TB and HIV

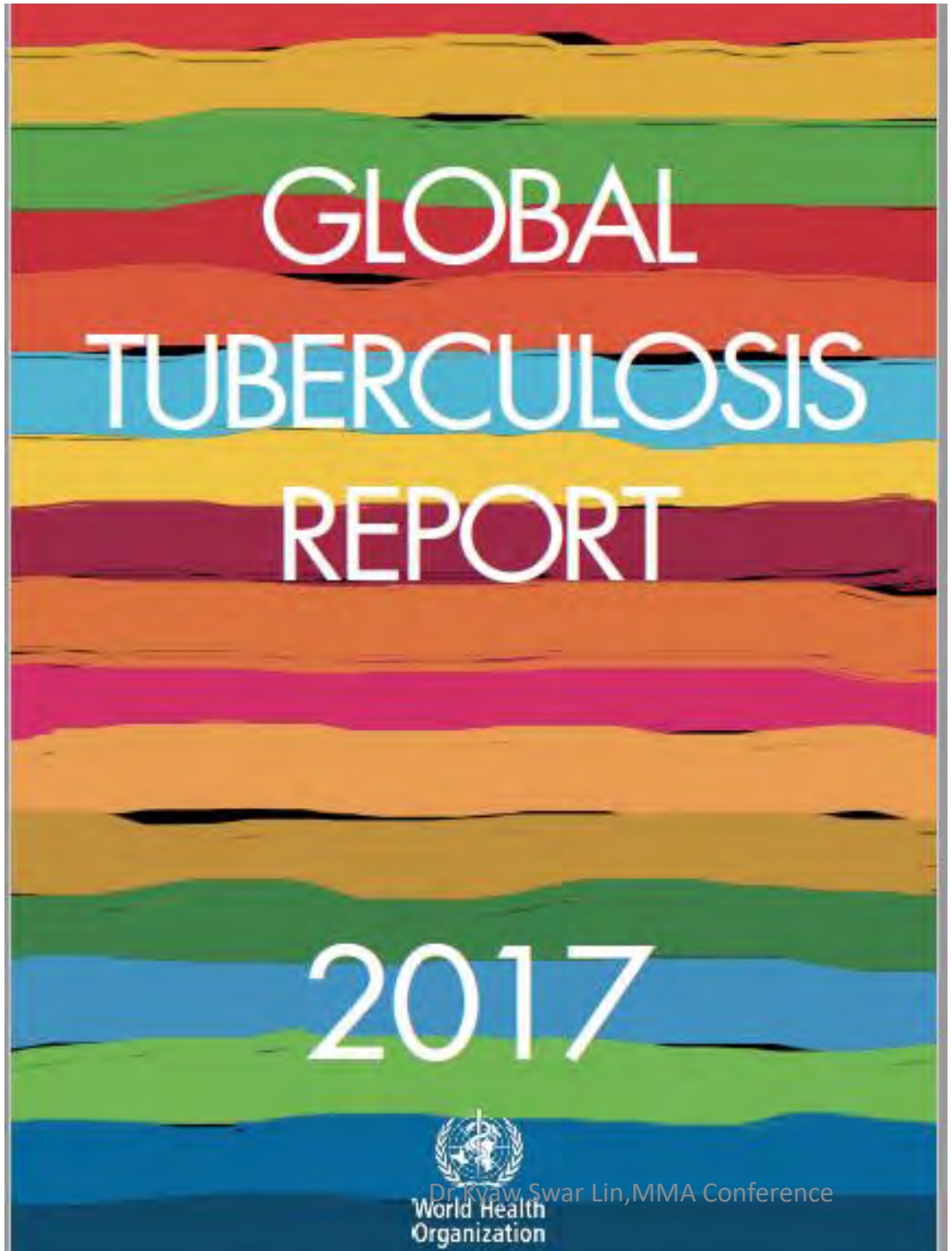
20/1/2018

Dr Kyaw Swar Lin

Outline of presentation

- Epidemiology
- Pathogenesis
- Clinical presentation
- Diagnosis
- Treatment
- DDI
- IRIS

Epidemiology


GLOBAL
TUBERCULOSIS
REPORT
2017
World Health
Organization

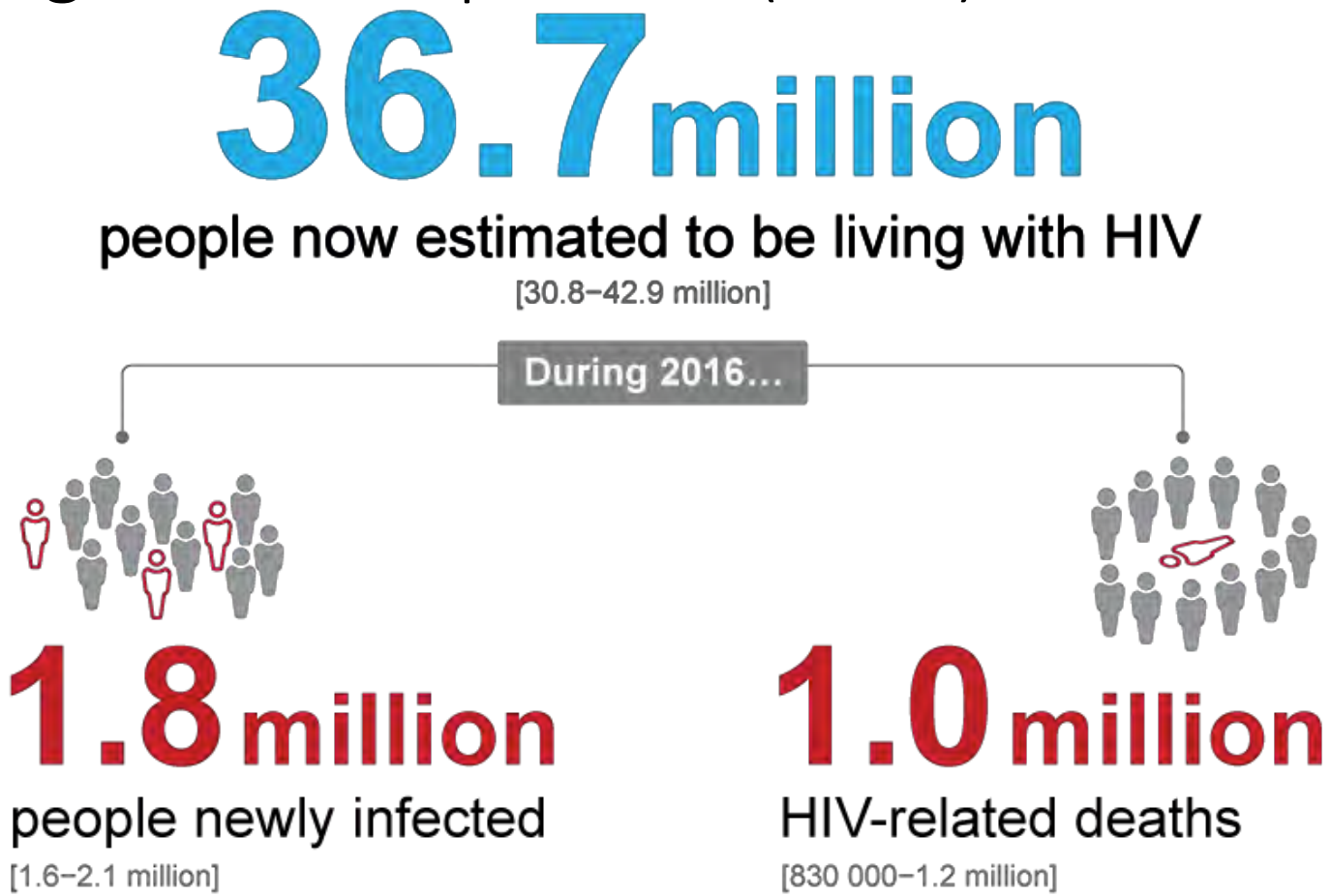
WHO global TB report 2017

- TB is the ninth leading cause of death worldwide and the
- Leading cause from a single infectious agent, ranking above HIV/AIDS.

- One-third of world's population is infected by TB (1.7 billion) and 5 – 15% of them will develop TB disease during their lifetime

- In 2016, 10.4 M fell ill with TB
  - 1.3 M death (non-HIV)
  - 375 000 deaths (HIV)

Summary of global HIV epidemic (2016)



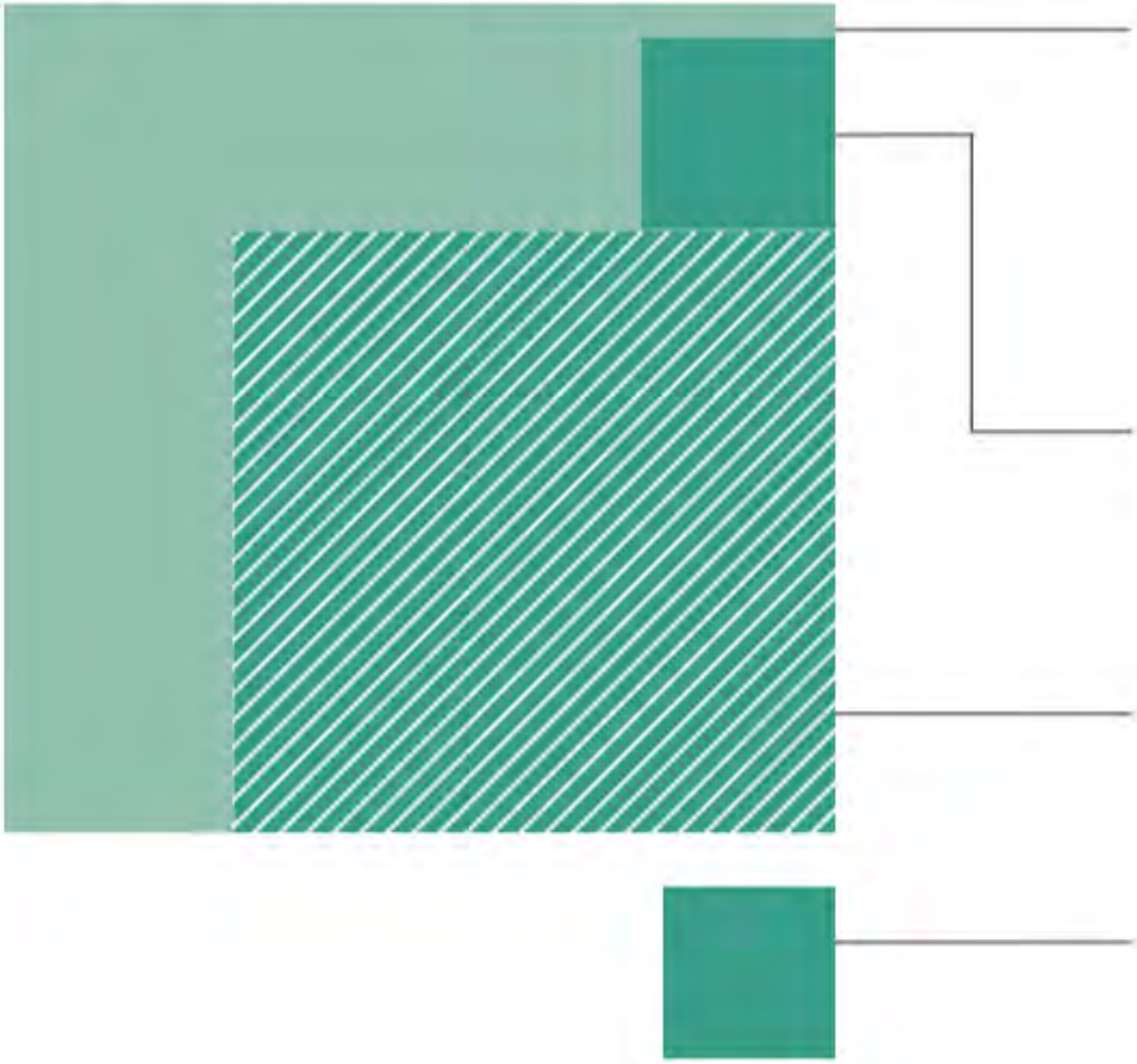
Myanmar TB data 2016 (WHO country profile)

- Total TB incidence = 191,000 or 361/100,000 population
- HIV prevalence in incident TB= 9.4 % OR 18,000

- Mortality , HIV-ve = 25,000
  HVI+ve = 4,900

Myanmar HIV profile 2017

0.6% prevalence



People living with HIV (PLHIV) **220 000**
Low estimate 200 000 High estimate 260 000

Women living with HIV **81 000**
Low estimate 69 000 High estimate 89 000

New HIV infections **12 000**
Low estimate 11 000 High estimate 13 000

People on ART (June 2016) **115 481**

AIDS-related deaths **9 700**
Low estimate 7 600 High estimate 12 000

Global & Myanmar TB and HIV epidemics in 2017

HIV

- **Globally:**
  - 36.7 million cases
  - 1.1 million deaths
- **Myanmar:**
  - 220 000 cases
  - 9 700 deaths

TB

- **Globally:**
  - 10.4 million cases
  - 1.6 million deaths
- **Myanmar:**

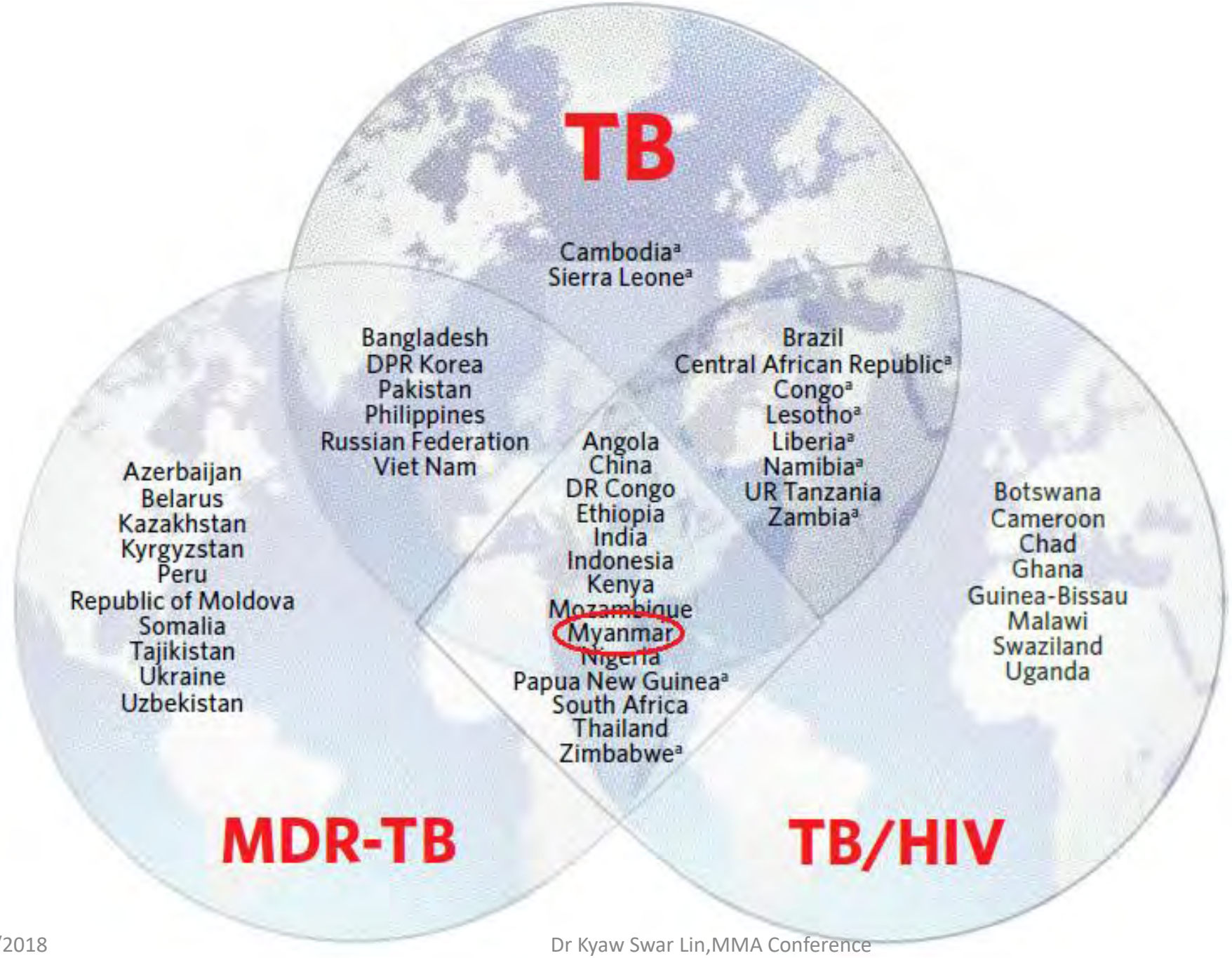
-191 000 cases (total)

-29,900 deaths (16% is HIV+)

TB - HIV co-infection

- **Globally:**
  - 1.8 million incident cases
  - 375,000 deaths
- **Myanmar:**
  - Incidence 18,000
  - Mortality 4,800 (26.7%)

THE 30 HIGH TB BURDEN COUNTRIES		THE 30 HIGH TB/HIV BURDEN COUNTRIES		THE 30 HIGH MDR-TB BURDEN COUNTRIES	
The top 20 by estimated absolute number (in alphabetical order):	*The additional 10 by estimated incidence rate per 100 000 population and with a minimum number of 10 000 cases per year (in alphabetical order):*	*The top 20 by estimated absolute number (in alphabetical order):*	*The additional 10 by estimated incidence rate per 100 000 population and with a minimum number of 1000 cases per year (in alphabetical order):*	*The top 20 by estimated absolute number (in alphabetical order):*	*The additional 10 by estimated rate per 100 000 population and with a minimum number of 1000 cases per year (in alphabetical order):*
Angola	Cambodia	Angola	Botswana	Bangladesh	Angola
Bangladesh	Central African Republic	Brazil	Central African Republic	China	Azerbaijan
Brazil	Congo	Cameroon	Chad	DPR Korea	Belarus
China	Lesotho	China	Congo	DR Congo	Kyrgyzstan
DPR Korea	Liberia	DR Congo	Ghana	Ethiopia	Papua New Guinea
DR Congo	Namibia	Ethiopia	Guinea-Bissau	India	Peru
Ethiopia	Papua New Guinea	India	Liberia	Kazakhstan	Republic of Moldova
India	Sierra Leone	Indonesia	Namibia	Kenya	Somalia
Indonesia	Zambia	Kenya	Papua New Guinea	Indonesia	Tajikistan
Kenya	Zimbabwe	Lesotho	Swaziland	Mozambique	Zimbabwe
Mozambique		Malawi		Myanmar	
Myanmar		Mozambique		Nigeria	
Nigeria		Myanmar		Pakistan	
Pakistan		Nigeria		Philippines	
Philippines		South Africa		Russian Federation	
Russian Federation		Thailand		South Africa	
South Africa		Uganda		Thailand	
Thailand		UR Tanzania		Ukraine	
UR Tanzania		Zambia		Uzbekistan	


TB
Cambodia[a]
Sierra Leone[a]
Bangladesh
DPR Korea
Pakistan
Philippines
Russian Federation
Viet Nam
Brazil
Central African Republic[a]
Congo[a]
Lesotho[a]
Liberia[a]
Namibia[a]
UR Tanzania
Zambia[a]
Azerbaijan
Belarus
Kazakhstan
Kyrgyzstan
Peru
Republic of Moldova
Somalia
Tajikistan
Ukraine
Uzbekistan
Angola
China
DR Congo
Ethiopia
India
Indonesia
Kenya
Mozambique
Myanmar
Nigeria
Papua New Guinea[a]
South Africa
Thailand
Zimbabwe[a]
Botswana
Cameroon
Chad
Ghana
Guinea-Bissau
Malawi
Swaziland
Uganda
MDR-TB
TB/HIV

Specialist hospital Mingaladon
About 1/3 of pts already have TB before ART

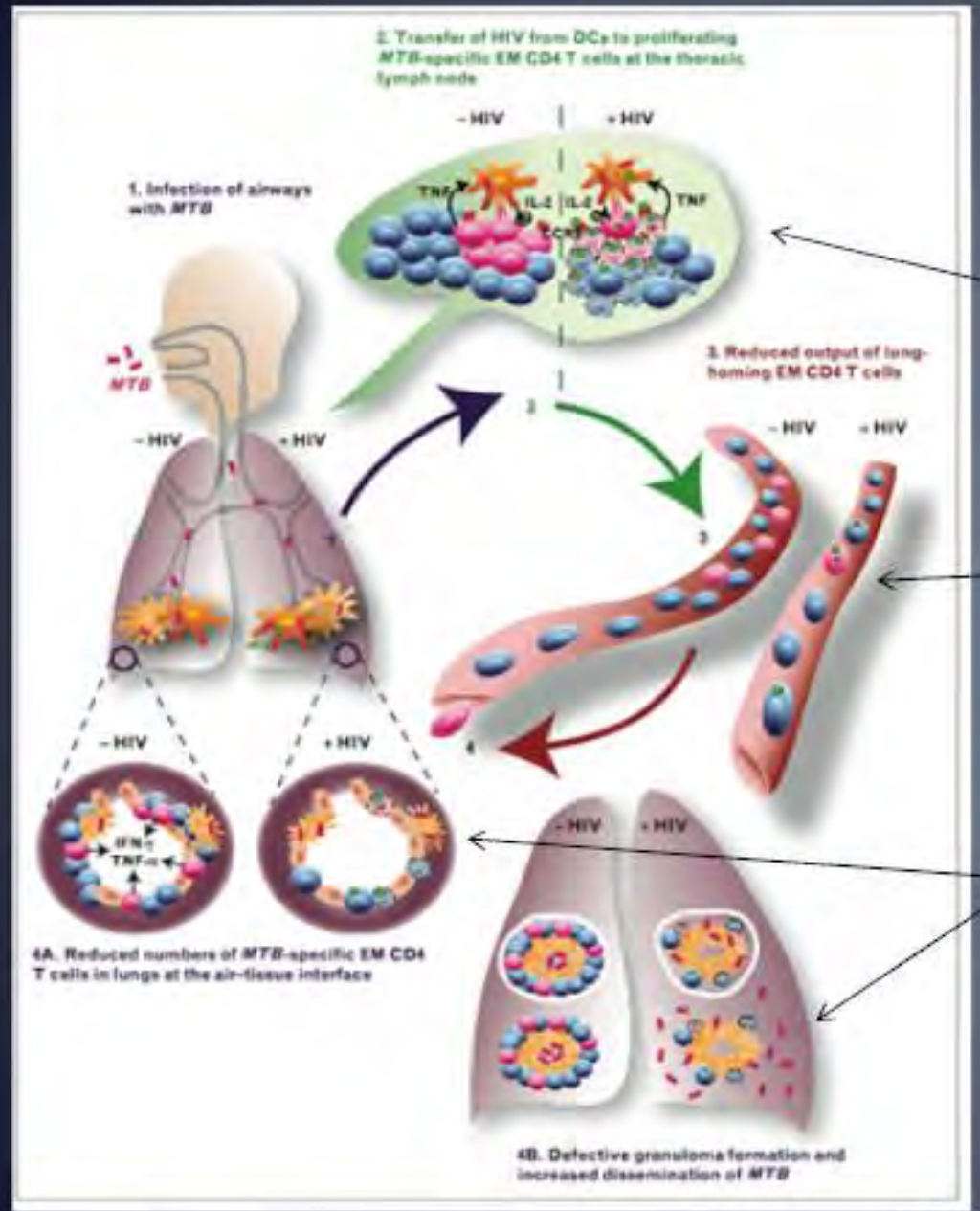
YEAR	Start ART		TB	
		CD4 average	N	%
2011	1165	136	430	37
2012	783	165	271	35
2013	1210	182	419	35
2014	1918	194	707	37
2015	2191	208	718	33

In 2015, there were 1853 admissions to SHM and 440 deaths

Disease	Prevalence	%	Mortality	%
TB (All) -TBM	811 250	43.8 30.8(of all TB)	222 126	50.5 56.7

Pathogenesis

Pathogenesis



HIV kills TB-specific CD4 cells
Impairs macrophage activation

Reduced numbers lung-homing CD4 cells

Defective granuloma formation
Loss of control of infection

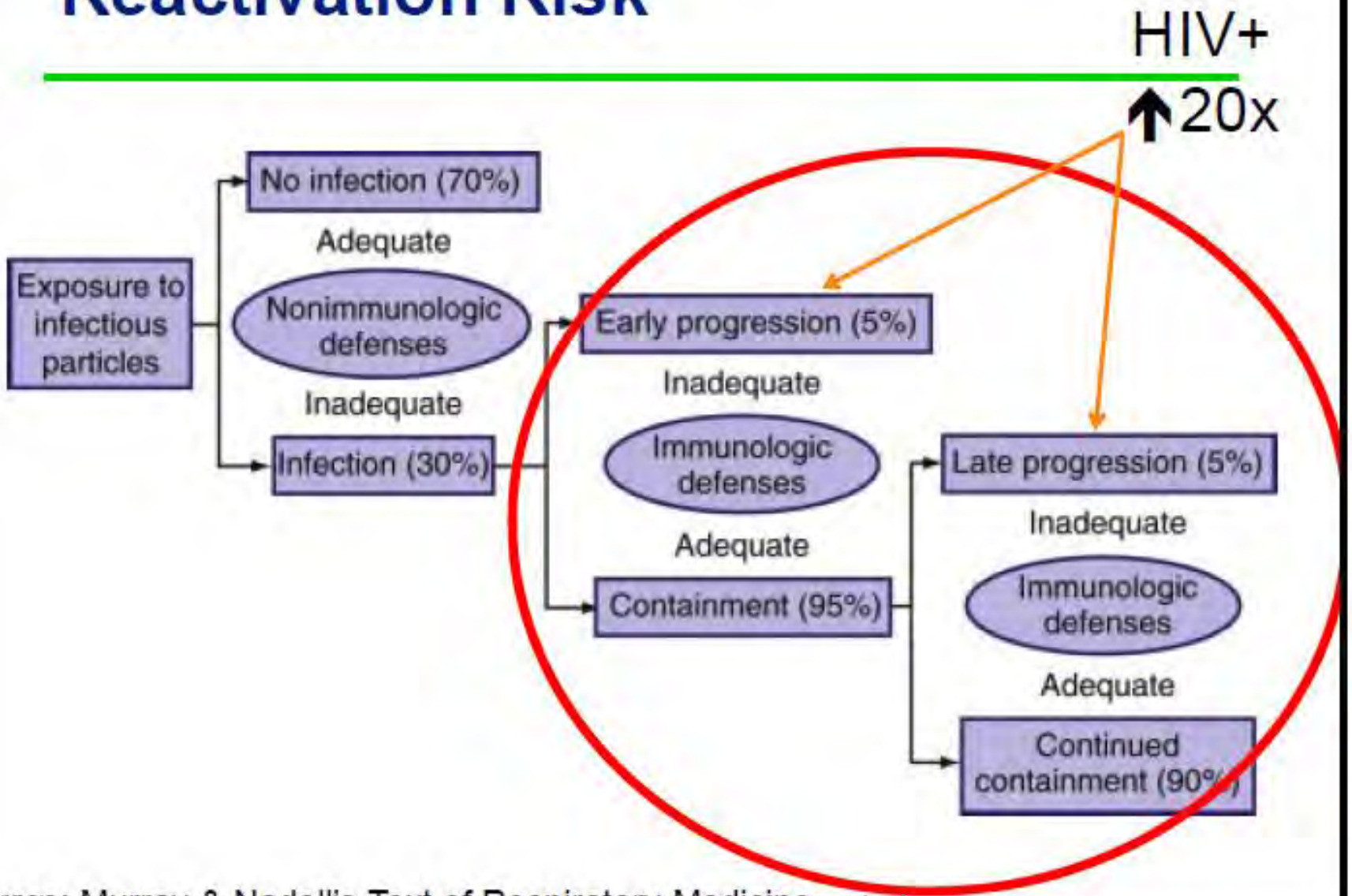
(Goldmacher, Curr Opin HIV AIDS, 2012)

Credit to Dr Robert Harrington

Exposed ⟶ Infection ⟶ Disease

- In more than 90% of persons infected with *M. tuberculosis,* the pathogen is contained as asymptomatic latent infection (LTBI)
- The risk of active disease is estimated to be approximately
  - 5% in the 18 months after initial infection and then
  - approximately 5% for the remaining lifetime.
- LTBI reduces the risk of reinfection on repeated exposure whereas
- Active TB is associated with an increased risk of a second episode of tuberculosis on re-exposure

Reactivation Risk



Source: Murray & Nadell's Text of Respiratory Medicine

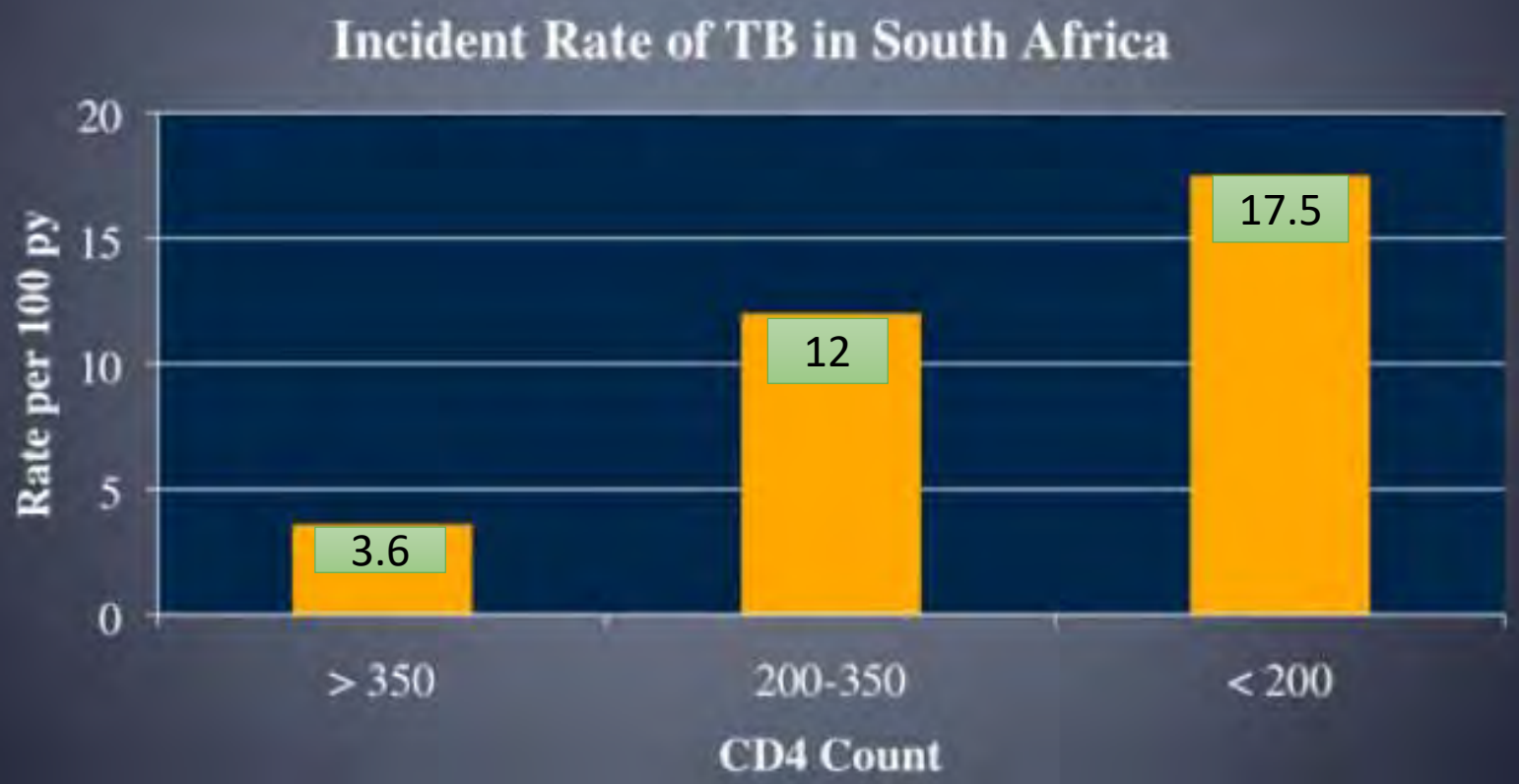
Table 1 Risk factors for TB activation

The usual quoted figure is 20 times

Risk factor	TB risk[a]	Reference(s)	WHO's recommendation for screening and treatment for LTBI[41]	
			Country A[b]	Country B[c]
High-risk factors				
HIV/AIDS	10–100	Landry *et al.*,[4] Hourburgh *et al.*[9] and WHO[14]	Required	Required
Close contacts	15	Landry *et al.*[4] and Sutherland *et al.*[15]	Required	Required for close contacts (<five years old)
Organ-transplantation recipients	20–70	Aguado *et al.*[16] and Sakhuja *et al.*[17]	Required	Not mentioned
Chronic renal failure requiring dialysis	6.9–52.5	Andrew *et al.*,[18] Lundin *et al.*,[19] Belcon *et al.*[20] and Hussein *et al.*[21]	Required	Not mentioned
TNF-alpha blockers	1.6–25.1	Solovic *et al.*[22]	Required	Not mentioned
Silicosis	2.8	Cowie *et al.*[23]	Required	Not mentioned
Moderate-risk factors				
Fibronodular disease on chest x-ray	6–19	Grzybowski *et al.*[24]	Not mentioned	Not mentioned
Immigrants from high-TB-prevalence countries	2.9–5.3	Baussano *et al.*[25]	Options to be considered	Not mentioned
Health-care workers	2.55	Chu *et al.*[26]	Options to be considered	Not mentioned
Prisoners, homeless persons, illicit drug users	–	–	Options to be considered	Not mentioned
Low-risk factors				
Diabetes mellitus	1.6–7.83	Harries *et al.*,[27] Dobler *et al.*,[28] Jeon *et al.*,[29] Boucot *et al.*,[30] Kim *et al.*[31] and Baker *et al.*[32]	Not recommended	Not mentioned
Smoking	2–3.4	Altet *et al.*,[33] Slama *et al.*[34] and Maurya *et al.*[35]	Not recommended	Not mentioned
Use of corticosteroids	2.8–7.7	Jick *et al.*[36]	Not recommended	Not mentioned
Underweight	2–3	Palmer *et al.*[37] and Comstock *et al.*[38]	Not recommended	Not mentioned

Pathogenesis and Natural History

Active Disease Rates Driven by Degree of Immunosuppression



(Wood, Int J of TB + Lung Dis, 2010)

Credit to Dr Robert Harrington

Impact of TB on HIV

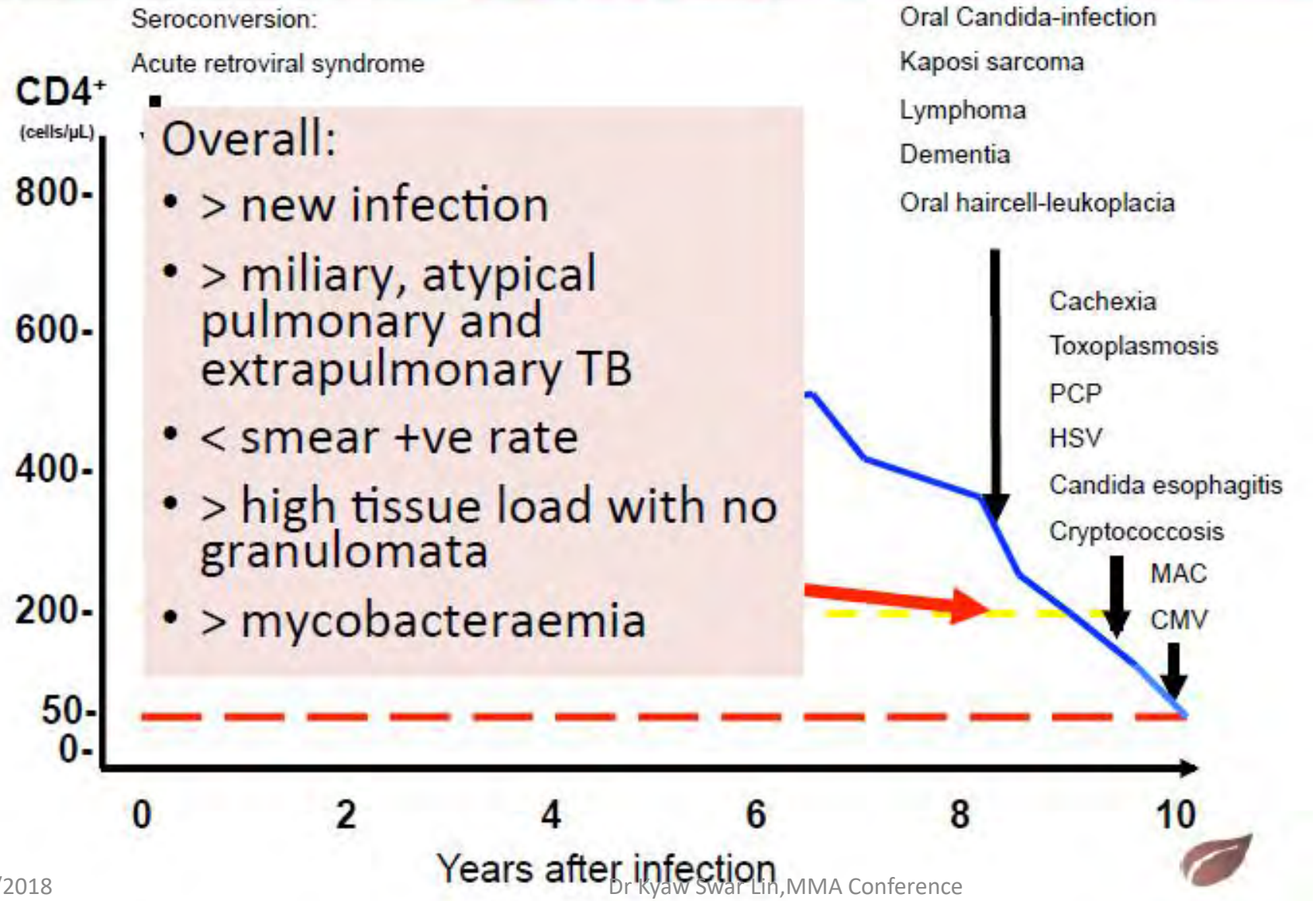
- Generalized immune activation → Increased expression of the HIV coreceptors CCR5 and CXCR4
- increases in plasma HIV viremia (up to160 fold increase in VL)
- Increases vertical transmission of HIV and increased congenital transmission of TB
- TB increases the risk of progression to AIDS or death

Impact of HIV on TB

- Increased risk of reactivation from latent infection
  - 10% lifetime risk if HIV-ve
  - 10% annual risk if HIV+ve, upto 50% during lifetime
- TB occurs at any time in course of untreated HIV, usually early.
- The risk of TB increases after HIV seroconversion, doubling within the first year
- Accelerated progression leading to outbreaks of MDR & XDRTB
- Duration of TB disease prior to diagnosis was three times shorter TB is a more subacute than chronic illness

- HIV infected at high risk for TB immediately after ART initiation

TB in the course of HIV-infection



Clinical Presentation

Depends on immune status

- Certain TB types occur more frequently (more dissemination)
  - EPTB (10 -20% in HIV-ve vs upto 40 – 80 % in HIV+ve
  - TB meningitis (< 2% in HIV-ve vs 5 -10 % in HIV+ve)
- Certain TB syndromes are recognized
  - Pulmonary, lymphadenopathy, serositis, constitutional
- Extreme of presentation
  - Subclinical disease (may account for 10% of cases in high burden countries)
  - Accelerated & exaggerated (esp IRIS)
  - Outbreaks with resistant strains

- Pulmonary tuberculosis in HIV-infected patients bears many similarities to childhood tuberculosis;
  - paucibacillary,
  - involve hilar and mediastinal lymph nodes,
  - lack cavitation, and
  - are smear negative

High Rates of Clinical and Subclinical Tuberculosis among HIV-Infected Ambulatory Subjects in Tanzania

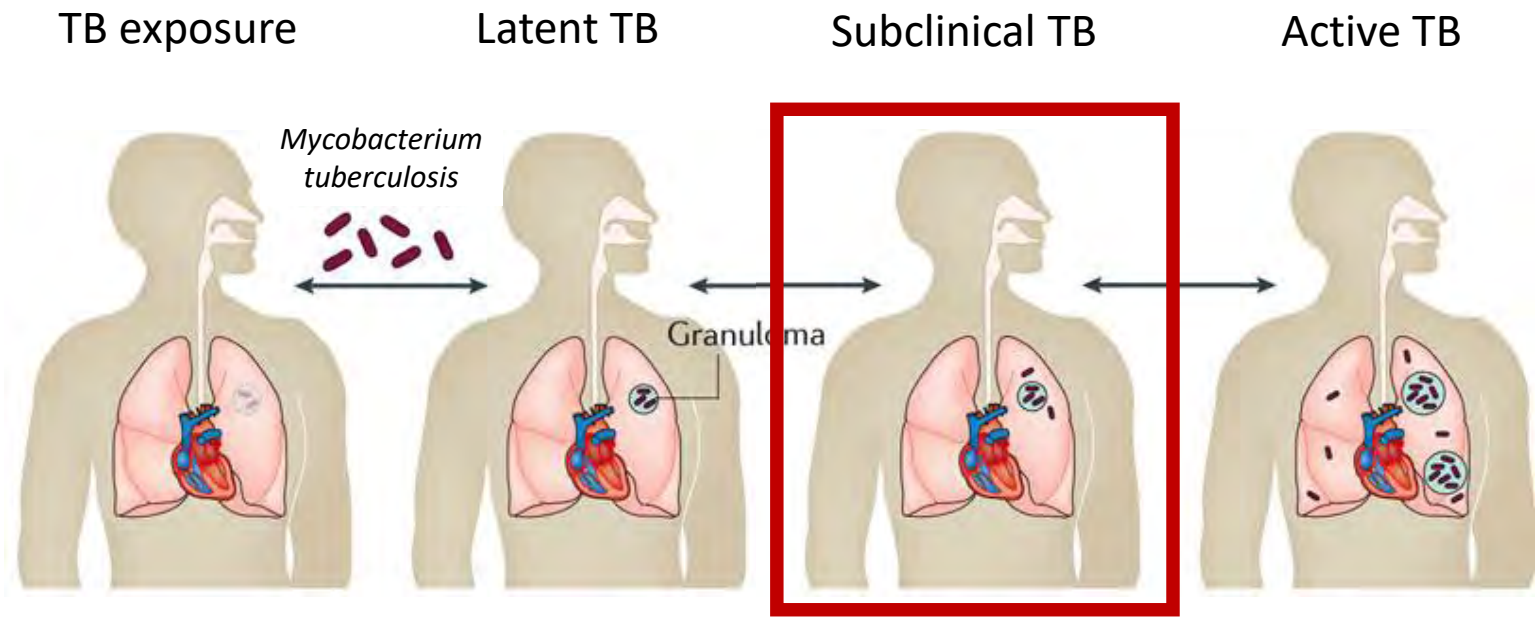
Clinical Infectious Diseases 2005; 40:1500–7

Lillian Mtei,[1] Mecky Matee,[1] Oliver Herfort,[2] Muhammad Bakari,[1] C. Robert Horsburgh,[4] Richard Waddell,[2]

- Ambulatory PLHIV with CD4>200, 93 pts, ART naïve
- 10 (10.7%) have subclinical TB (no -/S, either smear or culture +)

Patient	CD4 cell count, cells/mm^3	Symptom	TST reaction size, mm	Smear	culture
1	525	None	16	-	+
2	880	None	12	-	+
3	538	None	0	-	+
4	362	None	0	-	+
5	386	None	20	+	+
6	324	None	15	-	+
7	261	None	14	-	+
8	630	None	38	+	+
9	445	None	17	-	+
10	365	None	20	+	+

Spectrum of TB and subclinical disease



A total of 630 PLHIV were screened for TB by smear & culture from 2011-2014 in Durban, S Africa

Active TB 106(16%), Subclinical TB 34 (5%), No TB 490 (79%); FU 12 months

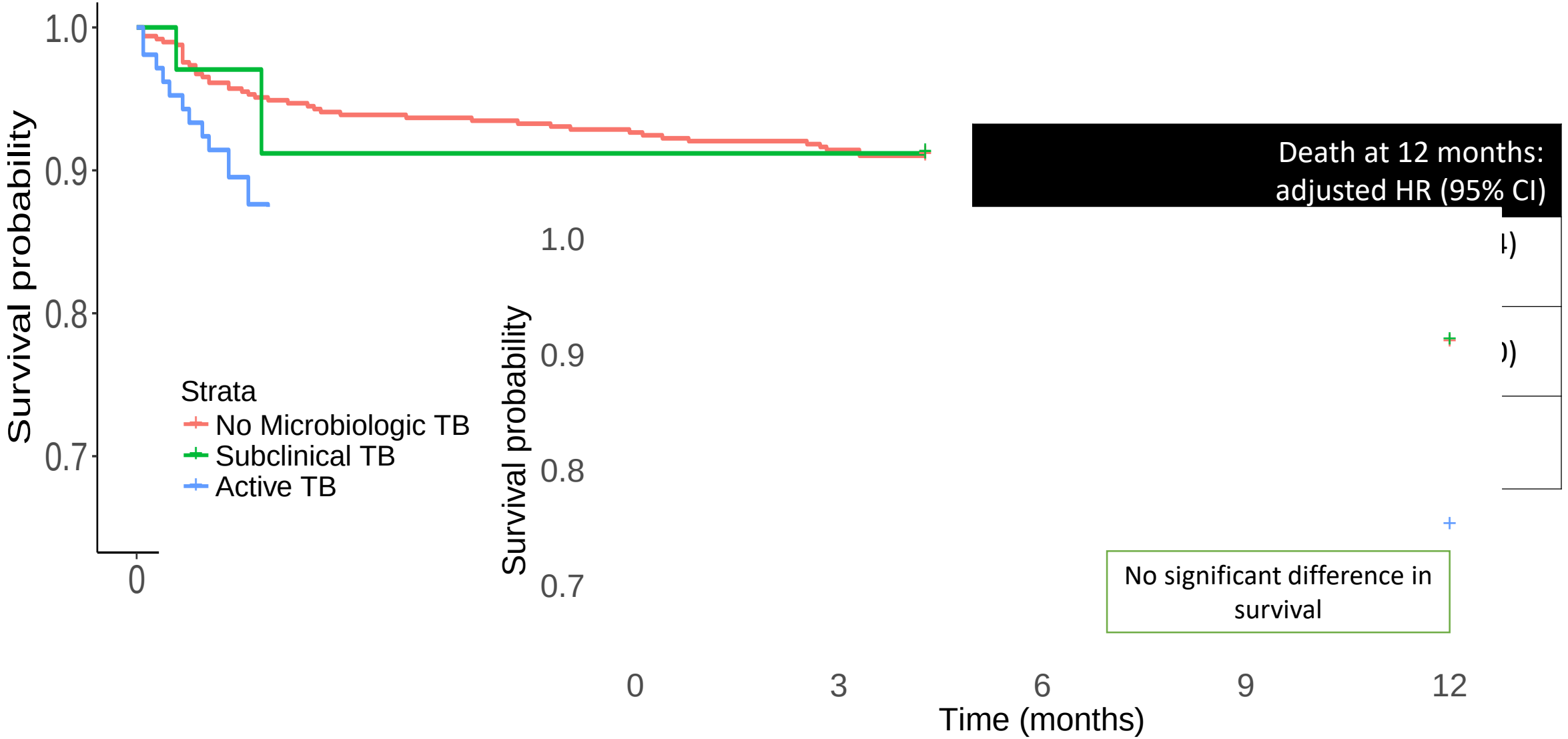
Pai, M. et al. Tuberculosis *Nat. Rev. Dis. Primers* 2016; 2:1-23.

Results

All are ART naive

	Active TB *N = 106 (16%)*	Subclinical TB *N = 34 (5%)*	No Microbiologic TB *N = 490*	P value
Mean age, years (SD)	35 (9)	33 (9)	34 (10)	*0.48*
Men	70 (66%)	16 (47%)	248 (51%)	*0.03*
Mean CD4 cell count (SD)	138 (144)	200 (162)	289 (214)	*<0.01*
AFB smear positive	23 (22%)	14 (41%)	--	*0.04*
AFB culture positive	96 (91%)	28 (82%)	--	*0.35*

c TB



THE 48TH UNION WORLD CONFERENCE ON LUNG HEALTH

ACCELERATING TOWARD ELIMINATION

11–14 OCTOBER 2017 | GUADALAJARA, MEXICO

Screening HIV positive pregnant women for TB in South Africa increased detection by 10-fold

- compare universal sputum testing with standard symptom-based testing in this population, about 1000 pts in each arm, from 2015 to 2017,FU 2M postpartum
- Samples were tested with Xpert/RIF & liquid MGIT culture
- FU --- 2 months post partum

	Universal	Symptom
Median age(yr)	30.2	29.5
gestational age (wks)	24.6	24.4
Past TB	9.8%	7.8%
CD4	426	451
On ART	99.5%	98.6%

	Universal	Symptom	P
TB diagnosed	34/941(3.6%)	4/1100 (0.36%)	
Infant mortality	1%	2.2%	0.13
Maternal mortality	0.1%	0.3%	0.87

Conclusion: Universal screening detects 10 time more TB patients, no significant effect on infant and maternal deaths

XDRTB outbreak in rural Africa 2005

Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Lancet 2006; 368: 1575–80

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

- Rural South Africa, KwaZulu Natal, 2005 -2006, 1539 pts,
- TB 35%, MDRTB 41% (of culture isolates)
- 53 people have XDRTB, 52 died within 16 days from specimen collection
- 90% were infected with genetically similar strain
- All 44 XDR TB patients with known HIV status were HIV-infected

Recurrence:
endogenous reactivation or exogenous reinfection?

Recurrence of TB

- HIV-negative patients with 4-drug therapy and DOT
  - 2-3% recurrence
- HIV-positive patients
  - 14+ % recurrence rate
    - Some relapse with original strain
    - Most re-infect with new strain
    - Recurrence may herald drug resistance

MAYO CLINIC

MAYO CLINIC CENTER FOR TUBERCULOSIS

HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers

Lancet 2001; 358: 1687–93

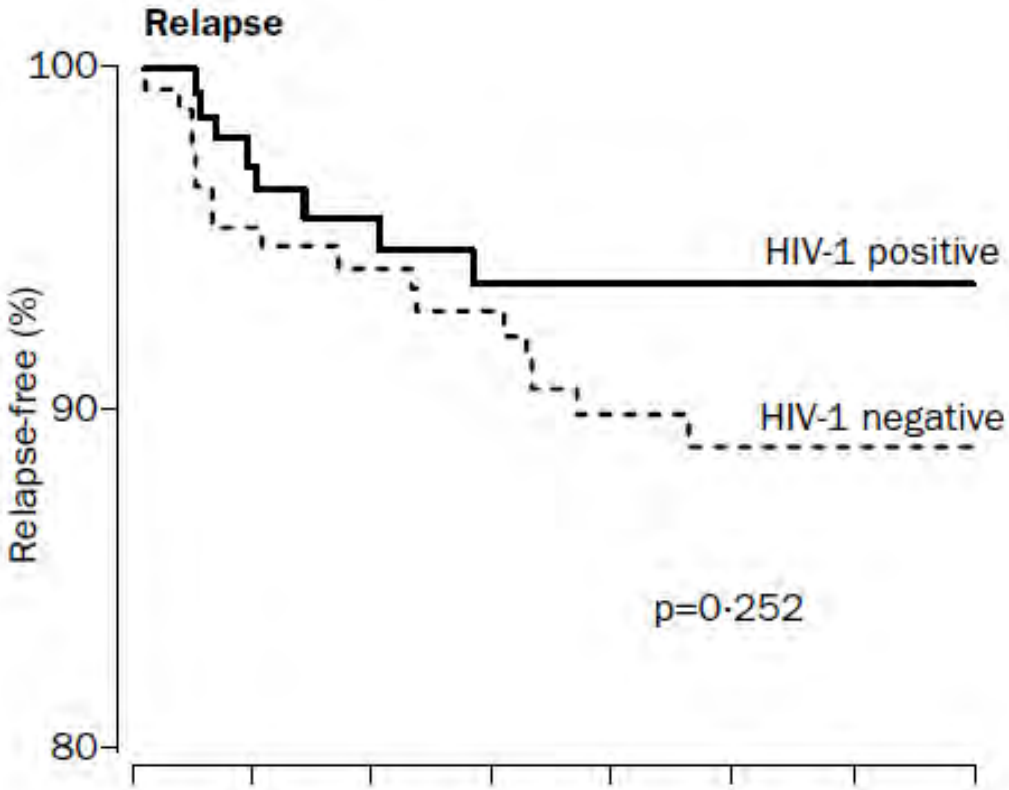
Pamela Sonnenberg, Jill Murray, Judith R Glynn, Stuart Shearer, Bupe Kambashi, Peter Godfrey-Faussett

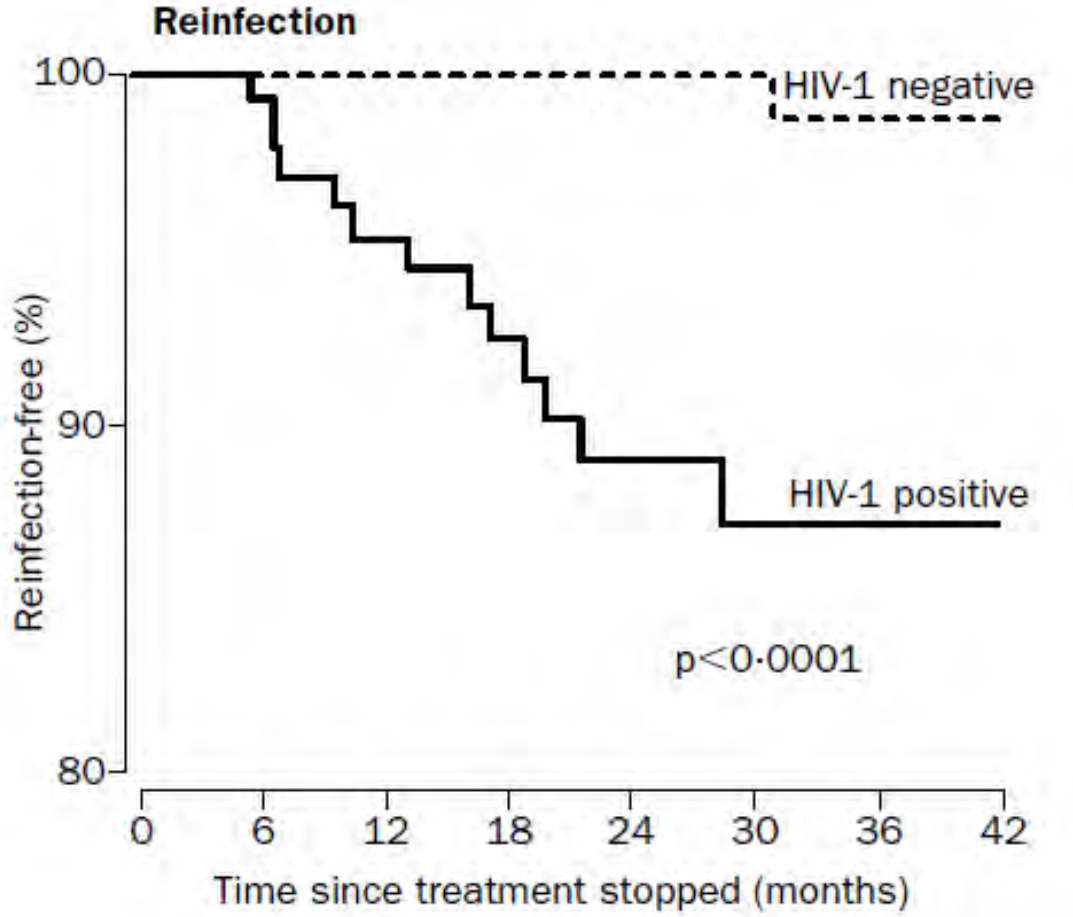
- 326 mineworkers in S Africa in 1998,both HIV +ve (151 pts) & -ve (175), TB cured 3 yrs ago , FU 3 year for incident TB
- 20% recurrence rate, 16 per 100PY in HIV+ve pts, which is 2.4 times higher than HIV-ve pts

Conclusion

In high TB burden setting, HIV-1 increases the risk of recurrent tuberculosis because of an **increased risk of reinfection**

Reinfection vs Relapse





Lancet 2001; 358: 1687–93

Recurrent Tuberculosis Risk Among HIV-Infected Adults in Tanzania With Prior Active Tuberculosis

Clinical Infectious Diseases 2013;56(1):151–8

- HIV-infected, BCG-immunized adults with CD4 counts ≥200 cells/Ml
- 979 subjects, 80 (h/o prior TB), 899 (no prior TB, given IPT),median FU 3.2 yrs
- TB recurrence in prior TB group 13.8% vs 4.6% , HR 3
- Conclusions.
  - Compared to subjects without prior tuberculosis, the hazard of active tuberculosis is increased 3-fold among HIV-infected adults with prior active tuberculosis

MAJOR ARTICLE

After cure

Impact of HIV Infection on the Recurrence of Tuberculosis in South India

The Journal of Infectious Diseases 2010; 201:691–703

Sujatha Narayanan,[1] Soumya Swaminathan,[1] Philip Supply,[2] Sivakumar Shanmugam,[1] Gopalan Narendran,[1]

- HIV+ arm --- 306 cured pts --- 44 recurred (14%)

ART % ---missing data

- HIV-ve arm --- genotype result of paired isolates were available for 23 pairs --- 21 recurrent from the same strain
- Recurrence was due to exogenous reinfection in 88% of HIV-infected and 9% of HIV-uninfected patients (P <0.05). Among recurrent isolates, the HIV-infected patients showed higher rate of multidrug resistance

Published in final edited form as:
Int J Tuberc Lung Dis. 2011 May ; 15(5): 571–581. doi:10.5588/ijtld.10.0483.

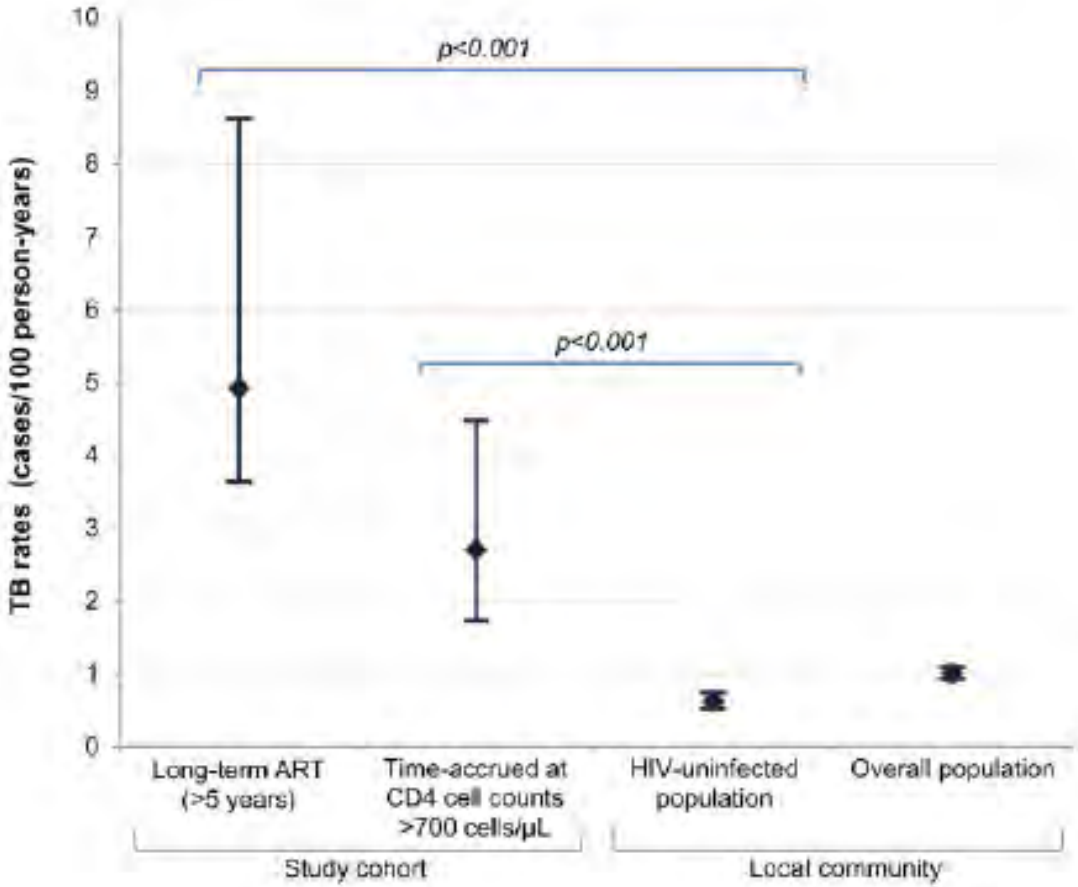
Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it?

S. D. Lawn[1,2], **A. D. Harries**[2,3], **B. G. Williams**[4], **R. E. Chaisson**[5], **E. Losina**[6], **K. M. De Cock**[7], and **R. Wood**[1]

- ART reduces
  - the risk of TB by 67%,
  - Recurrent TB 50%,
  - mortality 64–95%
  - prolongs survival in patients with HIV-associated drug-resistant TB.
- However, rates of TB remain substantial and above the background rates in HIV-uninfected populations despite ART use.
- The cumulative lifetime risk of TB in HIV infected individuals strongly depends on the amount of time that patients spend at low CD4 cell counts before and during ART.

ART reduces TB incidence, but still high

Meta-analysis: ART any CD4 HR 0.35 (0.28-0.44)
ART CD4>350 HR 0.43 (0.3-0.63)
Suthar Plos Med 2012



Gupta PLoS ONE 7(3): e34156

Risk of MDRTB

OPEN ACCESS Freely available online

PLOS | ONE

Association between HIV/AIDS and Multi-Drug Resistance Tuberculosis: A Systematic Review and Meta-Analysis

PLoS ONE 9(1): e82235. doi:10.1371/journal.pone.0082235

Yonatan Moges Mesfin[1], Damen Hailemariam[2], Sibhatu Biadglign[3], Kelemu Tilahun Kibret[4]*

- Meta-analysis of all 24 observational studies showed that HIV is associated with a marginal increased risk of MDRTB (OR 1.24)
- Sub-group analysis also showed that HIV infection was significantly associated with MDRTB in primary drug resistance group (OR 2.28)

MDRTB in HIV-infected patients is transmitted from others, rather than acquired by ineffective or insufficient therapy

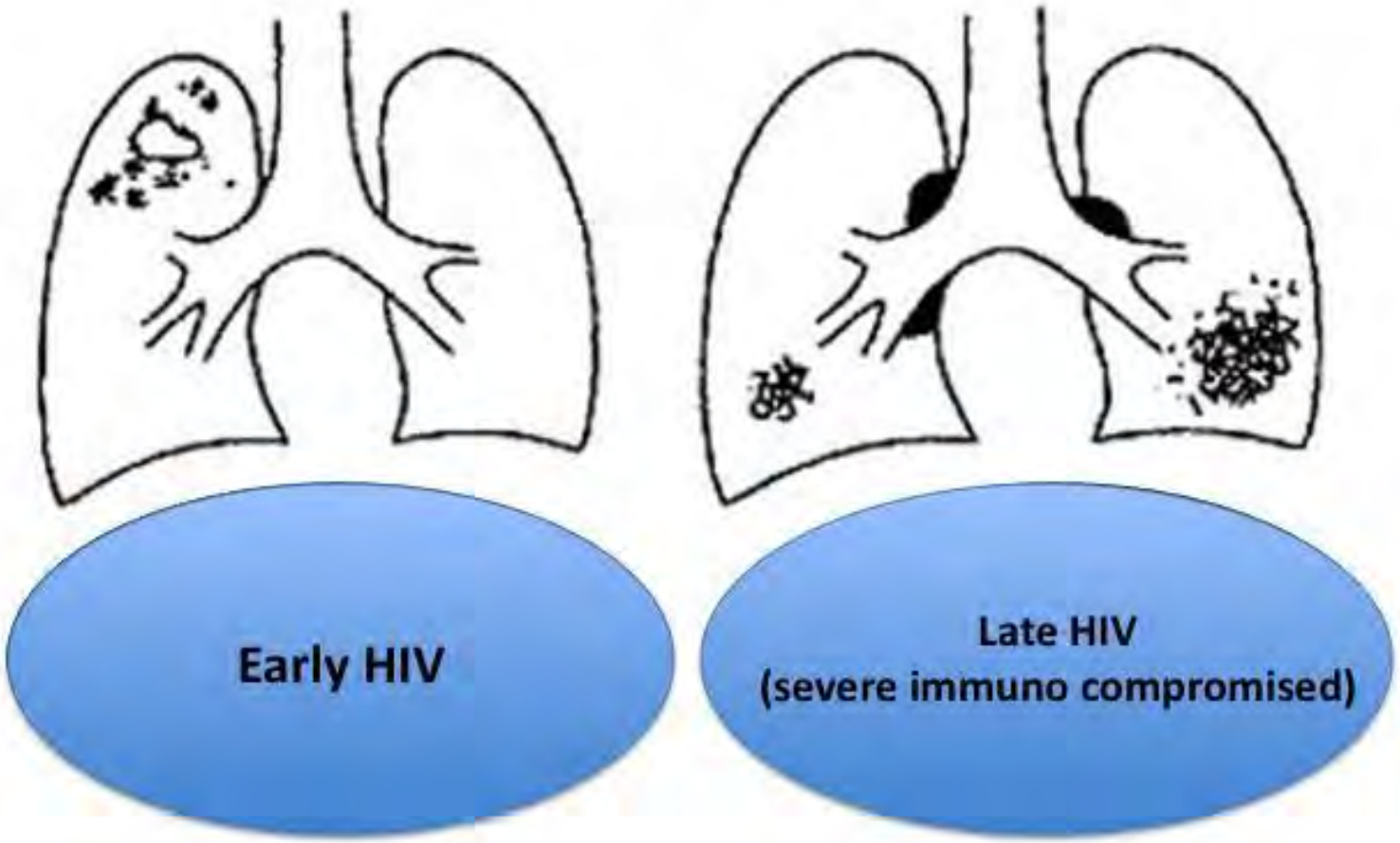
Diagnostic challenges

CXR

- At CD4>200, the radiographic pattern tends to be one of reactivation disease with upper-lobe infiltrates with or without cavities.
- If CD4 count <200, a pattern of primary disease with intrathoracic lymphadenopathy and lower-lobe infiltrates is seen.
- As chest radiographs may appear normal in up to 21% of those with culture-positive TB and CD4 counts of <50

High index of suspicion

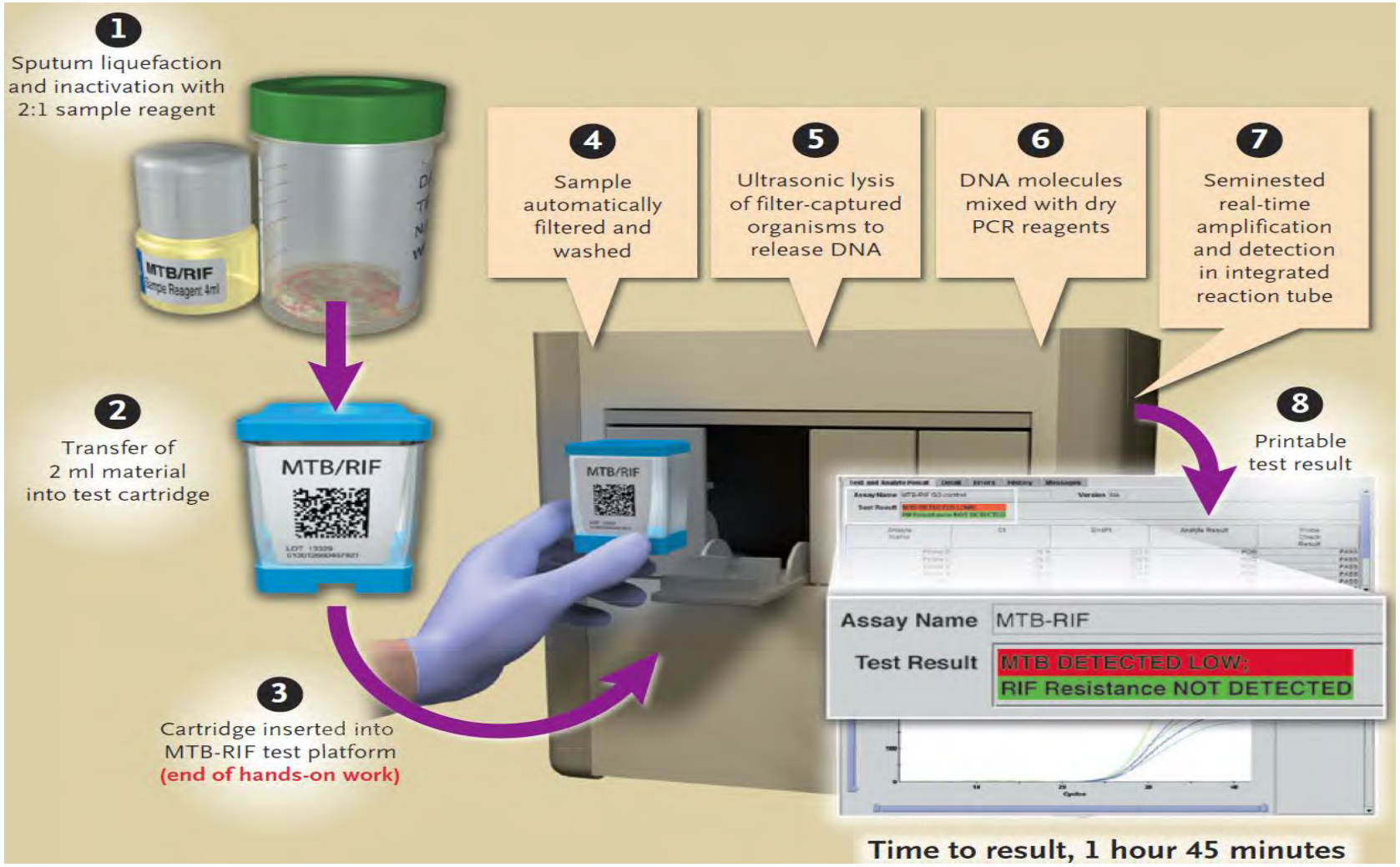
X-ray findings in TB patients with HIV infection



Smear microscopy & culture

- Traditional TB diagnostic tools perform poorly in PLHIV
  - smear microscopy ---- 39%
  - Lowenstein Jenson culture --- 48%

GeneXpert MTB/RIF



For diagnosing MTB
Sensitivity = 88% (= solid culture)
Specificity = 99%

For rifampicin resistance
Both S & S =99 %

(WHO TB standard compendium 2017)

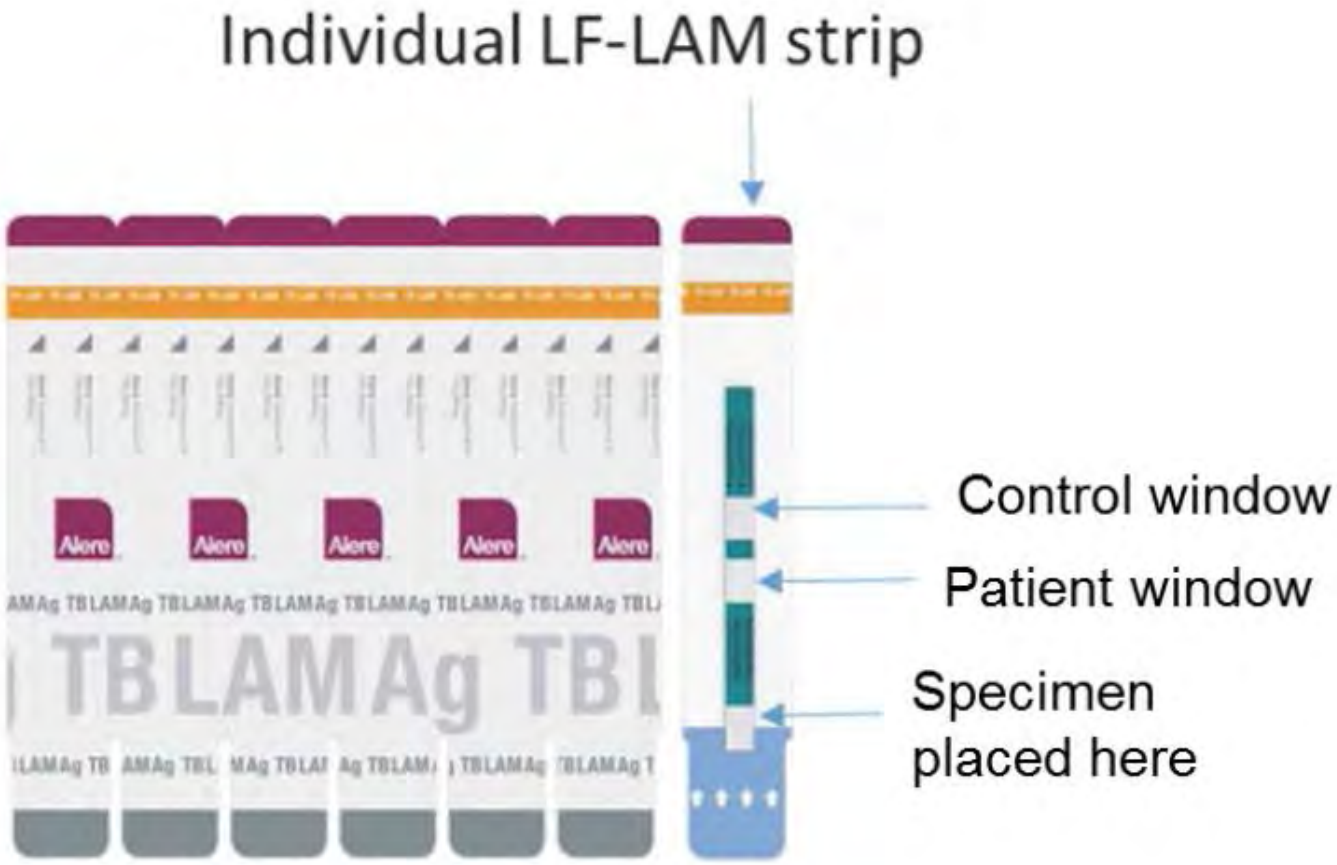
Xpert MTB/RIF Ultra

- Ultra performance approaches that of liquid culture
- Overall 5% higher sensitivity but 3.2% reduced specificity
- Benefit seen in most difficult cases
  - Smear –ve culture +ve cases (sensitivity ↑ 17%)
  - PLHIV (sensitivity ↑ 12%)
  - children
  - EPTB (esp TB meningitis)

33 WHO TB Standard of care

- WHO TB Standard 8. For persons living with HIV, the Xpert MTB/RIF Ultra assay should be used as an initial diagnostic test. The (LF-LAM) can be used to assist in the diagnostic process for HIV-positive patients who are seriously ill.
- WHO TB Standard 19. HIV testing should be routinely offered to all patients with presumptive TB and those who have been diagnosed with TB.
- WHO TB Standard 20. Persons living with HIV should be screened for TB by using a clinical algorithm.
- WHO TB Standard 21. Antiretroviral therapy (ART) and routine co-trimoxazole preventive therapy (CPT) should be initiated among all TB patients living with HIV, regardless of their CD4 cell count

LF-LAM – urine Lipoarabinomannan
(Sensitivity= 54%; Specificity = 90%)



Urinary LAM Ag should NOT be used as
- A screening test
- A diagnostic test

Except in 2 situations
1. S/S of TB and CD4<100
2. Seriously ill in-patients (4 danger signs: RR >30 , HR >120, T >39°C, unable to walk unaided)

Given its limited sensitivity, urine LAM has been proposed as a "rule in" test but appears inadequate as a stand-alone "rule out" test for TB.

Cochrane Database Syst Rev. 2016 May 10;(5):CD011420

LAM improves outcomes !!

-Multicenter
-2013 to 2014
-Hospitalized pts with at least one TB -/S

	LAM group	No LAM group
No of pt	1257	1271
8 W mortality	261(21%)	315(25%)

THE LANCET
Volume 387, Issue 10024, 19–25 March 2016, Pages 1187-1197

Articles

Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial

Jonny G Peter PhD [a, c, d, l, *], Lynn S Zijenah PhD [e, *], Duncan Chanda MD [a, h, m, *], Petra Clowes MD [i, j, *],

- RRR 17%; ARR 4%
- Bedside LAM-guided initiation of anti-tuberculosis treatment in HIV-positive hospital inpatients with suspected tuberculosis was **associated with reduced 8-week mortality**.

Treatment

-AntiTB regimen and duration (same as HIV-ve pts)

-ART (When and what to start)

-Drug-drug interaction

HIV/AIDS MAJOR ARTICLE

An Updated Systematic Review and Meta-analysis on the Treatment of Active Tuberculosis in Patients With HIV Infection

Faiz Ahmad Khan,[1] Jessica Minion,[2] Abdullah Al-Motairi,[1] Andrea Benedetti,[3,4] Anthony D. Harries,[5,6] and Dick Menzies[1]

Clinical Infectious Diseases 2012;55(8):1154–63

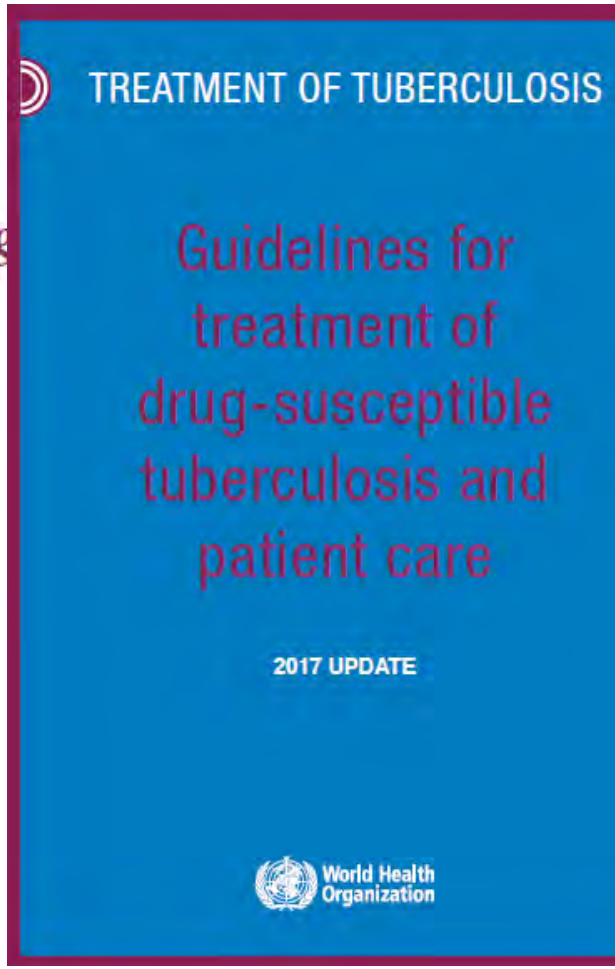
Conclusion

- OR for relapse 2 mth RIF Vs > 8 mth: 5.0
– OR for relapse 6 mth RIF Vs > 8 mth: 2.5
– OR for relapse No ARV Vs ARV: 14.3
– *Restricting the analysis to ARV studies: nothing else mattered*

1.5. The effectiveness of a TB treatment period of greater than 8 months compared to the standard 6-month treatment period for HIV co-infected patients with drug-susceptible pulmonary TB

Recommendation:

In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-month standard treatment regimen is recommended over an extended treatment for 8 months or more (Conditional recommendation/very low certainty in the evidence).



Treatment duration (expert opinion)

- 6 month for drug sensitive TB EXCEPT
  - Cavitary disease
  - month 2 sputum positive or
  - if PZA not included in the initial 2 months

9 months

- 9-12 month for bone & joint, CNS

Timing of ART

Immediate (< 2 wks)

Benefits:
- ↓ risk of other OI's

Risks:
- ↑ adverse effects
- ↑ incidence of IRIS

Early (2 months)

Benefits:
- ↓ risk of IRIS

Risks:
- ↑ incidence of OIs

Key characteristics of trials of timing of ART during TB treatment

Study	Setting	Key enrollment criteria	Median CD4 (IQR)	Primary endpoint
CAMELIA	Cambodia	Smear +, CD4 < 200	25 (10 - 56)	Death
STRIDE	Multi-national	Clinical TB, CD4 < 250	77 (36 – 145)	AIDS or death
SAPIT	South Africa	Smear +, CD4 < 500	150 (77 – 254)	AIDS or death

AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB

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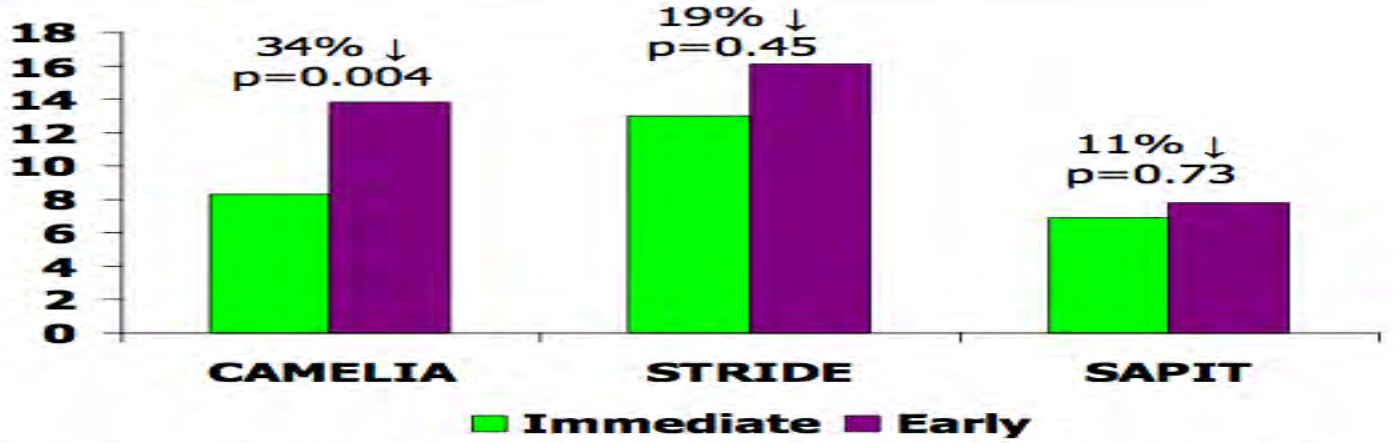
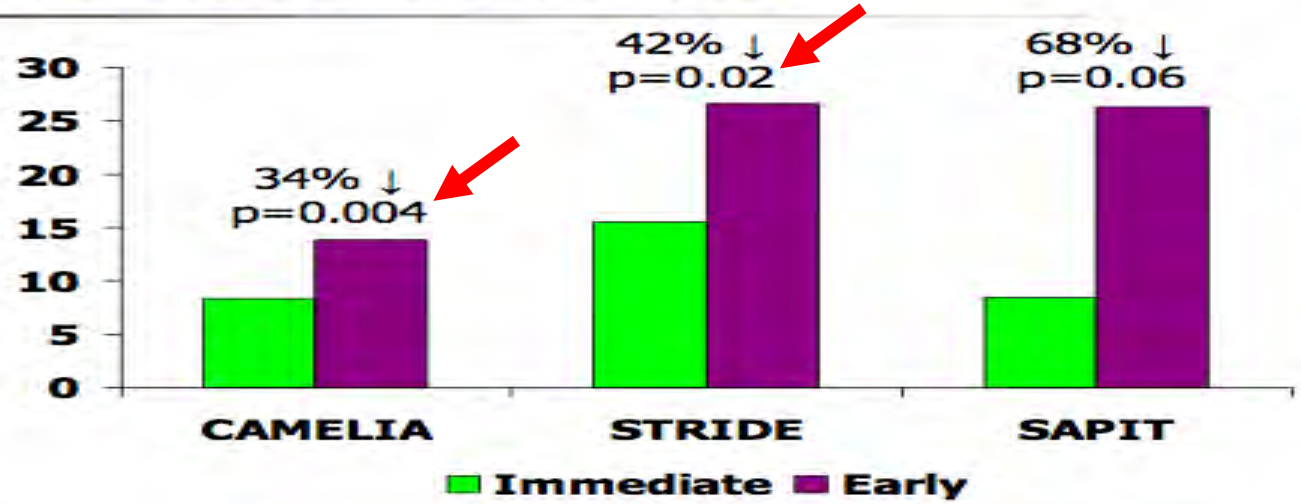
Blanc NEJM 2011, Havlir NEJM 2011, Abdool Karim NEJM 2011

Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)



Effects of ART timing on outcomes in CAMELIA and patients with **CD4 < 50** in STRIDE and SAPIT



AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB

WHO 2016 Guideline: when to start ART

4.3.5 Timing of ART for adults and children with TB	ART should be started in all TB patients living with HIV regardless of CD4 count (strong recommendation, high-quality evidence).[1] TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, high-quality evidence).[2] HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm^3) should receive ART within the first two weeks of initiating TB treatment.
	ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of antituberculosis treatment regardless of the CD4 cell count and clinical stage (strong recommendation, low-quality evidence).

Timing of Initiation of Antiretroviral Therapy in Human Immunodeficiency Virus (HIV)–Associated Tuberculous Meningitis

1374 d CID 2011:52 (1 June)

M. Estee Török,[1,2] Nguyen Thi Bich Yen,[3] Tran Thi Hong Chau,[4] Nguyen Thi Hoang Mai,[4] Nguyen Hoan Phu,[4]

	Immediate	Deferred ART	HR, P
Pts no	127	126	
CD4(median)	39	44	
9M mortality	76	70	**1.15, 0.5**
Grade 3 or 4 AE	90	89	0.84
Grade 4 AE	102	87	0.04

Conclusions.
Immediate ART initiation does not improve outcome in patients presenting with HIV-associated TBM . There were significantly more grade 4 adverse events in the immediate ART arm, supporting delayed initiation of ART in HIV-associated TBM.

British HIV Association guidelines for the management of TB/HIV co-infection in adults 2017

When to start ART

- We recommend that all individuals with TB should start ART as soon as is practicable, and within 8–12 weeks of the TB diagnosis. (GRADE 1A)
- We recommend that individuals with a CD4 cell count <50 cells/mm^3 start ART as soon as is practicable and within 2 weeks. (GRADE 1A)
- We recommend against the early initiation (<2 months) of ART in individuals with CNS TB. (GRADE 1A)

Drug-drug interactions (DDI)

Rifamycins & ART

	Rifampicin	Rifabutin
NRTIs	No problem	No problem
Efavirenz (EFV)	EFV AUC ↓ 26%	RFB AUC ↓ 38%
Nevirapine (NVP)	NVP AUC ↓ 40-60%	No problem
Etravirine/Rilpivirine	ETR/RPV ↓ 40-60%	NNRTI AUC ↓ 37%
PIs unboosted	PI AUC ↓ 80-90%	RFB AUC ↑ 200%
PIs boosted	PI AUC ↓ 60-75%	RFB AUC ↑ 300%
Raltegravir	Integrase AUC ↓ 40%	No problem
Dolutegravir	Integrase AUC ↓ 40%	No problem
Maraviroc	CCR5 AUC ↓ 60-70%	? No problem

Drug-drug interaction (DDI) b/t ART & AntiTB (Essentially b/t Rifampicin & NNRTI or PI)

- EFV --- No need to change dose
- NVP –not recommended (BUT still OK)
- LPV/r --- either rifampicin replaced by rifabutin 150mg OD
    - Or --- the dose of PI doubled (LPV/r from 2 bd to 4 bd)
- ATV/r – not recommended
    - OD dose ---- subtherapeutic level of ATV
    - Double dosing ---- high rate of liver injury
    - And aslo because ATV can cause unconjugated hyperbilirubinemia which can be confused with DILI due to antiTB drugs)

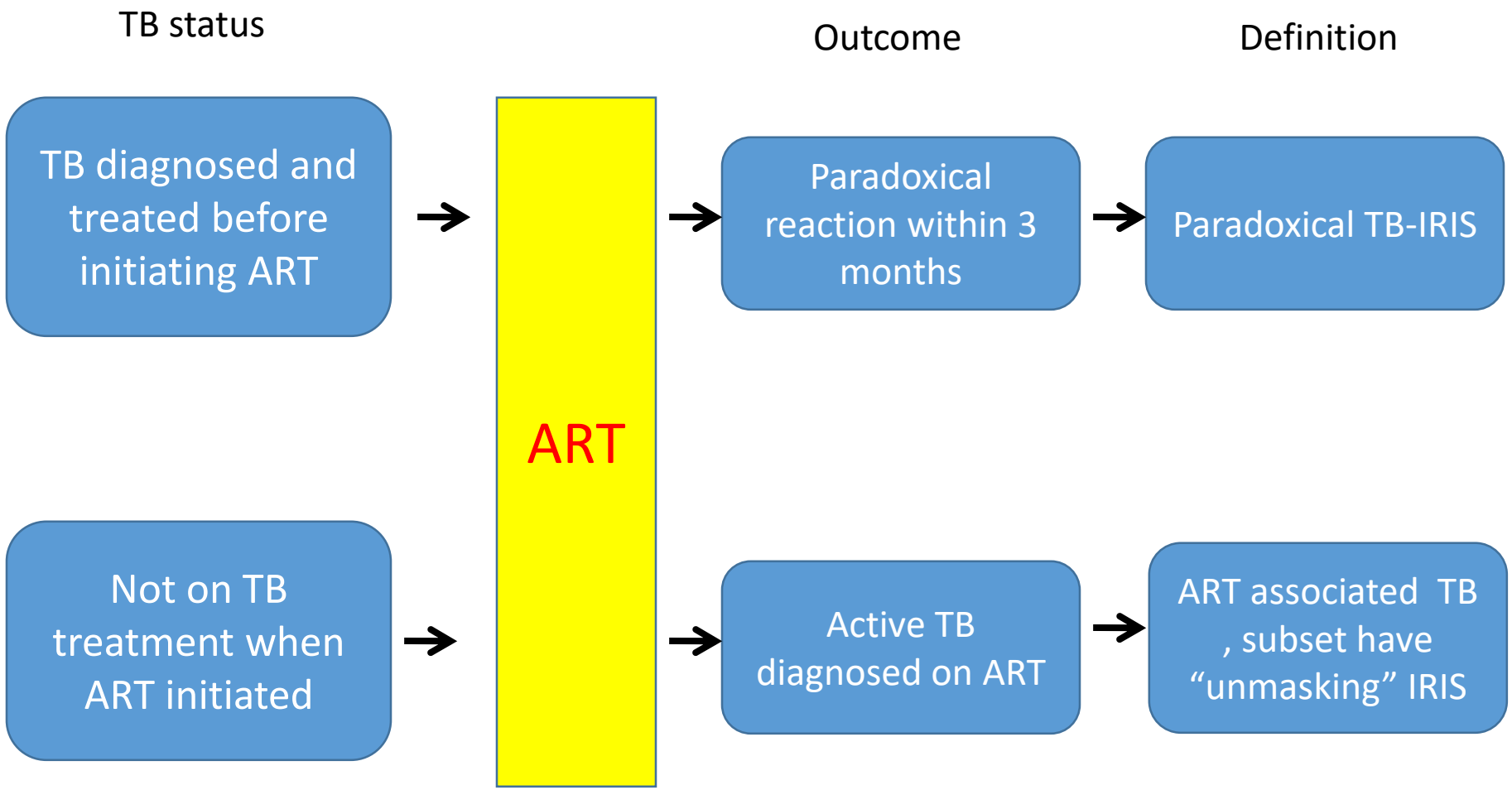
Summary of ART options with rifamycin-based TB Rx

- EFV + 2NRTIs* (preferred option) +RIF (*Not TAF)
  - Standard EFV dose (600mg daily)
- RAL + 2NRTIs* + RIF
  - Standard RAL dose (400mg bd)
- DTG + 2NRTIs* + RIF
  - Double DTG dose (50mg bd)
- PI + 2NRTIs* + RBT
  - Decrease rifabutin dose 150mg/daily

Immune Reconstitution Inflammatory Syndrome/ Immune Restoration Disease (IRIS/IRD)

- IRIS is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections such as TB, resulting in either:
- the deterioration of a treated infection (paradoxical IRIS) or
- a new presentation of a previously subclinical infection (unmasking IRIS).
- Is a diagnosis of exclusion. It is often transient in duration but can last many months

IRIS: Types



Lancet Infect Dis 2008;8:516

Paradoxical TB IRIS: INSHI Case definition

A. Antecedent requirement

Diagnosis of TB

Initial response to TB treatment

B. Clinical Criteria (within 3 months of initiation, re-initiation or change)

Major criteria

- New or enlarging nodes, focal involvement e.g. arthritis
- New or worsening radiological features
- New or worsening CNS TB
- New or worsening serositis

Minor Criteria

- New or worsening fever, night sweats, weight loss
- New or worsening respiratory symptoms
- New or worsening abdominal symptoms

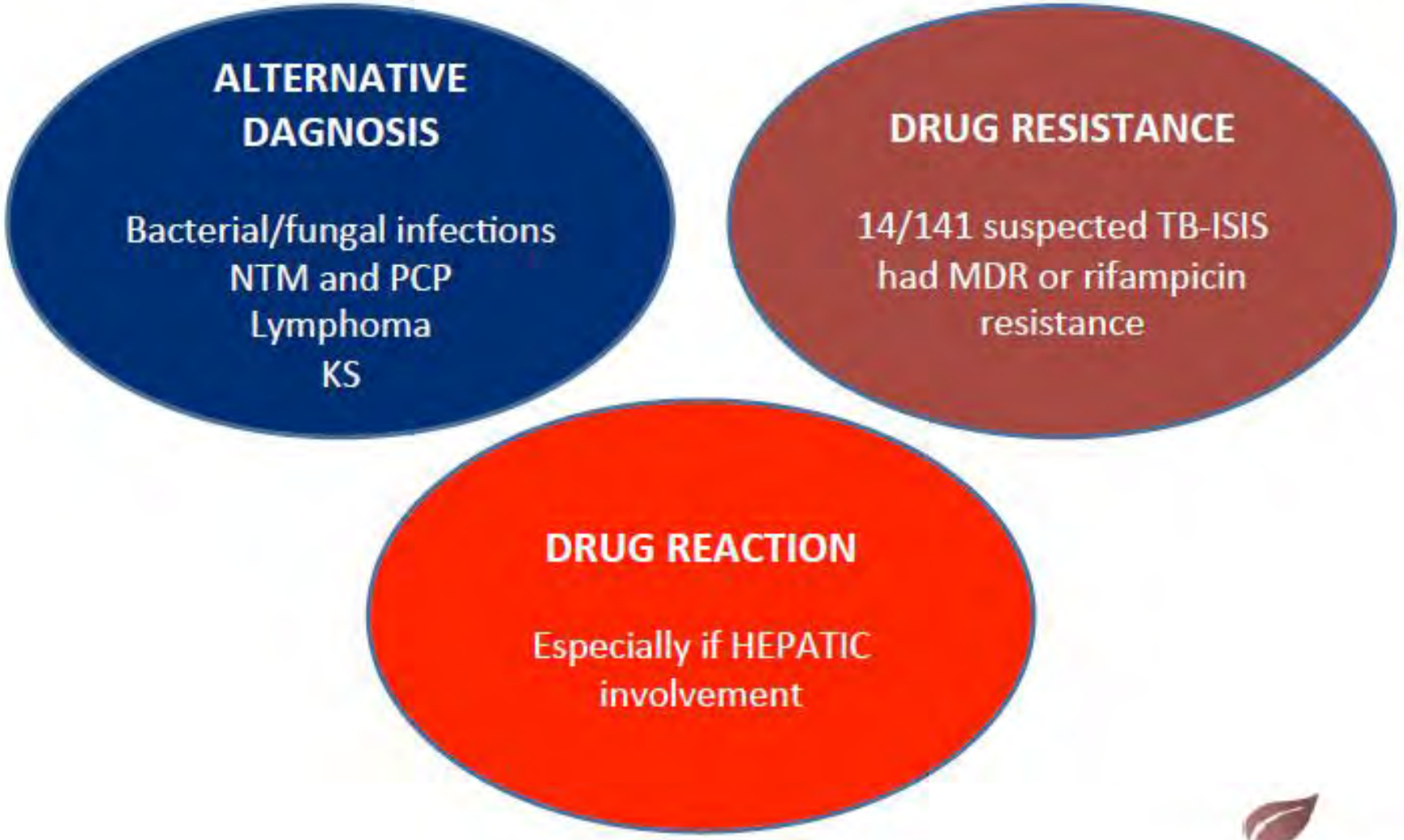
C. Alternative explanations should be excluded if possible (Tm F, other OI, drug toxicity)

Lancet Infect Dis 2008;8:516

Risk of IRIS

- Low baseline CD4+ cell count (esp <50) and rapid recovery
- High baseline VL and rapid decline
- Type of OI (CMV, Crypto & TB) and high pathogen burden
- Short time interval between start of OI treatment and initiation of ART.
- prednisone or methylprednisolone have been used at a dose of 1–1.5 mg/kg, with gradual reduction after 1–2 weeks

Challenges in differential diagnosis of IRIS



Management of IRIS

- Mild to moderate ---- NSAID
- Severe --- prednisone at 1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks ---- improves symptoms and quality of life

- Neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient

British HIV Association guidelines for the management of TB/HIV co-infection in adults 2017

12 Immune reconstitution inflammatory syndrome

- We recommend the use of corticosteroids tapered over 4–6 weeks in symptomatic IRIS. (GRADE 1C)

There is no consensus on what is an optimal and effective dose to use, although prednisone or methylprednisolone have been used at a dose of 1–1.5 mg/kg, with gradual reduction after 1–2 weeks.

Other treatment options:

Recurrent needle aspiration of lymph nodes or abscesses to remove pus and caseous material is appropriate if they become tense and/or inflamed. This can prevent spontaneous rupture, which may lead to long-term sinus formation and scarring

Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis

Lancet Infect Dis 2010; 10: 251–61

Monika Müller, Simon Wandel, Robert Colebunders, Suzanna Attia, Hansjakob Furrer, Matthias Egger, for IeDEA Southern and Central Africa

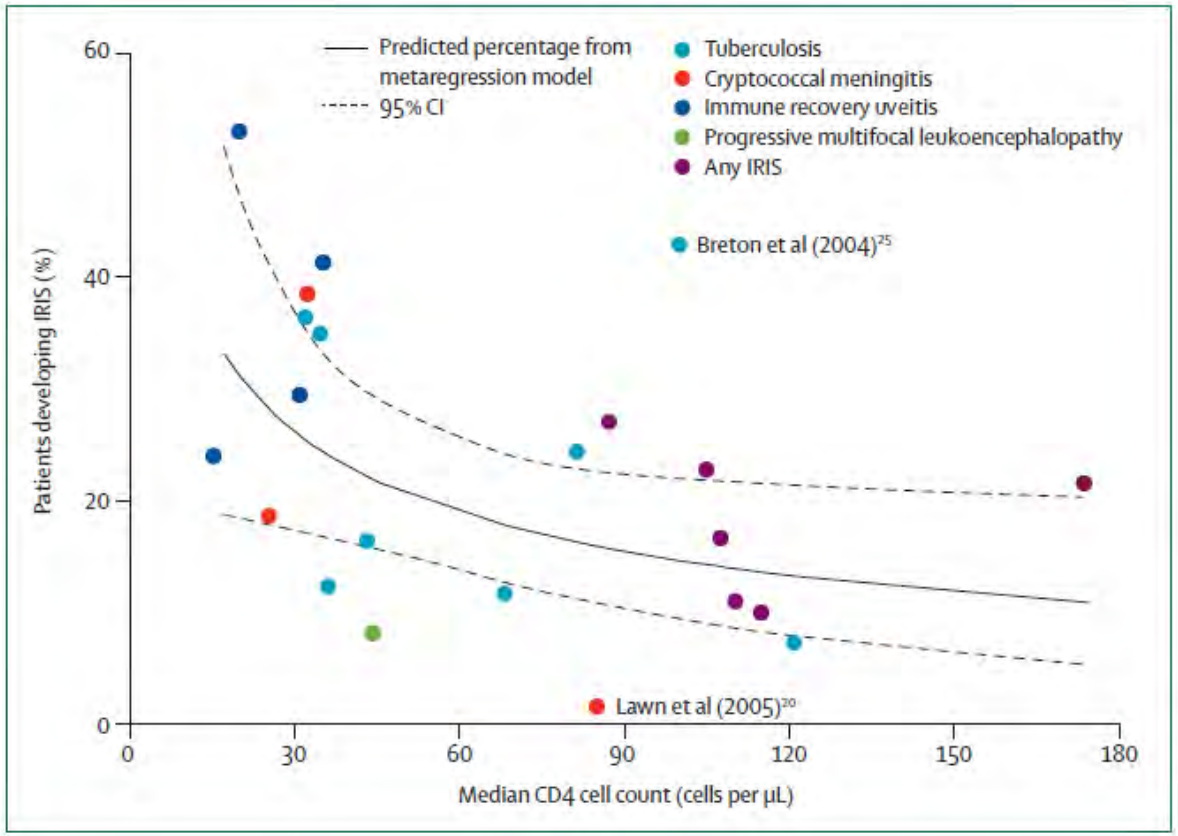
54 Cohorts, 13 103 pts, the relation between CD4 and IRIS

Previously diagnosed OI

Disease	IRIS	Mortality
CMV	37.7	
Crypto meningitis	19.5	20.8
PMLE	16.7	
TB	15.7	3.2
Herpes zoster	12.2	
Kaposi's sarcoma	6.4	

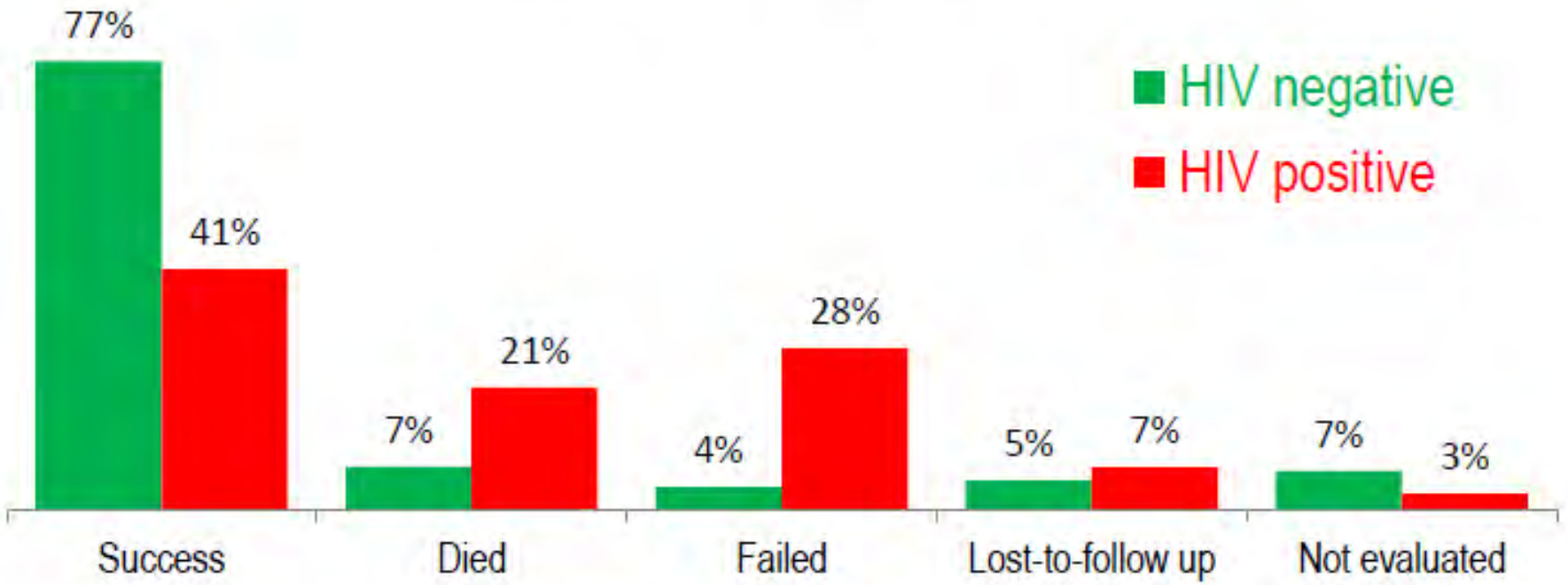
Undiagnosed OI,

-Any IRIS = 16.1%



People with TB/HIV are seven times at higher risk of failing treatment and three times at higher risk of dying than people with TB disease

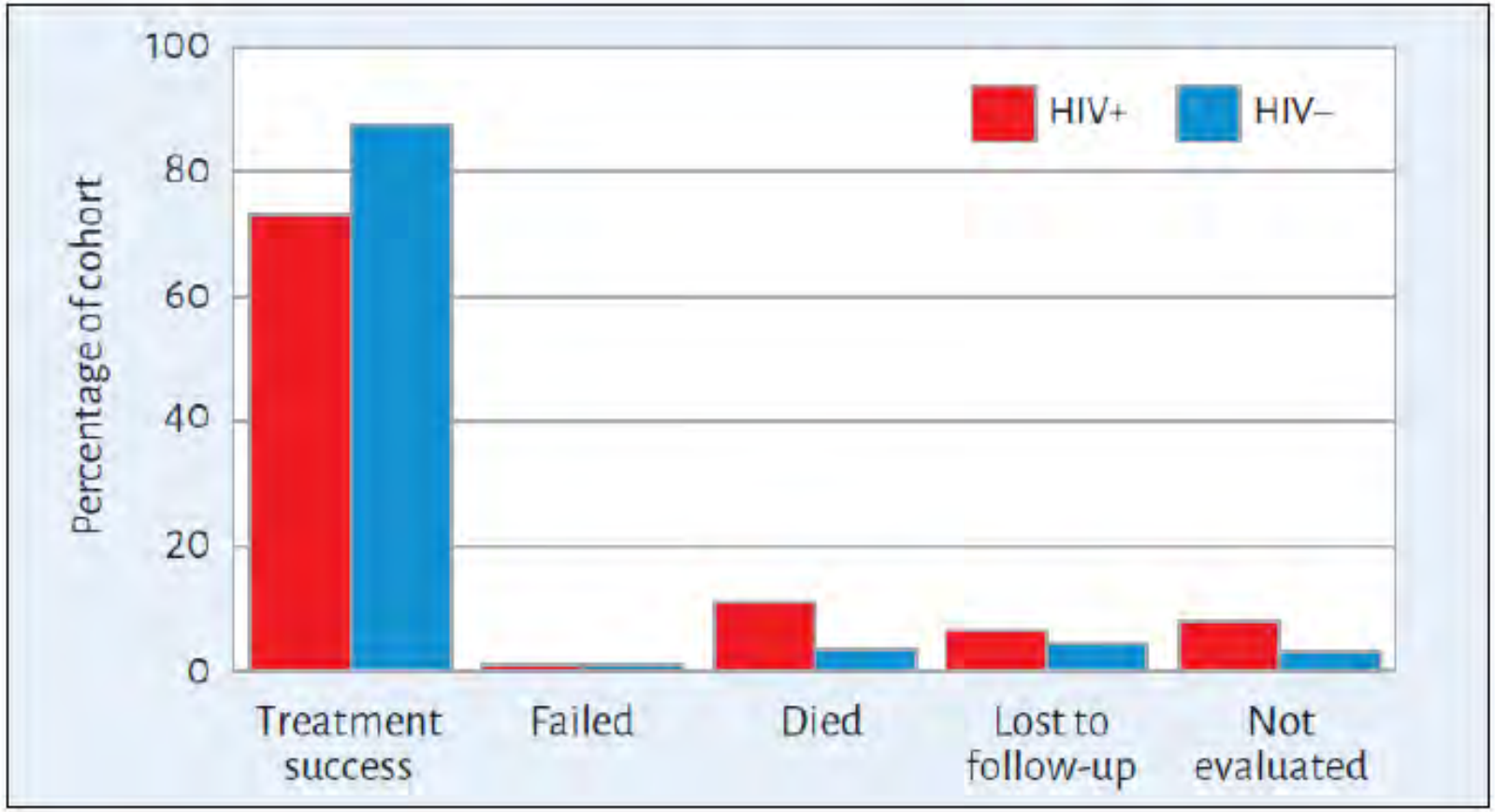
Treatment outcomes of new TB and relapses by HIV status, WHO European Region, 2015



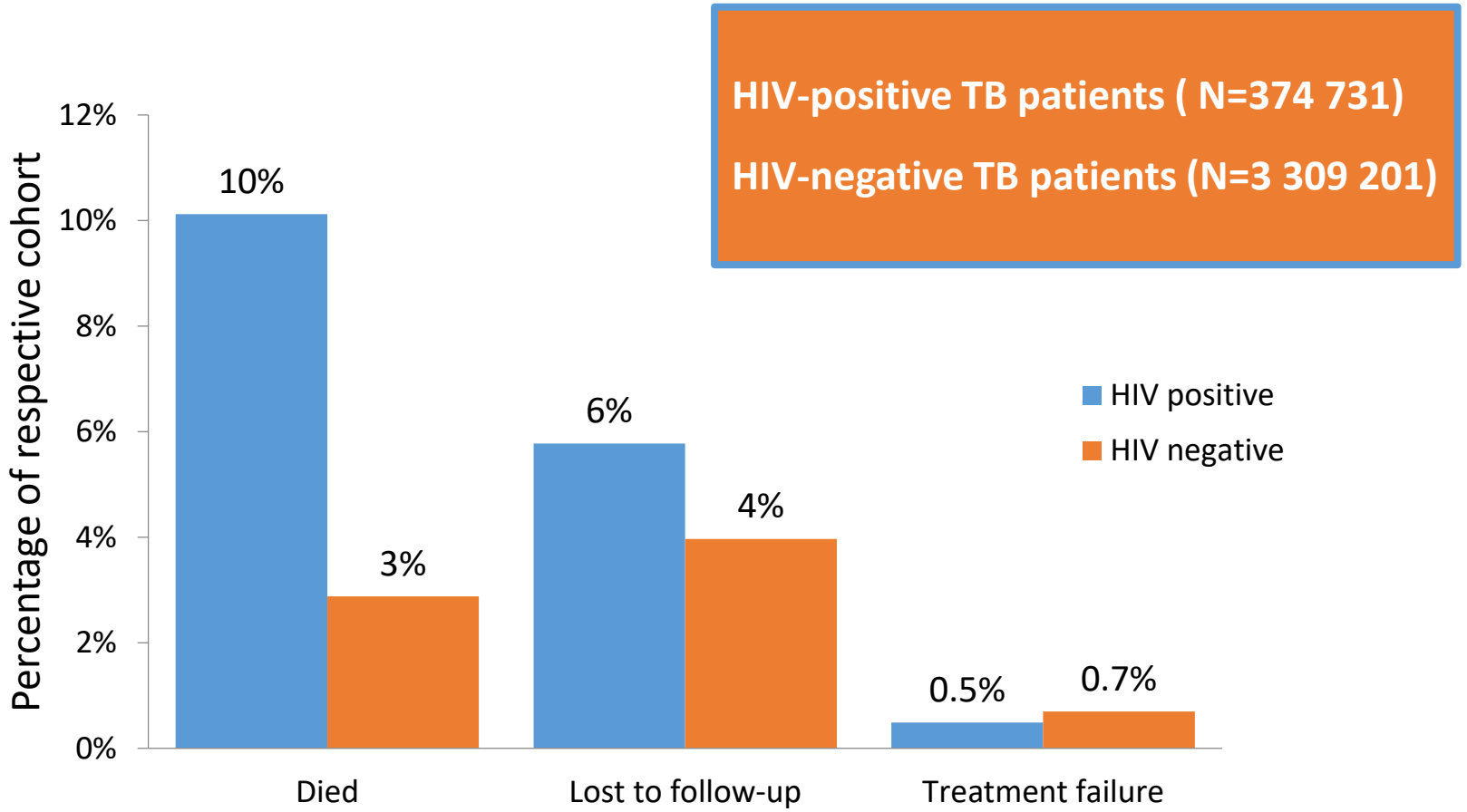
Source: Tuberculosis surveillance and monitoring in Europe 2017. European Centre for Disease Prevention and Control / WHO Regional Office for Europe.

World Health Organization Europe | Organisation mondiale de la Santé Europe | Weltgesundheitsorganisation Europa | Всемирная организация здравоохранения Европейское

TB treatment outcomes by HIV status, globally, 2013



TB Treatment Outcomes by HIV status in 14 reporting Countries*, 2014 Cohort



*TB treatment outcomes by HIV status not reported: Angola, DR Congo, Ethiopia, Mozambique, Malawi, Zambia

PLHIV 3 times more likely to die during TB treatment

Bad outcomes: How to improve it?

- Early ART ✓
- Empirical antiTB ?
- ART + IPT ?

The NEW ENGLAND JOURNAL of MEDICINE

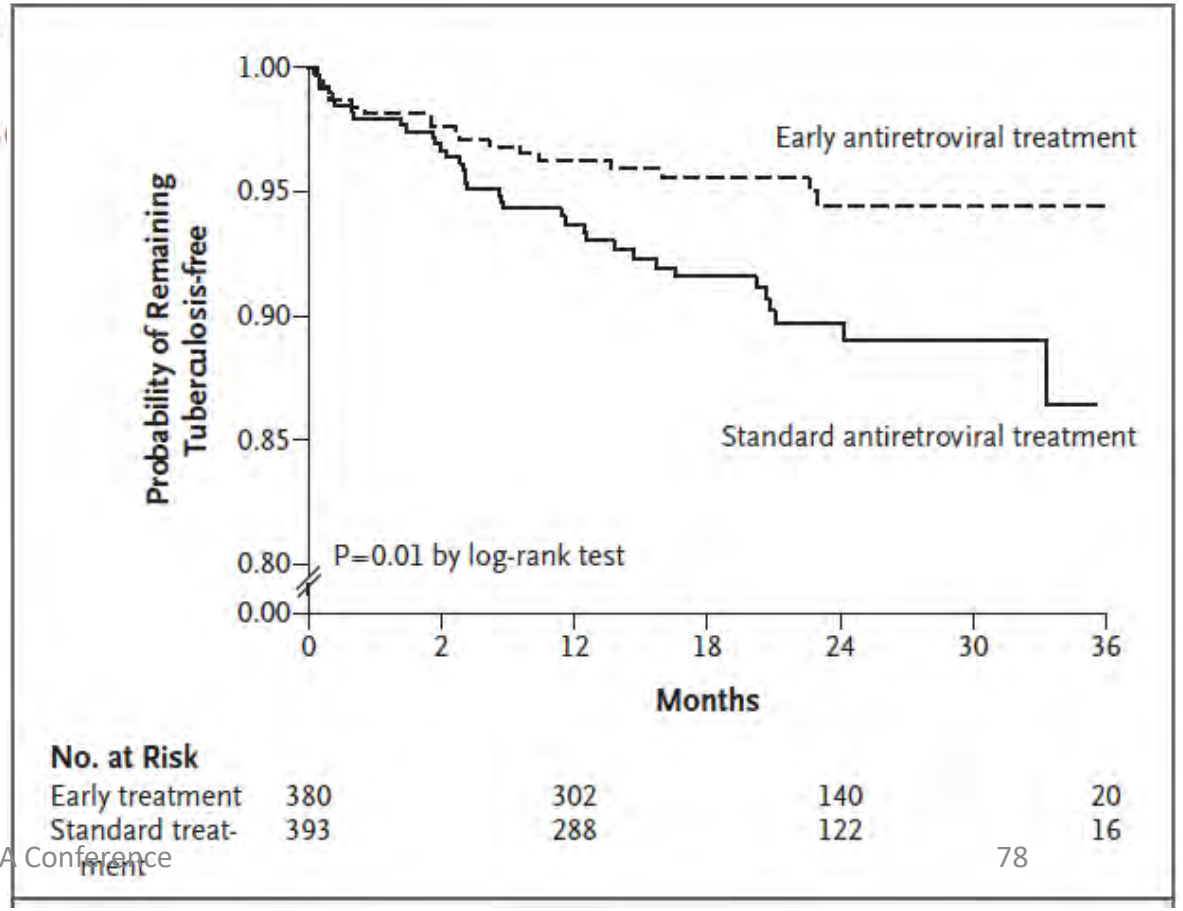
ORIGINAL ARTICLE

Early versus Standard Antiretroviral Therapy for HIV-Infected Adults in Haiti

Patrice Severe, M.D., Marc Antoine Jean Juste, M.D., Alex Ambrois

Early: ART started CD4 200 -350
Standard: ART started when CD4<200
About 400 pts in each group
Mean CD4 about 280 in each group

There were 36 incident cases of tuberculosis in the standard-treatment group, as compared with 18 in the early-treatment group (HR 2)



START: Results – does early ART protect against TB?

Endpoint	Immediate ART (n = 2326)		Deferred ART (n = 2359)		HR (95% CI)	*P* Value
	N	Rate/100 PY	N	Rate/100 PY		
Serious AIDS-related event	14	0.20	50	0.72	0.28 (0.15-0.50)	< .001
Serious non-AIDS–related event	29	0.42	47	0.67	0.61 (0.38-0.97)	.04
All-cause death	12	0.17	21	0.30	0.58 (0.28-1.17)	.13
Tuberculosis	6	0.09	20	0.28	0.29 (0.12-0.73)	.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01-0.71)	.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08-1.10)	.07
Non-AIDS–defining cancer	9	0.13	18	0.26	0.50 (0.22-1.11)	.09
CVD	12	0.17	14	0.20	0.84 (0.39-1.81)	.65

New Engl J Med 2015;373:795

REMEMBER: Key Results

- **Empiric TB treatment had no differential impact on risk of death or unknown status at 24 wks of follow-up vs IPT**

Primary Endpoint, n (%)	ART + Empiric TB Treatment (n = 424)	ART + IPT (n = 426)
Death	20 (4.8)	22 (5.2)
Unknown status	2 (< 0.5)	0 (0)
All primary endpoints	22 (5.3)	22 (5.2)

Absolute risk difference: -0.06% (95% CI: -3.05% to 2.94%; *P* = .97)

- Time to death or unknown status did not differ by treatment strategy
- IPT treatment was associated with reduced time to confirmed or probable TB (*P* = .01) vs empiric TB treatment
- Verified TB cases more frequent in empiric TB treatment arm vs IPT arm (33/424 vs 19/426, respectively)

Hosseinipour M, et al. IAS 2015. Abstract MOAB0205LB.

INT J TUBERC LUNG DIS 18(11):1340–1346

http://dx.doi.org/10.5588/ijtld.14.0153

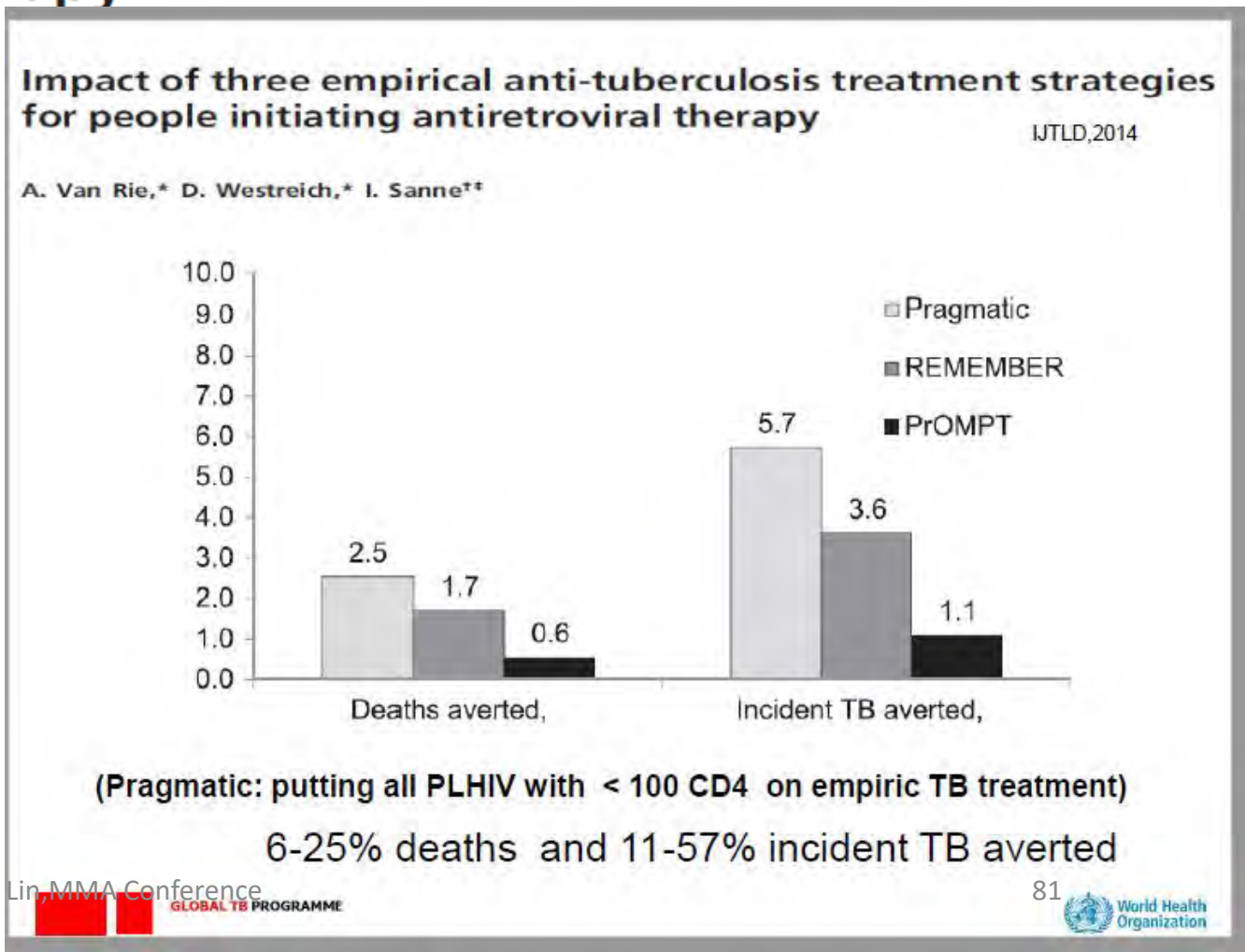
Impact of three empirical anti-tuberculosis treatment strategies for people initiating antiretroviral therapy

A. Van Rie,* D. Westreich,* I. Sanne†‡

NNT to avert one death
Pragmatic =21
REMEMBER=19
PROMT=13

Empiric TB therapy did not reduce mortality at 24 weeks compared to INH

- -Mortality low in both arms
- -No differences across arms by stratification factors



Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial

Molebogeng X Rangaka, Robert J Wilkinson, Andrew Boulle, Judith R Glynn, Katherine Fielding, Gilles van Cutsem, Katalin A Wilkinson, Rene Goliath, Shaheed Mathee, Eric Goemaere, Gary Maartens

***Lancet* 2014; 384: 682–90**

2008 -2011, IPT or placebo 12 months

37% reduction in incident TB
The effect of isoniazid preventive therapy was NOT restricted to patients who were positive on TST or IGRA

	IPT	Placeb	HR
No of pts	662	667	
CD4	218	214	
ART coverage (%(	70	74	
Incident TB	37	58	0.63
SE	19	10	1.9

IPT Effectiveness Related to ART

TB Incidence in 11,026 HIV-infected patients in Brazil

	No INH	**Yes INH**
No ART	4.01/100 person years	1.27/100 person years
Yes ART	1.90/100 person years	0.80/100 person years

Source: Golub JE, et al., Johns Hopkins University 2007.

76% reduction with both INH and ART when adjusted for age, previous TB diagnosis and CD4 count at baseline

15 July 2004, 15th IAS Conference Bangkok

Mandela urges action to fight TB

By Chris Hogg
BBC, Bangkok

Nelson Mandela has made an appeal at the international Aids conference for a greater effort to fight tuberculosis.

Mandela said fighting TB should be a top priority

> **"We can't fight Aids unless we do much more to fight TB as well"**
>
> Nelson Mandela

Any Questions
OR
Comments?