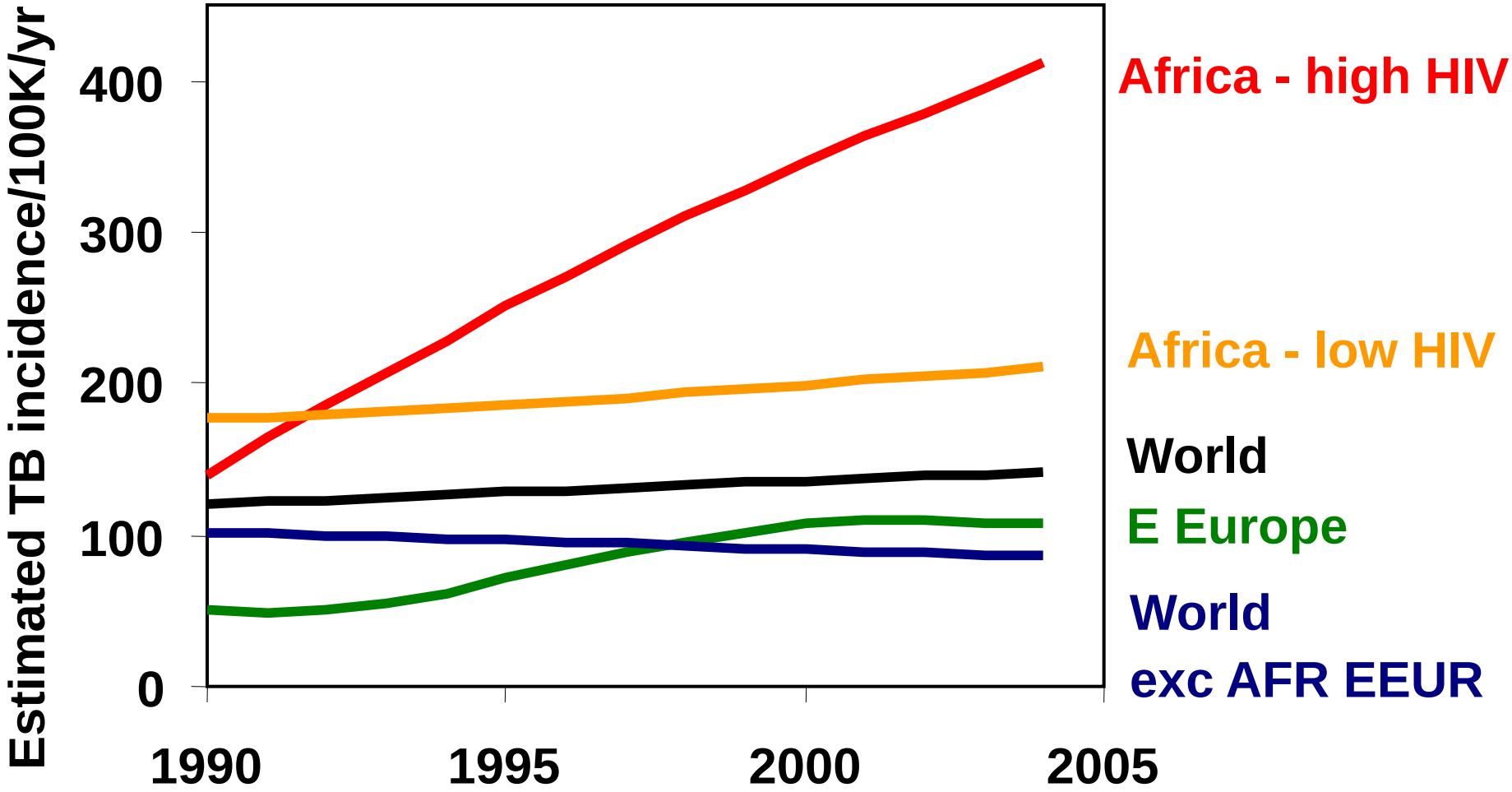
Barry et al , Nat Rev Biol 2009

Latent TB Infection (LTBI) – part of a continuum

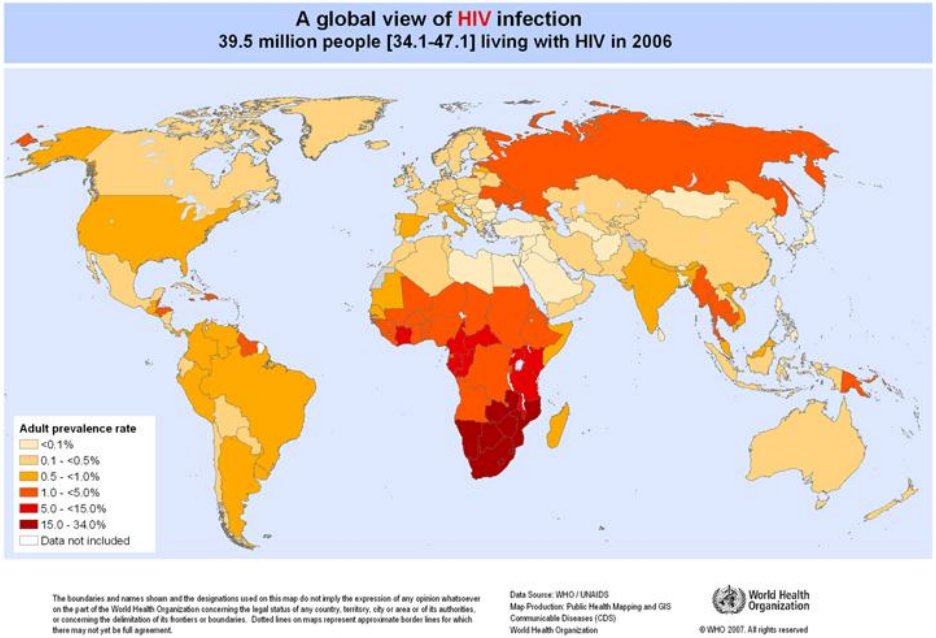


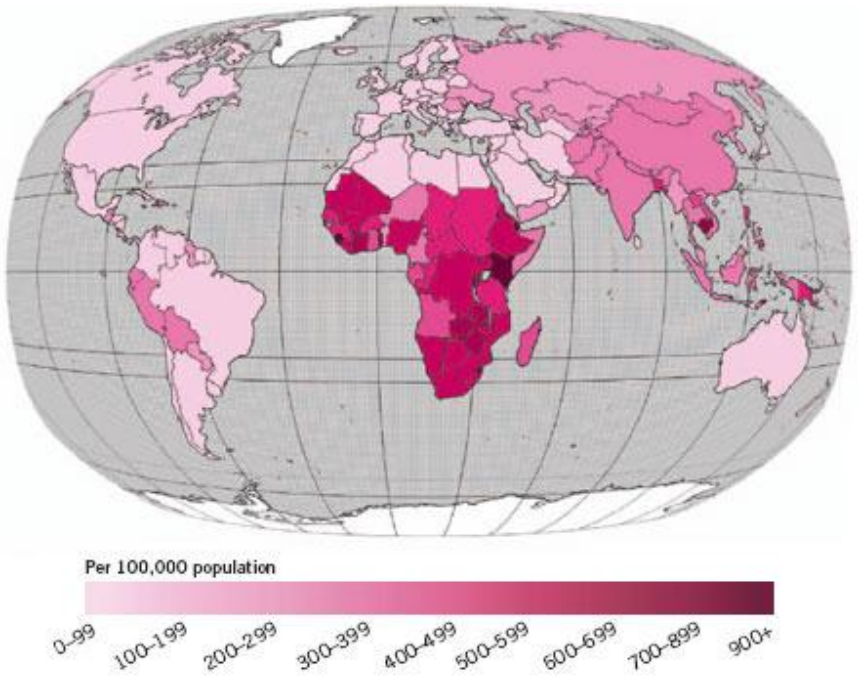
Barry et al , Nat Rev Biol 2009


HIV-pos with latent TB
HIV-neg with latent TB
Progression of 5-10% per year
Transmit TB to others
Progression of 5-10% per lifetime
HIV-pos with active TB
HIV-neg with active TB


Estimated TB incidence/100K/yr
400
300
200
100
0
1990
1995
2000
2005
Africa - high HIV
Africa - low HIV
World
E Europe
World
exc AFR EEUR

HIV and TB in the world





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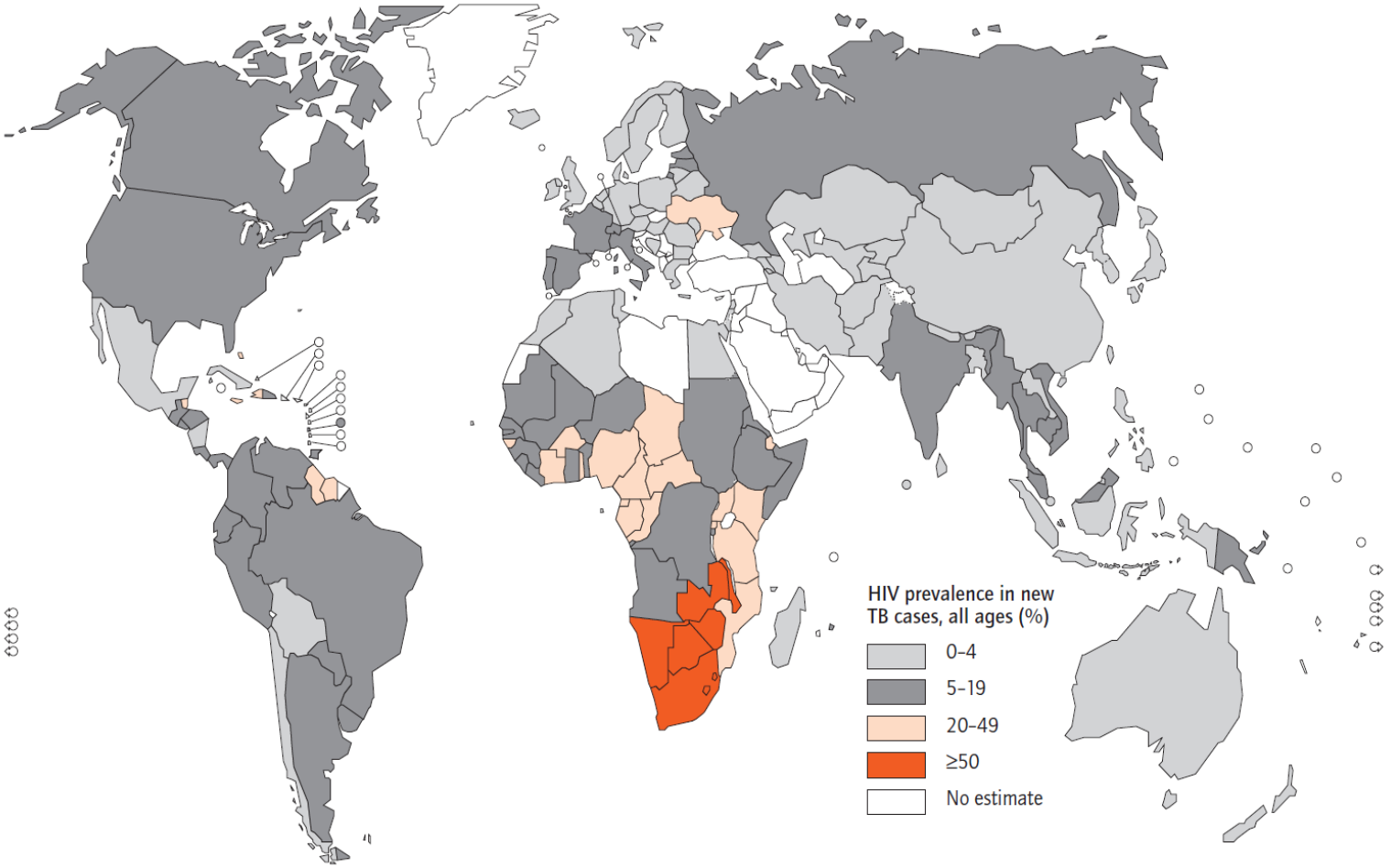
Source: WHO

HIV Prevalence in TB cases

FIGURE 1.3
Estimated HIV prevalence in new TB cases, 2007



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Source: Stop TB

Immunology

What are the mechanisms?

Impact of CD4 T cell depletion (and recovery on HAART)

Direct effects on innate immunity

Impact on other aspects of cellular immunity

HIV associated with impaired IFNg responses

Table 3 Effect of HIV on cytokine responses to tuberculin (PPD) (10 μg/ml) and culture filtrate proteins (CFP) (10 μg/ml)

Cytokine antigen	Number (%) with positive cytokine response: HIV+ (n = 22)	HIV− (n = 75)	Crude odds ratio (95% confidence interval)	P*	Adjusted odds ratio† (95% confidence interval)	P‡
IFN-γ						
PPD	3 (14)	46 (61)	0.10 (0.03–0.37)	<0.001	0.12 (0.03–0.40)	<0.001
CFP§	1 (4)	32 (45)	0.06 (0.01–0.46)	0.001	0.05 (0.01–0.46)	<0.001
IL-2						
PPD¶	4 (19)	17 (25)	0.69 (0.20–2.34)	0.76	1.15 (0.28–4.80)	0.84
CFP	1 (5)	12 (18)	0.23 (0.03–1.88)	0.26	0.26(0.03–2.55)	0.19
IL-5						
PPD	3 (14)	16 (21)	0.58 (0.15–2.22)	0.55	0.35 (0.08–1.56)	0.15
CFP	2 (9)	6 (8)	1.15 (0.22–6.14)	0.78	2.57 (0.35–18.97)	0.37
IL-10						
PPD	10 (45)	13 (17)	3.97 (1.42–11.14)	0.01	7.63 (1.91–30.48)	0.002
CFP	15 (68)	49 (65)	1.14 (0.41–3.14)	0.99	1.35 (0.43–4.22)	0.61
TNF-α						
PPD	5 (23)	19 (25)	0.87 (0.28–2.67)	0.97	0.82 (0.22–3.13)	0.77
CFP	10 (45)	39 (52)	0.77 (0.30–2.00)	0.77	0.50 (0.16–1.52)	0.21

*P value for crude odds ratio.
†Adjusted for BCG scar status, illness (well vs all illness, including probable/possible TB), lymphocyte count.
‡P value for the adjusted odds ratio.
§4 missing values (ELISA failed for 4 HIV-negative cases).
¶9 missing values (1 HIV-positive and 8 HIV-negative cases, excluded because of high, non-specific IL-2 production).

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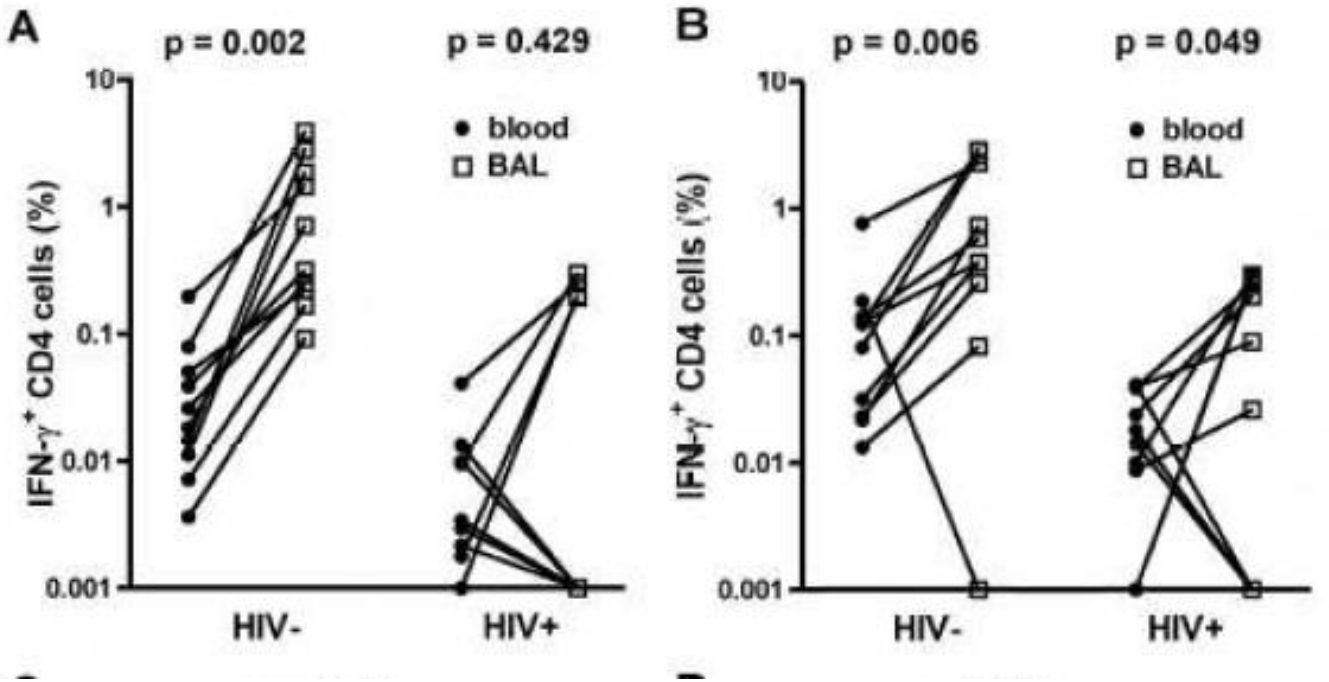
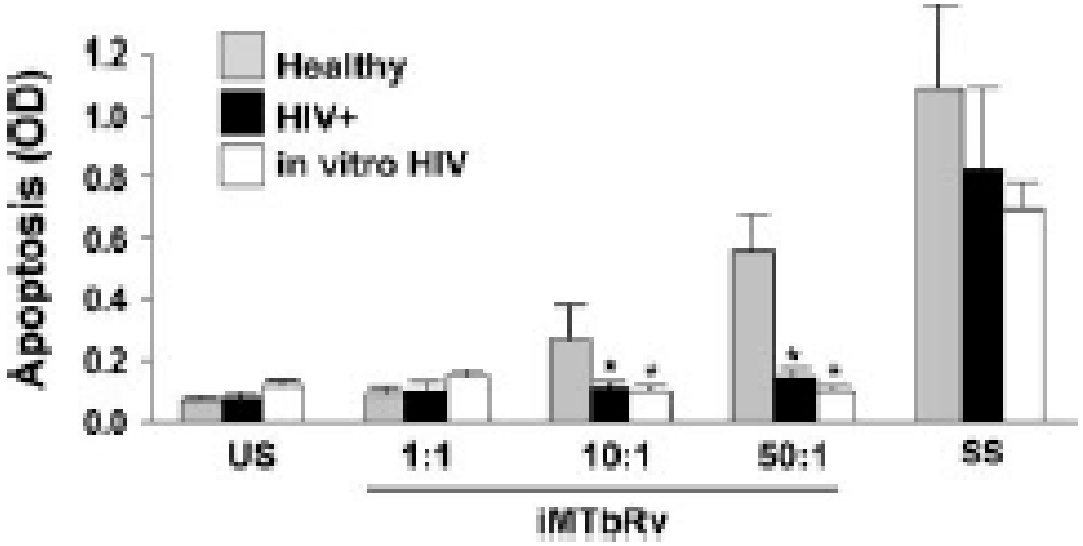
Elliott IJTLD 1999

HIV associated with impaired BAL T cell response



A- PPD, B- BCG-specific

HIV reduces apoptosis in human alveolar macrophages



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Patel JI 2007

Recent advances in diagnostics

Mainstays of traditional diagnosis

Clinical history
Chest X ray
Skin test
Smear microscopy
Culture, sensitivity and ID

In the setting of HIV…..

Clinical history	- Less likely to be classical
Chest X ray	- More likely extrapulmonary, X ray changes variable
Skin test	- More likely negative
Smear microscopy	- Less sensitive
Culture, sensitivity and ID	

Diagnosing TB in immunosuppressed patient

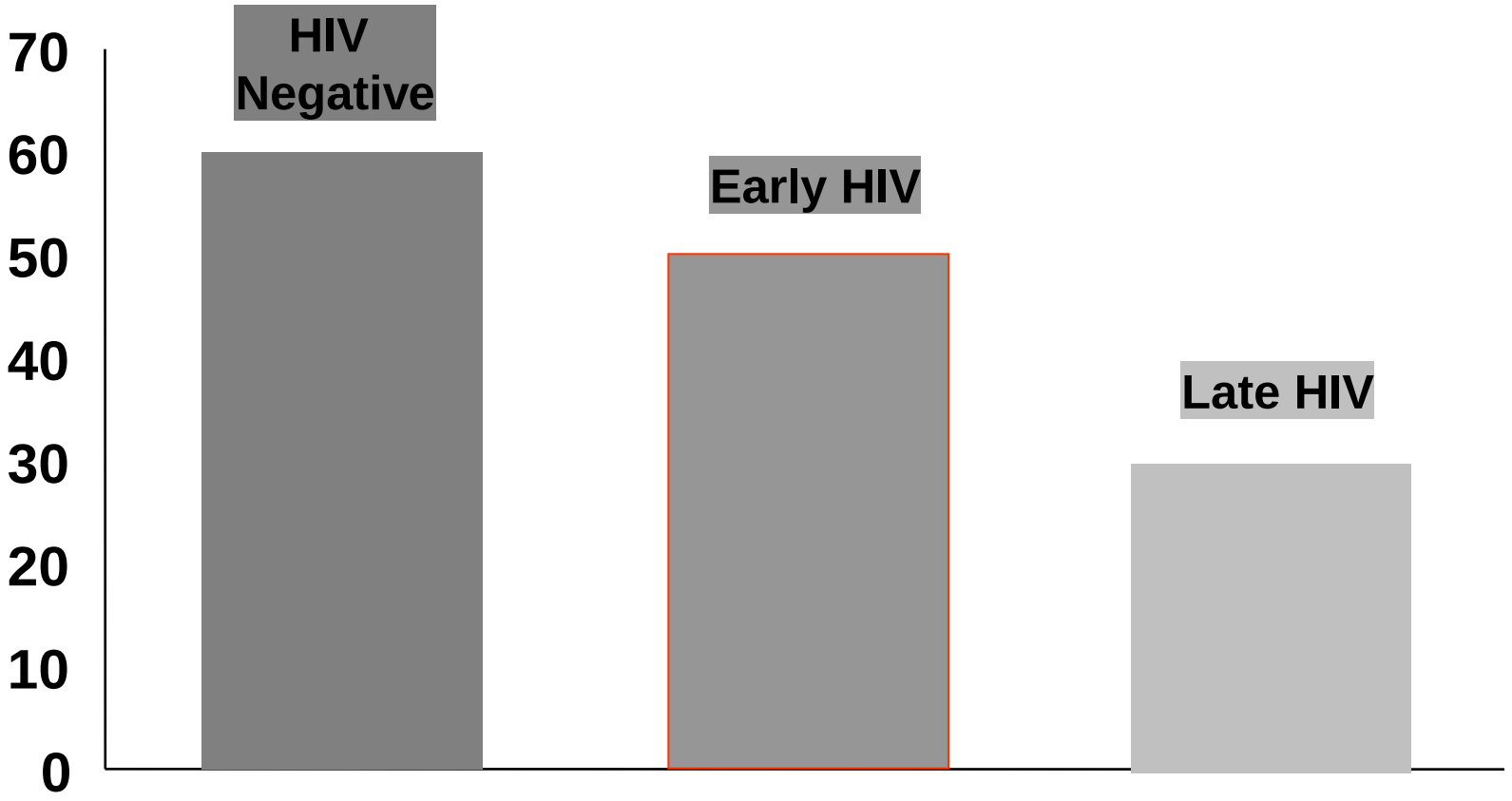
Symptoms and signs often absent in population with low CD4 count (data from a number of cohorts starting HAART in Africa)

Goletti et al PloS One 2008 Sensitivity of IGRAs for active tuberculosis

Quantiferon Gold 78.1% (95% CI 70.7, 84.3)

T SPOT 85.1% (95% CI 79.2, 89.9)

Smear negative disease more common with HIV



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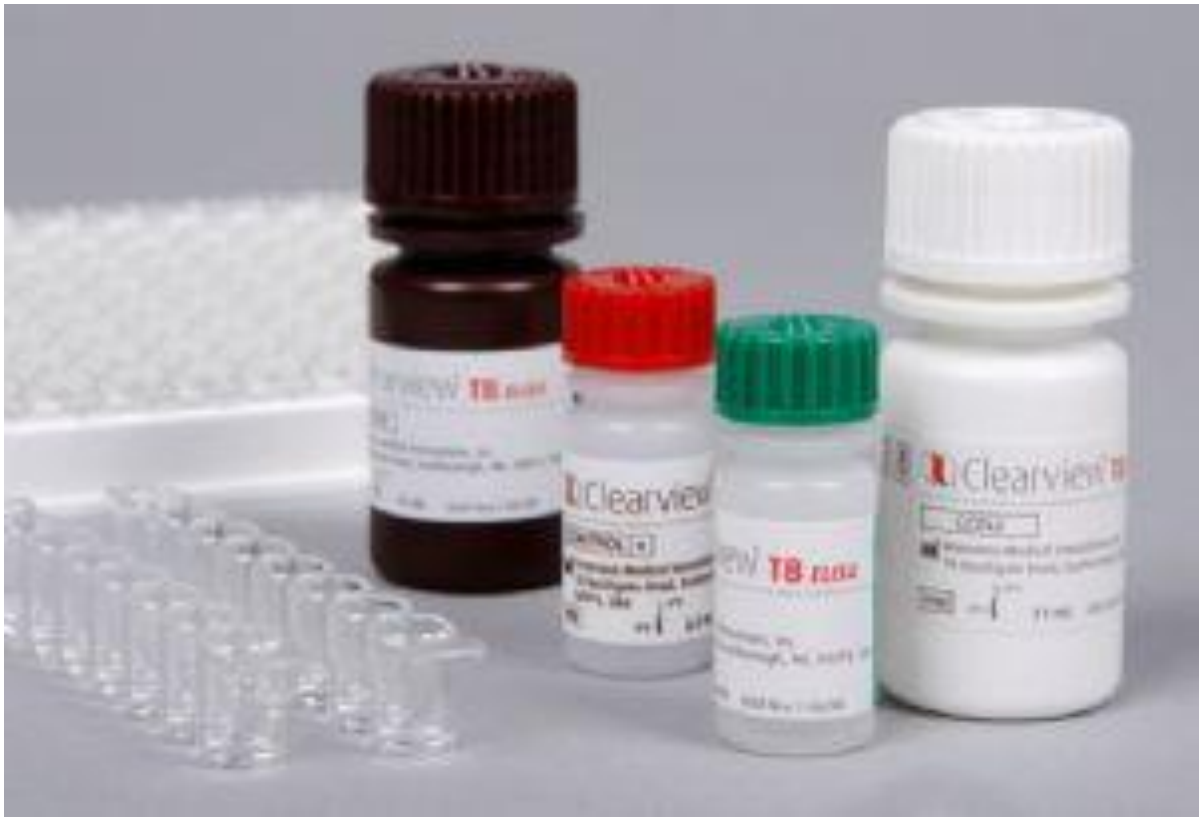
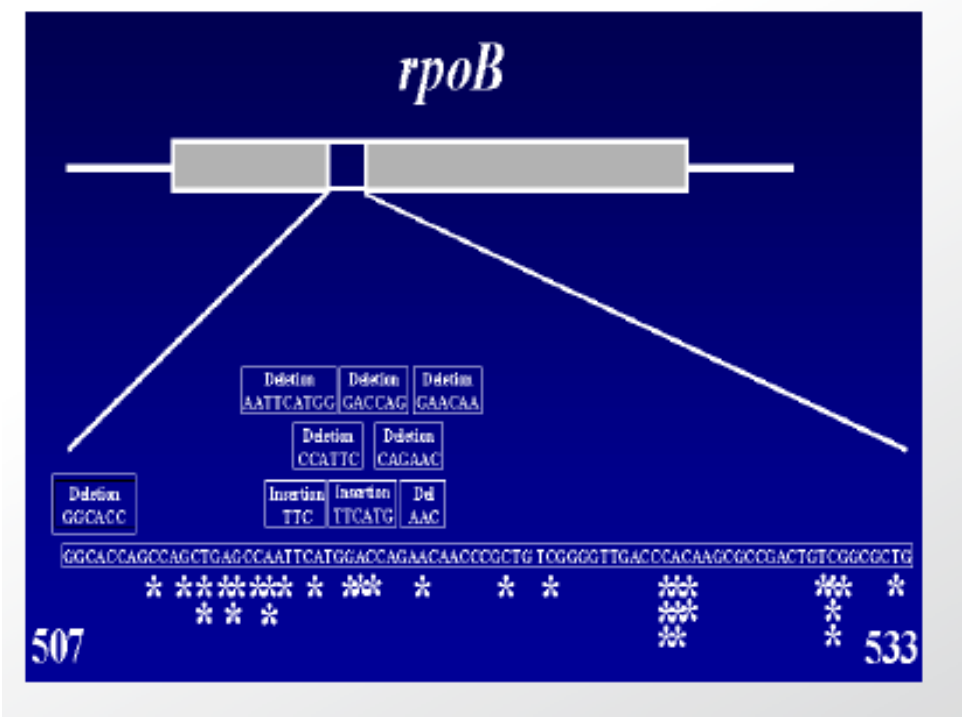
Source: USAID

Potential for urine diagnostics?



New molecular diagnostics

Current interest in applicability of new Molecular technologies to bring diagnosis closer to point of care



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Source: Cepheid, Boheme et al 2010

In well resourced settings modern diagnostics perform well

In resource poor settings very few are usable

GeneXpert is being scaled up in SA

Prevention of TB in PLWH

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HIV Prevention

- Reduce HIV transmission

    - Behavioural/partner interventions, condoms, etc
    - Biomedical prevention of HIV acquisition (vaccines, microbicides)
    - Biomedical prevention of transmission (HSV, antiretrovirals, etc)
    - HIV case detection (increasing VCT)

- Earlier initiation of antiretrovirals (POPART)

Biomedical Prevention of TB in setting of HIV

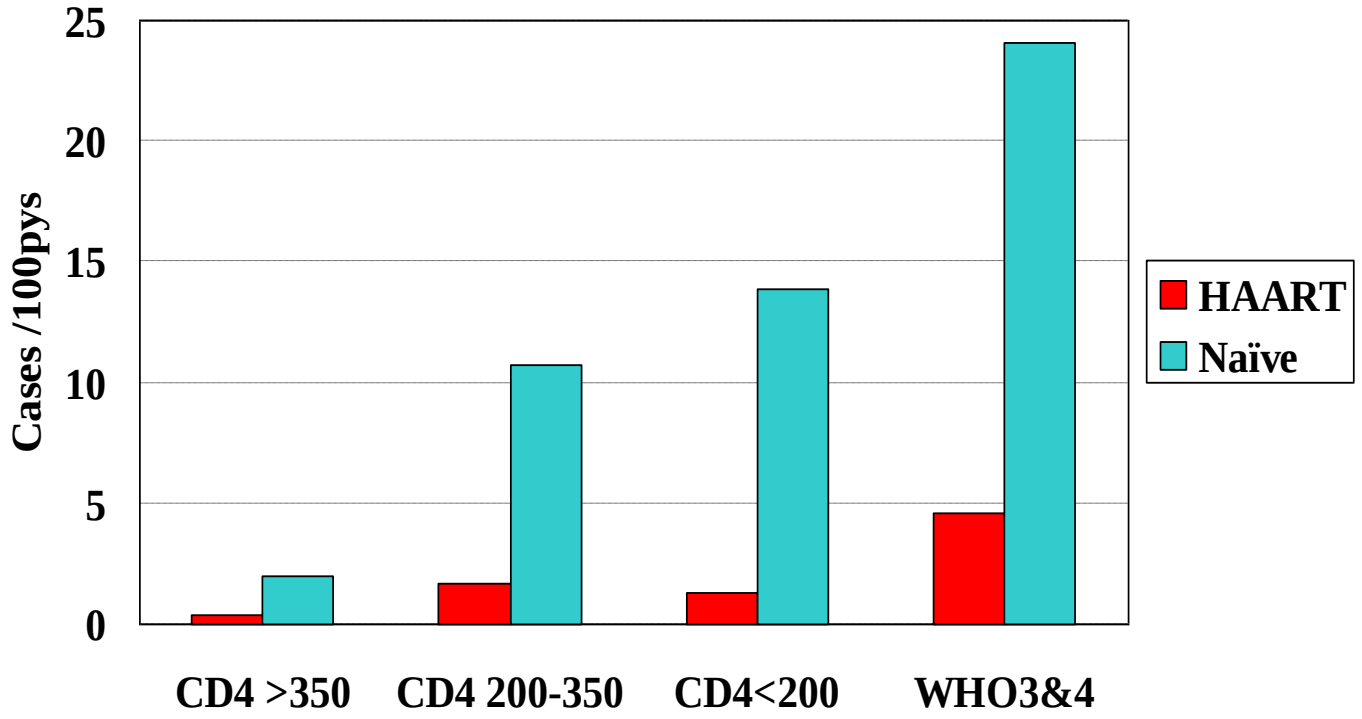
- Vaccination strategies
  - BCG
  - Subunit vaccine
  - Vaccine pipeline
  - M vaccae

- Antibiotics prevention

  - Early initiation of HAART
  - Isoniazid preventative therapy
  - Other preventative therapy
  - New drugs

  -Infection control (particularly healthcare settings)

TB incidence rates & cases prevented per 100 pys of HAART



Cases saved	**1.3**	**9.4**	**11.3**	**18.8**
95% CI	(0.3-2.9)	(3.8-14.3)	(6.2-19.1)	(13.2-26.1)

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Badri, Wilson, Wood *Lancet* 2002

Isoniazid Preventative therapy (IPT)

- Treatment of latent TB infection in HIV-infected reduces development of active TB (or can prevent re-infection)
- Debate over best way to implement IPT in both resource rich and resource poor settings
- Effort to prevent a single case of TB quite substantial

Needs exclusion of subclinical/active TB to prevent delivery of isoniazid to patients with disease…… that's a problem where the problem is worst

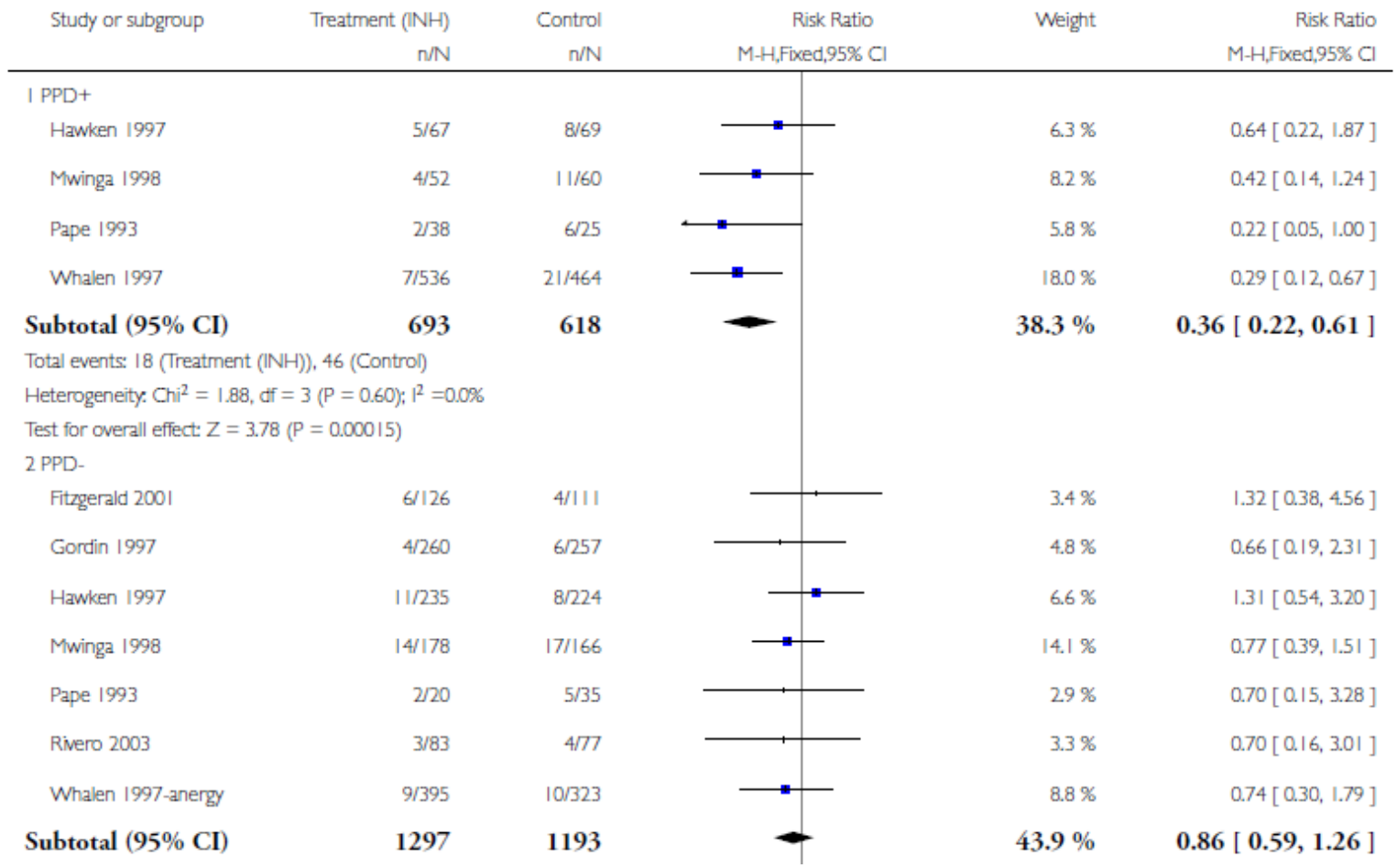
Two most popular regimens

Isoniazid for 6/12

Rifampicin and Isoniazid for 3/12

PPD +ve

PPD -ve



Study or subgroup	Treatment (INH) n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 PPD+					
Hawken 1997	5/67	8/69		6.3 %	0.64 [0.22, 1.87]
Mwinga 1998	4/52	11/60		8.2 %	0.42 [0.14, 1.24]
Pape 1993	2/38	6/25		5.8 %	0.22 [0.05, 1.00]
Whalen 1997	7/536	21/464		18.0 %	0.29 [0.12, 0.67]
Subtotal (95% CI)	**693**	**618**		**38.3 %**	**0.36 [0.22, 0.61]**
Total events: 18 (Treatment (INH)), 46 (Control)					
Heterogeneity: Chi^2 = 1.88, df = 3 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 3.78 (P = 0.00015)					
2 PPD-					
Fitzgerald 2001	6/126	4/111		3.4 %	1.32 [0.38, 4.56]
Gordin 1997	4/260	6/257		4.8 %	0.66 [0.19, 2.31]
Hawken 1997	11/235	8/224		6.6 %	1.31 [0.54, 3.20]
Mwinga 1998	14/178	17/166		14.1 %	0.77 [0.39, 1.51]
Pape 1993	2/20	5/35		2.9 %	0.70 [0.15, 3.28]
Rivero 2003	3/83	4/77		3.3 %	0.70 [0.16, 3.01]
Whalen 1997-anergy	9/395	10/323		8.8 %	0.74 [0.30, 1.79]
Subtotal (95% CI)	**1297**	**1193**		**43.9 %**	**0.86 [0.59, 1.26]**

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Akolo et al Cochrane

Treatment of TB/HIV

Challenges in TB/HIV management

Timing of treatment initiation

Drug interactions

Overlapping toxicity

Duration of treatment – adherence

Health care resources

Immediate or deferred ART?

Observational studies

Manosuthi et al., J Acquir Immun Defic Syndr 2006
Velasco et al., J Acquir Immun Defic Syndr 2009
Yotebieng et al., AIDS 2010

Randomised controlled trials

SAPIT trial (Abdool Karim et al., NEJM 2010, 2011)

CAMELIA trial (NEJM, 2011)

TBM/HIV Vietnamese (Torok et al , CID 2011)

ACTG A-5221 (Havlir, NEJM 2011)

TB HAART (WHO/TDR) n=1900 Africa

Uganda (NIAID) n=350

TIME trial (Thailand) n=210

Mexico (Instituto Nacional de Enfermedades Respiratorias), n=160

SAPIT 003

642 patients with TB starting ART

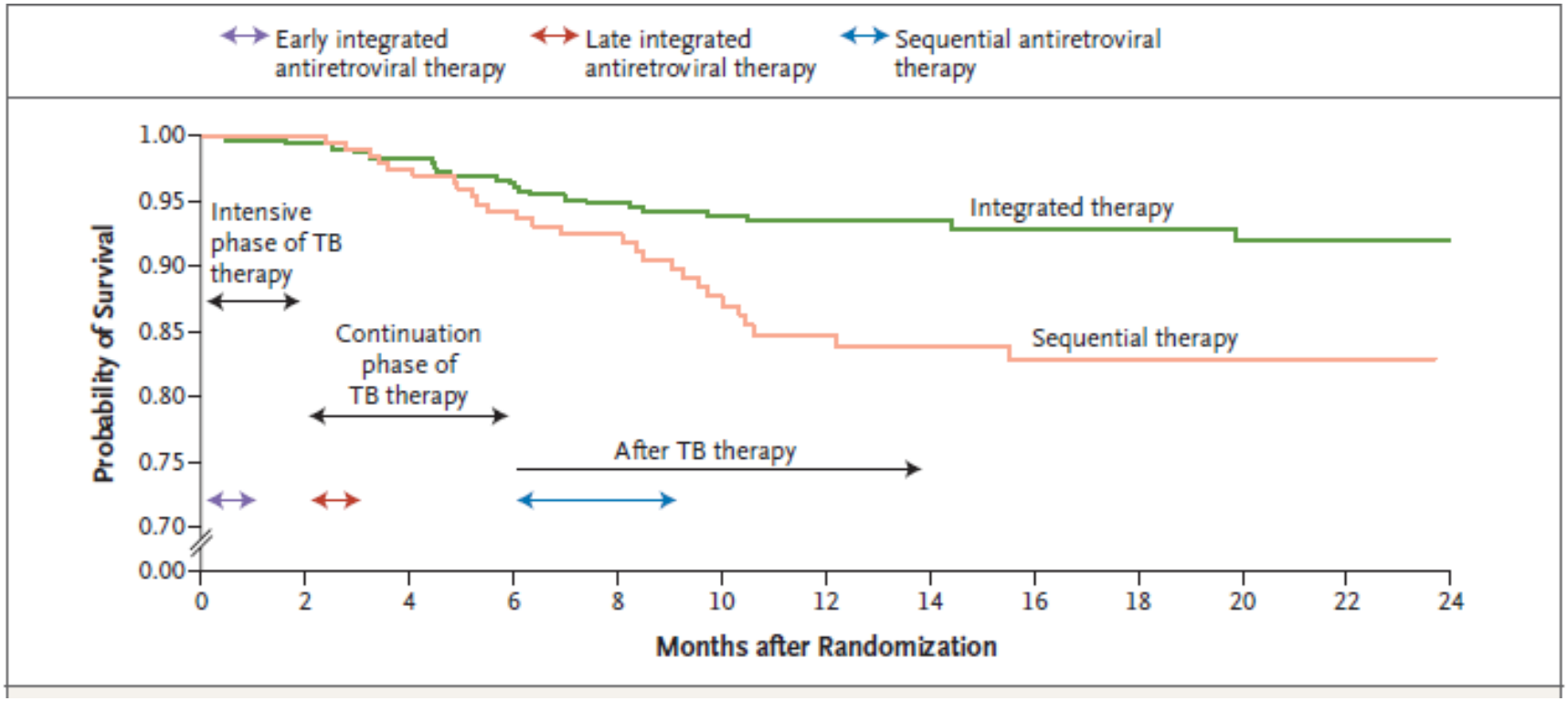
3 arms for randomisation :

Early integrated (HAART within 4 weeks of TB treatment)
Late integrated (HAART within 4 weeks of continuation)
Sequential

Stopped early due to increased mortality in sequential arm

Karim et al NEJM 2010 & 2011

SAPIT 003



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Karim et al NEJM 2010

A bit controversial…..

Expressed concern about the equipoise of the study….

Investigators argued that at time of study WHO guidelines were unclear on the timing

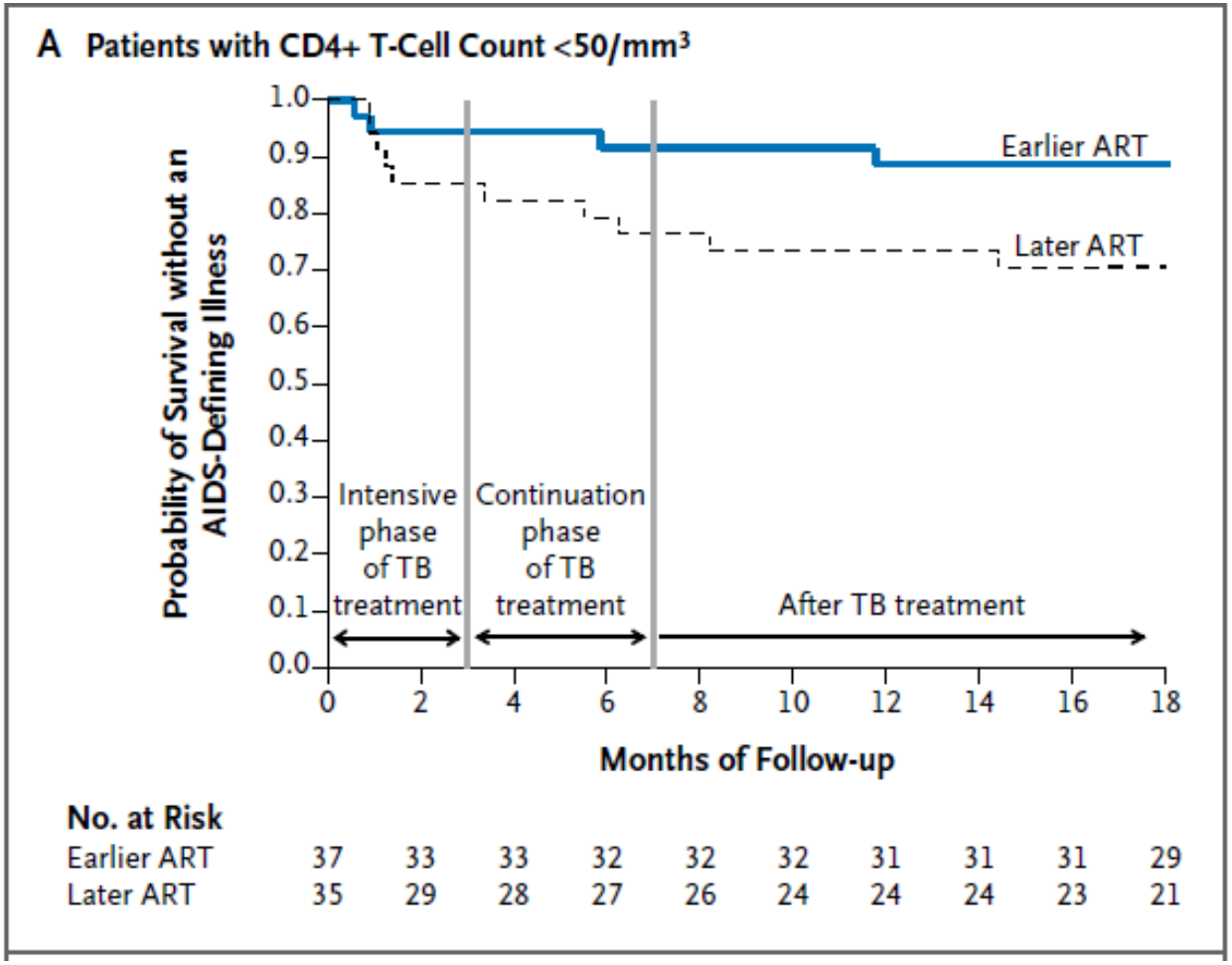
Others disagreed…

AIDS RESEARCH

Bioethicists Assail a Celebrated TB/HIV Treatment Trial

Science 2010

Follow-up study



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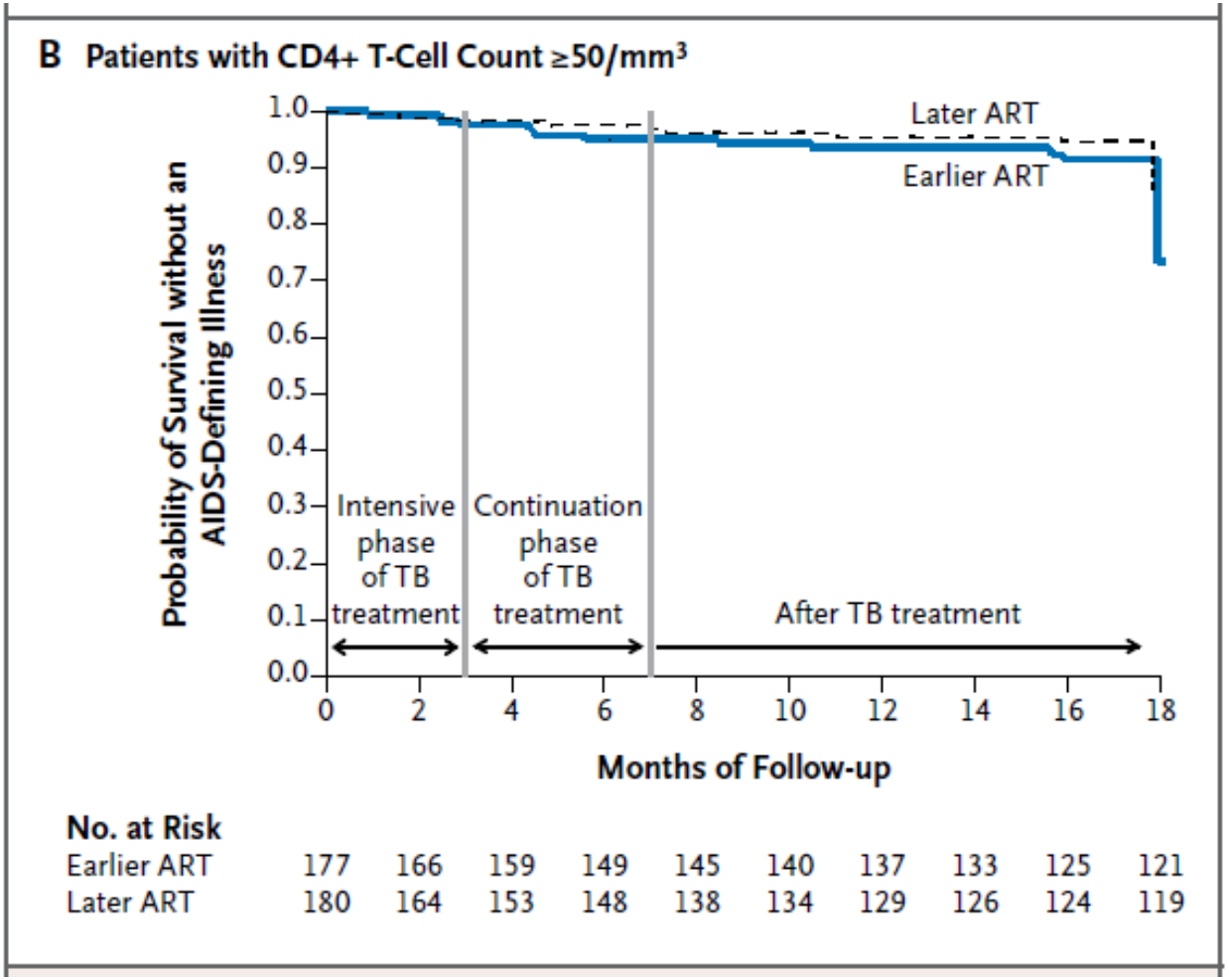
Science 2010

Follow-up study



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NEJM 2011

CAMELIA Study

RCT in Cambodia of 661 patients diagnosed with TB

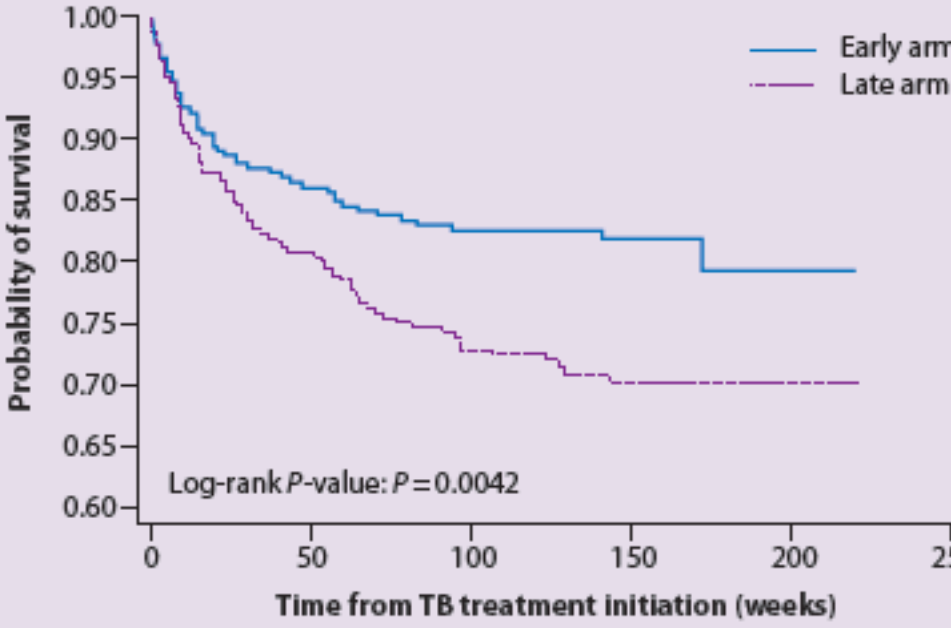
Low median CD4 count (25cell/ul)

Randomised to early (2 weeks) vs late (8 weeks) for ART

IRIS more common in early arm but easily managed

Blanc et al AIDS XVIII 2010

CAMELIA Study



Survival probability (95% CI)	EARLY arm	LATE arm	Log-rank *P*-value
Week 50	86.1 (81.8-89.4)	80.7 (76.0-84.6)	0.07
Week 100	82.6 (78.0-86.4)	73.0 (67.7-77.6)	0.006
Week 150	82.0 (77.2-85.9)	70.2 (64.5-75.2)	0.002

Figure 3. Kaplan-Meier Survival Curves: CAMELIA Study

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Blanc et al AIDS XVIII 2010

ACTG 5221

Open label RCT comparing

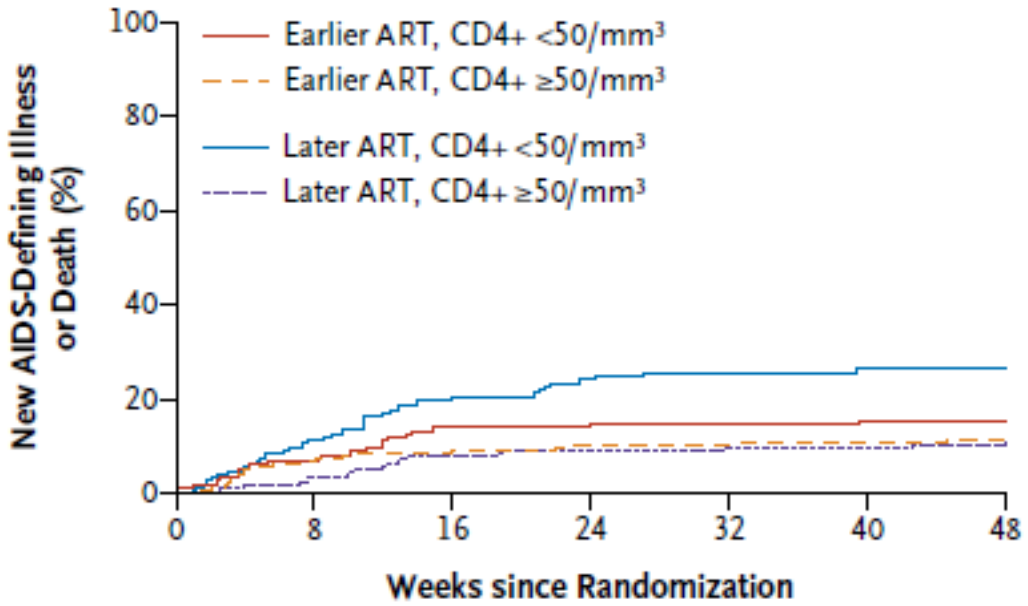
Early (within 2 weeks of TB treatment)
Late (within 8-12 weeks of TB treatment)

809 subjects in Africa, S America, N America and Asia

Median CD4 77

ACTG 5221

B



No. at Risk

Earlier therapy							
CD4+ <50/mm³	144	132	121	121	118	114	74
CD4+ ≥50/mm³	261	236	225	220	217	210	152
Later therapy							
CD4+ <50/mm³	141	125	110	103	101	98	69
CD4+ ≥50/mm³	260	246	232	226	224	220	149

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Havlir NEJM 2011

TB meningitis and HIV in Vietnam

To determine if early initiation of ART reduces mortality in HIV-associated tuberculous meningitis at 9 months

Conducted at 2 centres in Ho Chi Minh City, Vietnam

Randomised double-blind placebo-controlled trial with 2 parallel arms: immediate ART versus deferred ART (2 months) stratified by severity of disease

Adjunctive corticosteroids

- Grade 1 TBM 0.3mg/kg/day tapered over 6 weeks
- Grade 2 or 3 TBM 0.4mg/kg/day tapered over 8 weeks

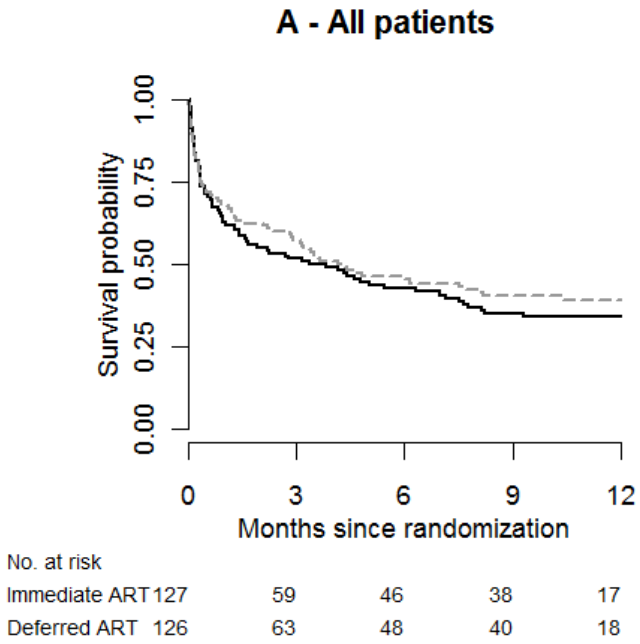
Pneumocystis prophylaxis

- Co-trimoxazole from week 4 if baseline CD4 <200 cells

Torok et al CID 2011

TB meningitis and HIV in Vietnam

- Mortality at 9 months (126 each arm)
  - 76 in immediate arm
  - 70 in deferred arm
- Hazard ratio 1.12 (95% CI 0.81 – 1.55), p = 0.52
- KM survival estimates at 9 months
  - 35.2% in immediate arm
  - 40.3% in deferred arm
- Similar in per protocol analysis



High rate of HCV co-infection

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Torok et al in press

MDR/XDR and HIV

Definitions

Some basics

First line medications

Rifampicin	(R)	MDR-TB
Isoniazid	(H)	
Pyrazinamide	(Z)	
Ethambutol	(E)	

Some basics

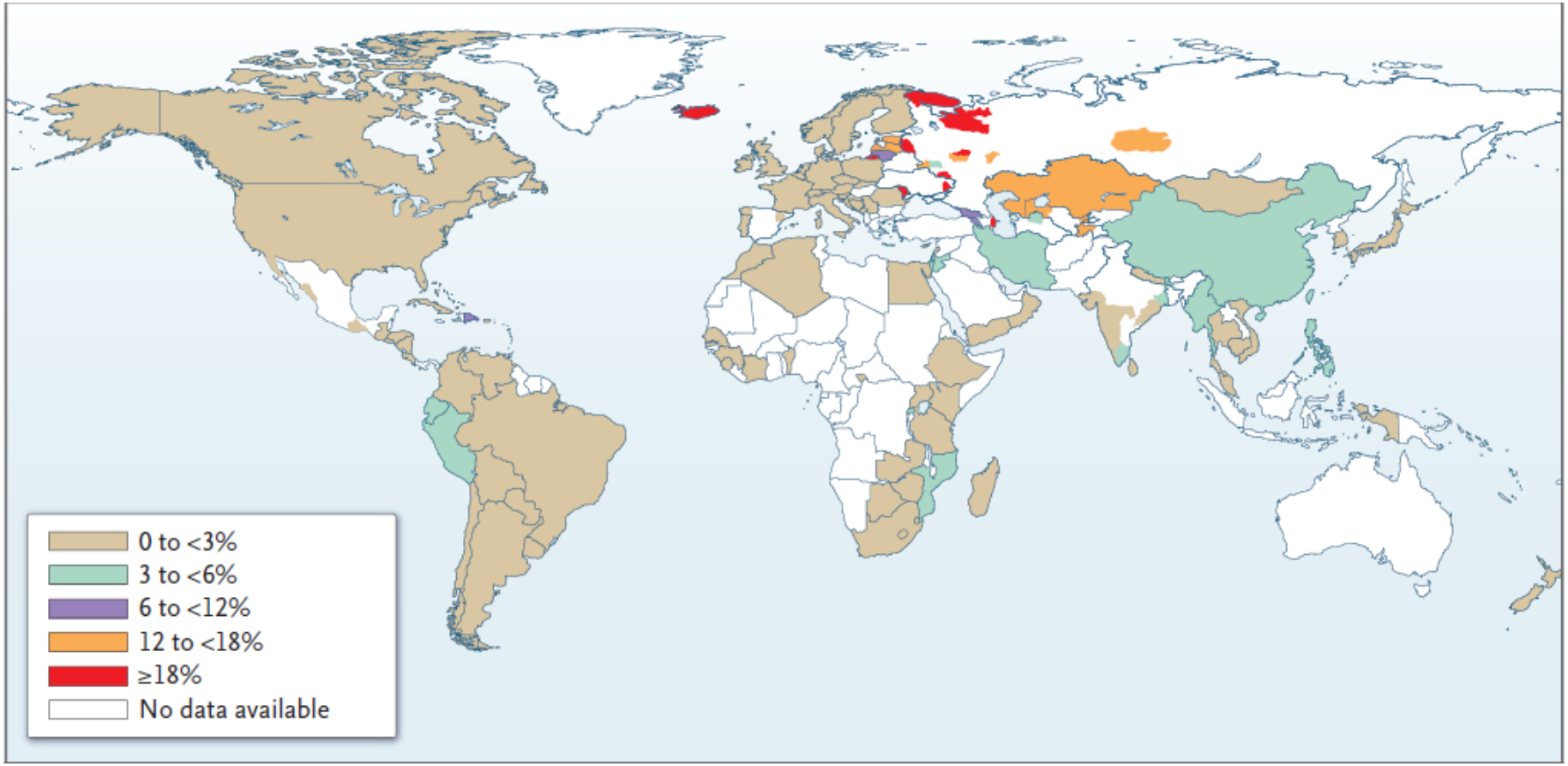
First line medications

Rifampicin	(R)	MDR-TB+
Isoniazid	(H)	
Pyrazinamide	(Z)	
Ethambutol	(E)	

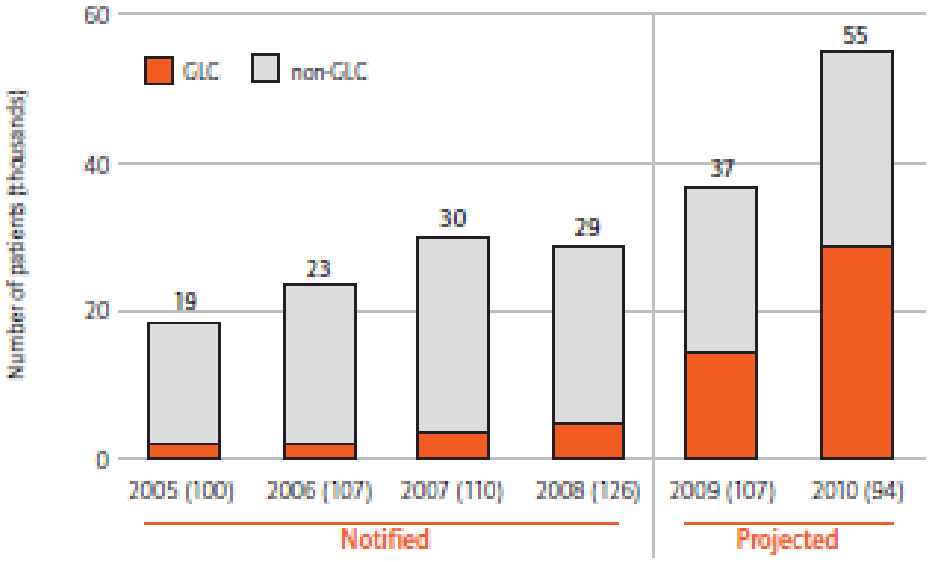
Second line medications

Quinolones	XDR-TB
Injectables (kana, ami)	
Ethionamide/Prothionamide	
Cycloserine	
PAS	
Linezolid	
Clofazamine	

Proportion of new TB cases with any MDR-TB 1994-2007 (WHO, 2008)

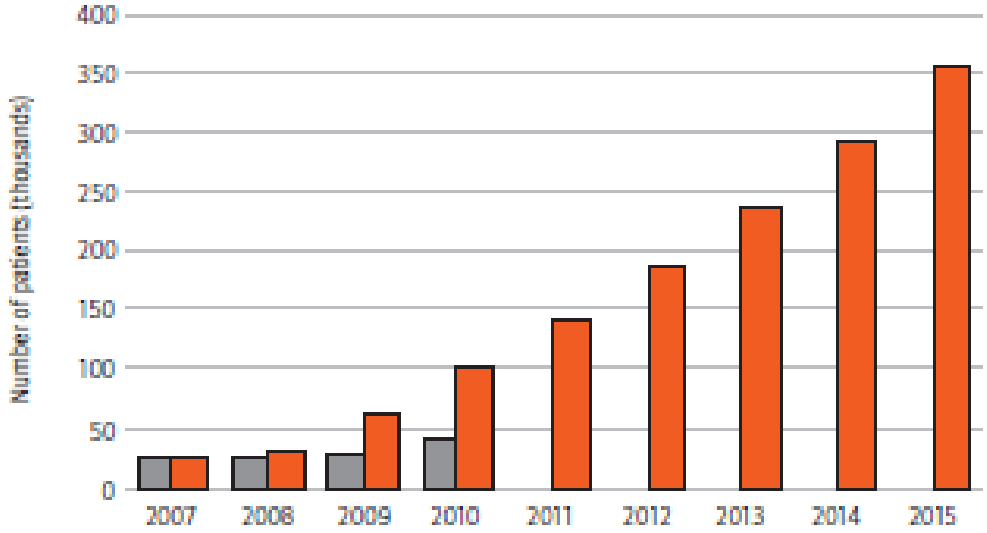


MDR is predicted to become more common: notifications



WHO (2009)

And will (probably) continue to increase

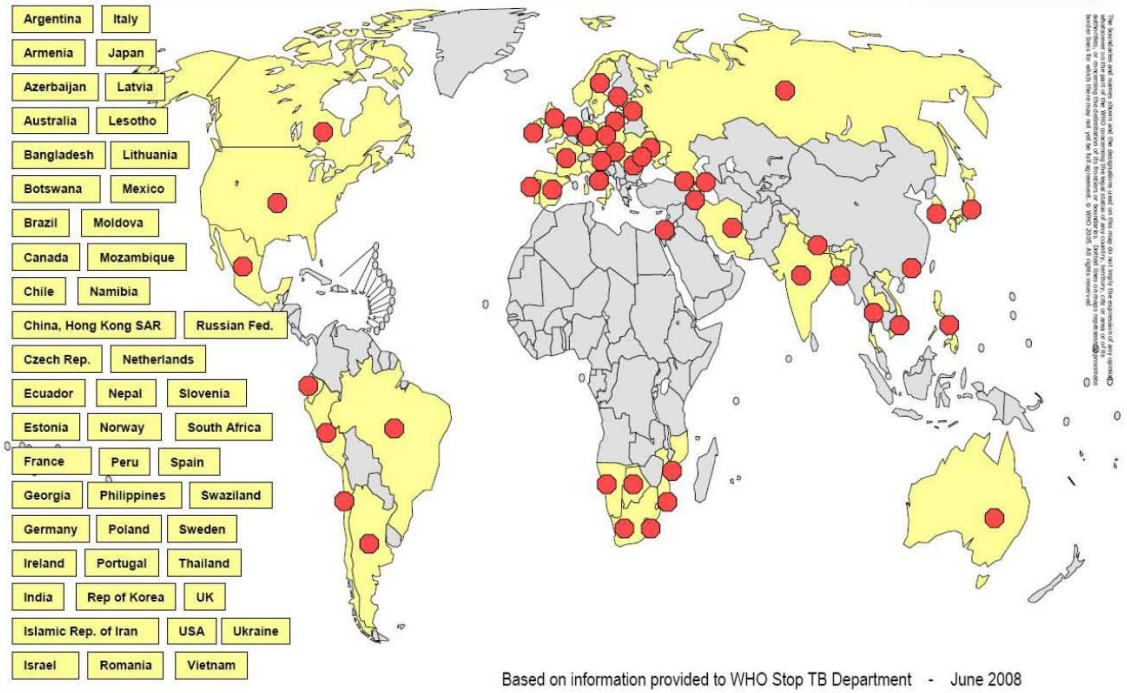


* The targets/milestones for scaling-up treatment of MDR-TB in the Global Plan are based on updated projections produced in March 2009, in preparation for a ministerial meeting on MDR/XDR-TB held in Beijing, China in April 2009.

WHO (2009)

Countries with confirmed cases of XDR-TB as of November 2008

WHO THE STOP TB DEPARTMENT



Based on information provided to WHO Stop TB Department - June 2008

Imperial College London

The bigger problem is MDR/HIV

	Tugela Ferry	KwaZulu Natal	South Africa
MDR	269	4,701	17,615
XDR	350	656	996
Total	619	5,357	28,611

2005-2007

Imperial College London

Source: Gerry Friedland

Date	Treatment	Started	Stopped	Event
16/9	R.H,Z,E	R,H,Z,E		TB diagnosis
24/9	R,H,Z,E,Lfx, Am	Lfx,Am		INNO-LIPA.rif
26/9	Z,E,Cm,Mfx, Pto	Cm,Mfx,Pto	R,H,Lfx,Am	ITU EFV/FTC/TV F
2/10	E,Cm,Cs	Cs	Z,Mfx,Pto	Hepatitis EFV>Kaletra
10/10	E,Cm,Cs,Lfx, Pto	Pto		LFT's normal
15/10	Cm,Cs,Lfx,P AS	PAS	E,Pto	H,E,Pto resistance
18/10	Cm,Cs,Lfx,L zd	Lzd	PAS	Unable to pass PAS down NGT
2/11	Cm,Cs,Mfx	Mfx	Lfx,Lzd	Lfx>Mfx Pancytopenic
12/11	Mfx,PAS,Lzd	PAS,Lzd	Cm,Cs	ARF/conf TVF stopped

New Drugs

Phase 2 Trial of TMC207 (Diacon,09)

8 week, multi-centre, placebo controlled trial

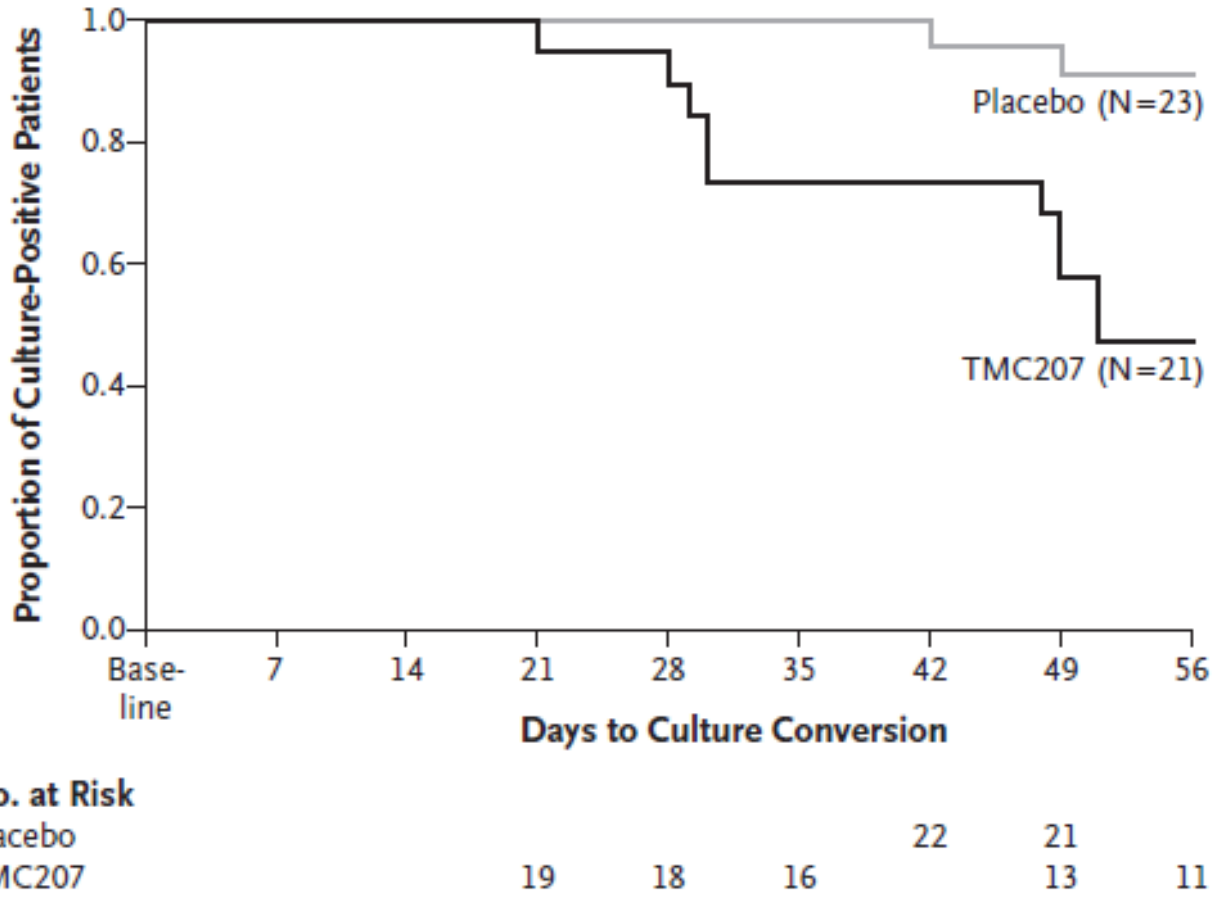
1 week lead in (TB treatment stopped)

Stratified by centre and extent of lung disease

Arm 1: TMC207 400mg od weeks 1 and 2, then 200mg 3/week
Arm 2: Placebo

Preferred background: kanamycin, ofloxacin, ethionamide, pyrazinamide and cycloserine or terizidone modified by DST

Phase 2 Trial of TMC207 (Diacon,09)



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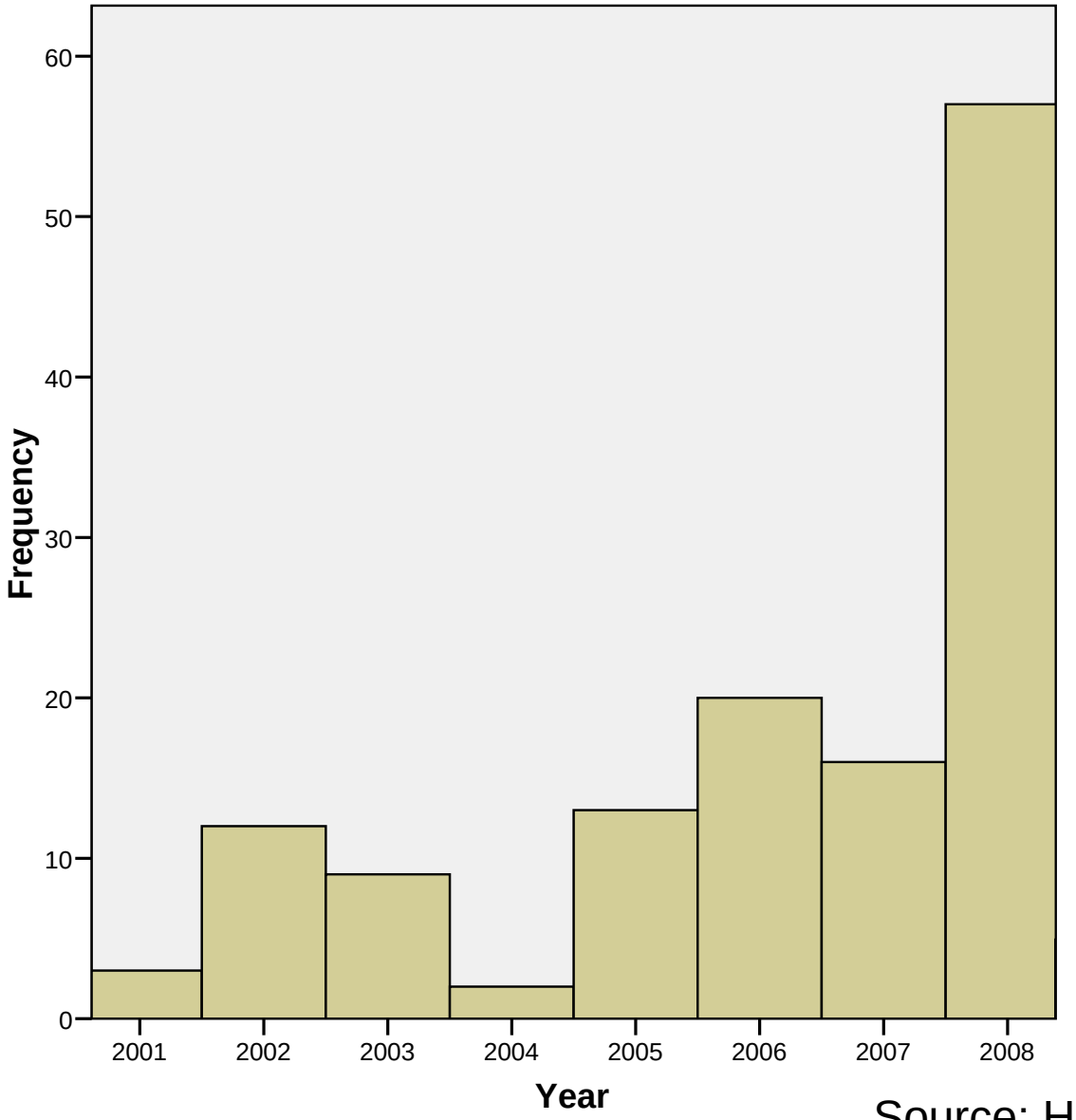
New Treatment Strategies

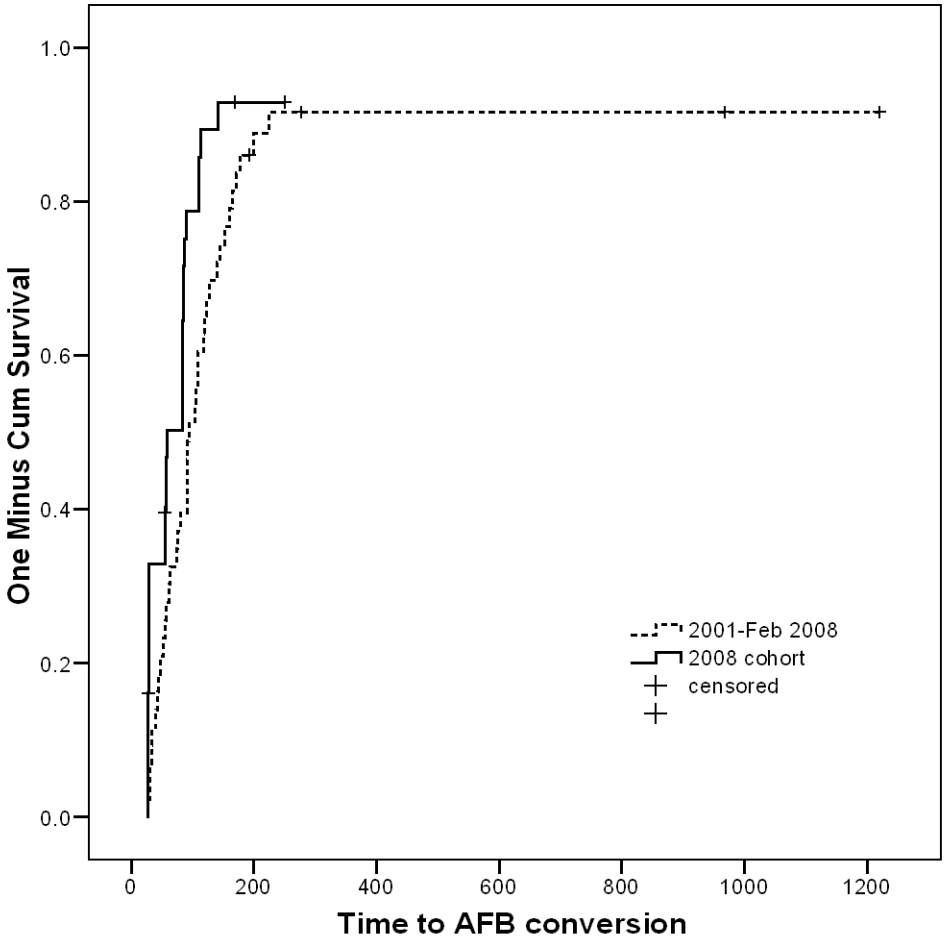
Renovated multi-story building

MDR Treatment Initiations Hlabisa 2001-8



Source: Heller et al (2010)

Decentralised MDR programme



Source: Heller et al (2010)

Conclusions

Diagnostics are improving but availability still limited by costs

Prevention by IPT probably underused

MDR increasingly important problem

Drug options limited but improving

Thank you

Questions?