MYCOBACTERIAL DISEASE

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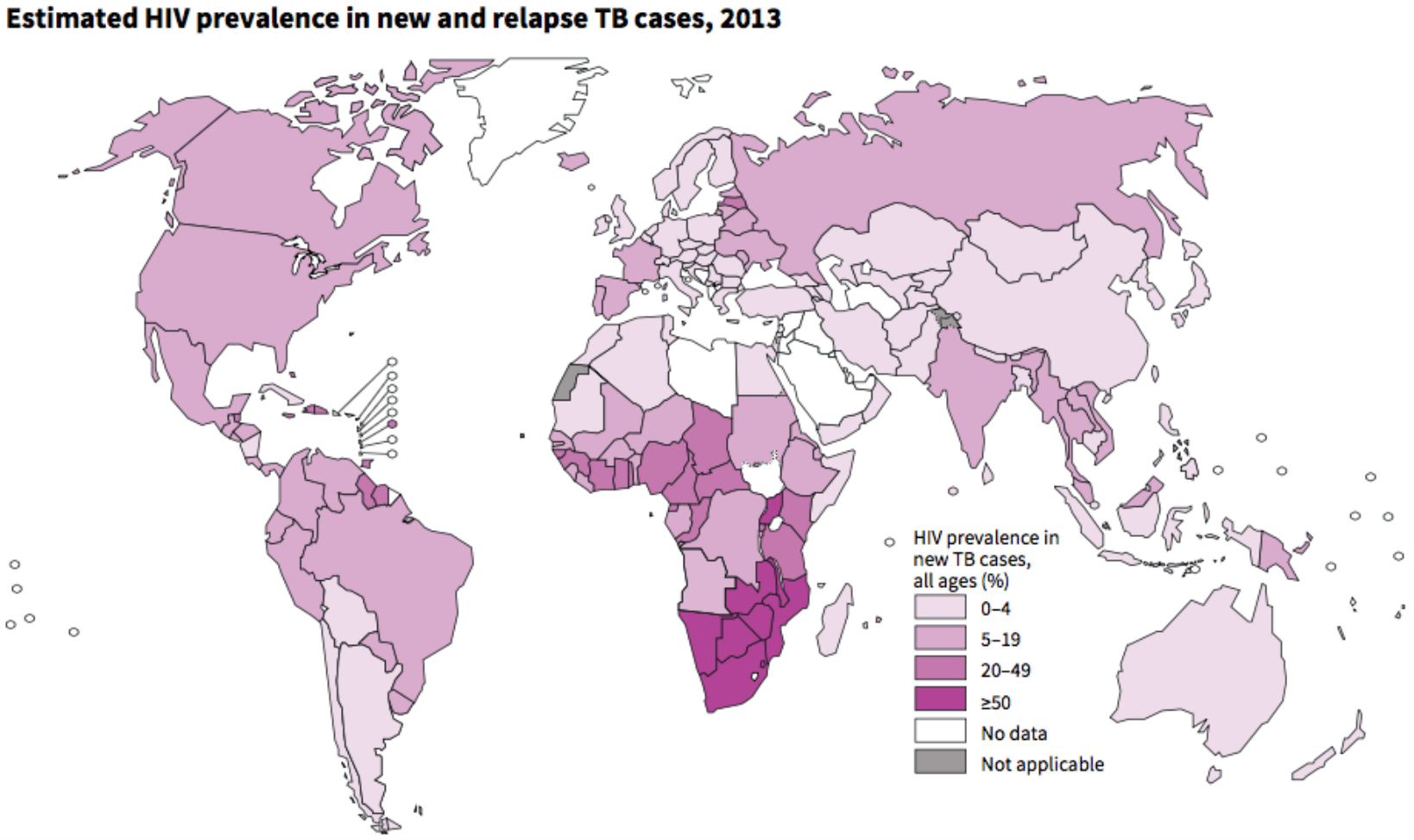
Outline

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

TB in HIV

- TB and HIV: main burden of ID in RLS
  - 13% of new TB patients in 2013 were coinfected with HIV *(Global TB report 2014)*
- Most common OI globally
- Leading cause of HIV/AIDS related morbidity and mortality *(curr opin HIV AIDS 2009;4:325)*
- RR of TB in PLHIV in the absence of ART *(lancet 2014 Jul)*
  - 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 2014

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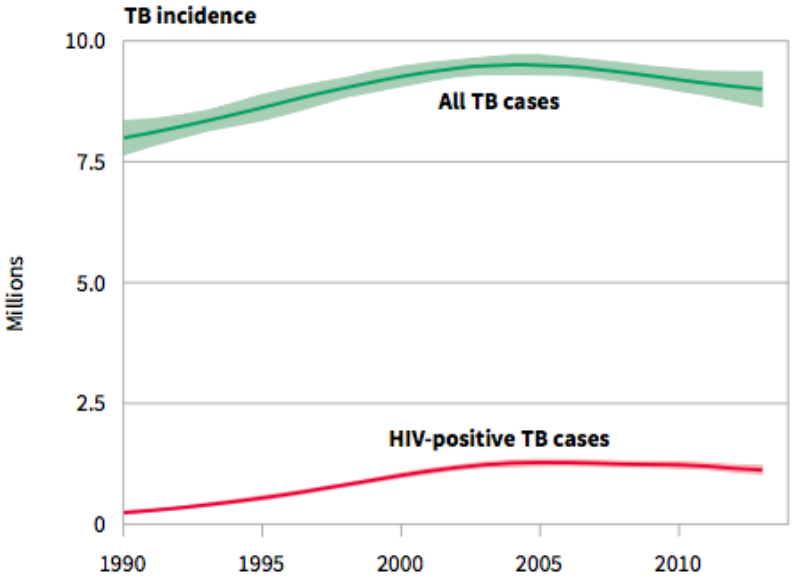
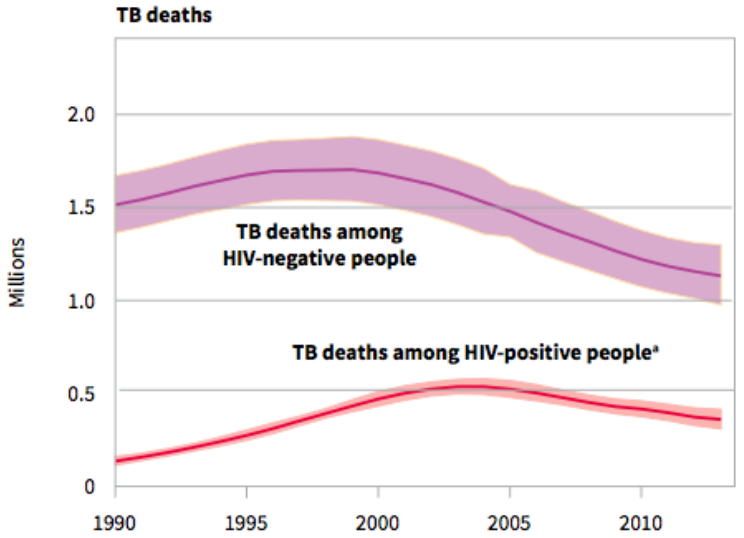
HIV associated TB: 1990-2103





WHO Global TB Report 2014

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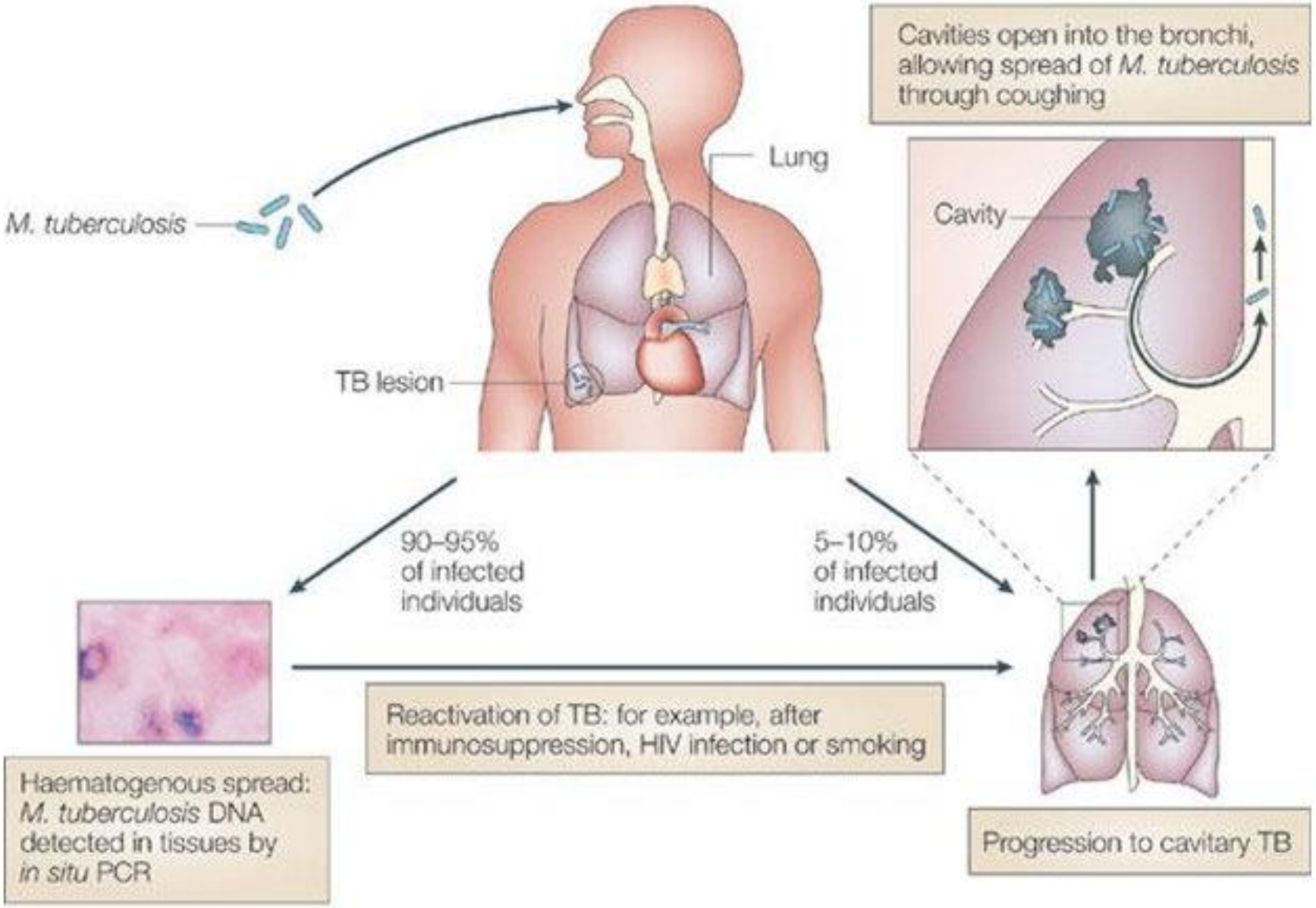


Nature Reviews | Immunology

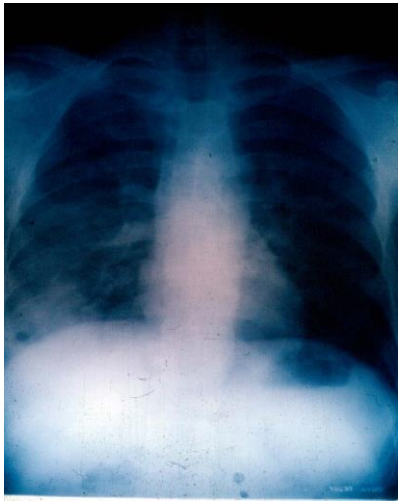
Pathogenesis

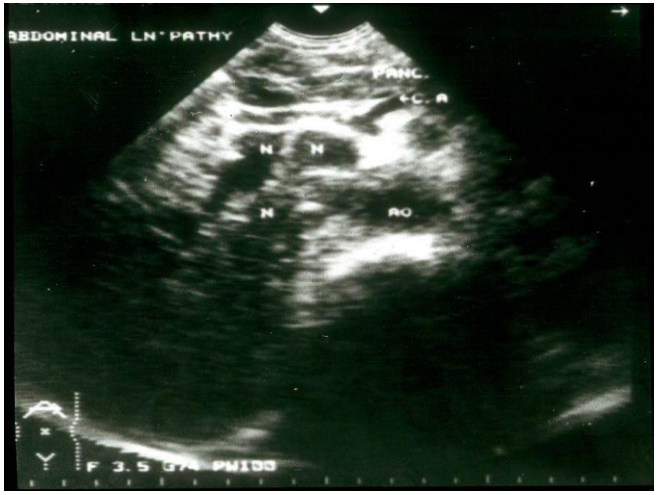
- Life time risk in immunocompetent: 5%-10% *(Clin Microbiol Infect 2004;388)*
- Annual risk in HIV+: 5%-15% *(Clin Microbiol Infect 2004;388)*
  - Further amplification with co-morbidities e.g. DM *(JAIDS 2014;66:108, Immunol Rev 2015;264:74)*
- Higher
  - Acquisition incl DRTB *(AIDS Res Human Retroviruses 2006;45,Lancet 2006; 368:1575)*
  - Rapid progression after infection
  - Reactivation disease
  - ART associated TB including IRIS

Pathogenesis to clinical presentation

- HIV mediated CD4 depletion
  - Impaired granuloma formation *(Pathol Res Pract 2008;155)*
    - Ineffective containment of MTB
    - Diminished formation of cavities *(Indian J Med Res 2005;550)*

- Clinically
  - CD4>350: similar to HIV –ve *(Clin Infect Dis 2010;51:823)*
  - CD4<200
    - 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)*

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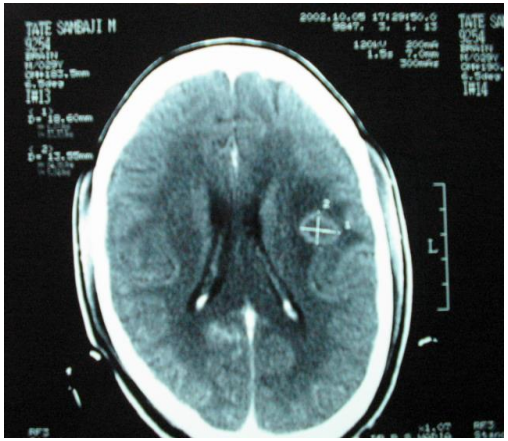
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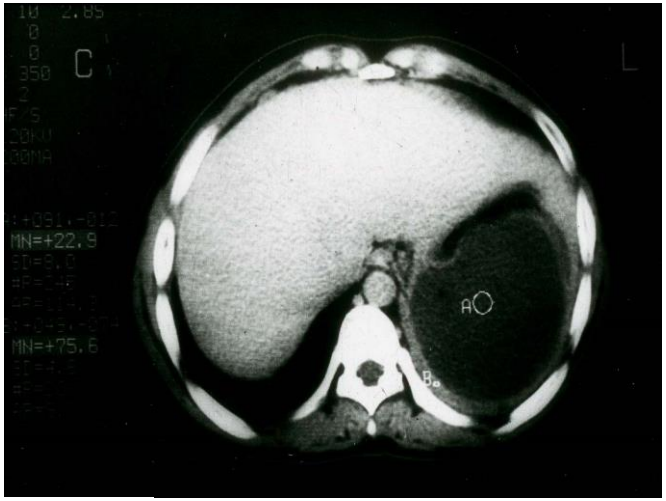
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MN=+22.9
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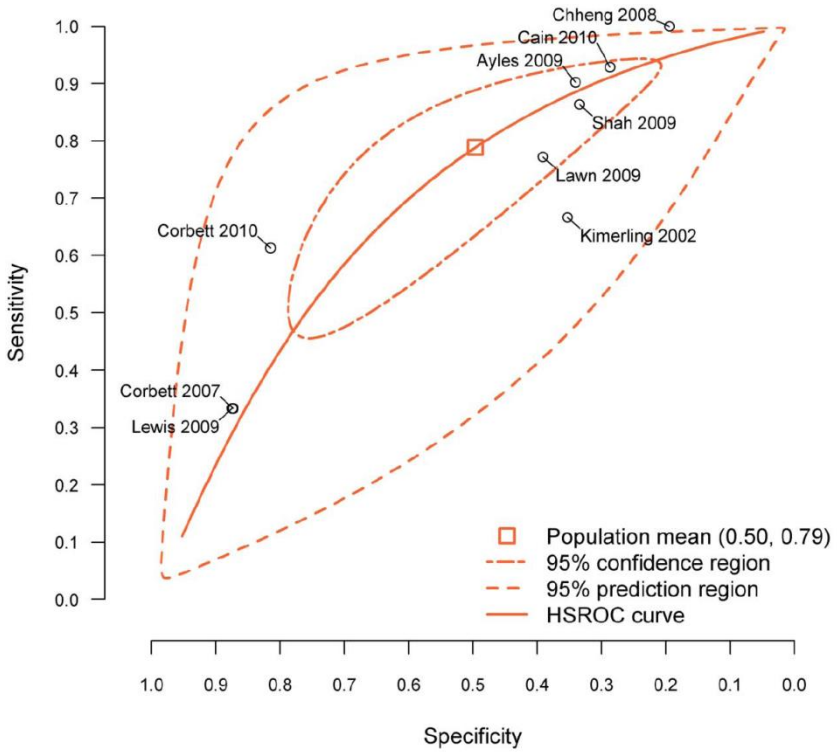
MN=+75.6

Clinical symptom screen for TB in HIV

HSROC curve for CFSW



PLoSOne 2011;e1000391

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)*

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Diagnosis

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

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

- Culture:
  - LJ medium, BACTEC, MGIT, MODS *(J Infect Dis 2007;Suppl 1:S15)*

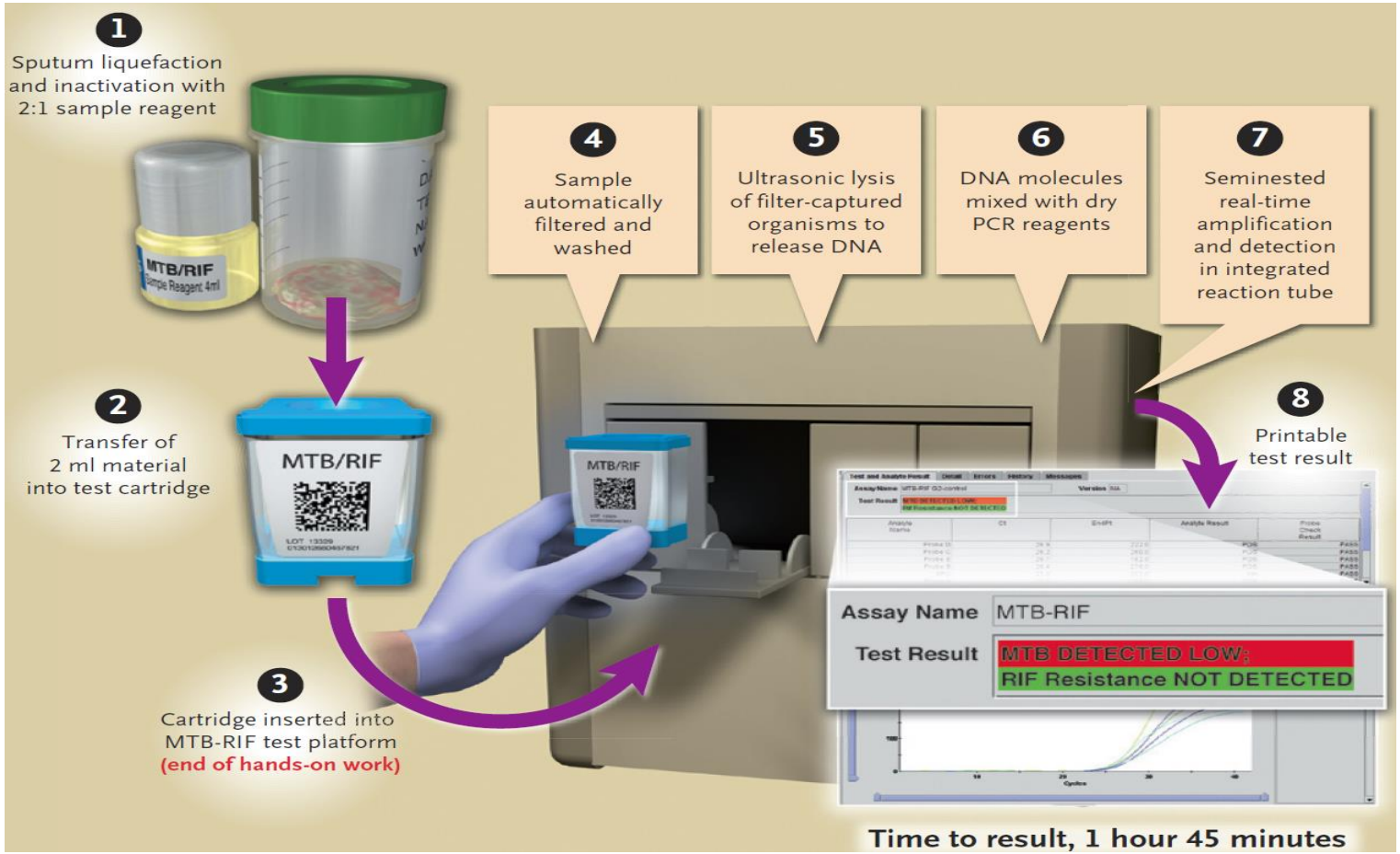
Diagnosis

- 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)*

Diagnosis

- Molecular
  - NAAT: Cobas Amplicor, BD Probe Tech
    - Lower sensitivity in Sm-
    - Poor performance for EPTB
    - Infrastructure
  - LAMP (Loop Mediated Isothermal Amplification)
    - Insufficient evidence in favor or against as replacement for microscopy *(WHO Expert group 2013)*
  - XpertMTB/Rif

Diagnosis: Xpert MTB/Rif

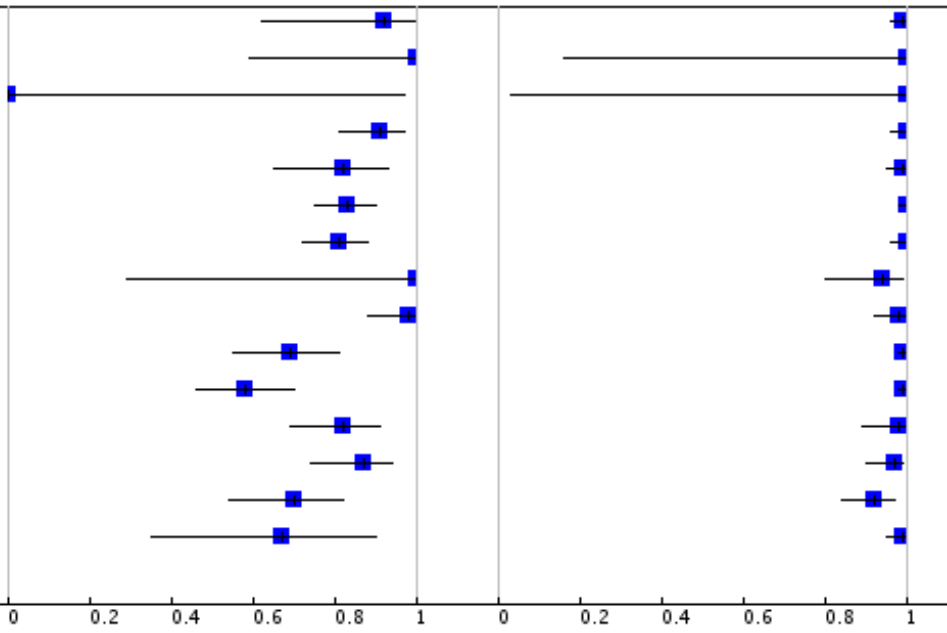


Can help in intensive case finding prior to initiation of ART *(PLOS One 2014;9:e85478)*

Xpert MTB/Rif: PTB

Review: Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults
Test: 5 HIV positive

Study	TP	FP	FN	TN	Sensitivity	Specificity
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Boehme 2010a	7	0	0	2	1.00 [0.59, 1.00]	1.00 [0.16, 1.00]
Boehme 2010b	0	0	1	1	0.0 [0.0, 0.97]	1.00 [0.03, 1.00]
Boehme 2010c	60	0	6	81	0.91 [0.81, 0.97]	1.00 [0.96, 1.00]
Boehme 2010d	27	2	6	141	0.82 [0.65, 0.93]	0.99 [0.95, 1.00]
Boehme 2011c	90	1	18	263	0.83 [0.75, 0.90]	1.00 [0.98, 1.00]
Boehme 2011d	80	0	19	88	0.81 [0.72, 0.88]	1.00 [0.96, 1.00]
Boehme 2011e	3	2	0	31	1.00 [0.29, 1.00]	0.94 [0.80, 0.99]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Hanrahan 2013	36	2	16	325	0.69 [0.55, 0.81]	0.99 [0.98, 1.00]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Rachow 2011	41	1	9	49	0.82 [0.69, 0.91]	0.98 [0.89, 1.00]
Scott 2011	45	3	7	84	0.87 [0.74, 0.94]	0.97 [0.90, 0.99]
Theron 2011	32	7	14	77	0.70 [0.54, 0.82]	0.92 [0.84, 0.97]
Van Rie 2013	8	1	4	99	0.67 [0.35, 0.90]	0.99 [0.95, 1.00]



Cochrane Database Syst Rev 2014;CD0095 93

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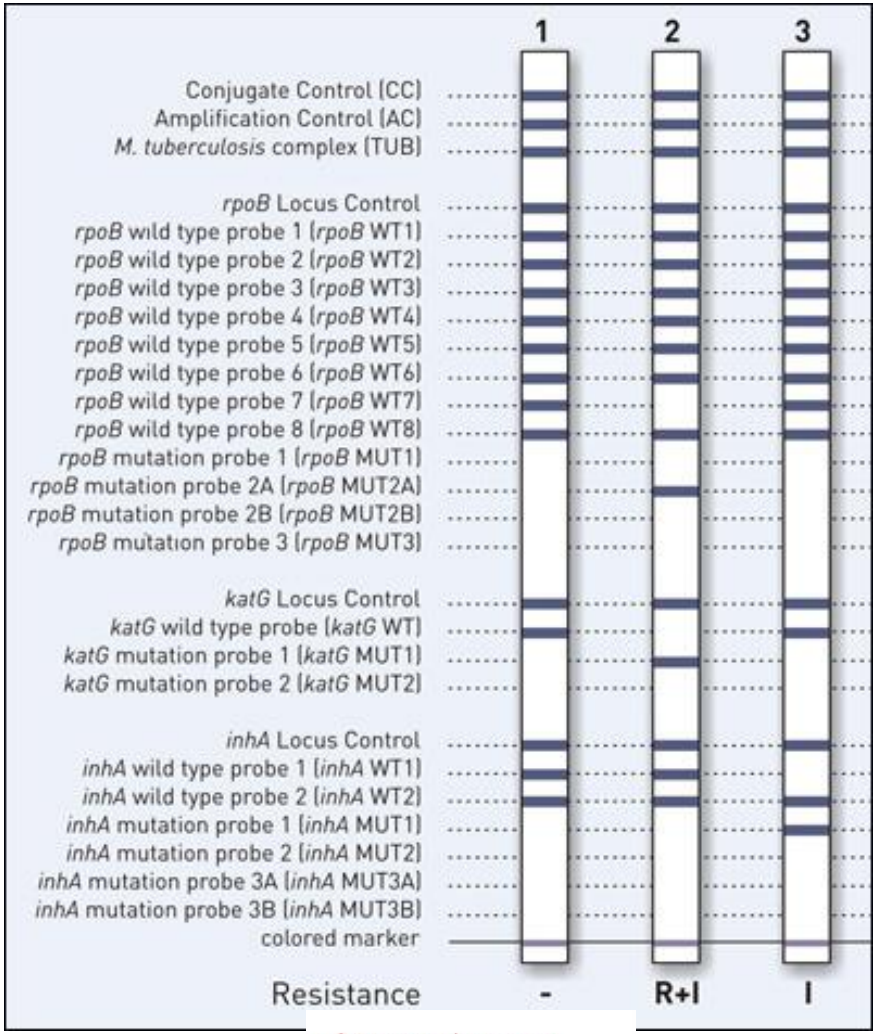
Xpert MTB/Rif

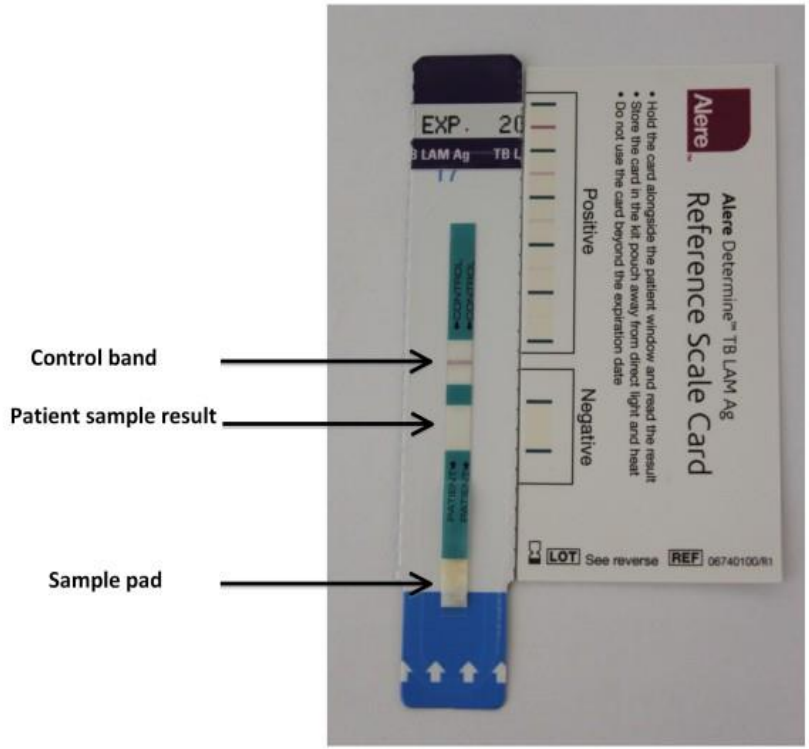
- EPTB
  - In high prevalence setting (e.g. India), sensitivity *(J Clin Micro 2011;49:2540)*
  - Pleural: 63%
  - Lymphadenitis: 73%
  - TBM: 29%, recommended initial CSF test *(WHO policy update 2013)*
  - Urine: irrespective of renal involvement, more sensitive with CD4<200, routine microbiological screening of inpatients *(JAIDS 2012;60:289, BMC Med 2015;13:192)*
- Rif resistance: Sens: 93%, Spec:97% *(Cochrane Database Syst rev 2014;1:CD009593)*
- Limitations
  - Misses 1/4th-1/3th sm-ve (1 sample)
  - Does not assess resistance to other drugs
- Recommended as initial diagnostic test for TB in HIV+ pts and those suspected of MDRTB *(WHO policy update 2013)*

DRTB: Line Probe Assay



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)*
  - May be useful to monitor treatment response *(BMJ Open 2015;5:e00683)*
  - New more sensitive LAM in development *(PLOSOne 2015;10)*
  - Urinary LAM+Xpert have higher sensitivity than each alone *(AIDS 2014;28:1307)*



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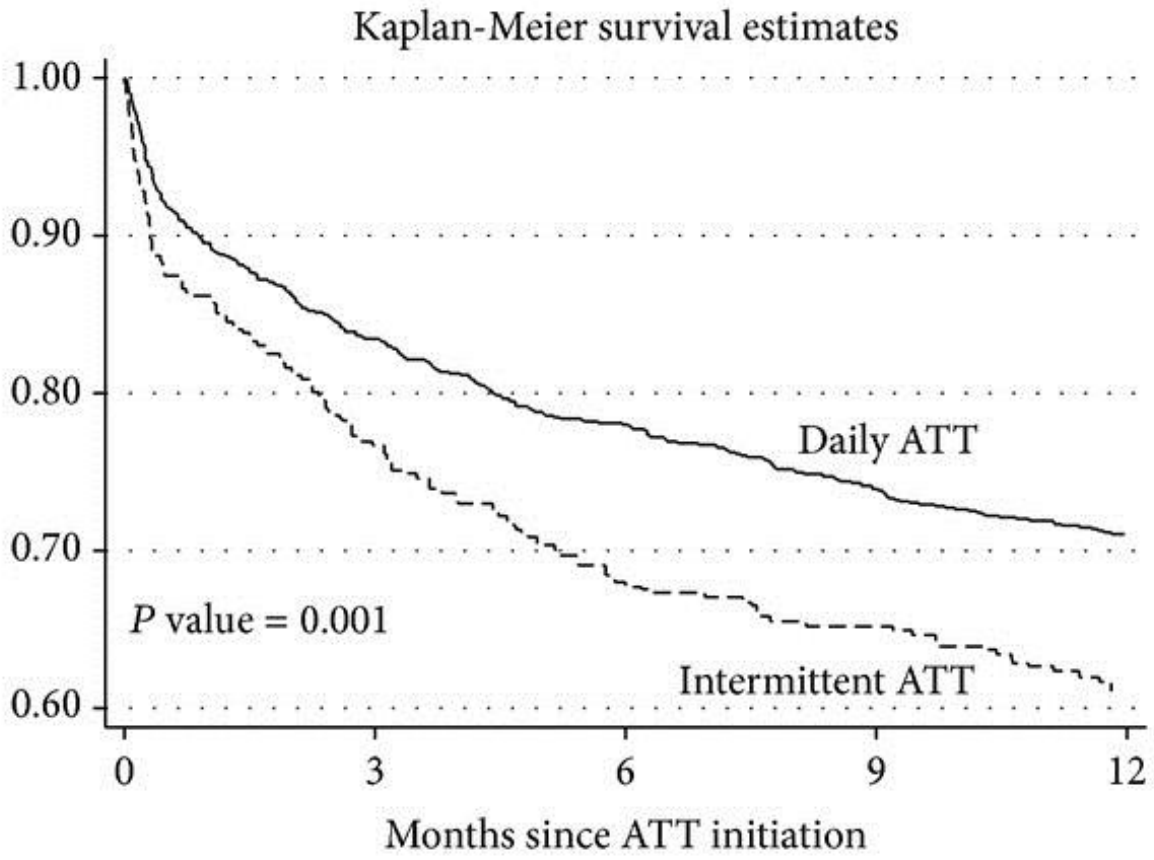
HIV-TB treatment (1)

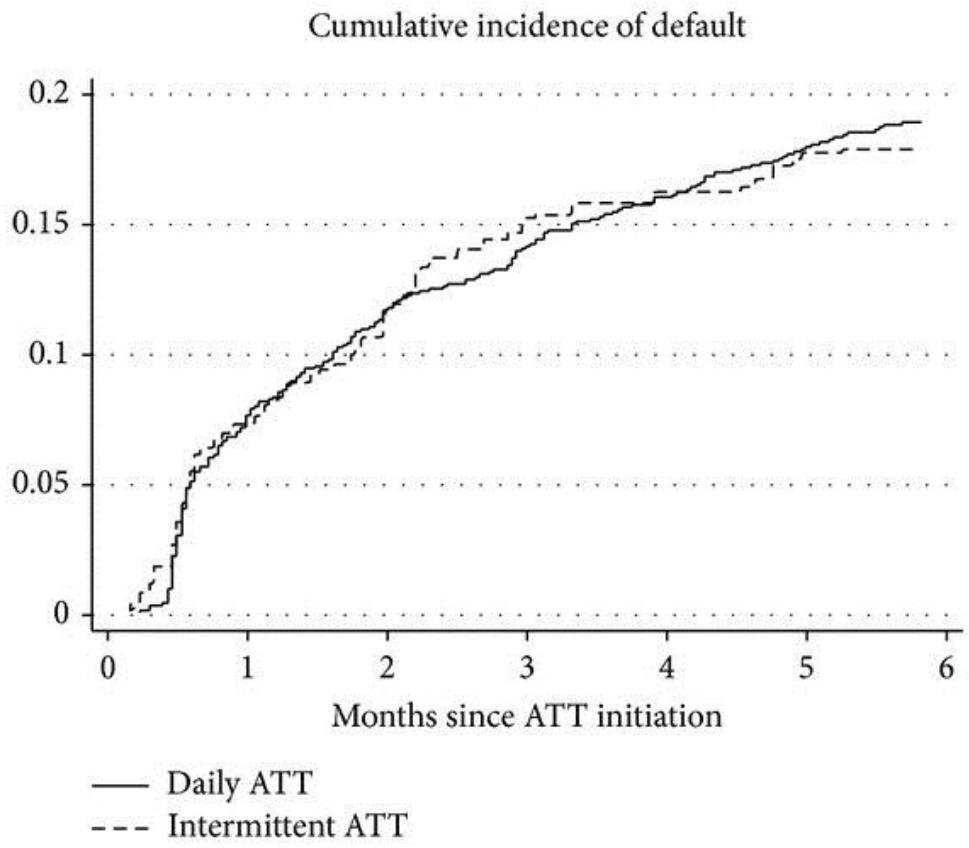
- What ATT regimen should be used?
  - Rifampicin based *(WHO TB treatment guidelines)*
  - Rifabutin based *(JAIDS 2015;68:e84)*
- Should we continue EMB in maintenance phase?
  - Yes, incidence of primary INH resistance is high
- What is the duration of ATT?
  - 6 (? ≥8 mo's) months except for CNS TB, non use of RMP/PZA
- Is intermittent treatment ok?
  - No, daily treatment throughout the course *(PLOSMed 2009;6:e1000146)*
  - ? Lower rifampicin exposure and acquired rifampicin resistance *(Int J Tub Lung Dis 2015;19:805,Clin Infect Dis 2014;59:1798)*

Intermittent vs Daily ATT in intensive phase



Biomed Res Int 2014;937817

Intermittent vs Daily ATT in intensive phase



Biomed Res Int 2014;937817

HIV-TB treatment (2)

- Is the incidence of ATT toxicity high?
  - Perhaps higher *(PLOSOne 2011;6:e19566, Thorax 2006;61:791)*
- Can steroids be safely used?
  - Yes in TBM, adrenal and paradoxical IRIS *(Indian J Chest Dis Allied Sci 2010;52:153)*
  - Pericardial TB: No *(New Engl J med 2014;371:1121)*
- 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)*

Pre-emptive TB treatment (REMEMBER):

- 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)
All primary endpoints	22 (5.3)	22 (5.2)

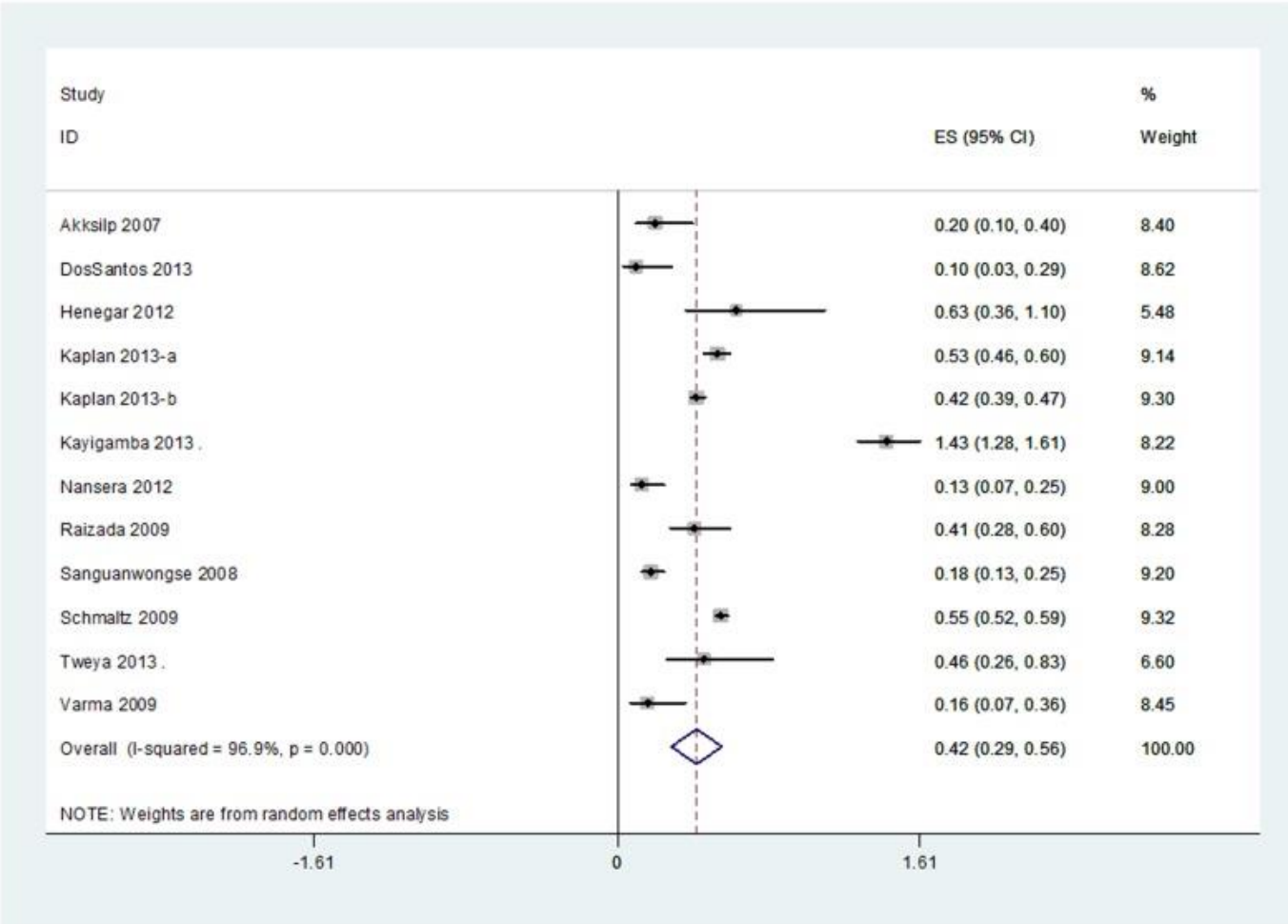
Absolute risk difference: -0.06% (95% CI: -3.05% to 2.94%; *P* = .97)

IAS 2015; Abstr MOAB0205LB

HIV-TB treatment (3)

- When is ART indicated in HIV-TB?
  - All patients irrespective of CD4 counts *(WHO ART guidelines 2013)*
    - Improves morbidity and mortality *(PLOS One 2014;9:e112017)*
      - Without ART 50% of PLHIV with TB die within 6-8 mo's *(JAIDS 2006;42)*
    - 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 mortality in HIV/TB



PLOSOne 2014;9:e112017

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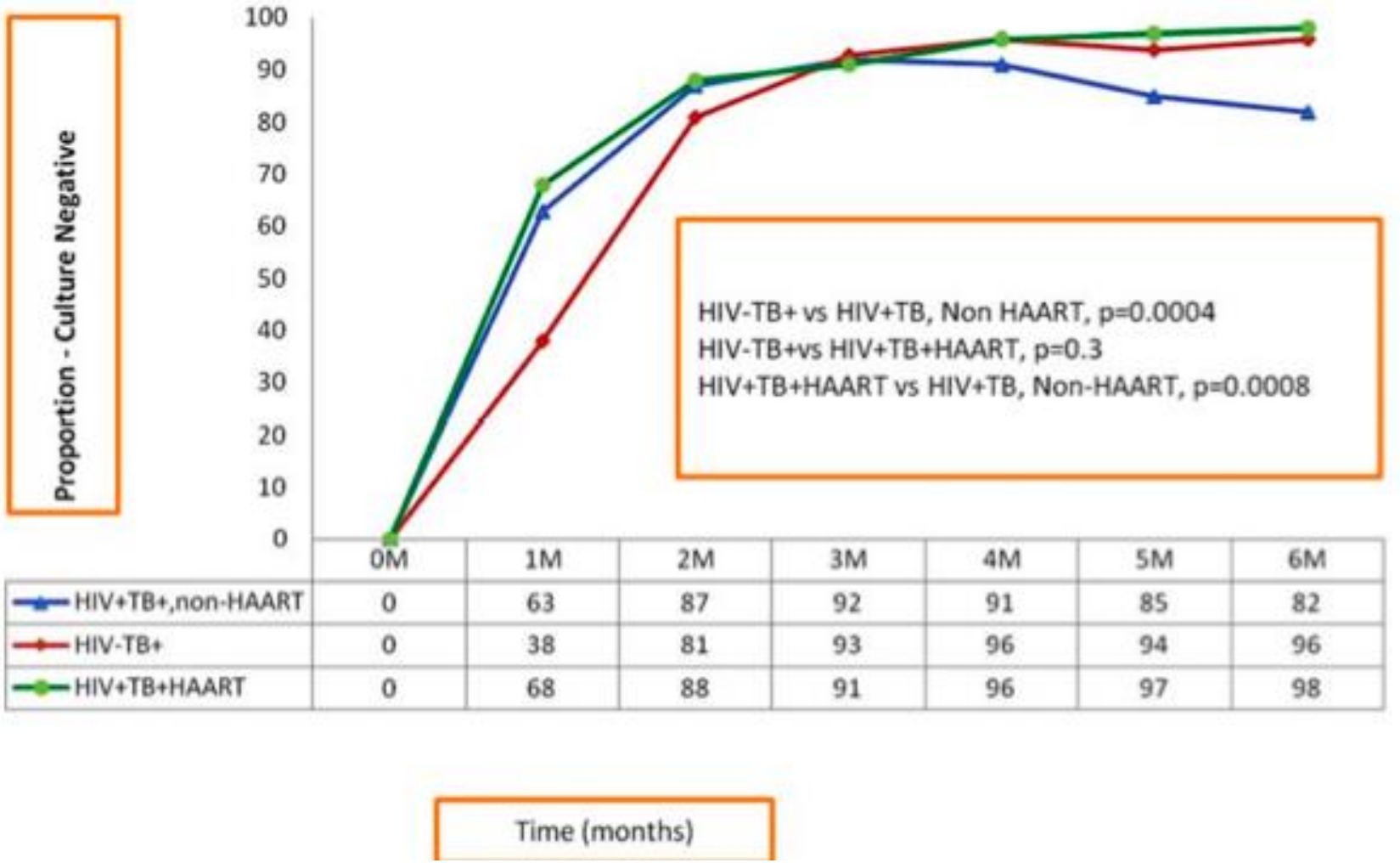
Impact of ART on TB culture conversion and ARR



	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

Clin Infect Dis 2014;59:1798

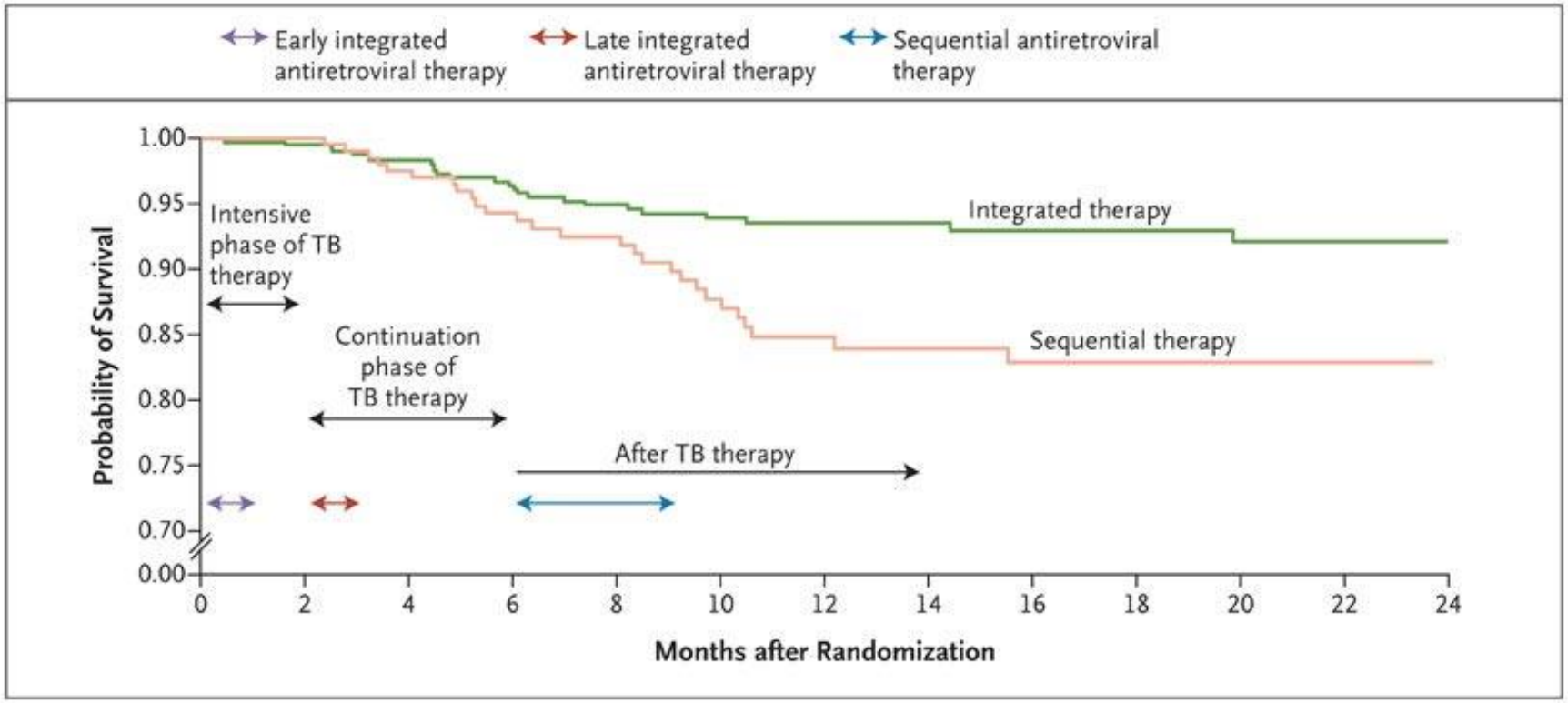
Initiating ATT and ART

Early ART

Deferred ART

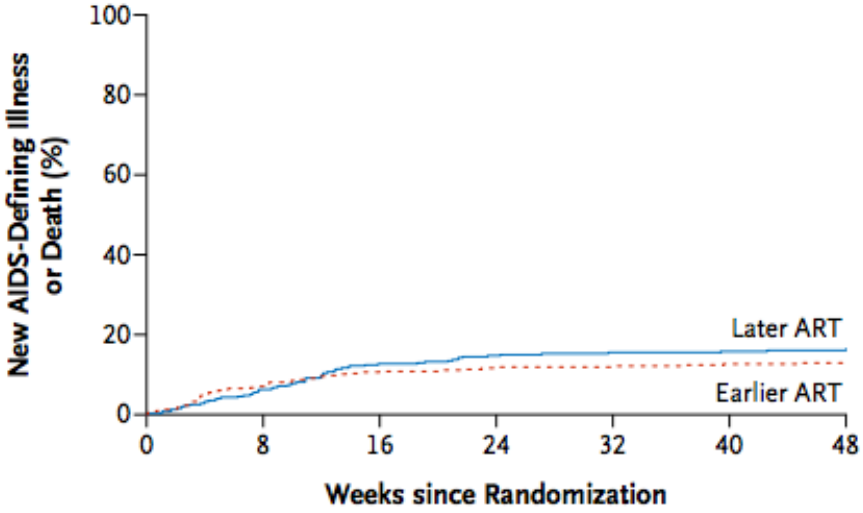
- Drug-Drug interactions
- Additive and overlapping toxicities
- Paradoxical IRIS
- High pill burden
- Ongoing clinical progression of HIV infection

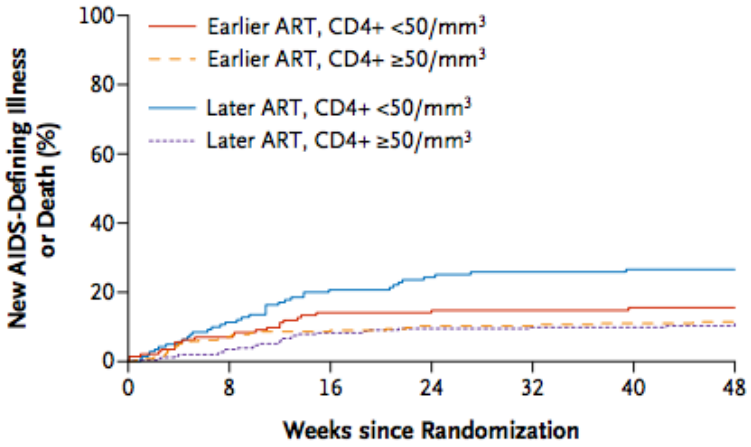
ART in TB: Don’t wait until ATT completion



New Engl J Med 2010;362:967

ART timing in TB





New Engl J Med 2011:365:1482

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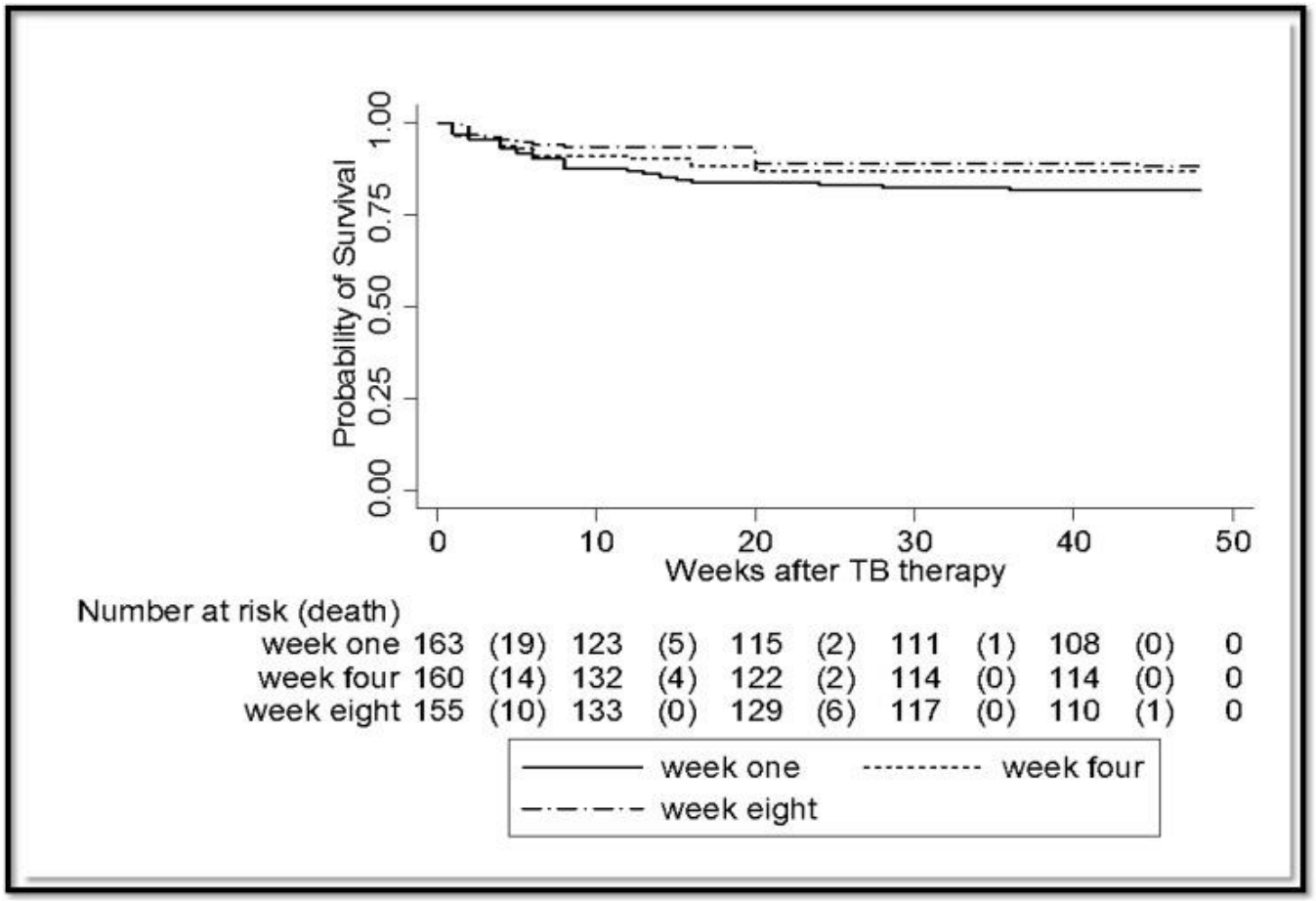
When to initiate ART in HIV/TB?

- Early ART: 1-4 weeks
  - CD4<50/mm^3
    - Improves survival
    - 2 fold increase in IRIS
  - CD4>50/mm^3
    - Evidence insufficient for or against survival benefit

Annals Intern Med 2015;163:32

Early ART amongst HIV/TB



PLOSOne 2015;10:e0122587

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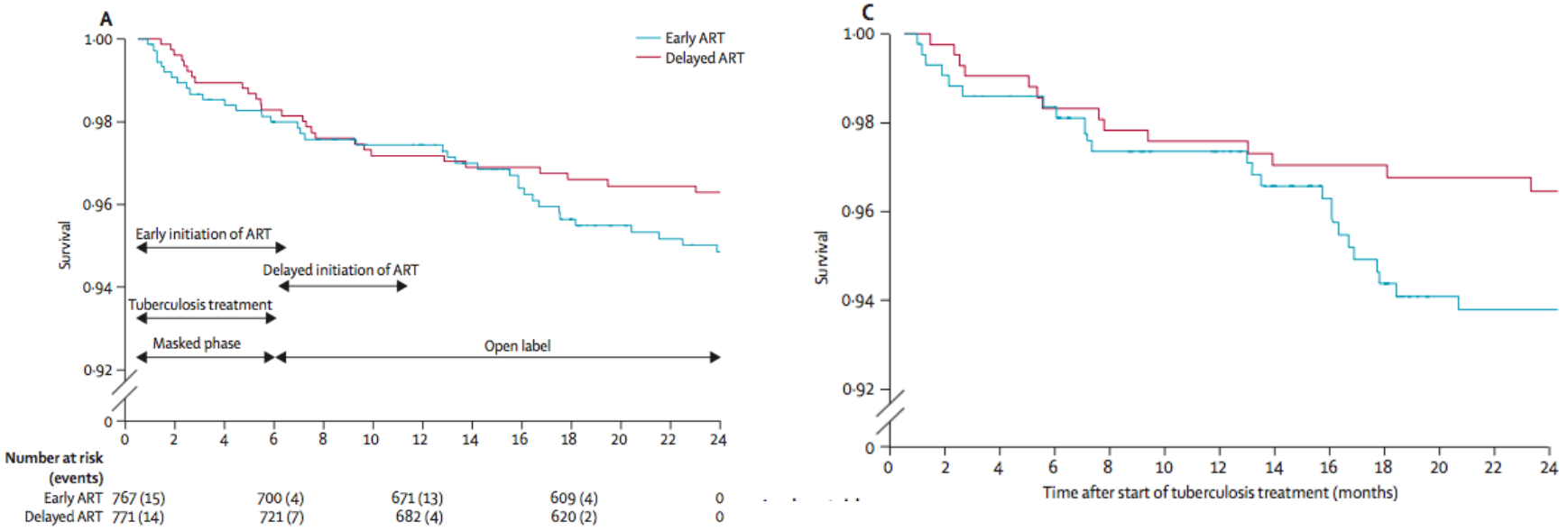
TB-HAART (CD4>220) study: Surprising results



Lancet Infect Dis 2014;14:563

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

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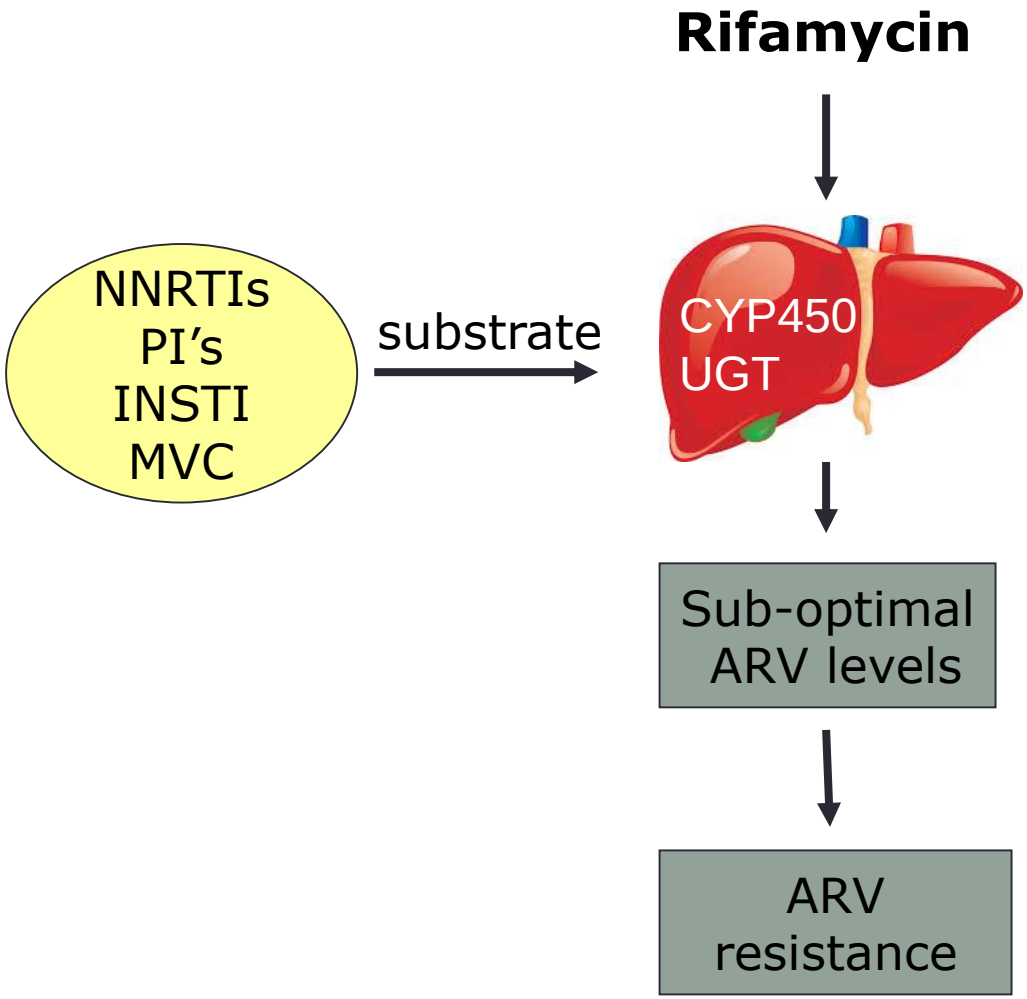
Drug-Drug interactions



Rifampicin and ARVs

- EFV: recommended option *(Lancet Infect Dis 2013;13:303,)*
  - 600 mg (Pharmacogenomics 2015;!, PLOSOne 2014;9:e90350, Clin Infect Dis 2013;57:586)
- NVP
  - Risk of Virologic failure *(J Antimicrob Ther 2015;70:225)*
  - No lead-in if on ATT>7 days (Int Infect Dis 2014;130)
  - More DILI *(Lancet Infect Dis 2013;13:303)*
- Increase doses of
  - RAL ? (Clin Infect Dis July 2015; advance access)
  - DTG *(JAIDS 2013;62:21)*
  - MVC *(Selezentry package insert)*
- Contraindicated
  - RPV, ETV, PI/r, TDF/FTC/COB/EVG

Rifabutin and ARVs

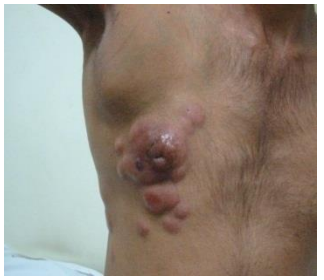
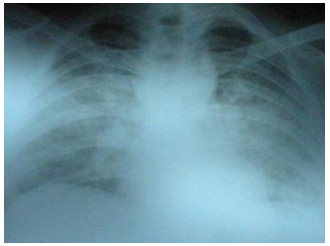
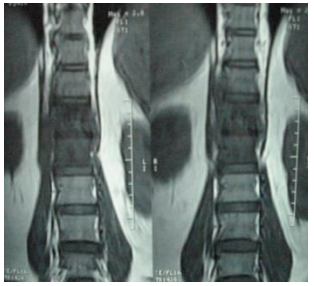
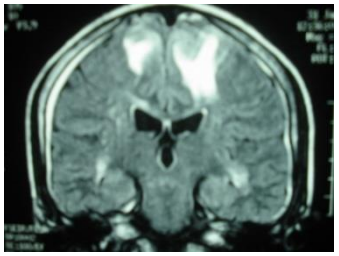
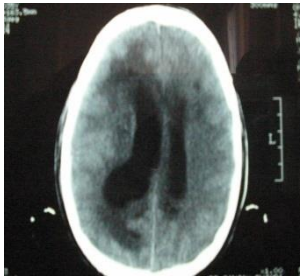
- Change RBT dose
  - PI/r: 150 mg qd (Clin Infect Dis 2009;49:1305, Clin Infect Dis 2009;48:1471)
  - EFV: 450-600 mg od *(DHHS 2015)*
  - ETV: 300 mg qd *(J Antimicrob Chemother 2014;69:728)*
- No change in RBT dose
  - NVP *(NVP package insert)*
  - RAL *(J Clin Pharmacol 2011;51:943)*
  - DLV *(JAIDS 2013;62:21)*
- Change ARV dose
  - RPV: 50 mg od *(AIDS Rev 2013;15:87)*
- Not recommended
  - TDF/FTC/COB/EVG *(Clin Pharmcokinetik 2011;50:229)*
  - MVC

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 (18%) *(Future Microbiol 2015;10:1077)*
- 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)*
- Outcome: 2% deaths *(Future Microbiol 2015;10:1077)*
  - CNS IRIS higher *(Clin Infect Dis 2009;48:96)*
- Treatment: Steroids *(AIDS 2010;24:2381)*

Outline

- The problem
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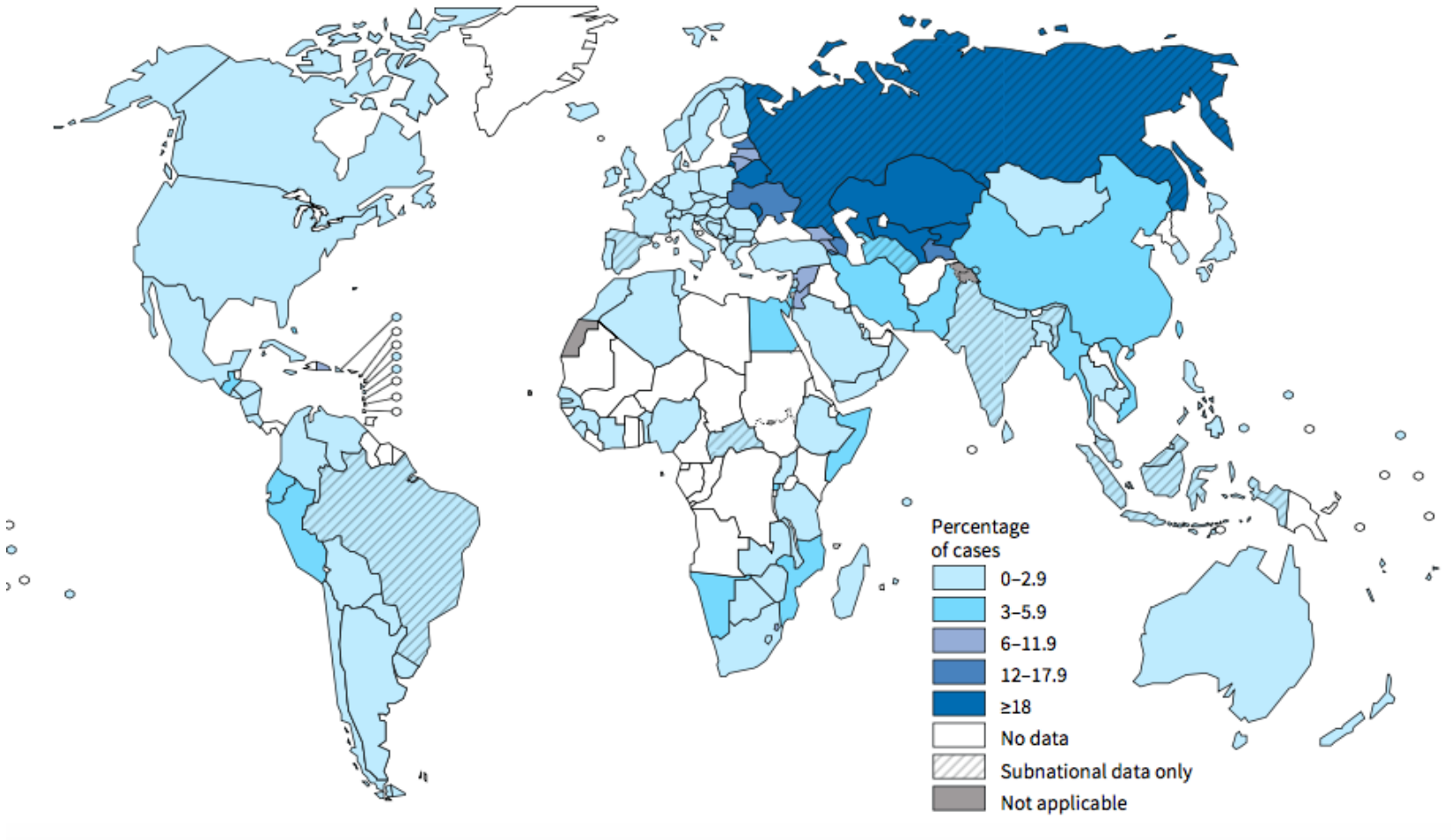
What is DRTB?

- 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
  - RR-TB: Rifampicin resistant TB
- XDR-TB
  - MTB isolate that is MDR + FQ + one or more injectable *(WHO XDR-TB definition meeting 2006)*
    - Pre-XDR TB
- 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



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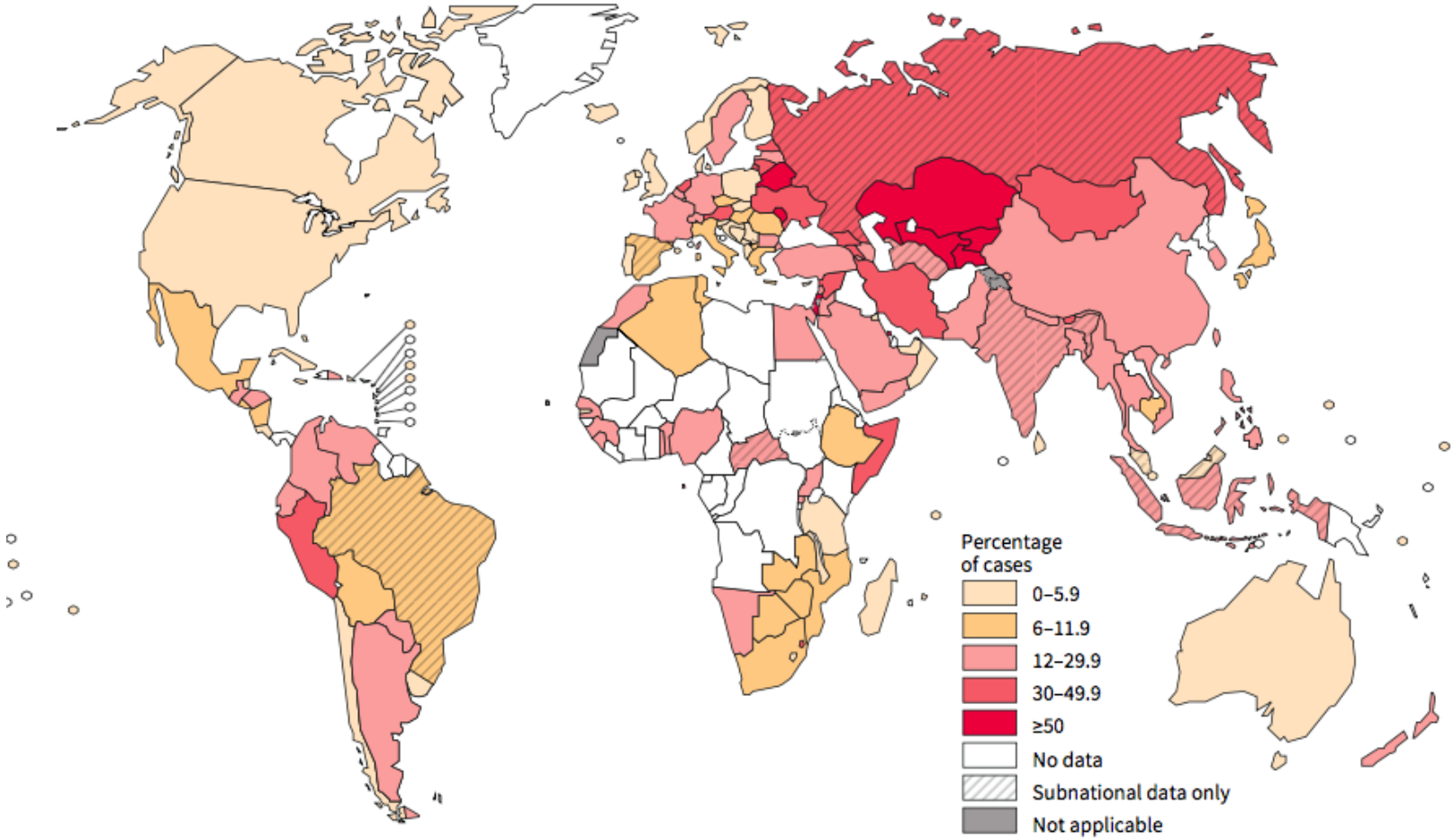
MDR-TB amongst retreated cases



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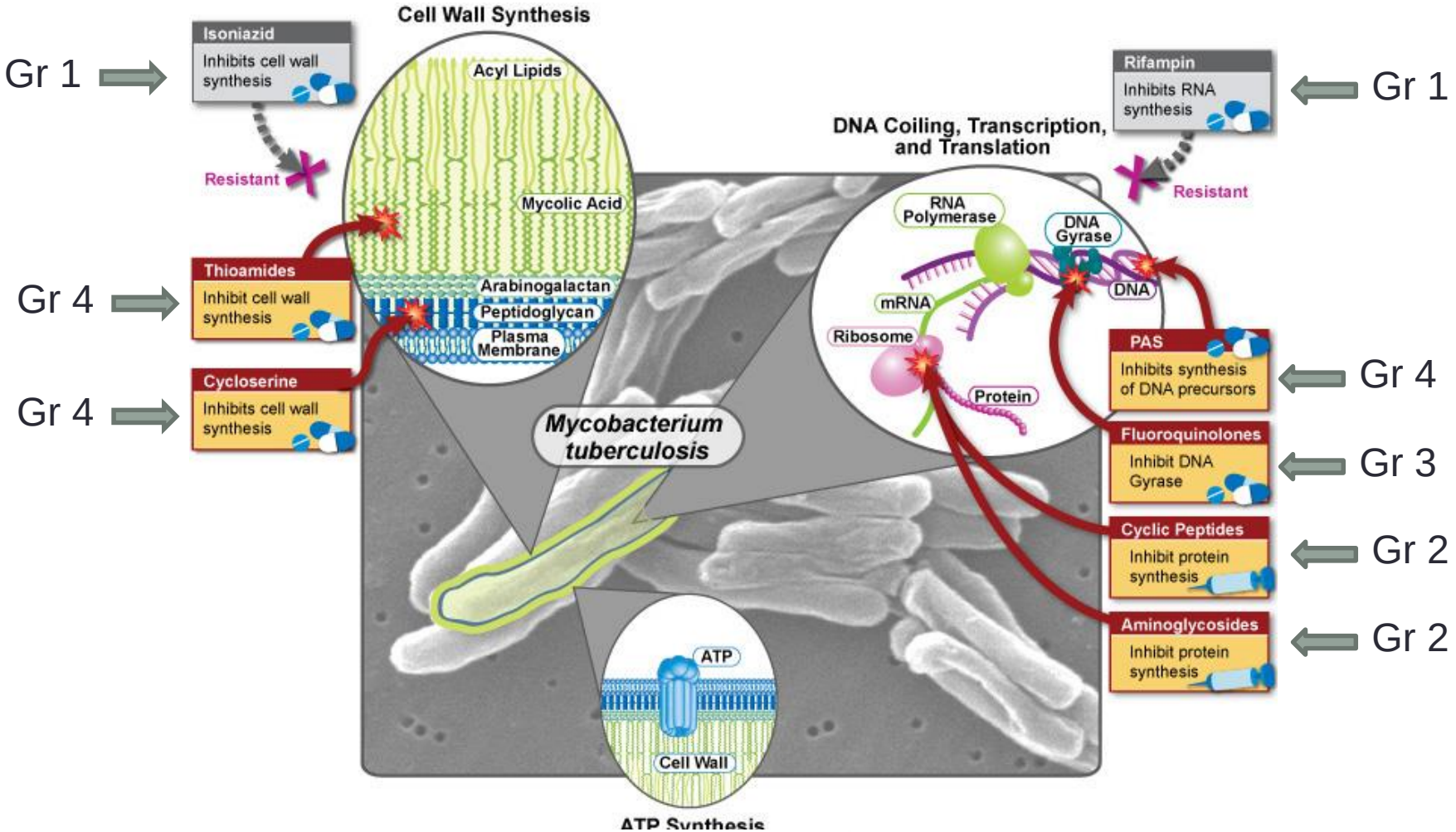
Molecular basis for DR-TB

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, gyrB
ETM *(Science 1994;263:277)*	inhA

MDR-TB options



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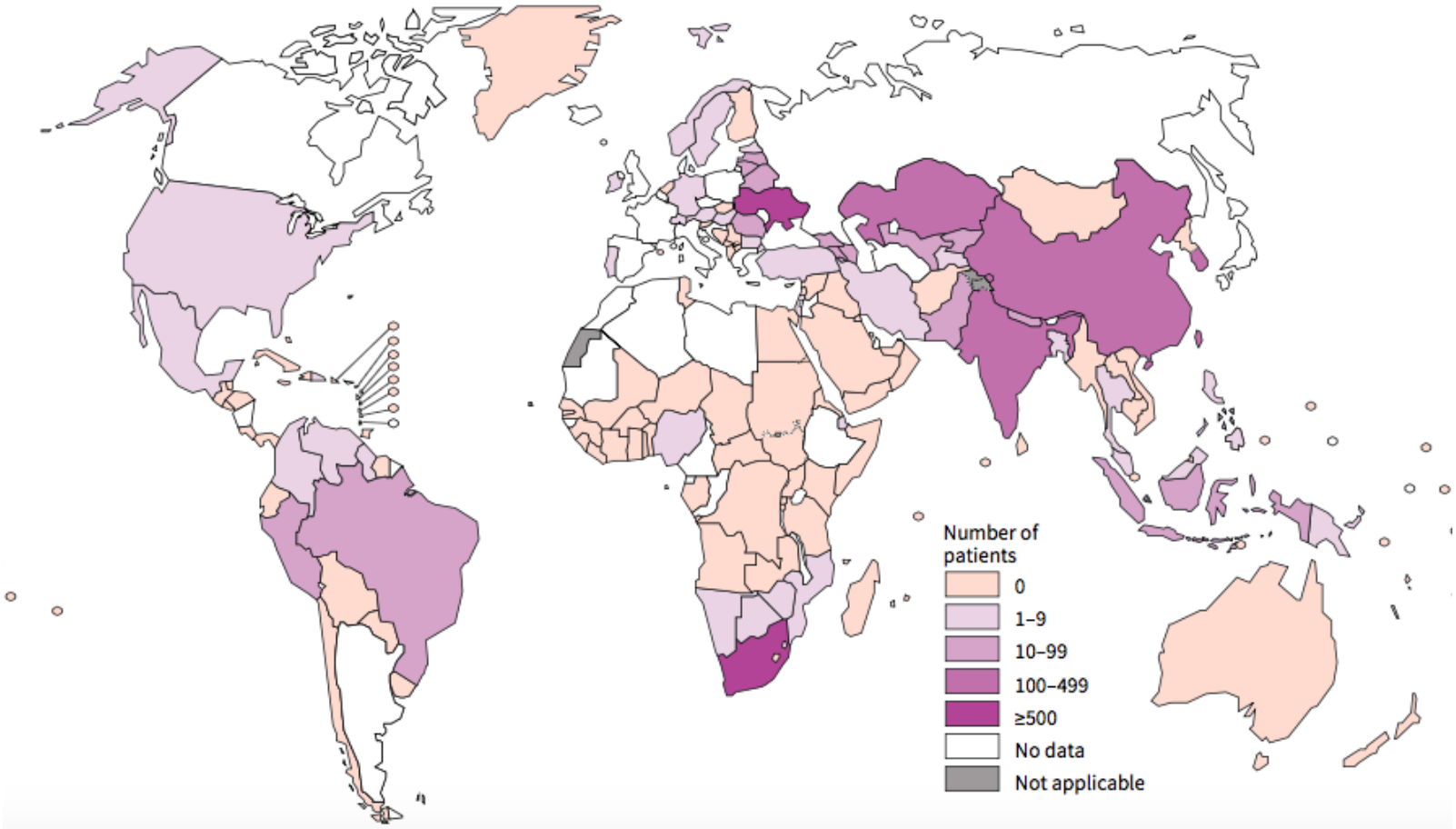
Treating HIV+MDRTB

- 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)*
- Outcomes: 56.9% success, however mortality higher *(Int J Tuberc Lung Dis 2015;19:969)*

XDR-TB: number of patients in 2013



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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 69:3103)*
    - Bedaquiline (76% conversion) *(Int J Tuberc Lung Dis 2015;19:979)*
  - 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
    - ?18 mo's post immune recovery (CD4>100/mm^3)

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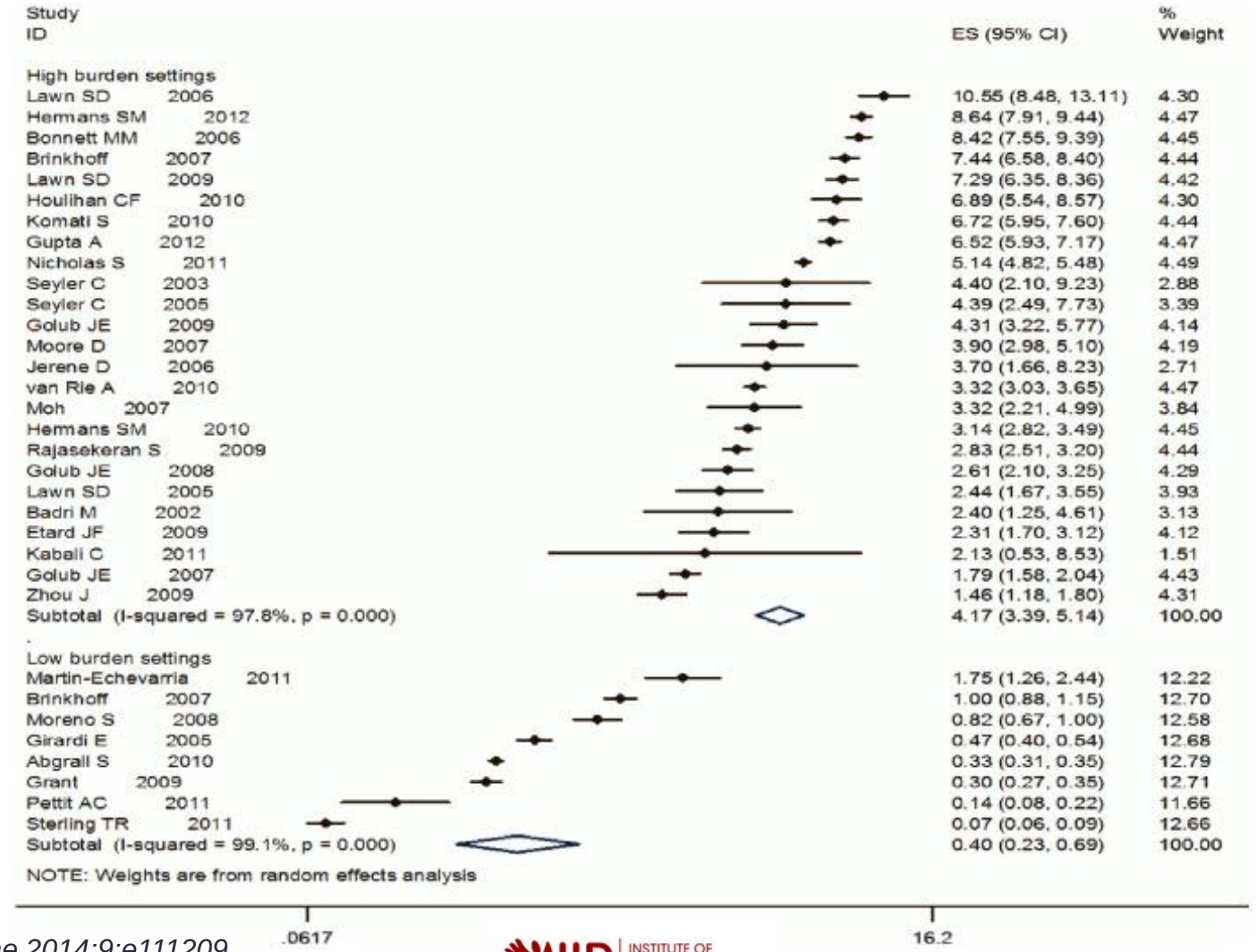
Prevention and control of TB in HIV

- 3 Is *(Int J Tuberc Lung Dis 2014;18:1159)*
  - 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

TB amongst HIV on ART



PLOS One 2014;9:e111209

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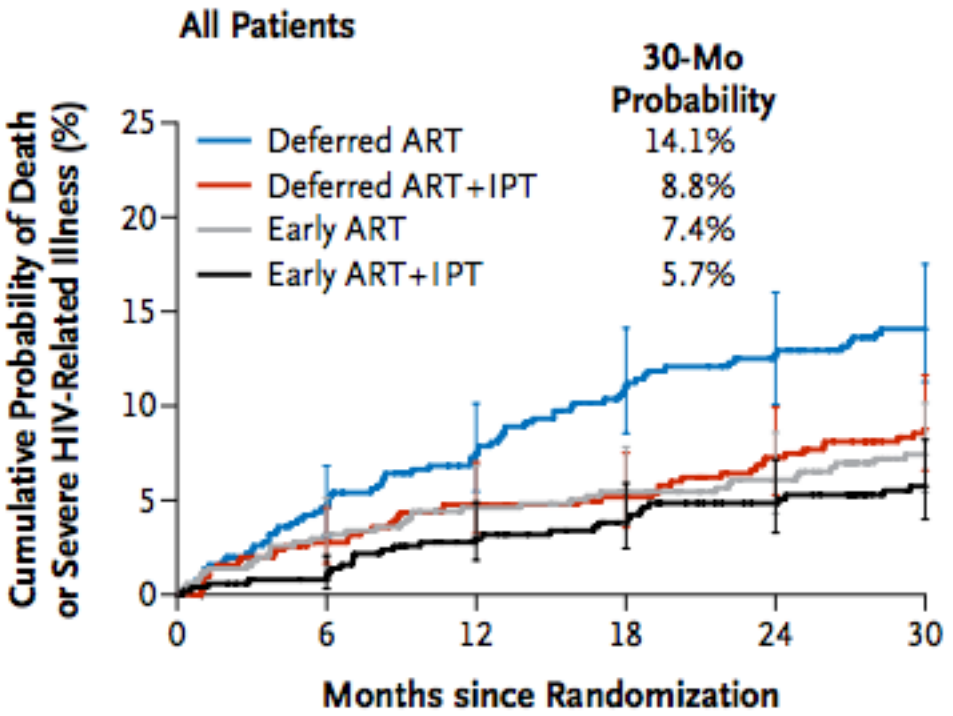
ART + INH: TEMPRANO ANRS 12136

A Primary Outcome



No. at Risk

Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418

New Engl J Med July 2015;

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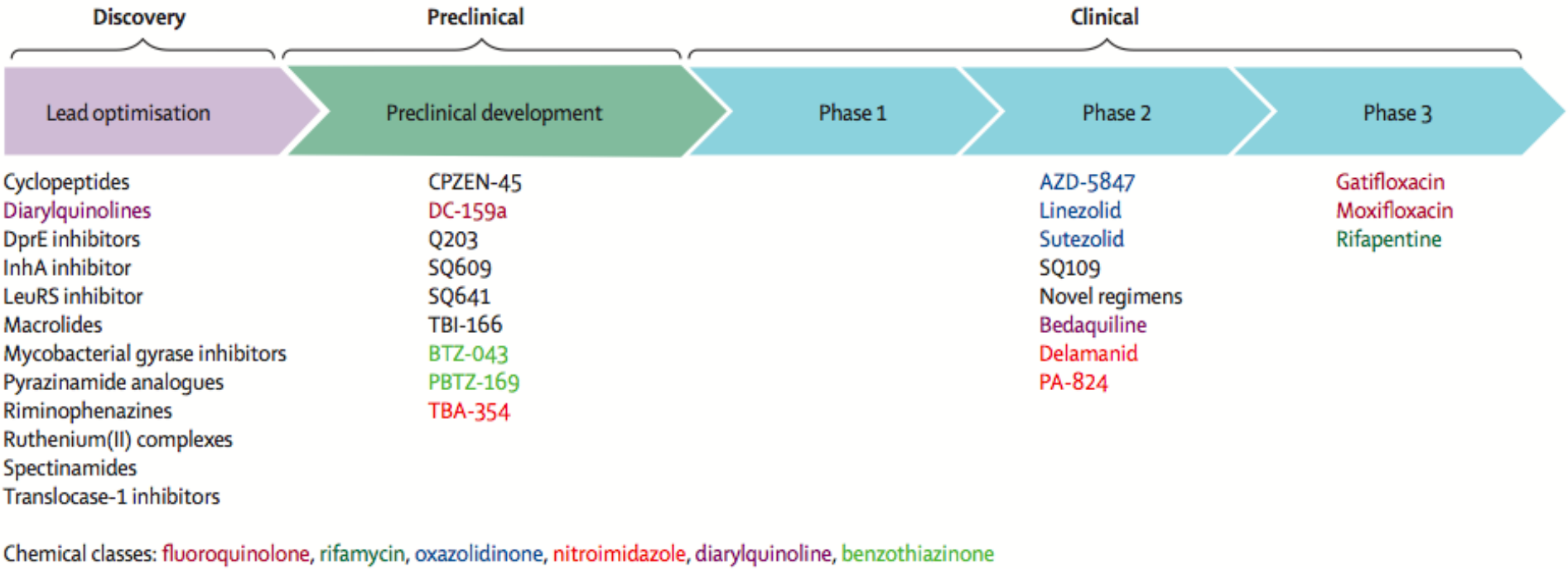
Prevention

- 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)*
  - MVA85A: disappointing *(Lancet Resp Med 2015;3:190)*
  - M72/AS01
    - Safe and immunogenic in PLHIV on cART *(AIDS 2014;28:1769)*

Anti-TB drugs: the pipeline



Lancet Infect Dis 2014;14:327

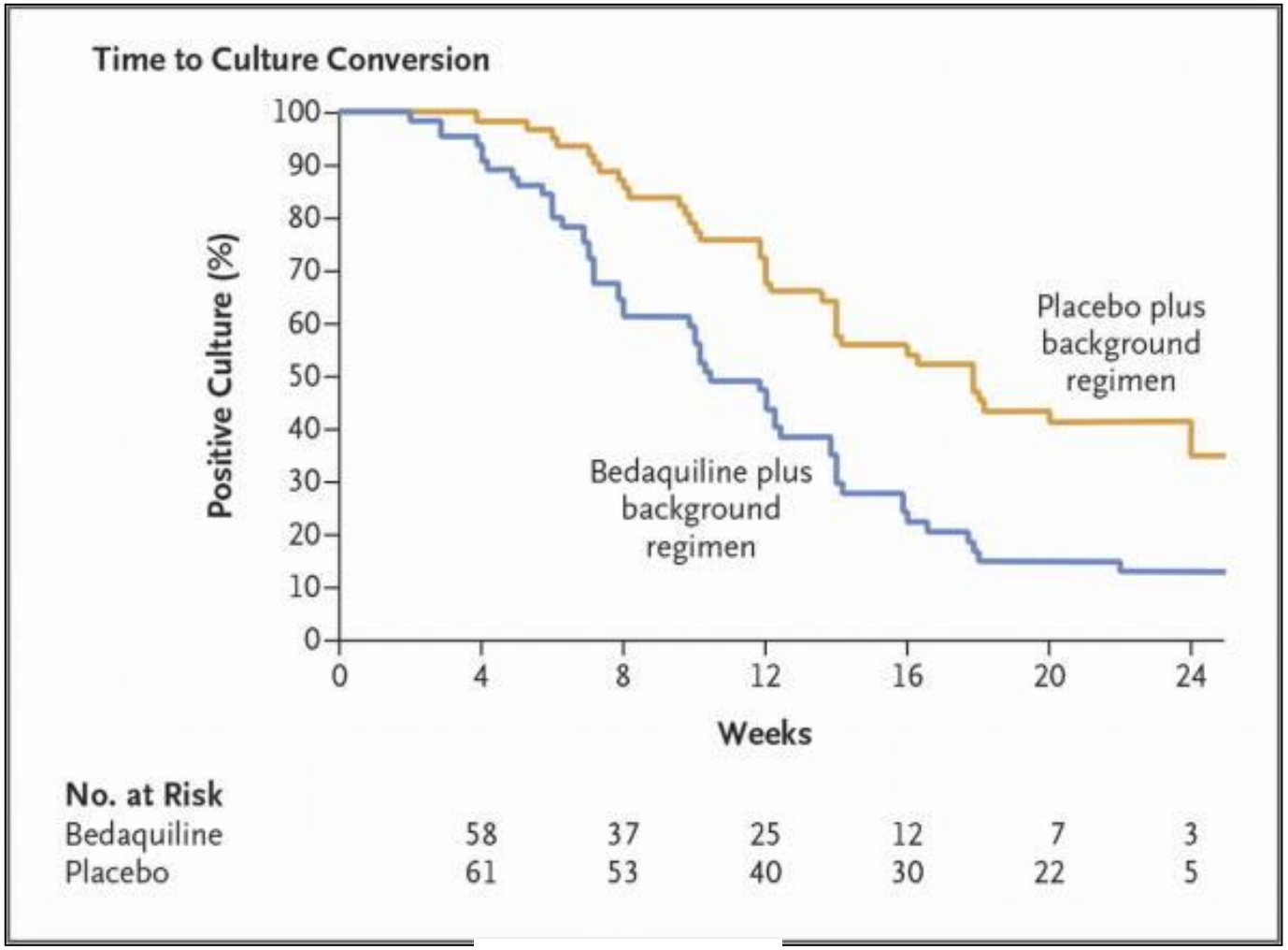
Future

- Incorporating FQ: reducing duration of TB treatment
  - ReMoxTB, OfloTub, Rifaquin studies *(New Engl J Med 2014;371:1577, ;New Engl J Med 2014;371:1588, New Engl J Med 2014;371:1599)*
  - None being studies specifically in HIV-TB

- Newer Drugs and combinations
  - Bedaquiline *(New Engl J Med 2014;371:723)*
  - Delaminid *(Drugs Today 2015;51:117)*
  - PA-824 (Pretominid)

- Repurposing and redosing
  - Rifamycins: RMP (upto 35 mg/kg), Rifapentine
  - Clofazamine *(Clin Infect Dis 2015;60:1361)*

Bedaquiline efficacy



New Engl J Med 2014;371:723

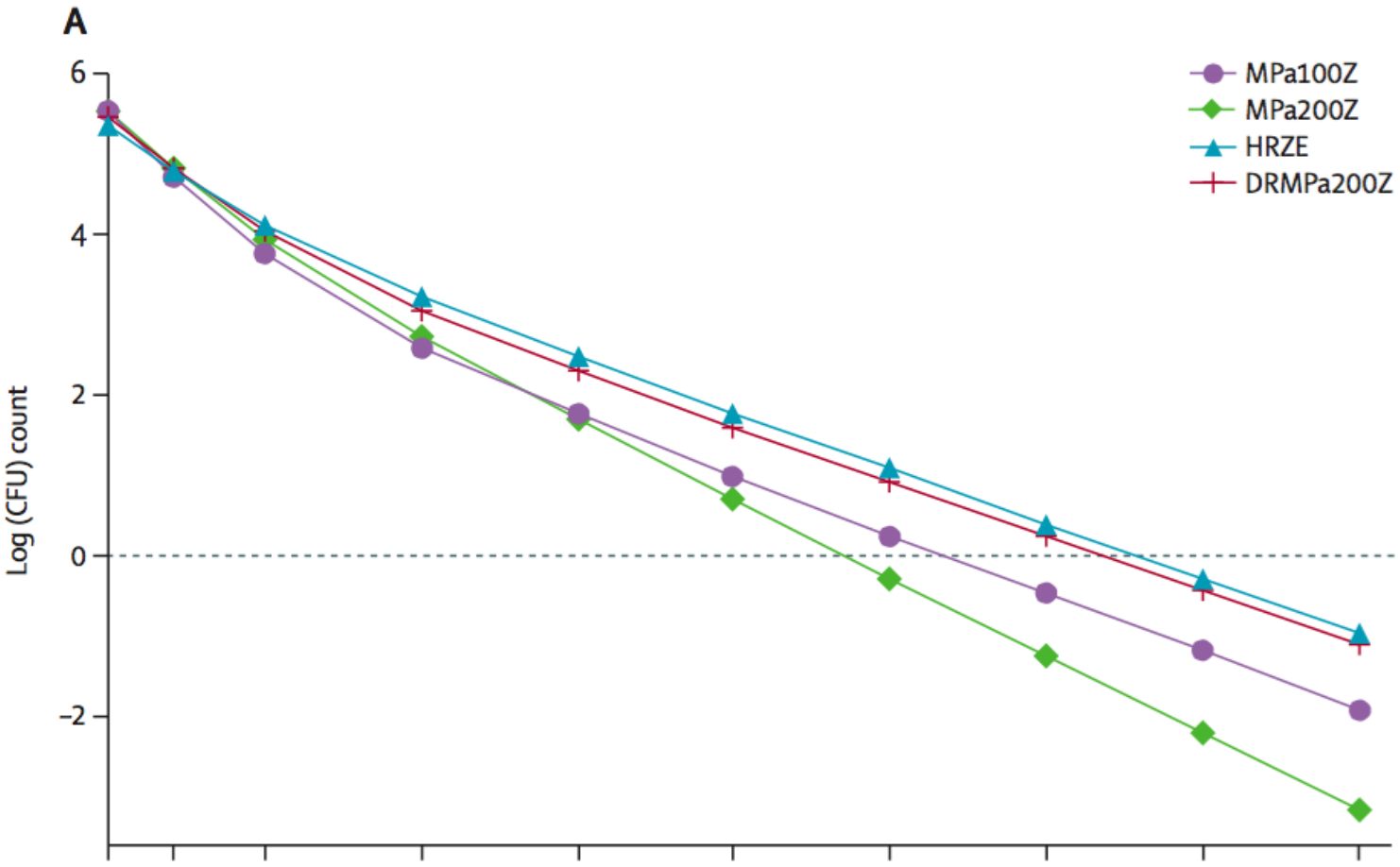
Bedaquiline: Use

- Added to a WHO recommended MDRTB regimen, if
  - Inability to design a 4 drug regimen including PZA
  - Documented FQ resistance (pre-XDRTB)

  - Use in caution amongst HIV pts

WHO interim policy recommendation 2013

Novel regimen: Pretominid+Mox+PZA

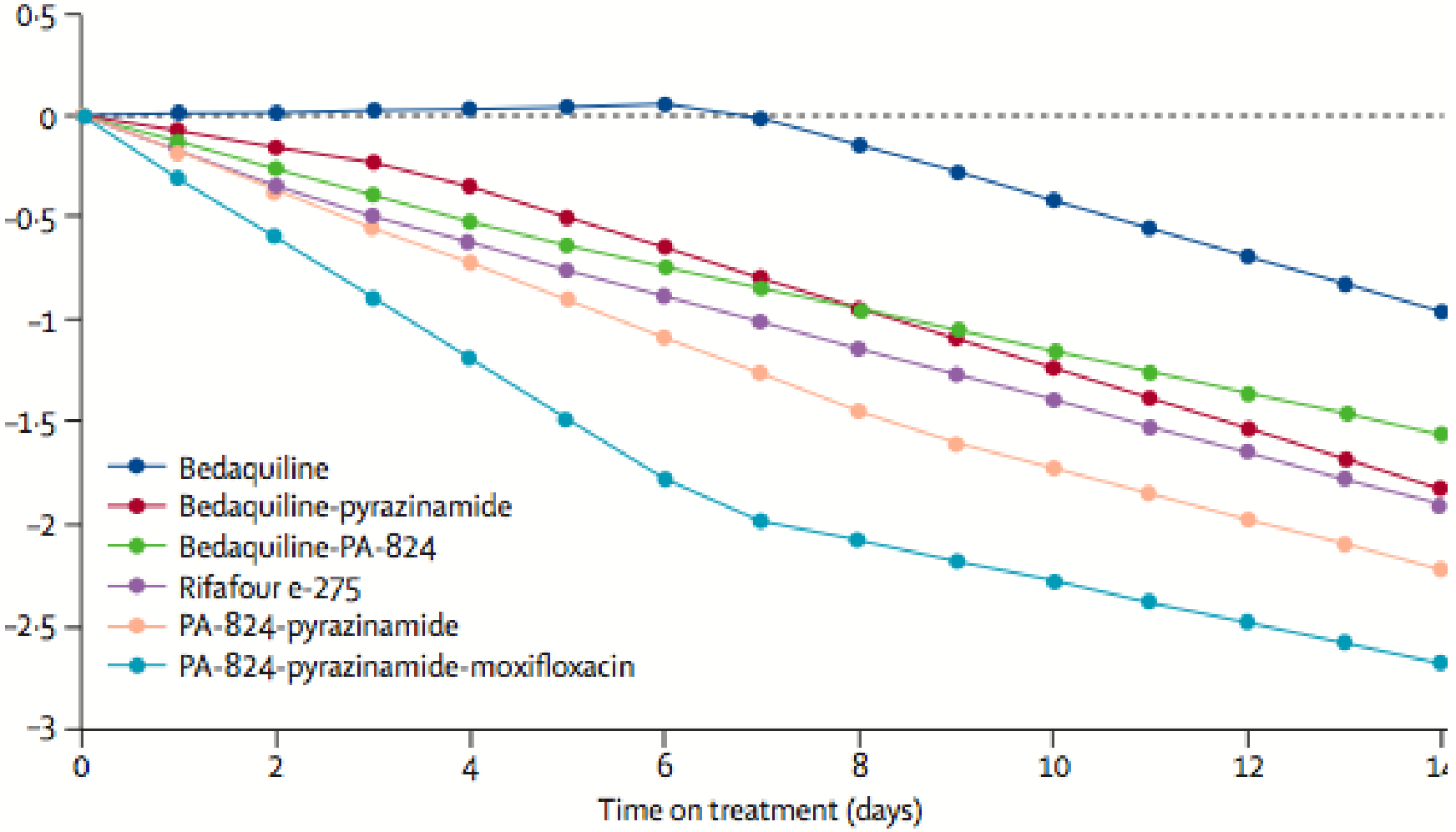


Lancet 2015;385:1738

Summary

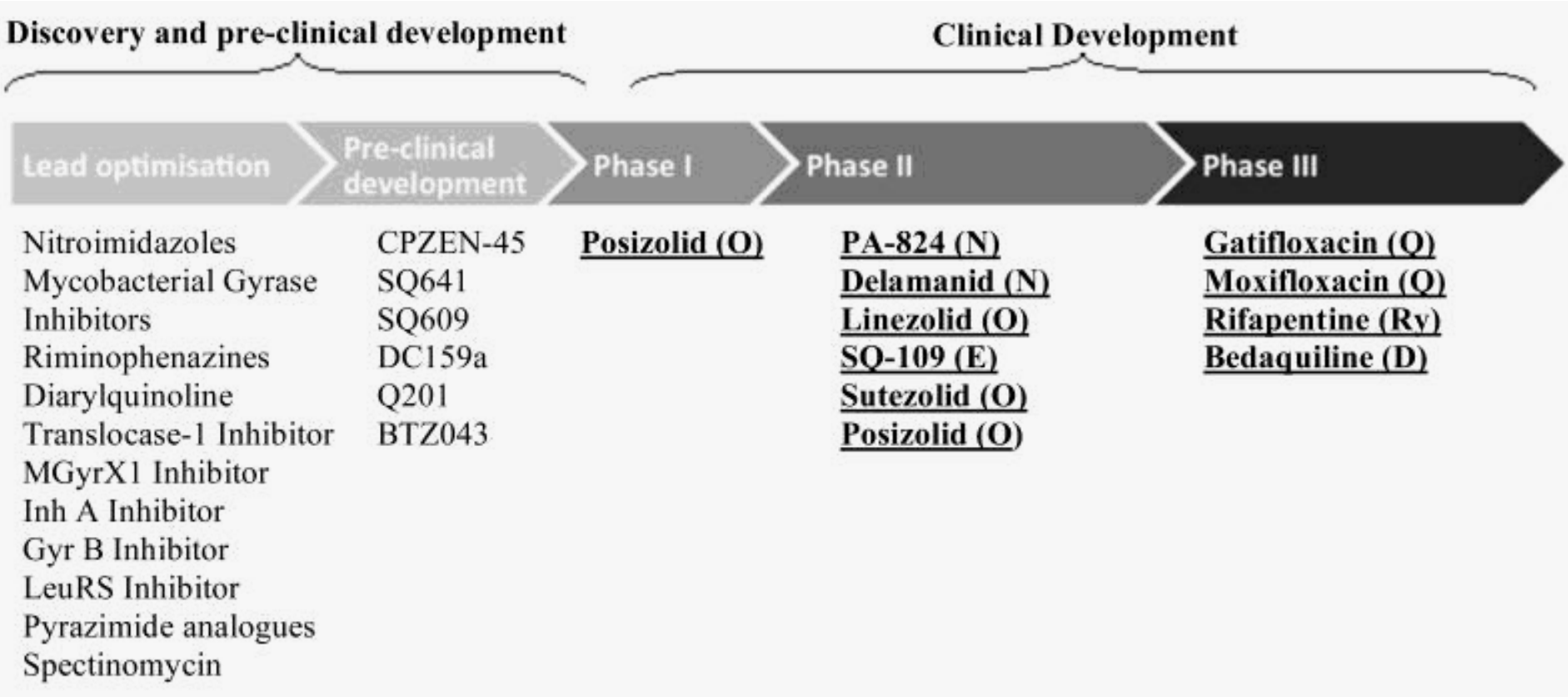
- Deadly synergy
- Screening for active TB critical for all HIV +
  - Implement Rapid molecular DST
- ART for all TB patients
  - Timing stratified by CD4 count
- Understanding ARV-ATT interactions and toxicities
- Prevent and treat DR-TB

ATT: Future regimen?



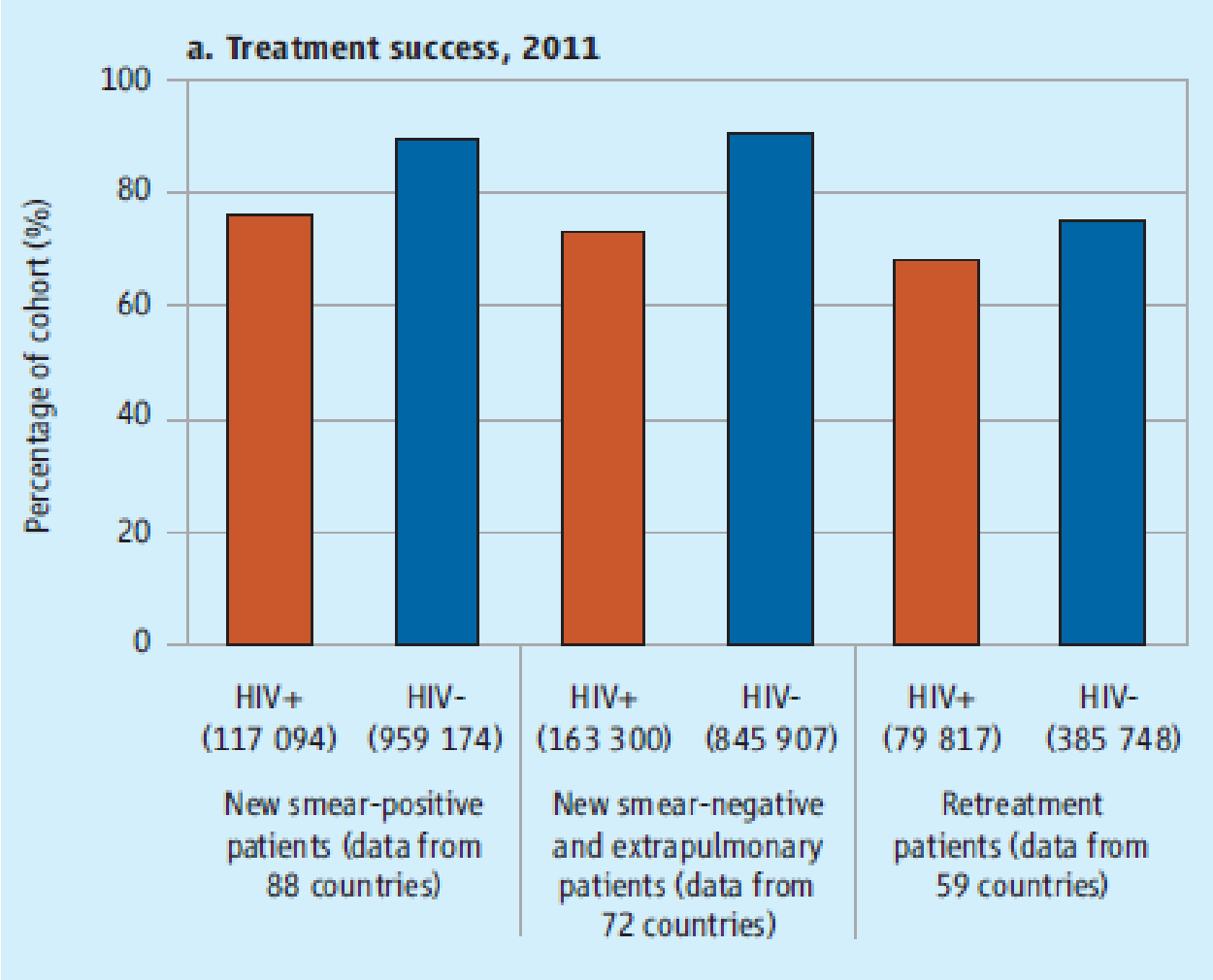
Lancet 2012;380:986

TB drug pipeline



Curr Resp Med Rev 2013;9:200

The problem: TB treatment success and HIV



WHO Global TB Report 2013

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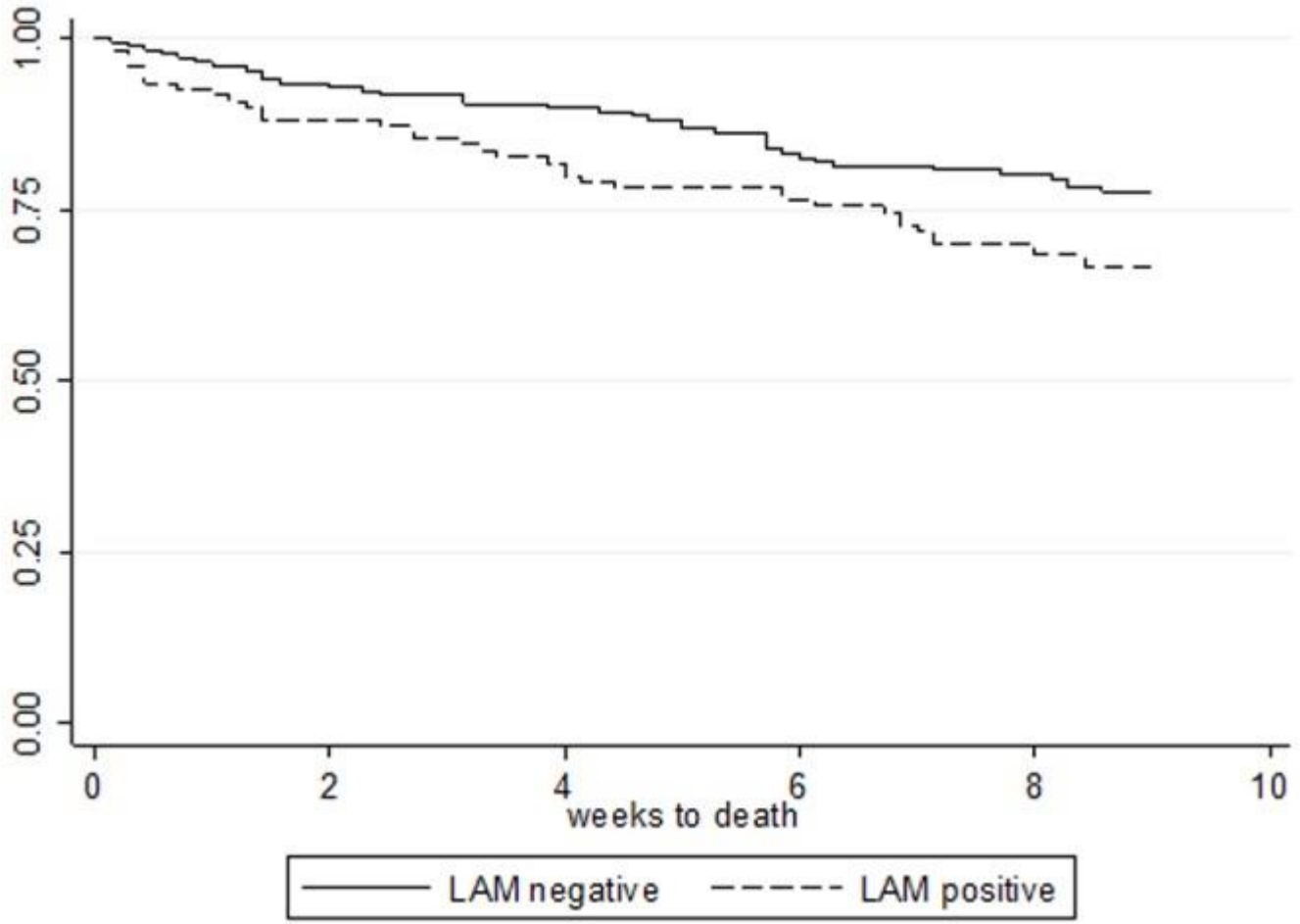
HIV and MDR-TB

- 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



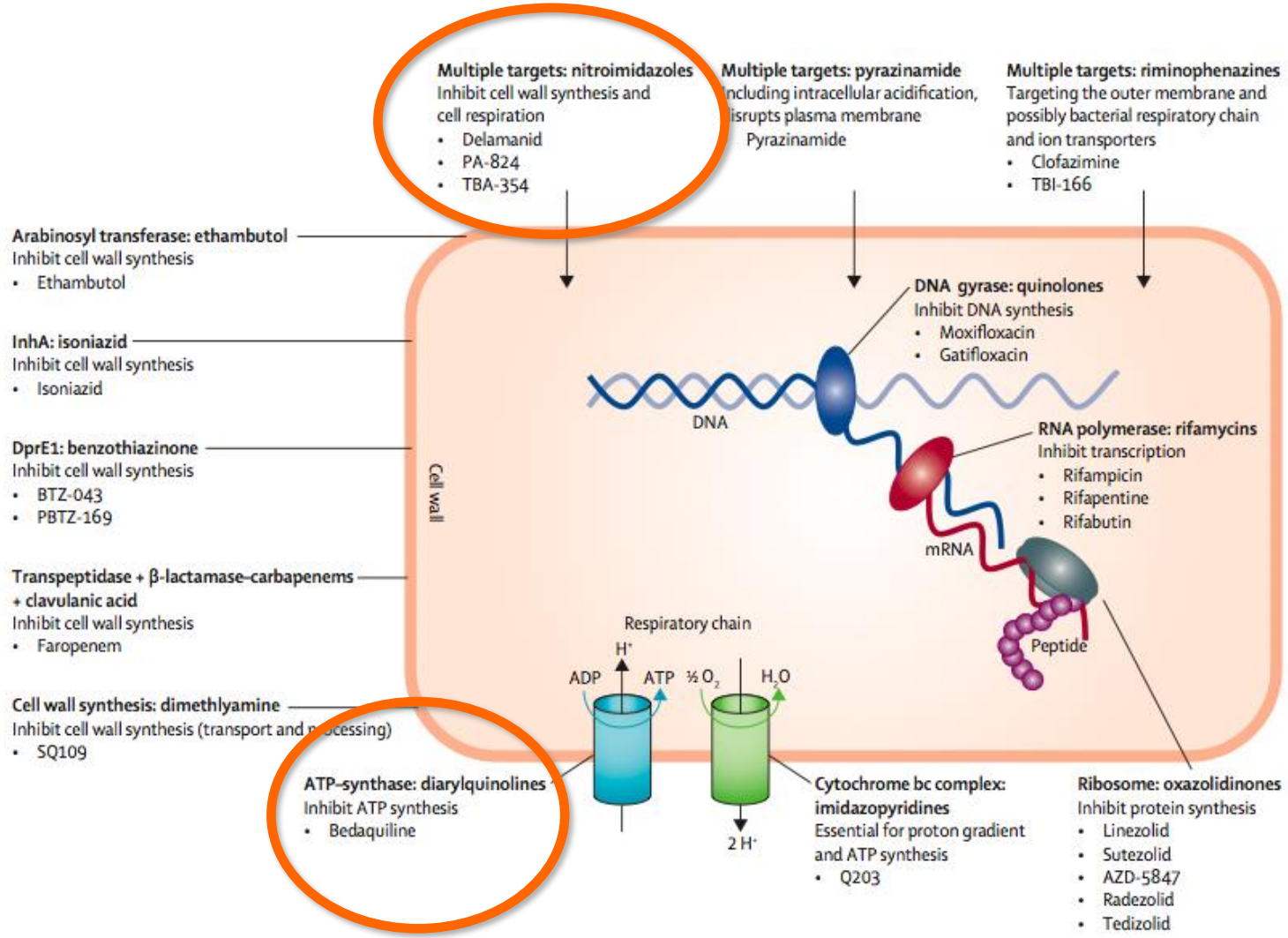
PLOS One 2014;9:e101459

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)*

Anti-TB drugs: Mechanism of action



Lancet Infect Dis 2014;14:327

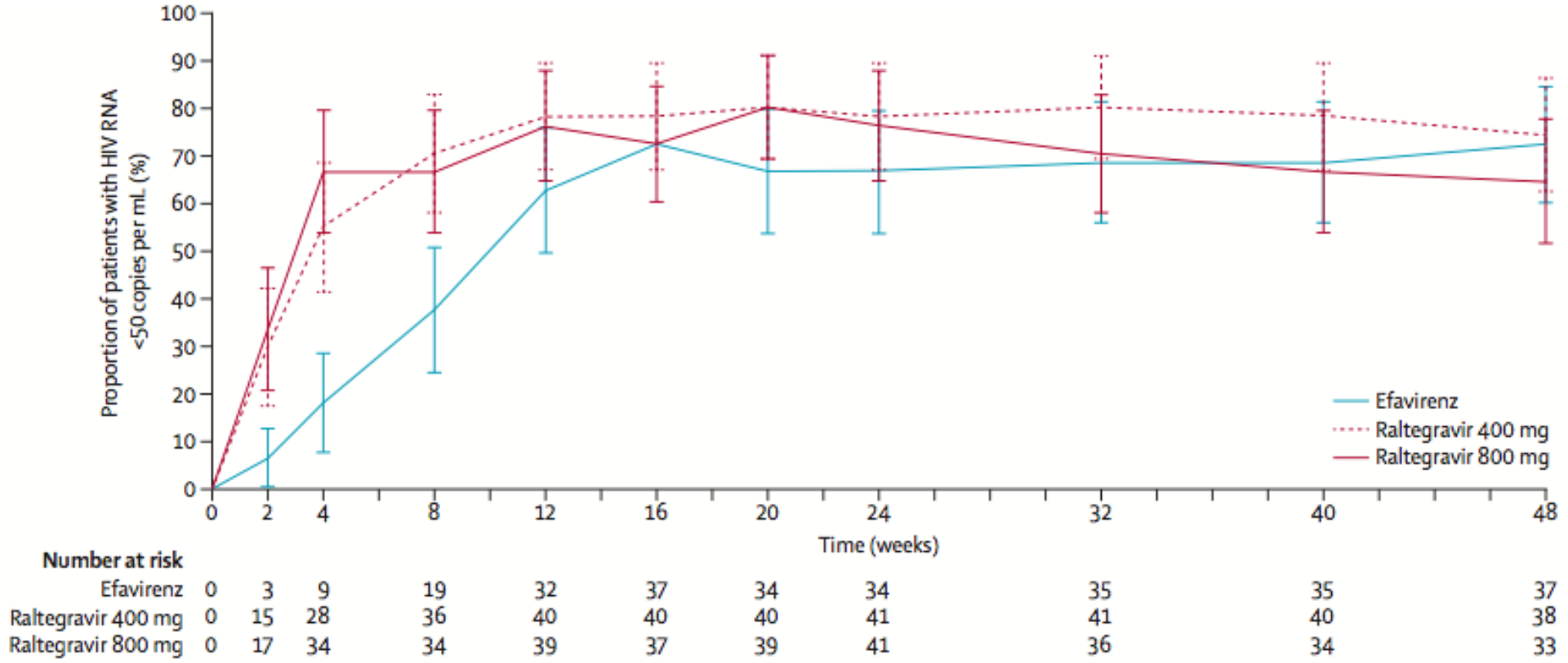
ART on CD4 improvement with/out TB

- Similar improvements in CD4 counts (AIDS 2015;29:1363)

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)*

RAL with RMP: REFLATE

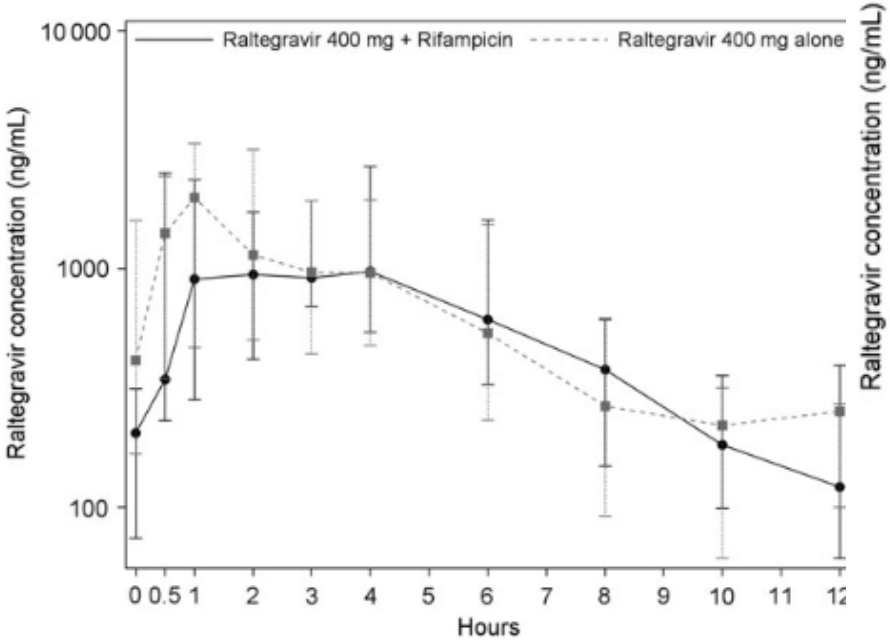


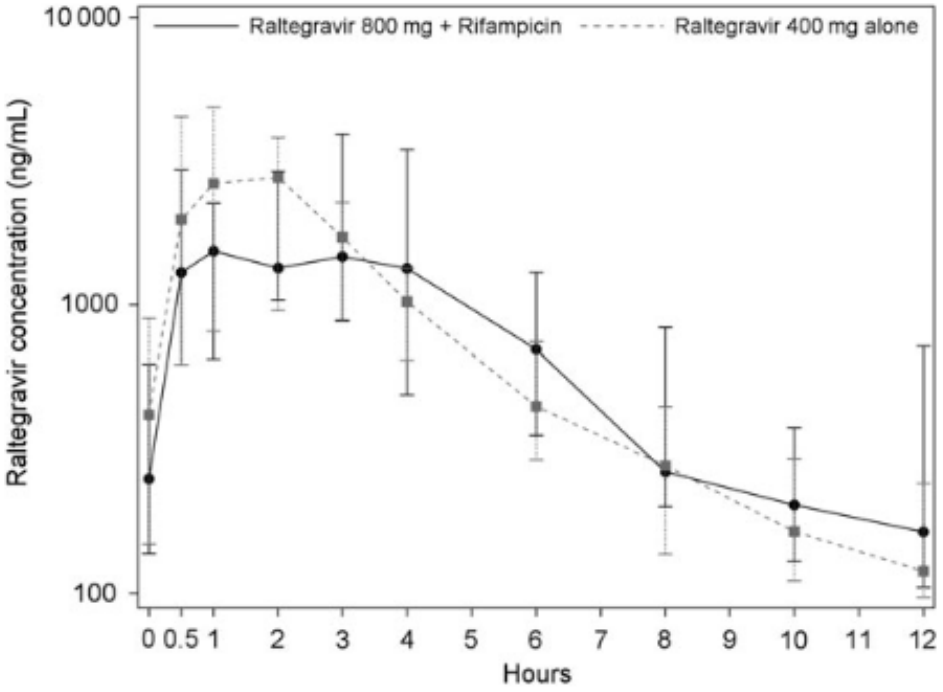
Number at risk

Efavirenz	0	3	9	19	32	37	34	34	35	35	37
Raltegravir 400 mg	0	15	28	36	40	40	40	41	41	40	38
Raltegravir 800 mg	0	17	34	34	39	37	39	41	36	34	33

Lancet Infect Dis 2014;14:459

RAL 400 vs 800 mg





Clin Infect Dis July 2015;advance access

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-DTV/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

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

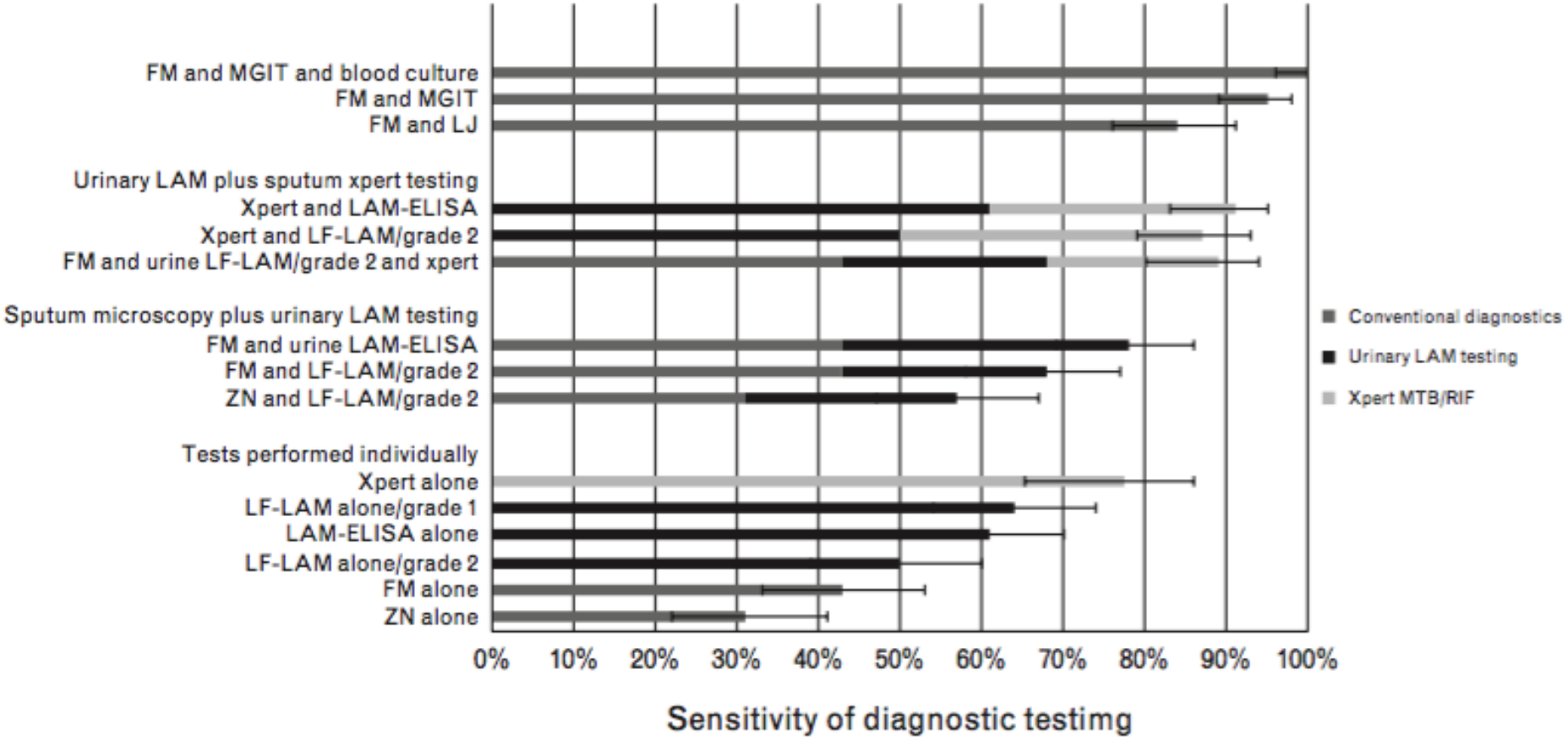
- Practically incurable

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/RFP qd x 4 weeks (with EFV) (Clin Infect Dis Jun 2015; epub)
  - INH+RMP for 3 mo

LAM+XpertTB better than either alone



AIDS 2014;28:1307