HIV AND TUBERCULOSIS

Sanjay Pujari, MD

Institute of Infectious Diseases, Pune India

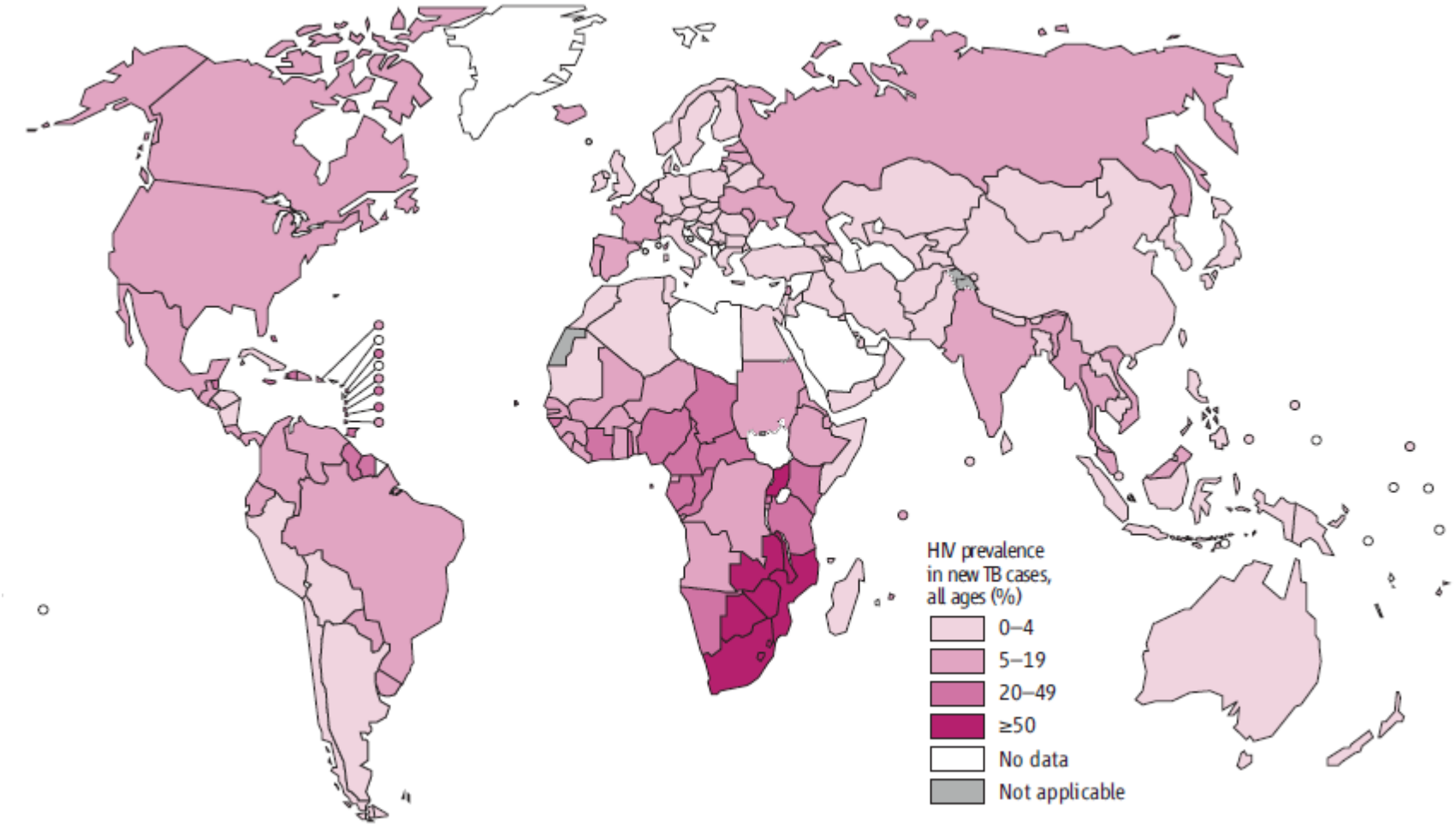
Outline

- The problem
- Pathogenesis and clinical manifestations
- Diagnosis
- HIV/TB treatment
- Drug-Resistant TB
- Prevention, control and future

TB in HIV

- Most common OI globally
- Leading cause of HIV/AIDS related mortality *(curr opin HIV AIDS 2009;4:325)*
- RR of TB in PLHIV in the absence of ART *(lancet 2014 Jul epub)*
  - 8.7%(95% CI 5.9-11.7)
  - 15.7% (10.6-21.1) for CD4<200
  - 10.8% (7.3-14.5) for CD4 200-350
  - 3.2% (2.2-4.3) for CD4>350
- RR of TB in PLHIV on ART
  - 1.7% (1.2-2.3)

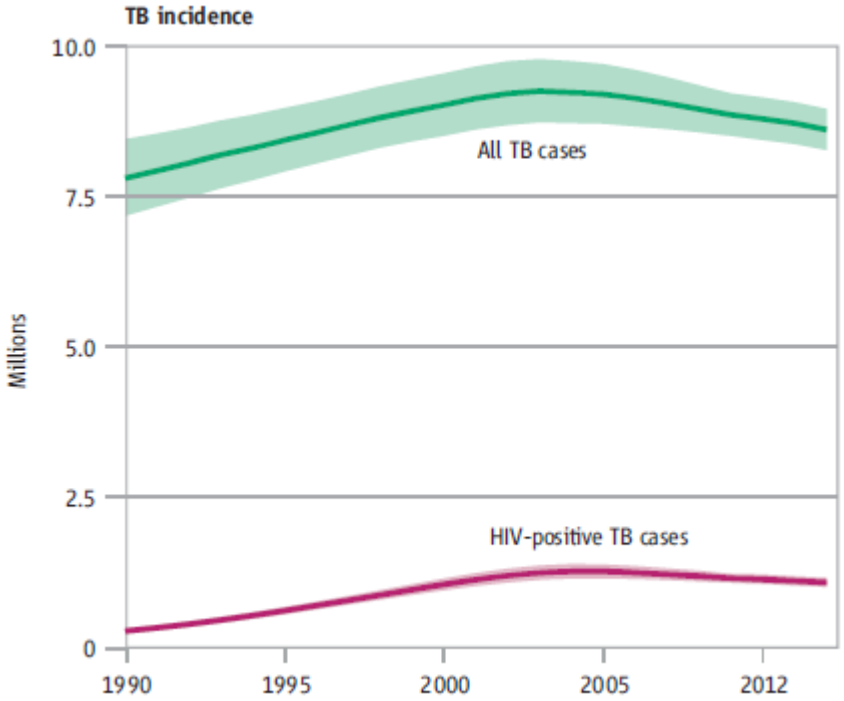
HIV prevalence amongst TB

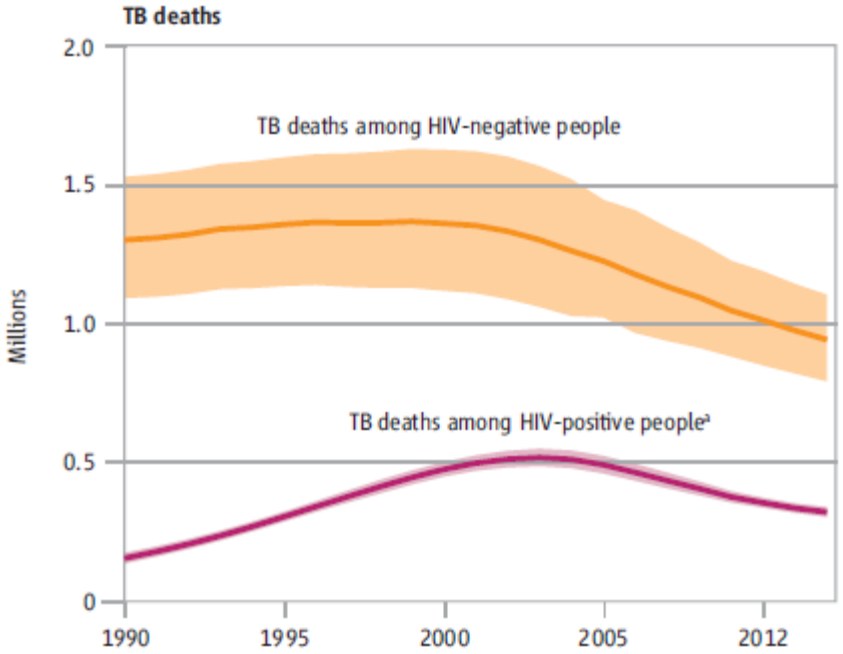


WHO Global TB Report 2013

IID INSTITUTE OF INFECTIOUS DISEASES

HIV associated TB





WHO Global TB Report 2013

IID INSTITUTE OF INFECTIOUS DISEASES

Outline

- The problem
- Pathogenesis and clinical manifestations
- Diagnosis
- HIV/TB treatment
- Drug-Resistant TB
- Prevention, control and future

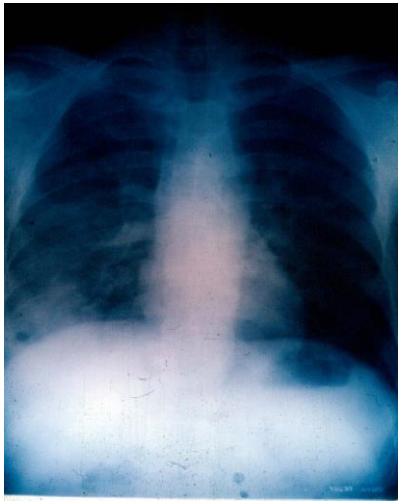
Pathogenesis

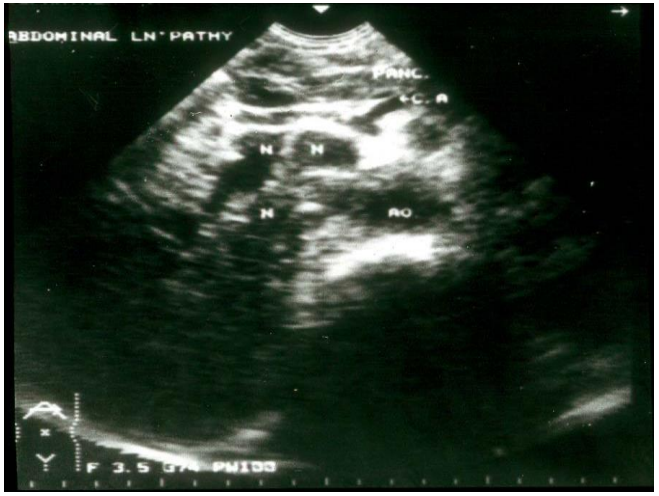
- Life time risk in HIV-ve: 10%
- HIV+ incidence: 5-16/100 person-years *(AIDS 2000, 14)*
- Increased risk of
  - Higher susceptibility for infection
  - Rapid progression after infection
  - Reactivation disease
  - ART associated TB including IRIS

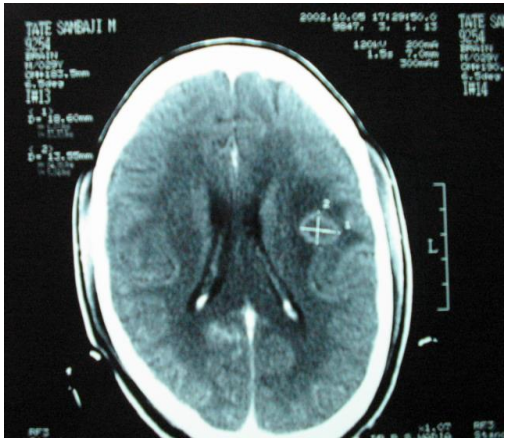
Pathogenesis to clinical presentation

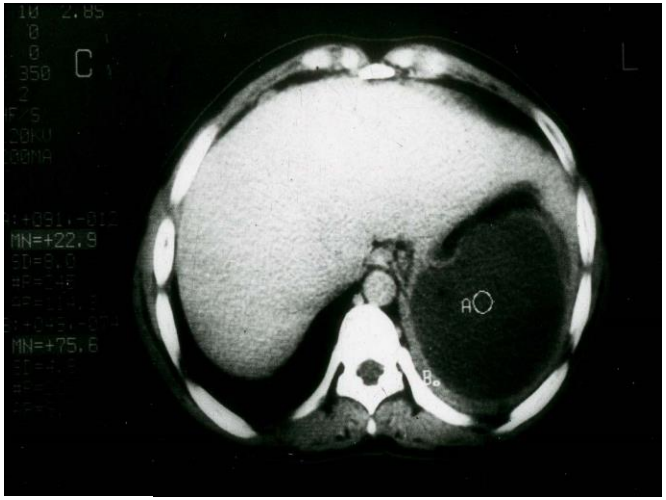
- HIV mediated immune suppression
  - Impaired granuloma formation
    - Ineffective containment of MTB
    - Diminished formation of cavities

- Clinically
  - Frequent EPTB *(Lunng 2012;Nov 23 epub ahead of print)*
  - Greater involvement of LL
  - Atypical chest radiographic findings, incl WNL *(Int J Tuberc Lung Dis 2008;12:397)*
  - More frequent smear –ve disease *(Int J Tuberc Lung Dis 1999;3:330)*



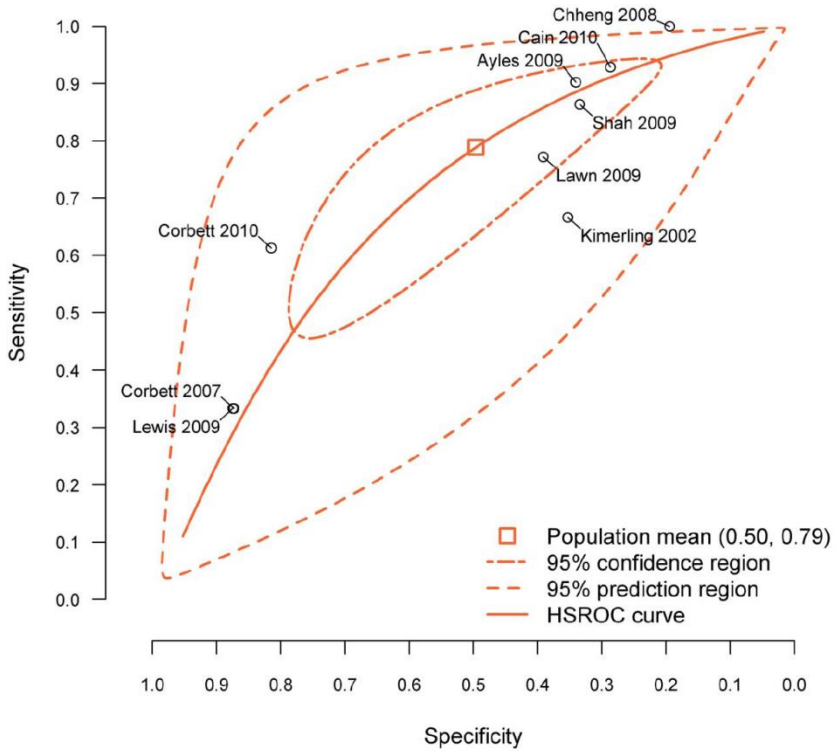

ABDOMINAL LN*PATHY
PANC.
+C.A
AO


TATE SAMBAJI M


MN=+22.9
MN=+75.6
AO

Screening rule for TB

HSROC curve for CFSW



Conclusions

- CFSW rule
  - Overall
    - Sens: 78.9%, Spec:49.6%
  - Clinical settings
    - Sens: 90.1%
  - Not previously screened for TB
    - Sens: 88.0%
  - NPV
    - 97.7% (5% TB prevalence)
    - 90.0% (20% TB prevalence)
  - CXR
    - Increases Sens by 11.7%
    - Decreased Spec by 10.7%
  - Performs poorly in pts on ART *(AIDS 2014; 28:1463)*

PLoSOne 2011;e1000391

Outline

- The problem
- Pathogenesis and clinical manifestations
- Diagnosis
- HIV/TB treatment
- Drug-Resistant TB
- Prevention, control and future

Diagnosis

- Diagnosing LTBI: CMI response
  - Tuberculin test
  - IGRA assays: QuantiFERON-TB Gold, T Spot-TB
    - Perform similarly to TST *(J Acquir Immune Defic Syndr 2011;56:230)*
    - Sub-optimal accuracy for confirming/ruling out active TB *(PLOS One 2012;7:e32482)*

- Radiology
  - CxR: atypical, can be normal
  - USG/CT: HPE/micro

- Serology (TB ELISA): No role

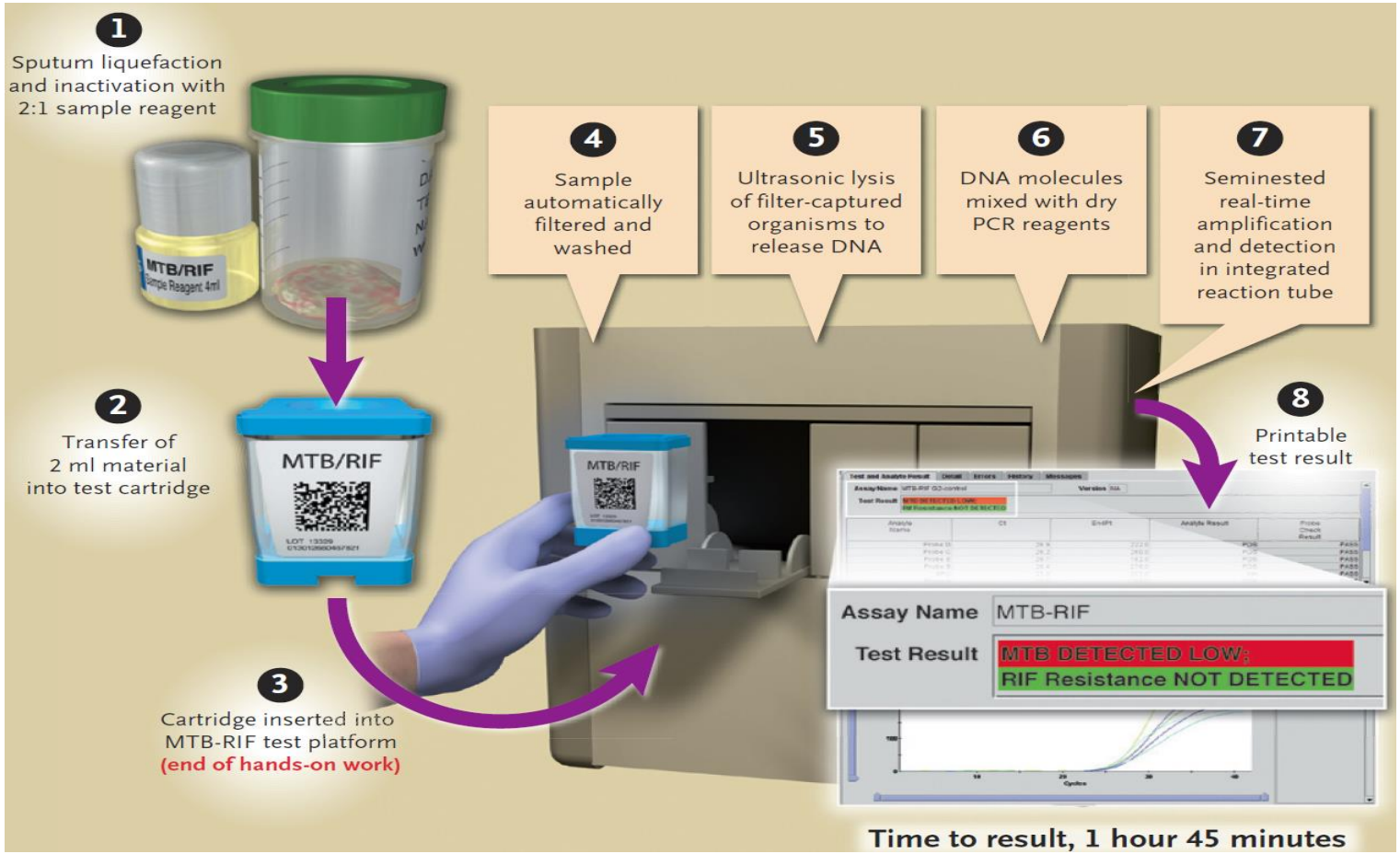
Diagnosis

- Sputum AFB:
  - lower yield as HIV –ve sens: 35% *(Lancet Infect Dis 2003;3:288)*
  - BAL/TBLB better yield *(lung India 2010;27:122)*

- NAAT:
  - Amplicor MTB PCR, Gen-Probe MTB, SDA (BD)
  - DST: Genotype MTBDR, INNO-LiPA. Rif TB, GeneExpertMTB/Rif
  - Useful in sputum smear +ve, but also EPTB e.g. TBM *(J Clin Microbiol Jul 2014 epub)*

- Culture:
  - LJ medium, BACTEC, MGIT, MODS

Diagnosis: GeneXpert MTB/Rif

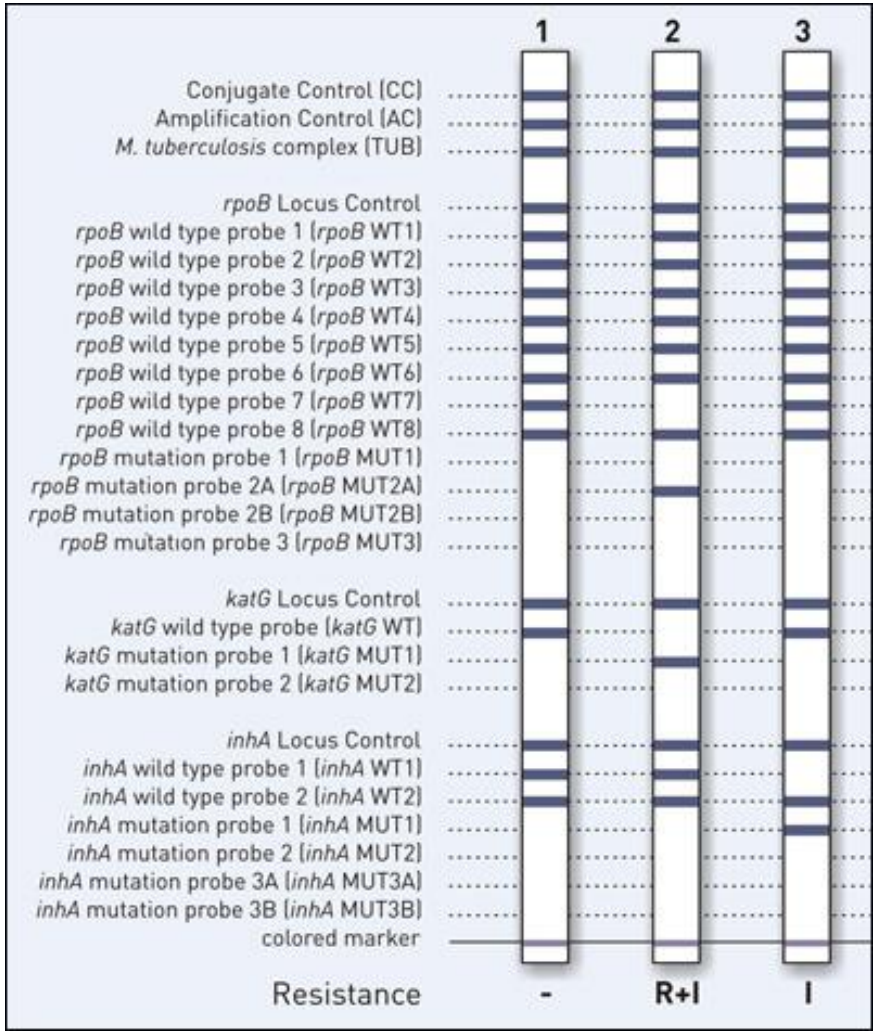


Can help in intensive case finding prior to initiation of ART *(PLOS One 2014;9:e85478)*

GeneXpertMTB/Rif

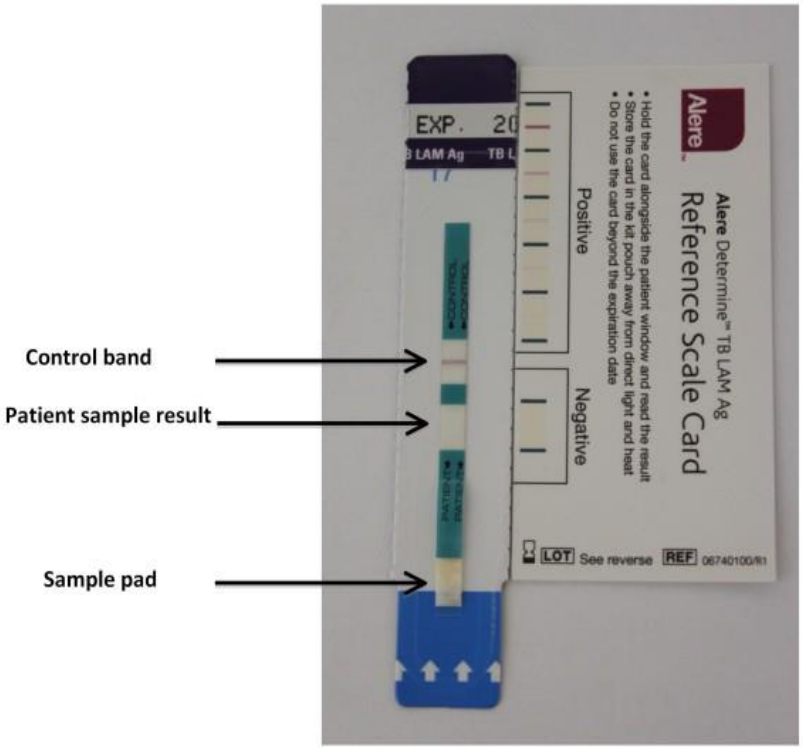
- More Sensitive/ specific for PTB regardless of HIV status than smear microscopy *(Cochrane Database Syst Rev 2014;C000593)*
  - Replaced smear microscopy as initial test for TB diagnosis in South Africa
- Higher sensitivity in smear +ve
- Initial Rif resistance: MDR regimen until culture/DST
- Can be used for wide variety of EPTB specimens *(Lancet Infect Dis 2013;13:349)*

Line Probe Assay



Diagnosis: Urinary LAM

- Urinary LAM
  - Lipo-arabinomanan: cell wall antigen
  - Detected in urine in TB
  - >95% specificity
  - Sensitivity inversely correlates with CD4 counts
    - HIV + with CD4< 200 *(JAIDS 2014 Mar epub)*
  - Quantification may have prognostic value *(PLOSOne 2014;9:e103285)*
  - Urinary LAM+Xpert have higher sensitivity than each alone *(AIDS 2014;28:1307)*



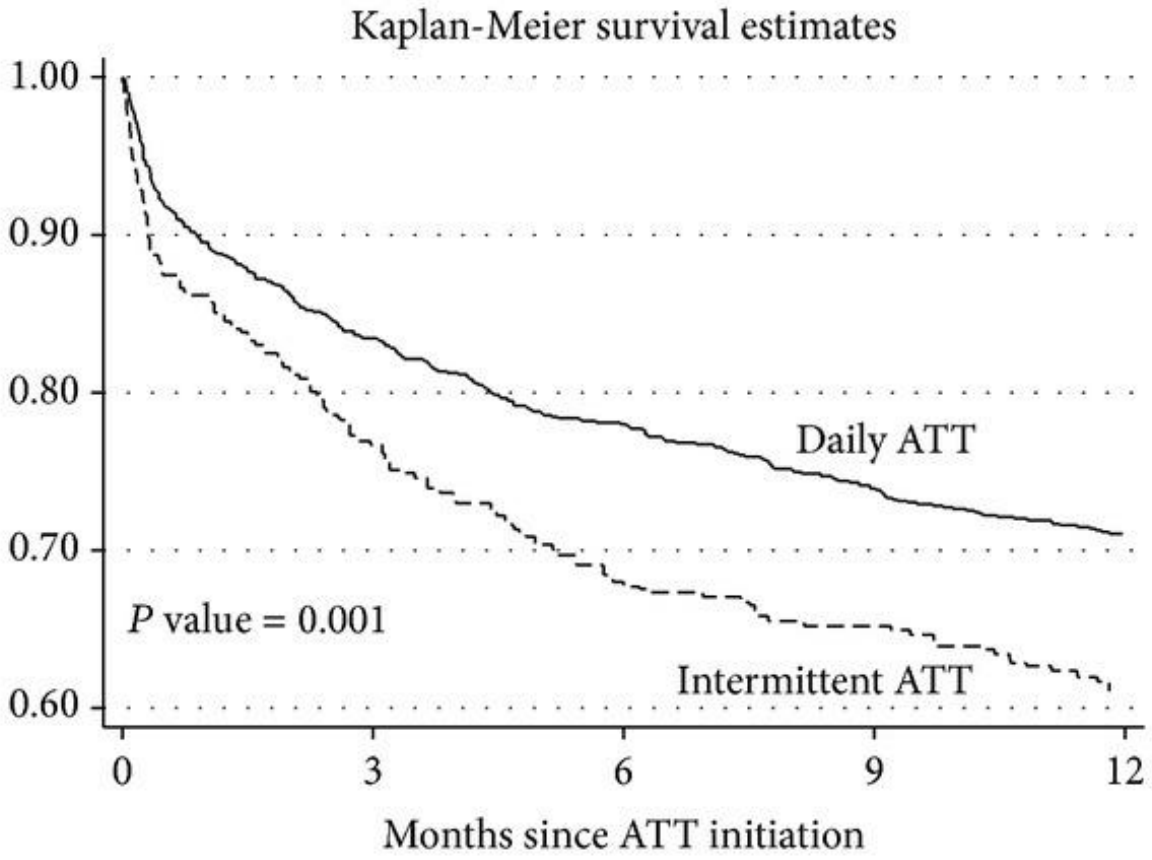
Outline

- The problem
- Pathogenesis and clinical manifestations
- Diagnosis
- HIV/TB treatment
- Drug-Resistant TB
- Prevention, control and future

HIV-TB treatment (1)

- What ATT regimen should be used?
  - Rifampicin based *(WHO TB treatment guidelines)*
- Should we continue EMB in maintenance phase?
  - Yes, incidence of primary INH resistance is high
- What is the duration of ATT?
  - 6 (? ≥8 mo's) months except for CNS TB, non use of RMP/PZA
- Is intermittent treatment ok?
  - No, daily treatment throughout the course *(PLOSMed 2009;6:e1000146)*

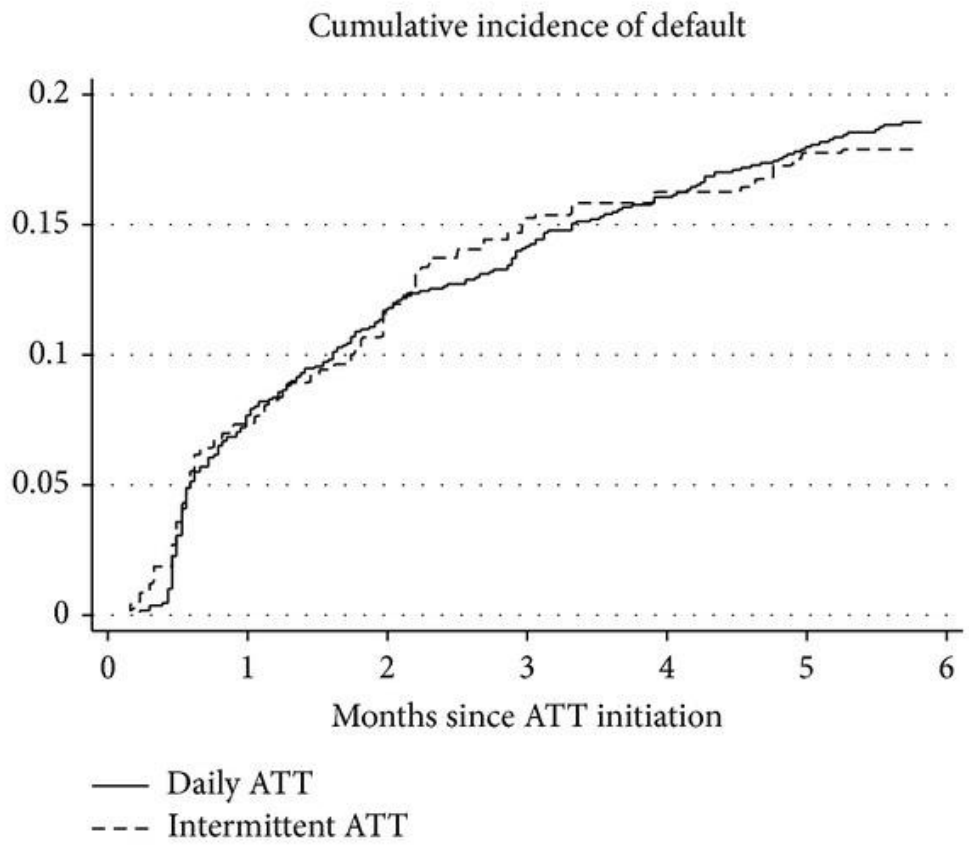
Intermittent vs Daily ATT in intensive phase



Biomed Res Int 2014;Epub 2014 Jun

IID INSTITUTE OF INFECTIOUS DISEASES

Intermittent vs Daily ATT in intensive phase



Biomed Res Int 2014;Epub 2014 Jun

IID INSTITUTE OF INFECTIOUS DISEASES

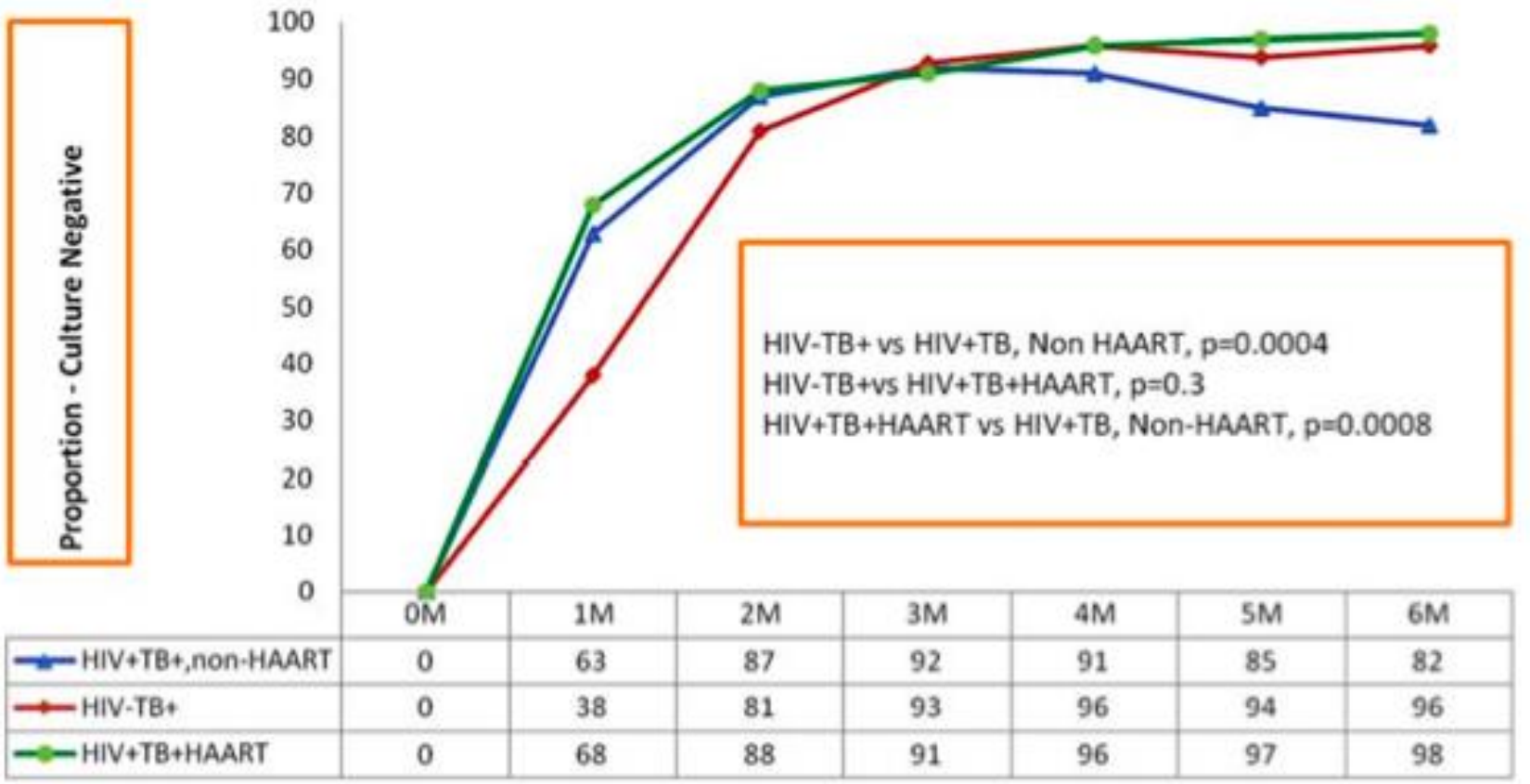
HIV-TB treatment (2)

- Is the incidence of ATT toxicity high?
  - Mixed evidence, but no change in practice *(PLOSOne 2011;6:e19566, Thorax 2006;61:791)*
- Can steroids be safely used?
  - Yes in TBM, pericardial, adrenal and paradoxical IRIS *(Indian J Chest Dis Allied Sci 2010;52:153)*
- Which concomitant treatment is recommended?
  - TMP-SMX *(WHO Consolidated ARV guidelines 2013*, *(Int J Tub Lung Dis 2009;13;6-16)*
- Is DST essential prior to initiating ATT?
  - Yes , incidence of DR-TB high in HIV + *(WHO TB Guidelines 2010)*

HIV-TB treatment (3)

- When is ART indicated in HIV-TB?
  - All patients irrespective of CD4 counts *(WHO TB/ART guidelines 2010)*
    - Improves morbidity and mortality *(Clin Chest Med 2009;30:685)*
    - Rapid smear and culture conversion *(Am J Respir Crit Care Med 2007;175:1199)*
    - Reduces recurrences of TB *(Clin Infect Dsis2012; AIDS 2009;4:325-333)*

Impact of ART on TB culture conversion



	0M	1M	2M	3M	4M	5M	6M
HIV+TB+,non-HAART	0	63	87	92	91	85	82
HIV-TB+	0	38	81	93	96	94	96
HIV+TB+HAART	0	68	88	91	96	97	98

Time (months)

Clin Infect Dis 2014;Aug advance access

Initiating ATT and ART

Early ART

Deferred ART

- Drug-Drug interactions
- Additive and overlapping toxicities
- Paradoxical IRIS
- High pill burden
- Ongoing clinical progression of HIV infection

When to initiate ART in HIV-TB?

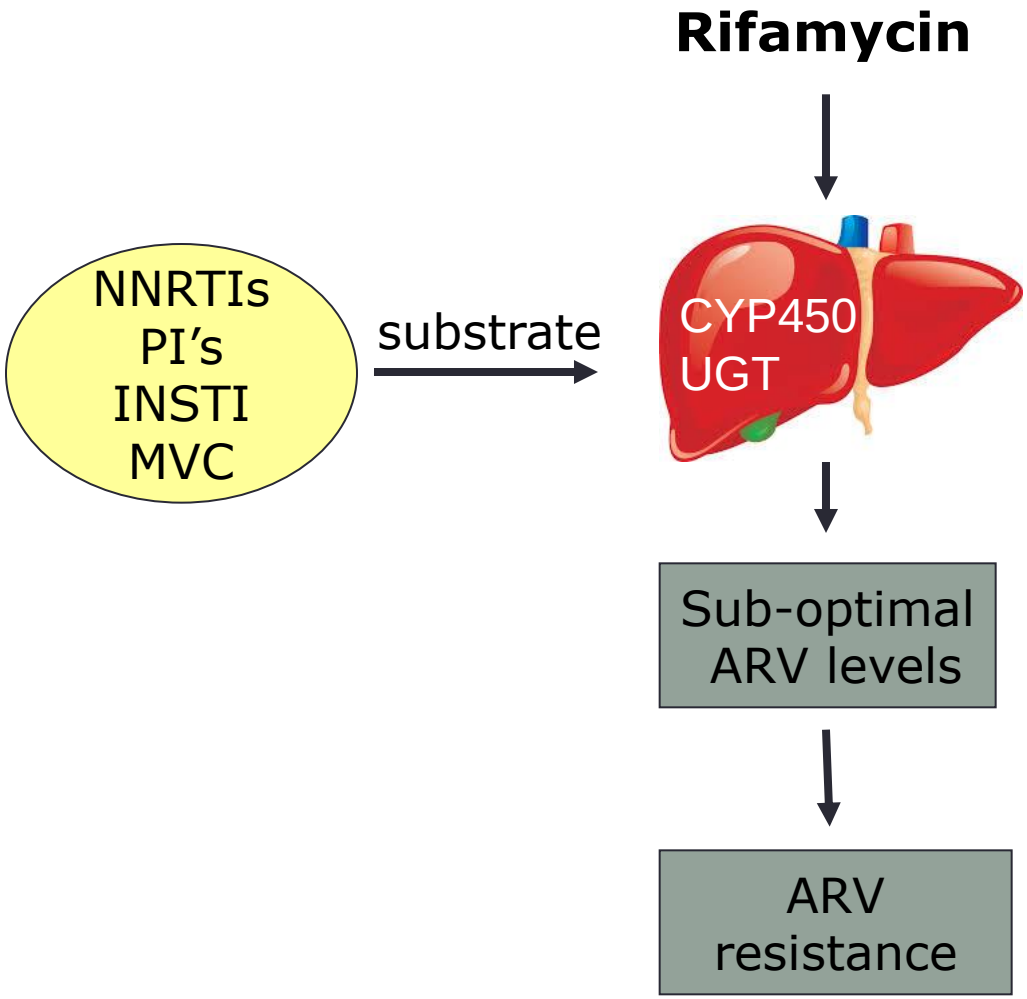
CD4 count	Timing within ATT initiation
<50/mm^3	<2 wks
>50/mm^3 Without severe disease With severe disease	 > 2-4 wks, but < 8-12 wks Within 2-4 wks

- TBM: higher incidence of AE if ART initiated within 8 weeks *(Clin Infect Dis 2011;52:1374)*
- severity of CNS IRIS *(Clin Infect Dis 2013;56:450)*

New Engl J Med 2011;365:1471,1482,1492

IID INSTITUTE OF INFECTIOUS DISEASES

Drug-Drug interactions



First line ART regimen with TB

- Preferred
  - 2 NRTI + EFV *(Lancet Infect Dis 2013;13:303)*
    - Standard EFV dose 600 mg hs *(PLOSOne 2014;9:e90350, Clin Infect Dis 2013;57:586)*

- Alternative
  - 2 NRTI + NVP *(Int J Infect Dis 2014;130, ;Lancet Infect Dis 2013;13:303)*
    - NVP (full dose) if already on ATT > 7 days *(BMC Infect Dis 2013;11:253)*
    - More DILI *(Lancet Infect Dis 2013;13:303)*
  - 2 NRTI + RAL (800 mg bid, 400 mg bid) *(Lancet Infect Dis 2014;14:459)*
  - 2NRTI + DTG (50 mg bid)?

ART and TB regimens for ARV experienced

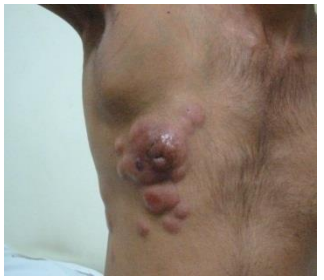
- 2n(t)RTI + PI/r
  - Rifabutin 150 mg od *(Clin Infect Dis 2009;49:1305, Clin Infect Dis 2009;48:1471)*
- RAL/MVC+PI/r
  - Rifabutin 150 mg od
- With RMP
  - DTG (50 mg bid and without INSTI resistance)
  - Double dose LPV/r *(Int J Tuber Lung Dis 2014;18:689)*
    - Hepatic Safety
- Rifapentine should not be used

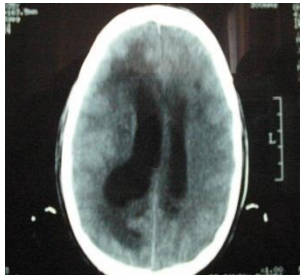
Shared toxicities of ARVs and ATT

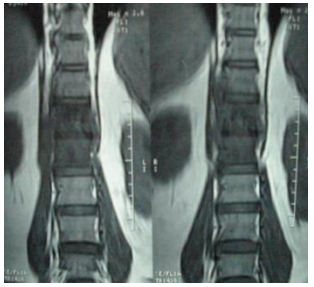
Toxicity	ARVs	ATT
GI disturbance	AZT, PIs	R,H, Z,Eto,PAS,Cfz,Lzd
Liver injury	NVP, EFV, PIs	R,H,Z, Eto,FQs,PAS
Peripheral neuropathy	d4T,ddI	H,Eto, Cs, Lzd
Neuropsychiatric	EFV	Cs,Eto,FQs, H
Renal impairment	TDF	AGs, Cm
Rash	NVP, EFV, ABC	R,H,Z,E,Sm,FQs,PAS,Cfz
Blood dyscrasia	AZT, 3TC	Lzd, Rbt, H,R
Cardiac conduction abnormalities	PIs	Bedaquiline, FQs, Cfz
Pancreatitis	d4T, ddI	Lzd
Lactic acidosis	d4T, ddI	Lzd

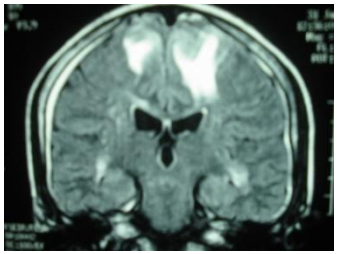
Immune Reconstitution Inflammatory Syndrome

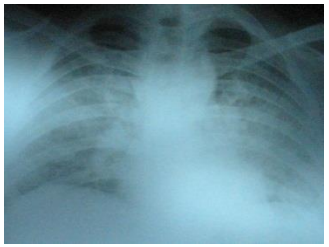
- Inflammatory response
- Usually within 3 mo
- Two types *(Lancet Infect Dis 2008;8:516)*
  - Unmasking
  - Paradoxical worsening
- Risk factors *(New Engl J Med 2011;365:1471, 1482)*
  - Lower CD4 count
  - Shorter time to ART initiation/antigen load *(Clin Infect Dis 2014 Aug epub)*
- Majority: Favorable outcome *(Int J Tuber Lung Dis 2012;16:1365)*
- Treatment: Steroids *(AIDS 2010;24:2381)*











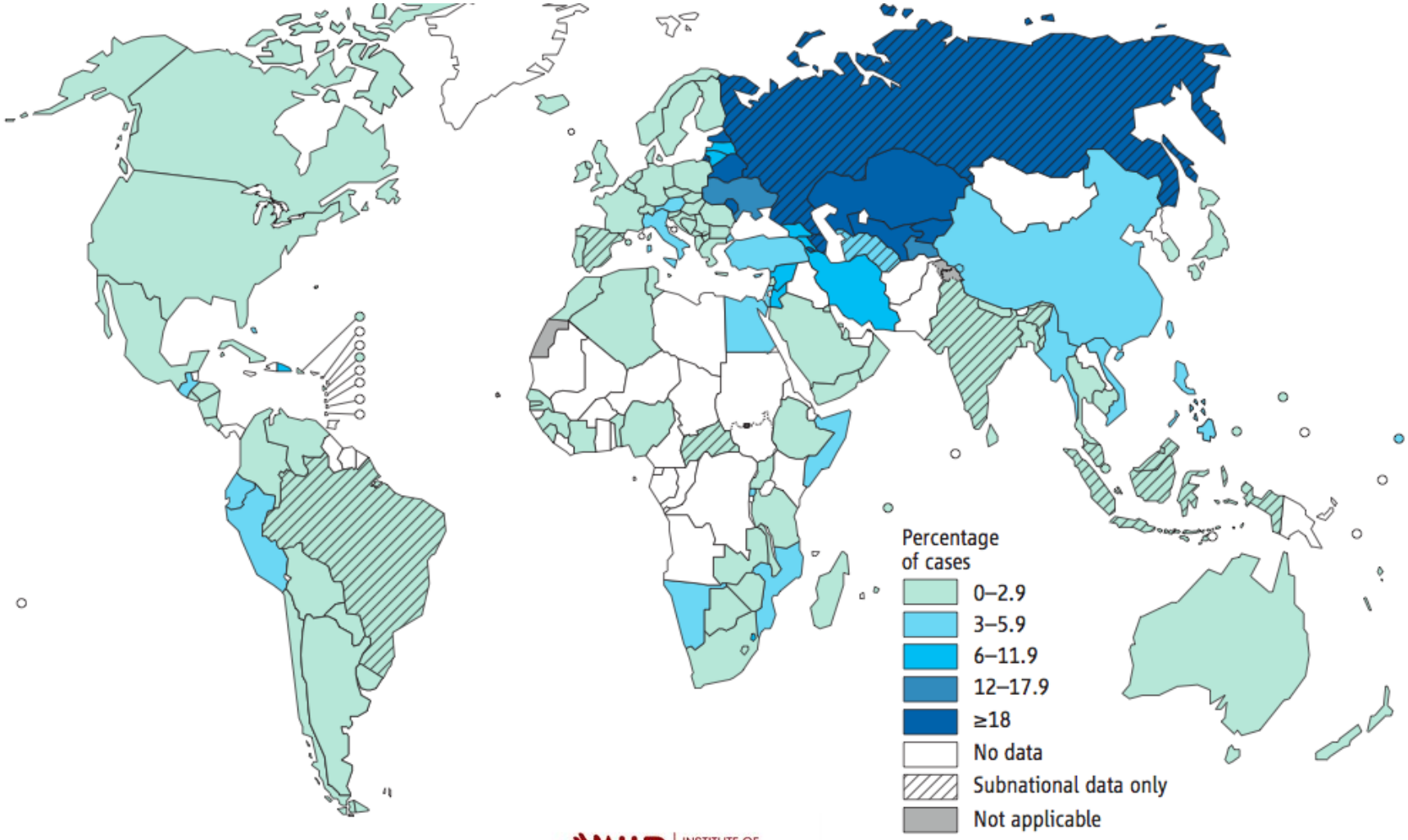
Outline

- The problem
- Pathogenesis and clinical manifestations
- Diagnosis
- HIV/TB treatment
- Drug-Resistant TB
- Prevention, control and future

What is DRTB?

- DRTB
  - MTB isolate resistant to one of H, R, Z, E
    - Mono resistant to H or R
    - Poly-resistant: other than H and R
- MDR-TB
  - MTB isolate resistant to at least H and R
- XDR-TB
  - MTB isolate that is MDR + FQ + one or more injectable *(WHO XDR-TB definition meeting 2006)*
- TDR-TB
  - MTB isolate resistant to all locally tested meds *(Chest 2009;136:420, Clin Infect Dis 2012;54:579)*

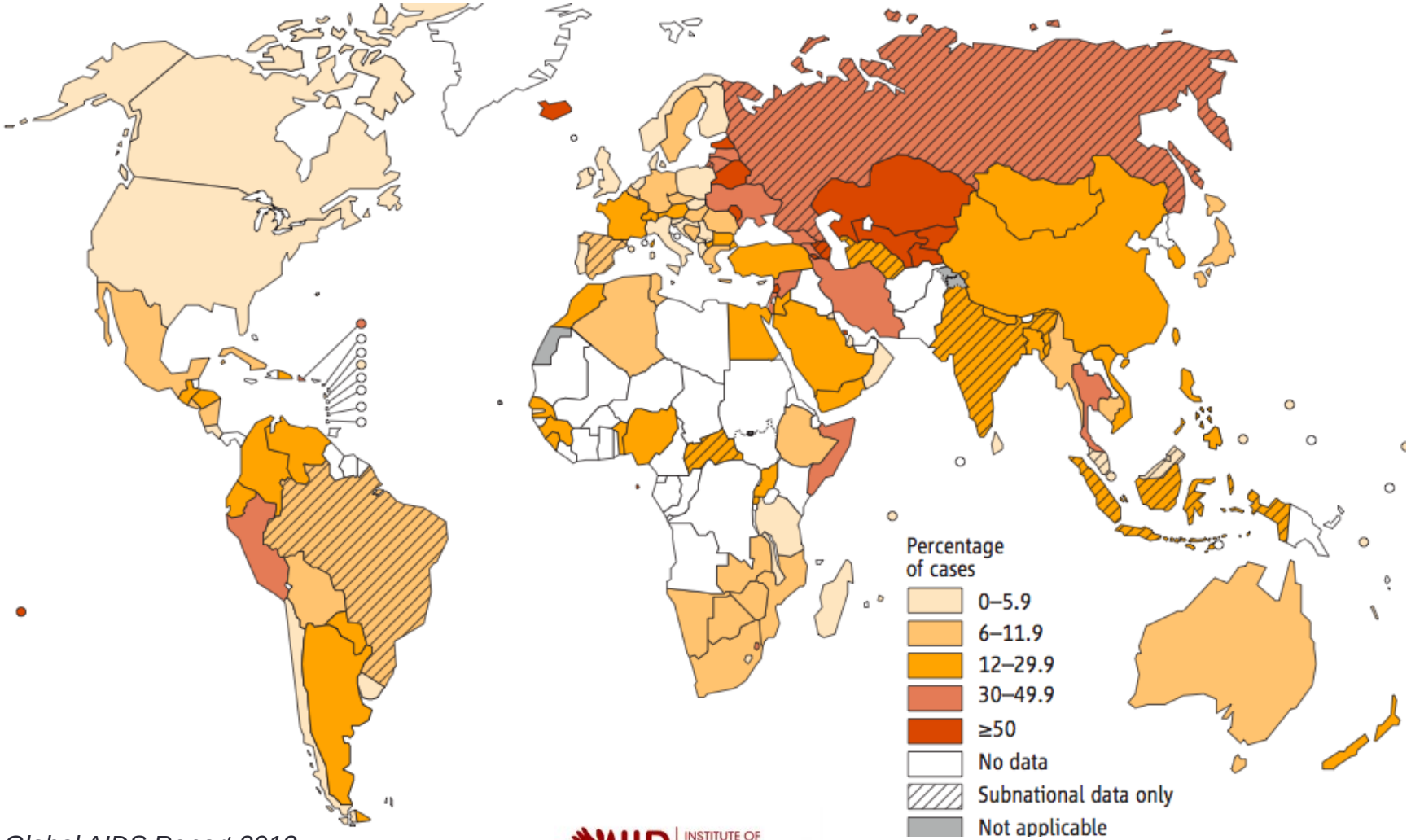
MDR-TB amongst new cases



Global AIDS Report 2013

IID INSTITUTE OF INFECTIOUS DISEASES

MDR-TB amongst retreated cases



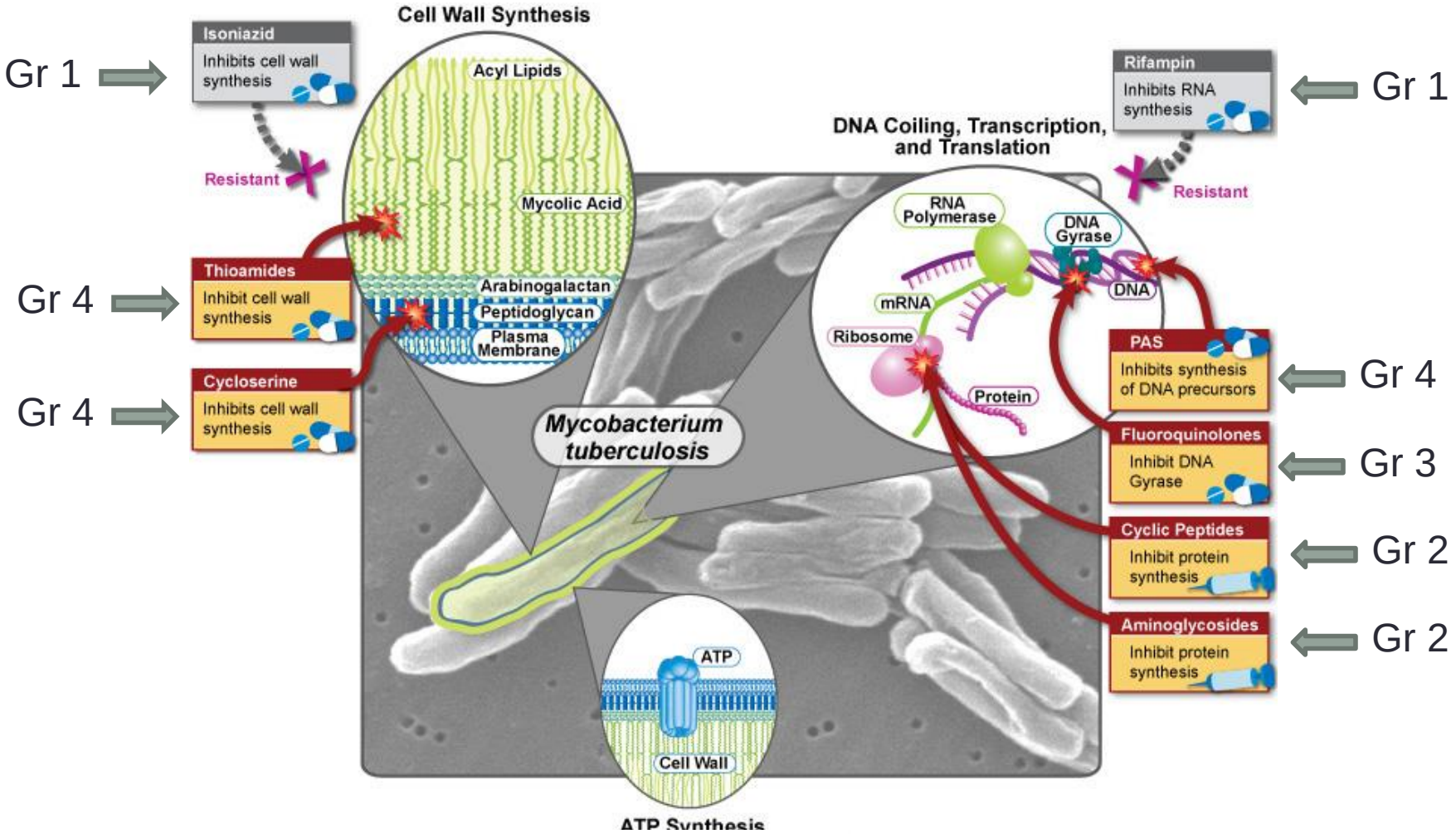
Global AIDS Report 2013

IID INSTITUTE OF INFECTIOUS DISEASES

Molecular basis for DR-TB

DRUG	MUTATIONS (in genes)
INH *(Nat Med 2006;12:1027, Science 1994;263:224)*	inhA, katG, kasA
RMP *(Lancet 1993;341:647)*	rpoB
PZA *(Nat Med 1996;2:662)*	pncA
EMB *(Tuber Lung Dis 1998;79:3)*	embB
Sm *(Antimicrob Agents Chemother 1994;38:238)*	rpSL, rrs
FQs *(J Infect Dis 1994170:479)*	gyrA, gyr
ETM *(Science 1994;263:277)*	inhA

MDR-TB options

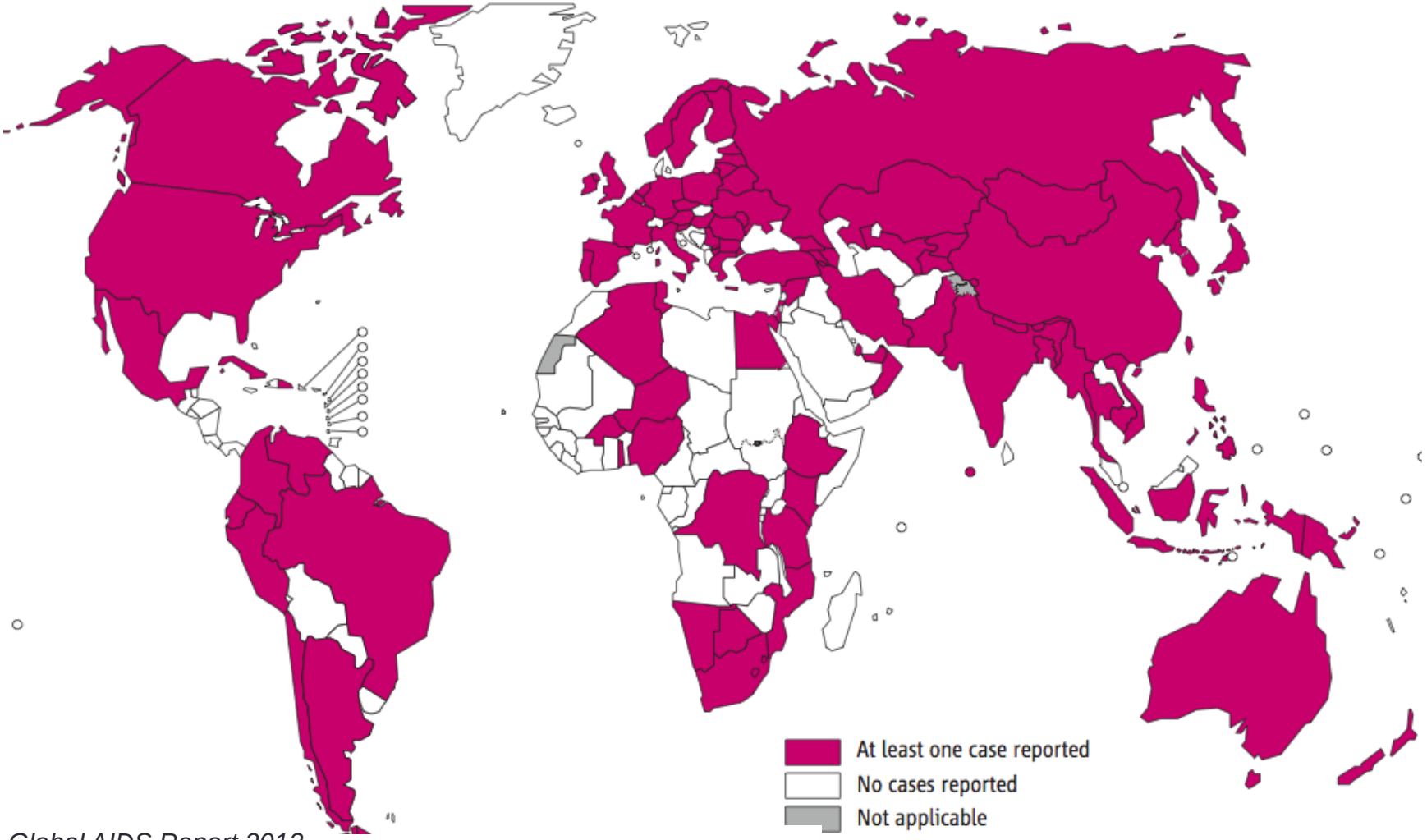


IID INSTITUTE OF INFECTIOUS DISEASES

Treating HIV+MDRTB

- Not based on good quality RCTs
- At least 4 fully active drugs should be included (DST and past h/o) *(PLOS One 2009;4:e6914, Lancet Infectious Dis 2010;910:621)*
  - Injectable: Km, Cm, Amk
  - FQ: Mfx=Gfx, Lfx, Ofx
  - Other drugs: Eto, Cs, PAS
  - Z and E may be included
  - Weight (weight band) based dosing
- Duration: 18 months after culture conversion or at least 24 months
- Initiate ART: within 2-4 weeks *(Lancet 2010;375:1798)*

XDR-TB: Countries reporting at least one case



Global AIDS Report 2013

IID INSTITUTE OF INFECTIOUS DISEASES

XDR-TB

- Definition *(WHO 2013)*
  - MDR-TB, and resistance to
  - One of the second line injectables, Am, Km, Cp
  - One of the fluroquinolones

- Risk factors
  - HIV infection
  - Incorrect TB treatment *(Lancet Infect Dis 2013;13:529)*
    - Intermittent treatment, prescription errors, poor compliance and substandard quality of drugs
  - Two or more previous courses of ATT *(PLOS One 2008;3:e2957)*
  - Bilateral/cavitary lesions in MDR-TB *(AM J Resp Crit Care Med 2010;182:426)*

XDR-TB

- Rules for constructing regimen
  - Empiric regimen (until DST available)
    - May use > 4 drugs in the intensive phase *(Clin Epidemiol 2014;6:111)*
    - Existing MDR-TB regimen+ Inj (Am) + not used Group 4 + 2 group 5 (Cfx, Amx/Clv, Lzd)
    - Cfx has better culture conversion rates *(J Antimicrob Chemother Jun 2014 epub)*
  - Individualise according to DST
  - High dose INH (if inhA resistance) *(Int J Tuberc Lung Dis 2008;12:129)*
  - Duration: 18 mo's post culture conversion

TDR-TB

- Few reports of MTB resistant to 1st/2nd line *(Chest 2009;136:420, Clin Infect Dis 2012;54:579)*

- Problematic terminology *(WHO TDR definition report 2012)*
  - DST for many drugs not standardized
  - Capacities of sites for testing and drug availability varies
  - Newer drugs may still be effective

- Practically incurable

Outline

- The problem
- Pathogenesis and clinical manifestations
- Diagnosis
- HIV/TB treatment
- Drug-Resistant TB
- Prevention, control and future

Prevention and control of TB in HIV

- 3 Is
  - Intensive case finding and treatment
  - Isoniazid preventive therapy
  - Infection control
    - Workplace/administrative, environmental, respiratory protection
- ART *(PLOSMed 2012;9:e1001270)*
  - Reduction in incidence across oll CD4 strata

IPT

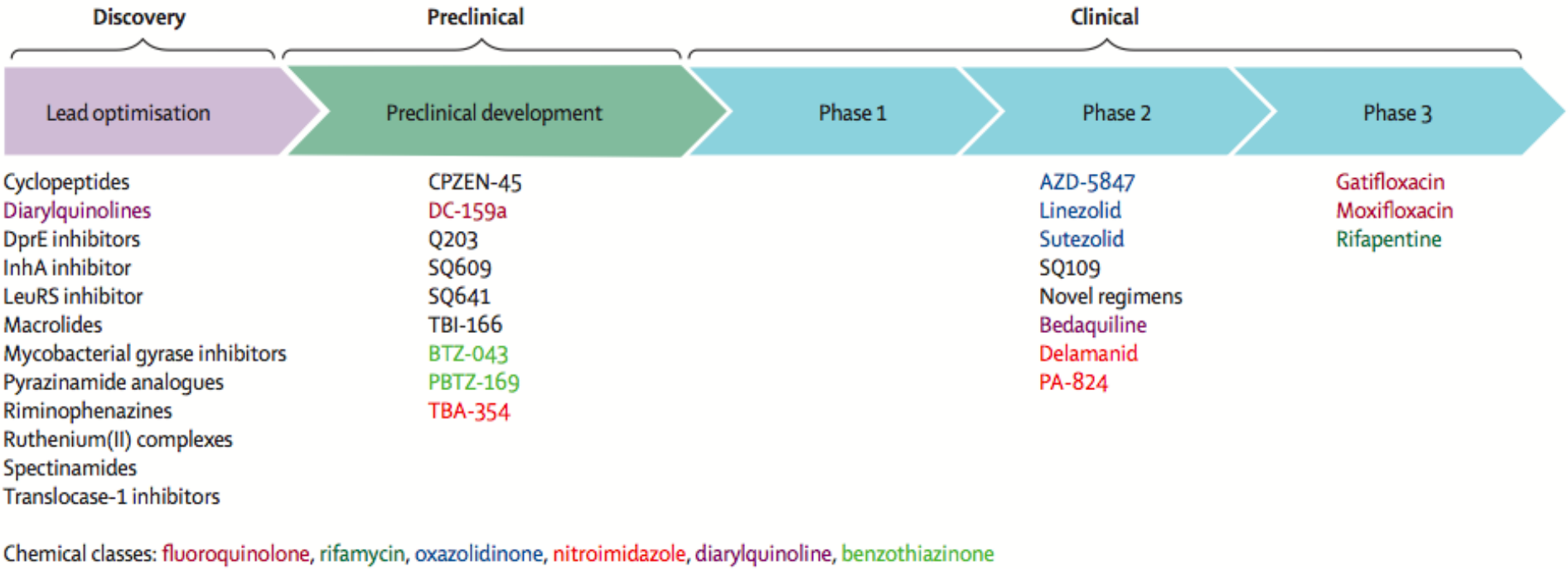
- ART + INH (12 mo)
  - 37% decrease in incident TB *(Lancet May 2014, online)*
  - Irrespective of tuberculin/IGRA status
  - Greatest benefit in the first year
  - Non significant increase in ALT
  - Did not increase risk of DR-TB
  - Significant effect on TB incidence under programmatic conditions *(PLOS One 2014;e104557)*

- Alternative *(BHIVA HIV/TB guidelines 2011)*
  - INH/RFP q1wkly for 3 months (without ART)
  - INH+RMP for 3 mo

Prevention

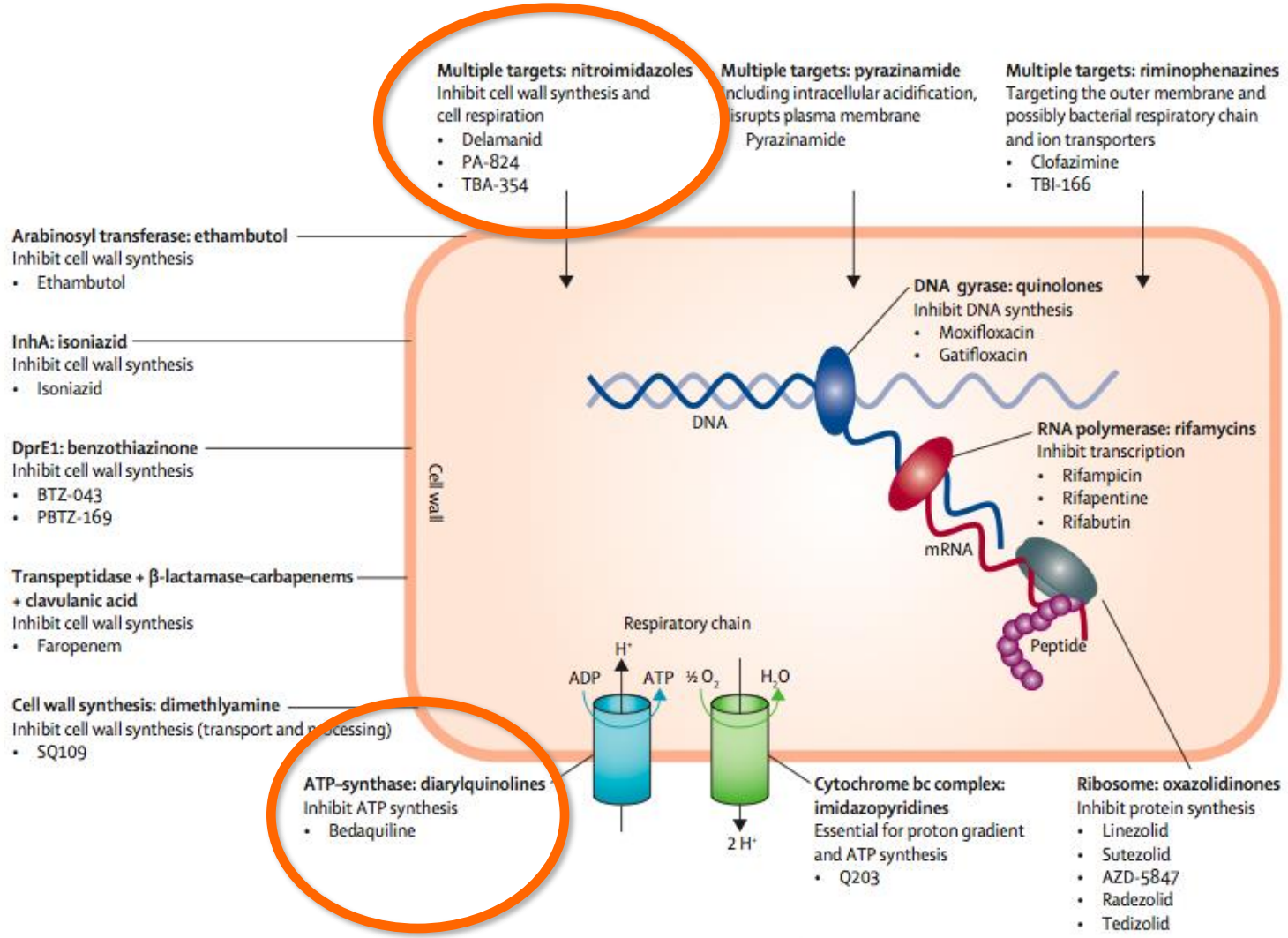
- Vaccines
  - BCG
    - Recommended at birth for HIV exposed infants in LMIC
    - Delaying by 8 weeks (until HIV status resolved): immunogenic *(J Infect Dis 2014 Aug epub)*
  - M72/AS01
    - Safe and immunogenic in PLHIV on cART *(AIDS 2014;28:1769)*
  - RUTI *(PLOS One 2014;9:e89612)*

Anti-TB drugs: the pipeline



Lancet Infect Dis 2014;14:327

Anti-TB drugs: Mechanism of action



Lancet Infect Dis 2014;14:327

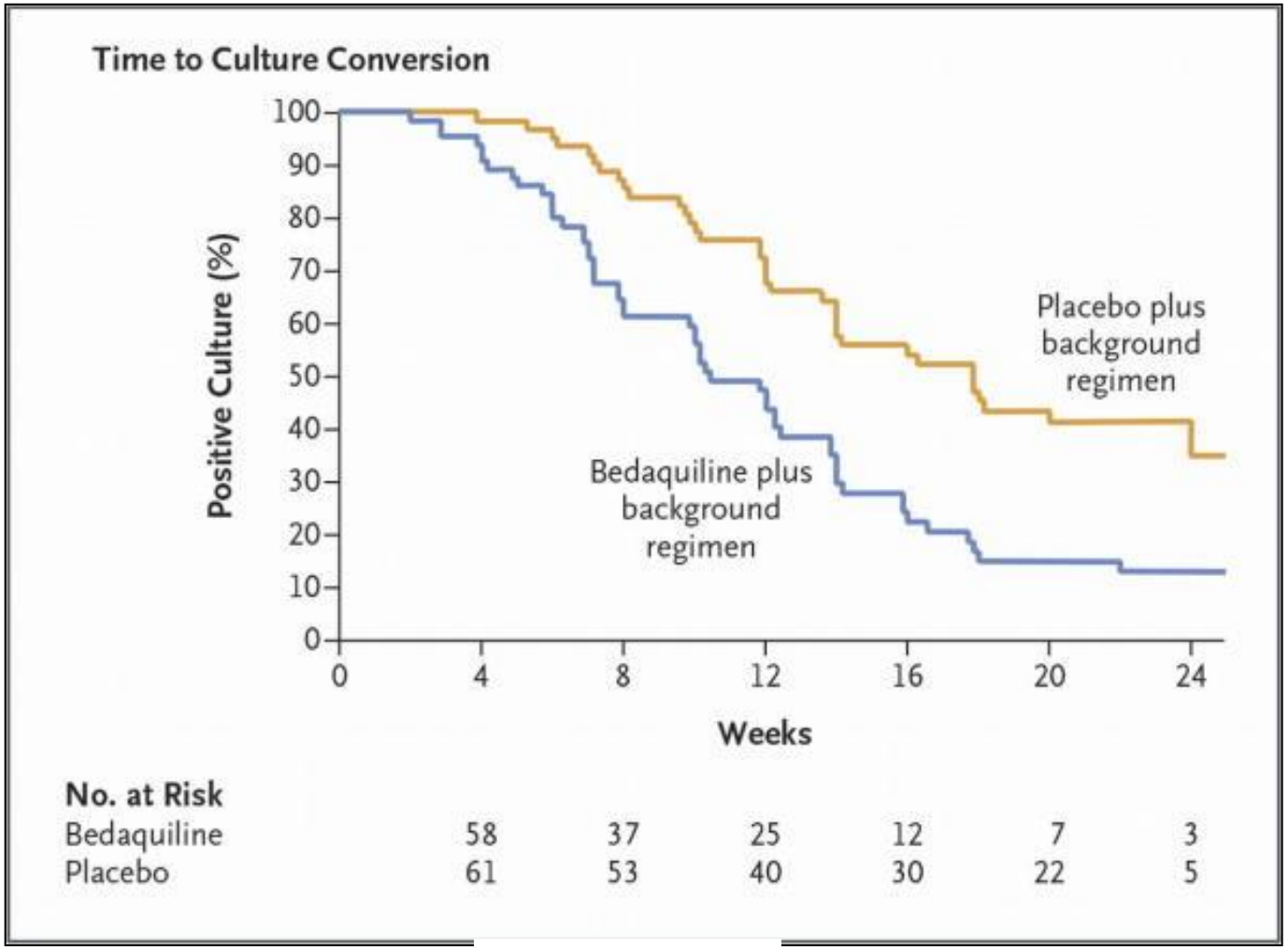
Future

- Incorporating FQ: reducing duration of TB treatment
  - ReMoxTB, OfloTub, Rifaquin studies *(20th CROI 2013;Abstr 147LB)*
  - None being studies specifically in HIV-TB

- Newer Drugs and combinations
  - Bedaquiline *(New Engl J Med 2014;371:723)*
  - Delaminid
  - PA-824

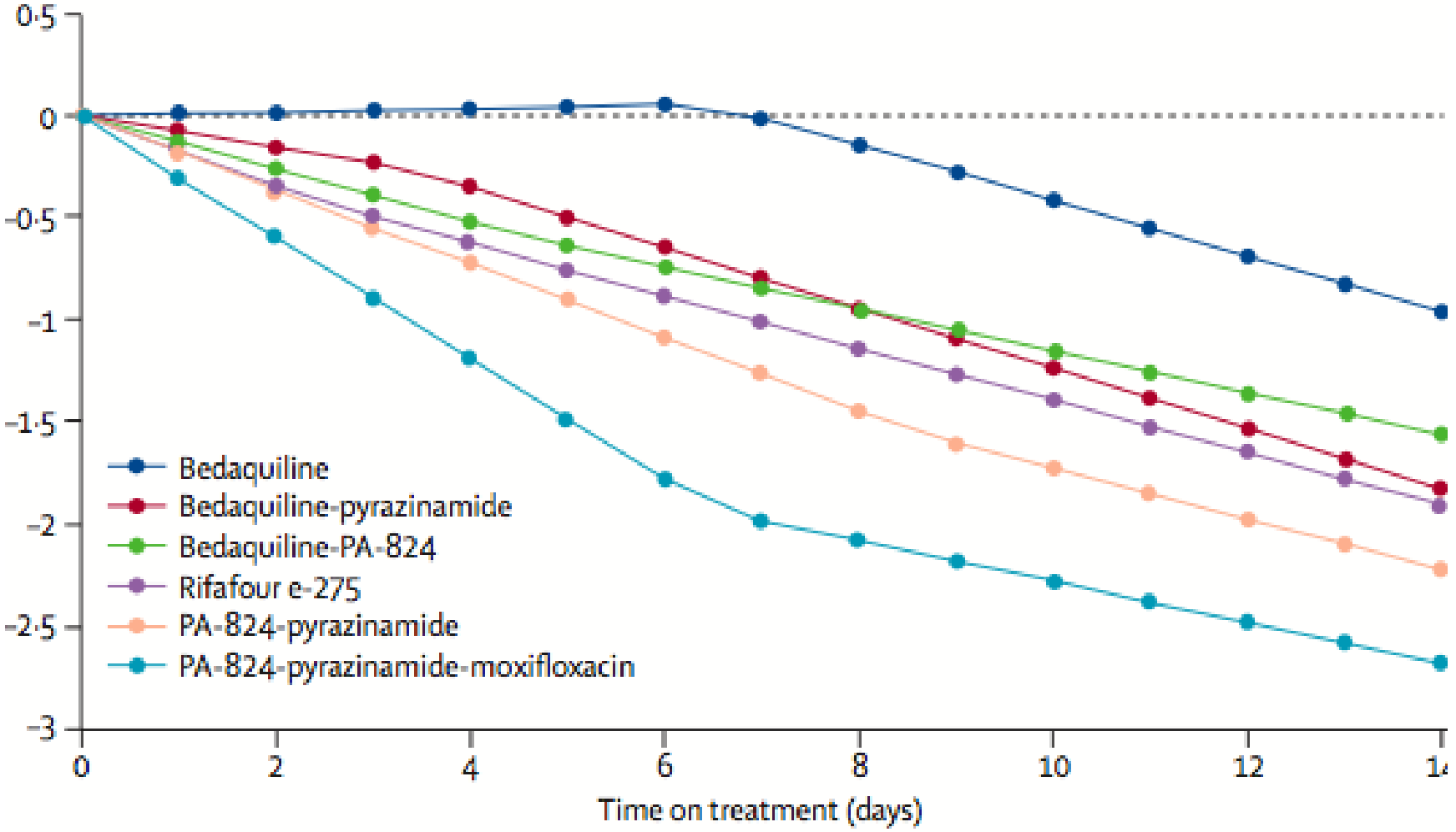
- Repurposing and redosing
  - Rifamycins: RMP (upto 35 mg/kg), Rifapentine
  - Clofazamine

Bedaquiline efficacy



New Engl J Med 2014;371:723

ATT: Future regimen?

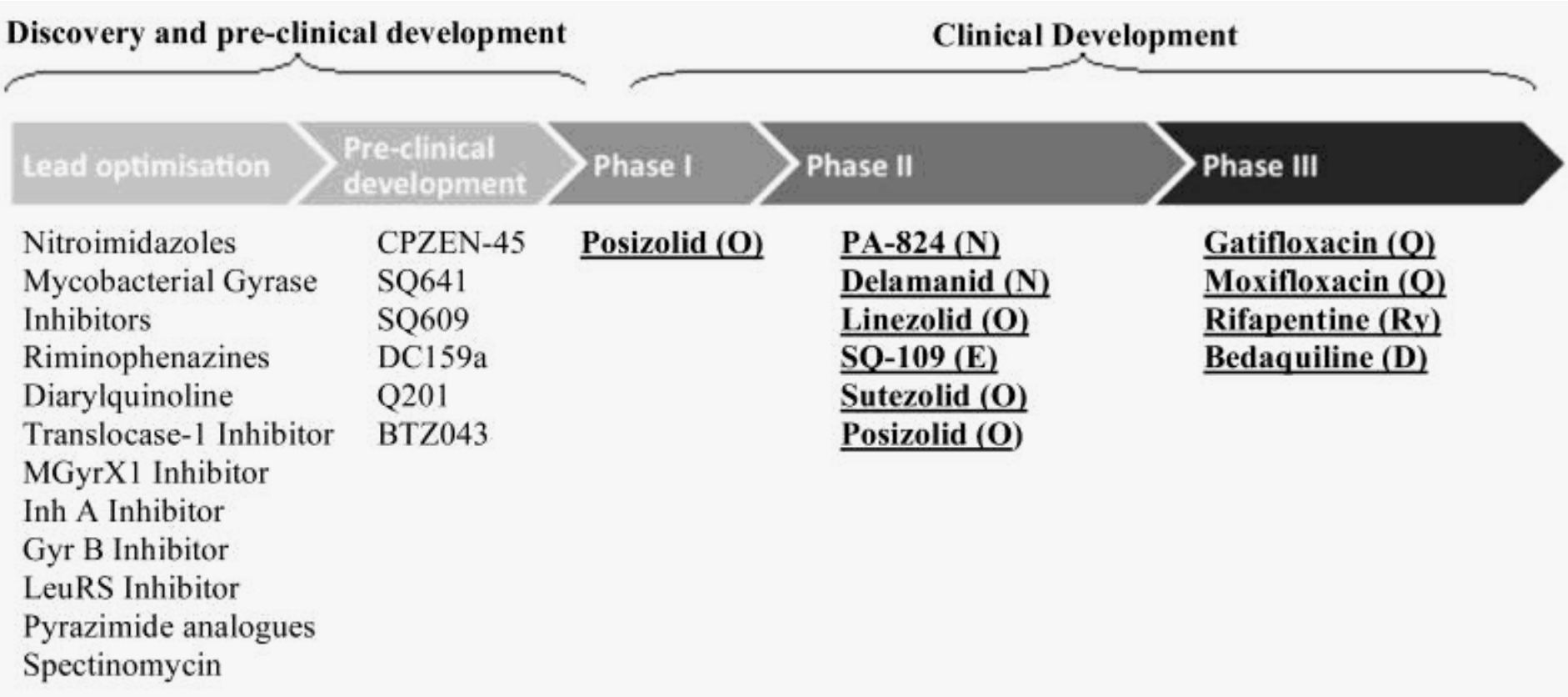


Lancet 2012;380:986

Summary

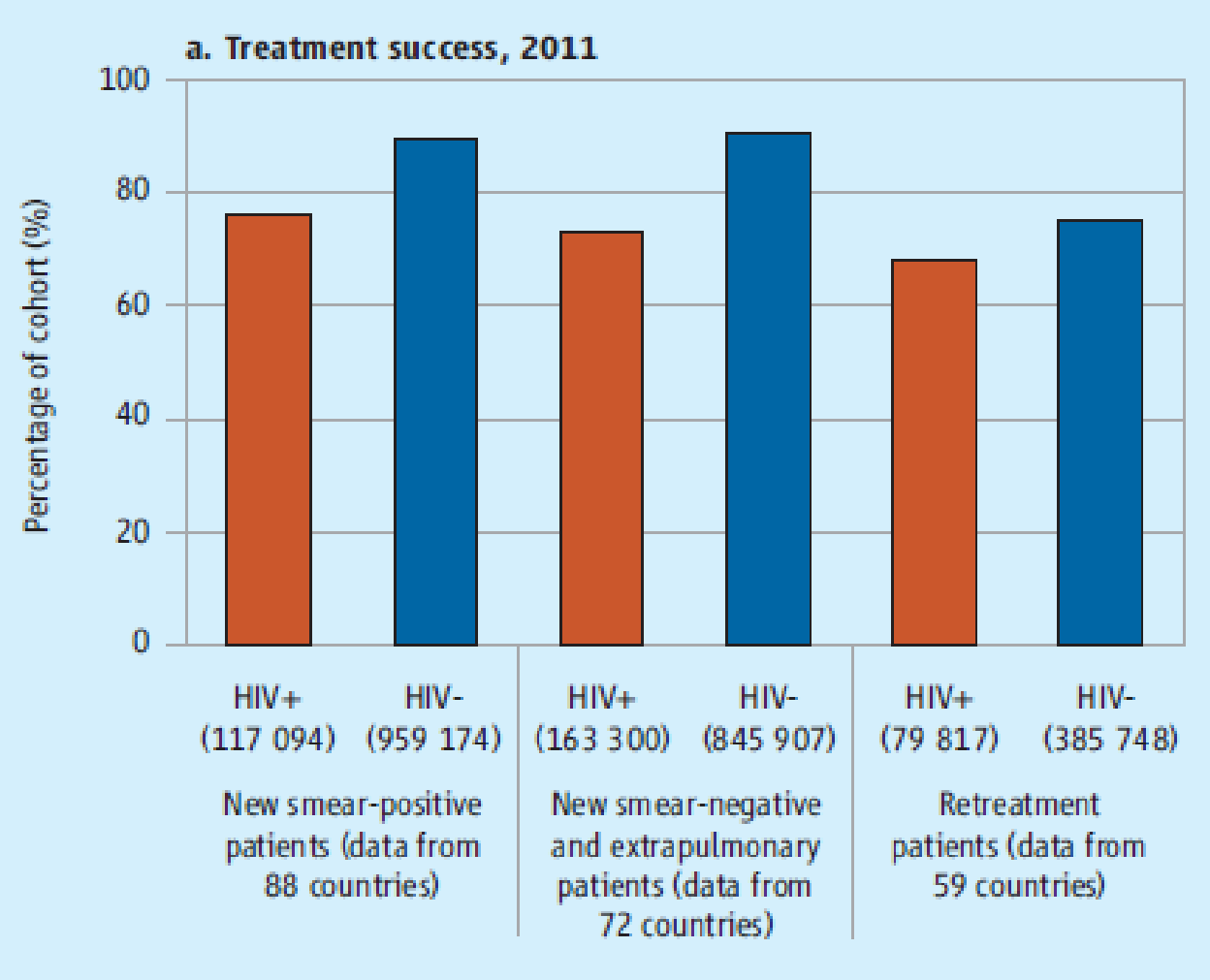
- Cursed synergy
- Screening for active TB critical for all HIV +
  - Implement Rapid molecular DST
- ART for all TB patients
  - Timing stratified by CD4 count
- Understanding ARV-ATT interactions and toxicities
- Prevent emergence of DR-TB

TB drug pipeline



Curr Resp Med Rev 2013;9:200

The problem: TB treatment success and HIV



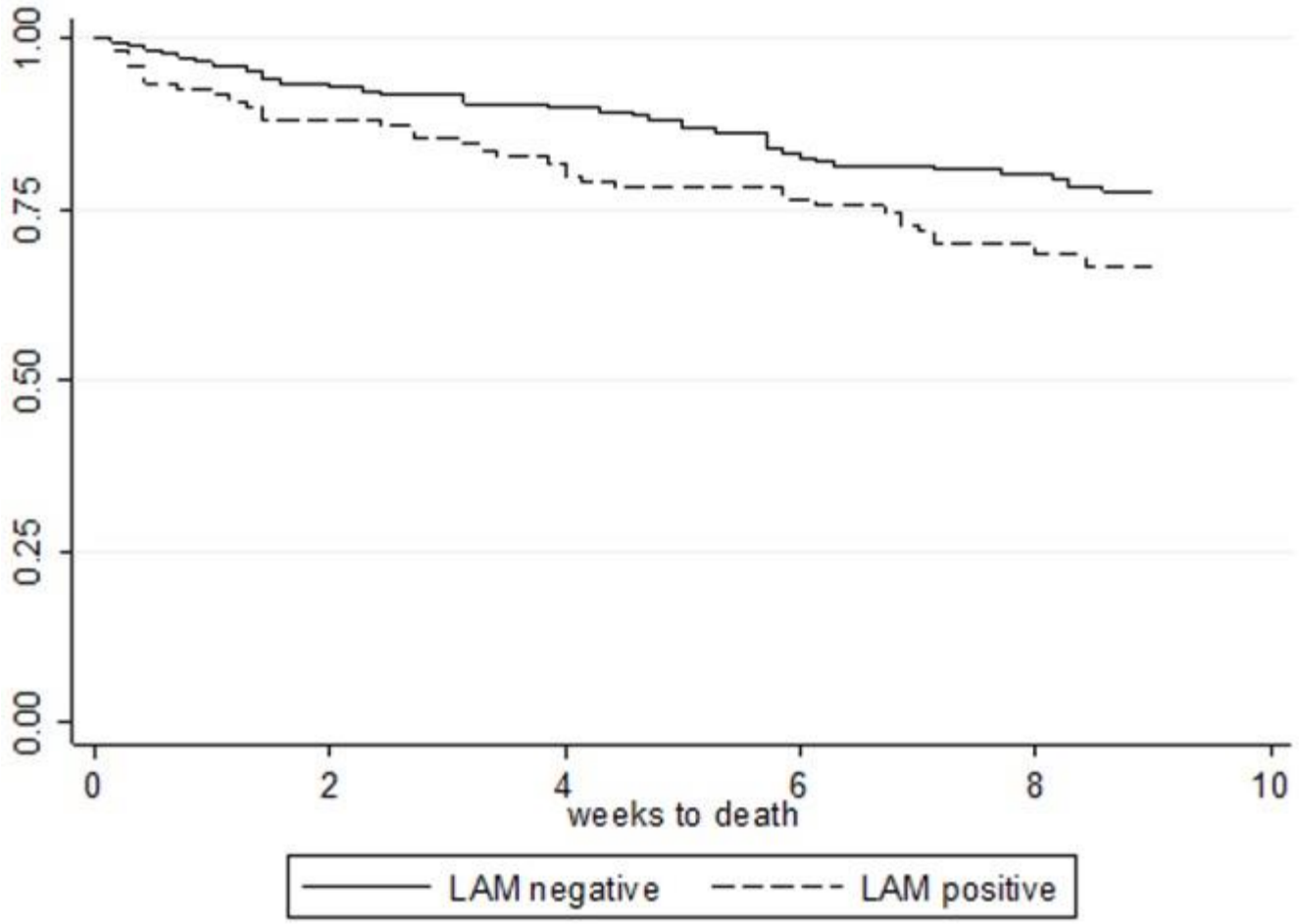
WHO Global TB Report 2013

IID INSTITUTE OF INFECTIOUS DISEASES

HIV and MDR-TB

- Prevalence is higher in HIV +
- Rapid DST for all TB
  - GeneExpert MTB/rif, LPA
- ATT Regimen
  - 4 second line ATT (Injectables, FQs, Eto, Cs or PAS) + PZA
  - Induction: 8 mo
  - Total duration: 20-24 mo's
- ART
  - Timing of initiation same
  - Adverse events: TDF with Inj's, Neuropsychiatric

Urinary TB/crypto LAM associated with mortality



PLOS One 2014;9:e101459