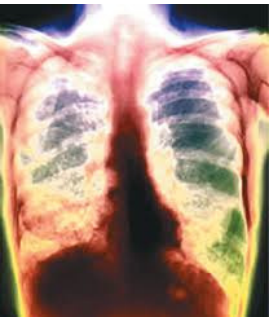
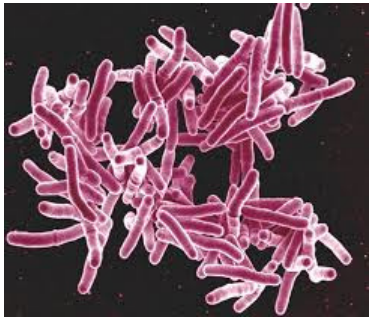
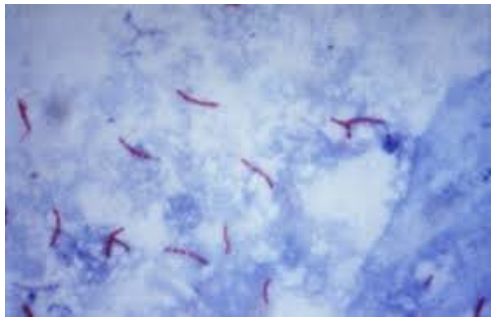
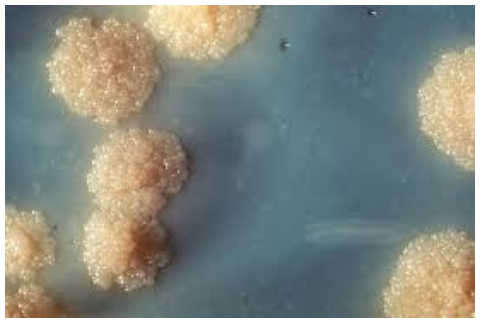
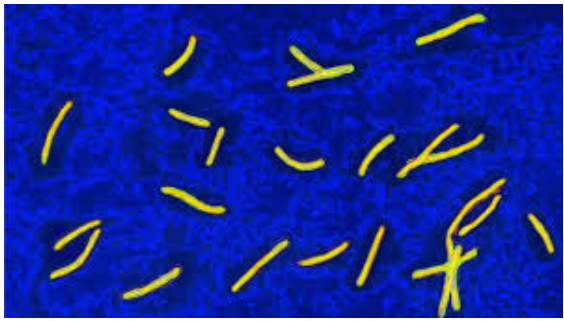
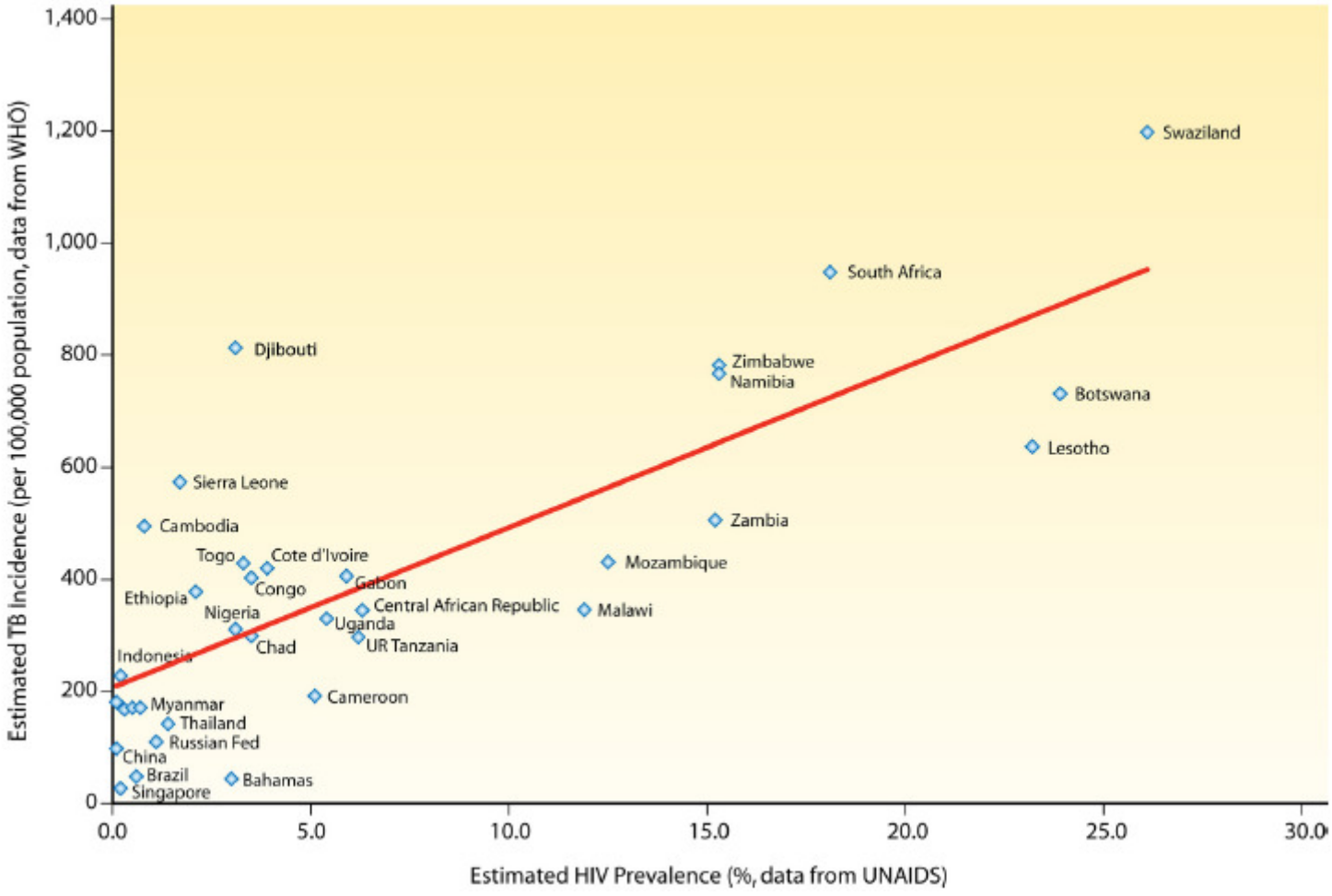






Using new antiretroviral agents and dosing with TB treatment

Samantha Potgieter

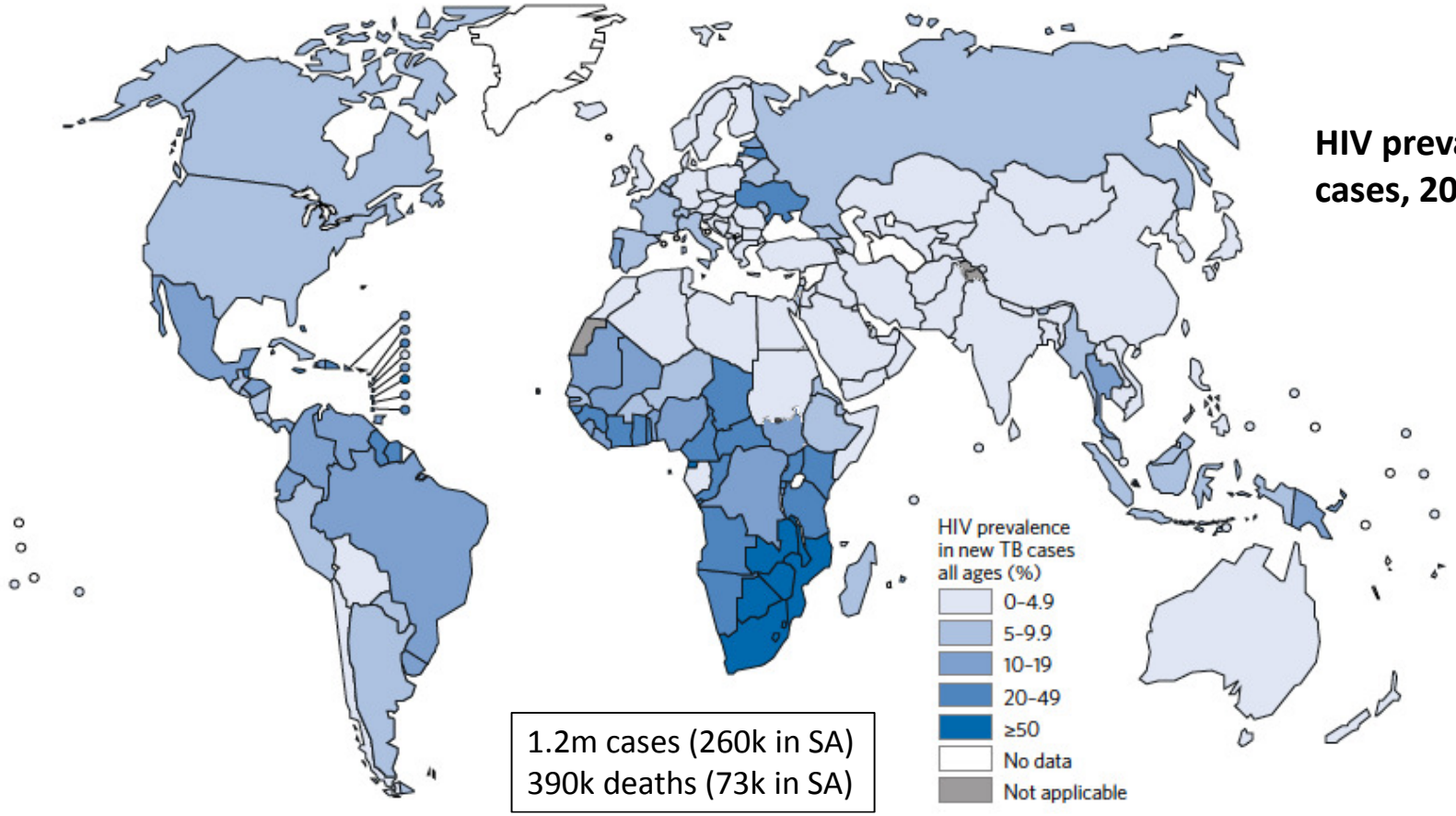
Sean Wasserman University of Cape Town

HIV drives TB incidence



Kwan CMR 2011

High burden of HIV-associated TB

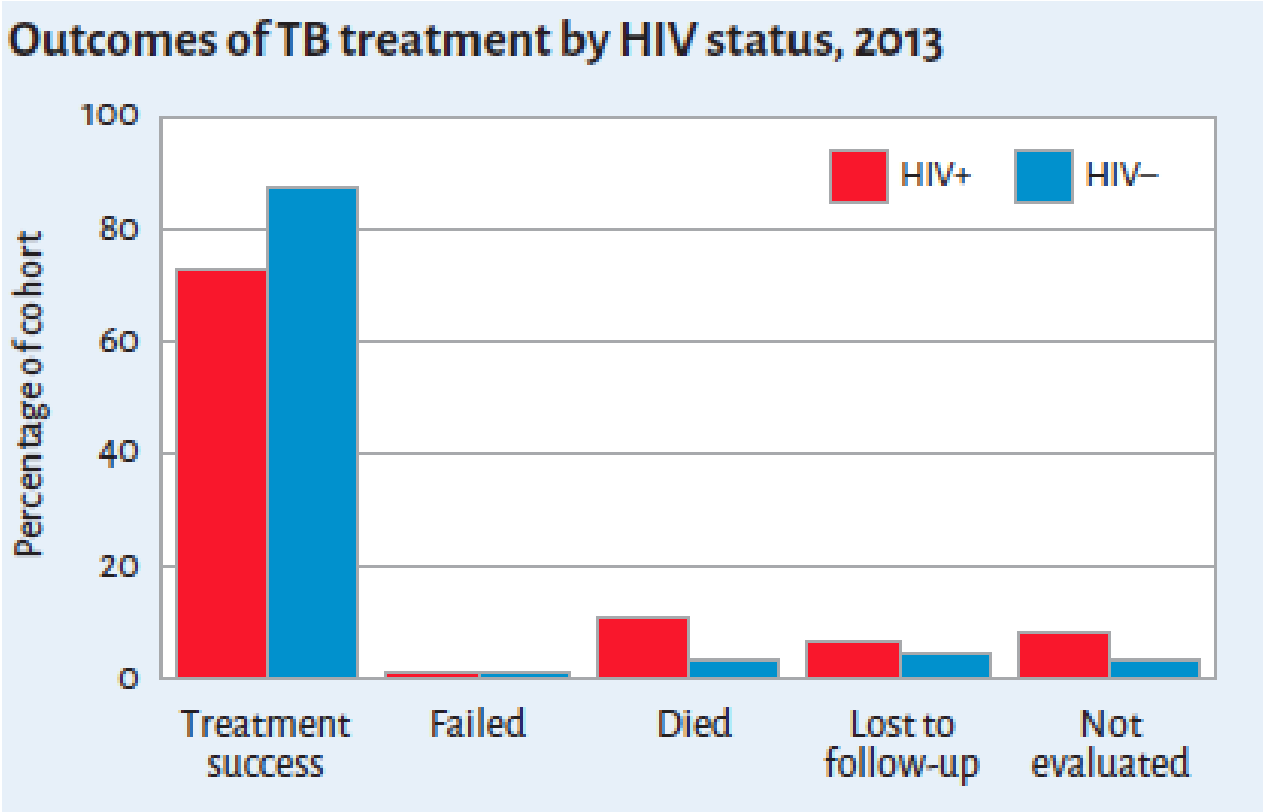


HIV prevalence in TB cases, 2015

1.2m cases (260k in SA)
390k deaths (73k in SA)

WHO Global Report 2016

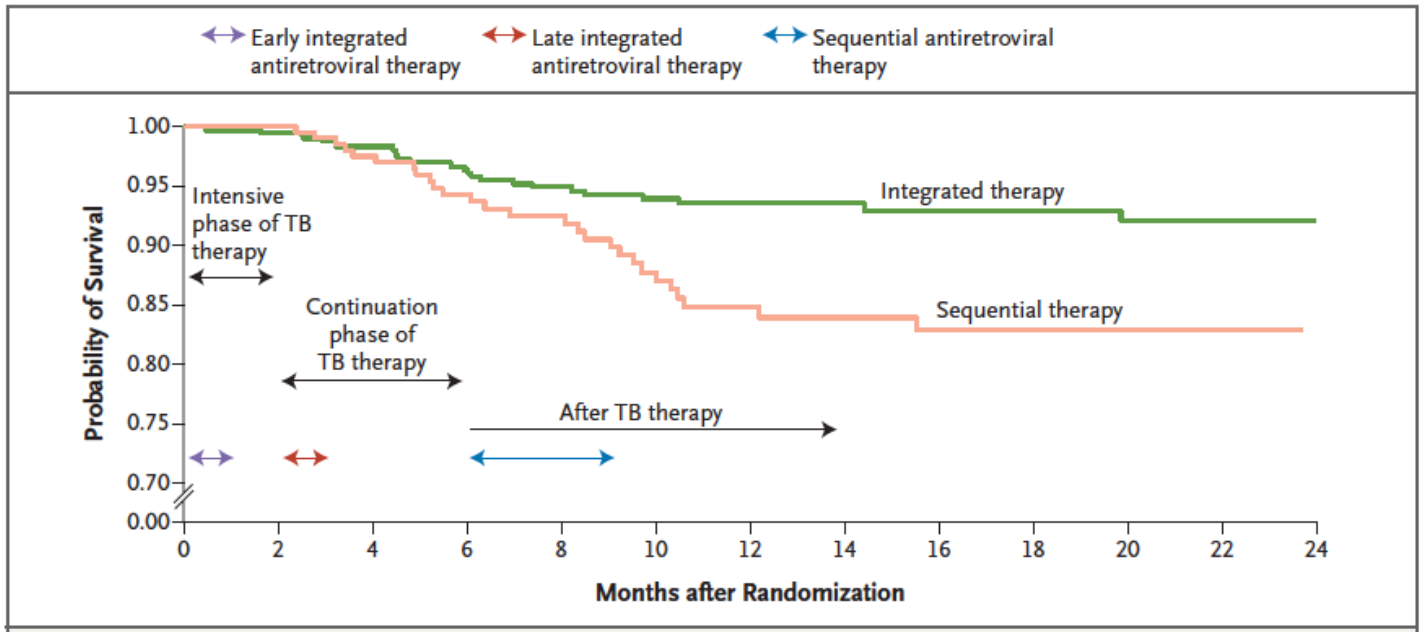
HIV-associated TB has worse outcomes



WHO Global report 2015

Improved outcomes on ART

- Observational studies: 64 - 95% reduced mortality
- SAPIT: 56% reduced mortality when ART started during TB Rx (median CD4 ~150)



Abdool Kariem NEJM 2010

All HIV-infected people should start ART

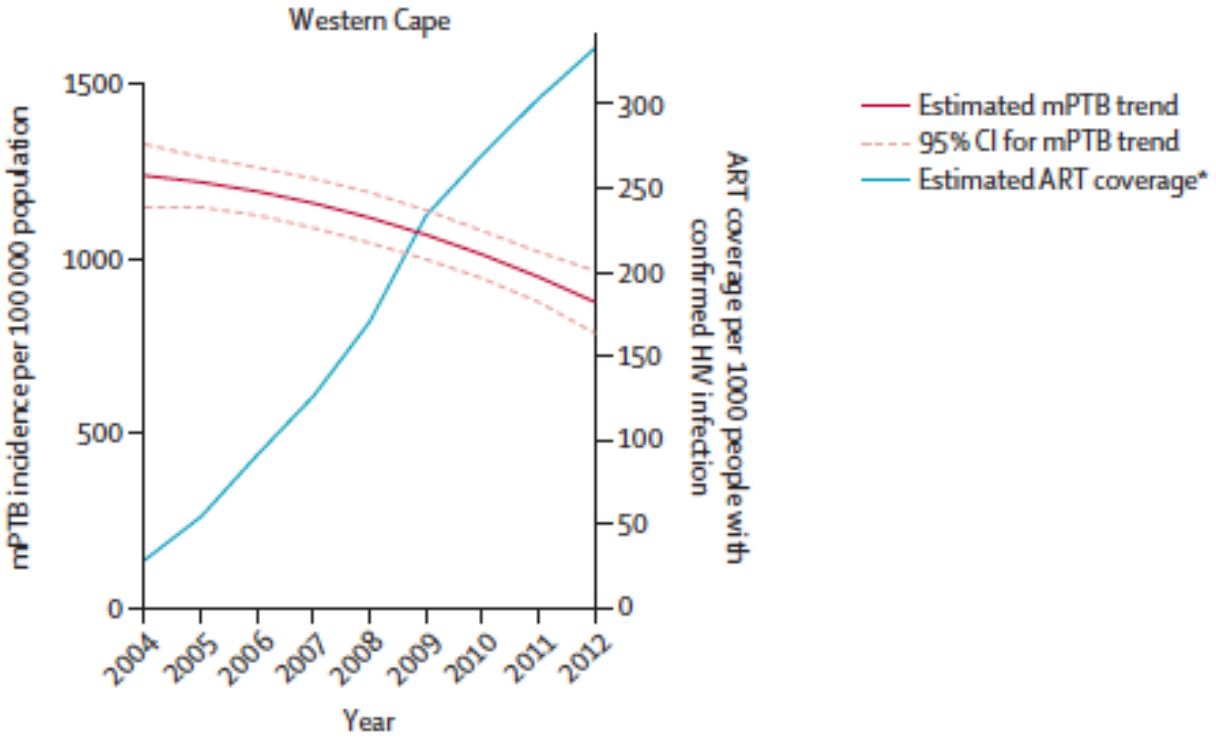
World Health Organization

Recommendation 1: When to start ART among people living with HIV			
Target population	Specific recommendation	Strength of the recommendation	Quality of the evidence
Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*

health

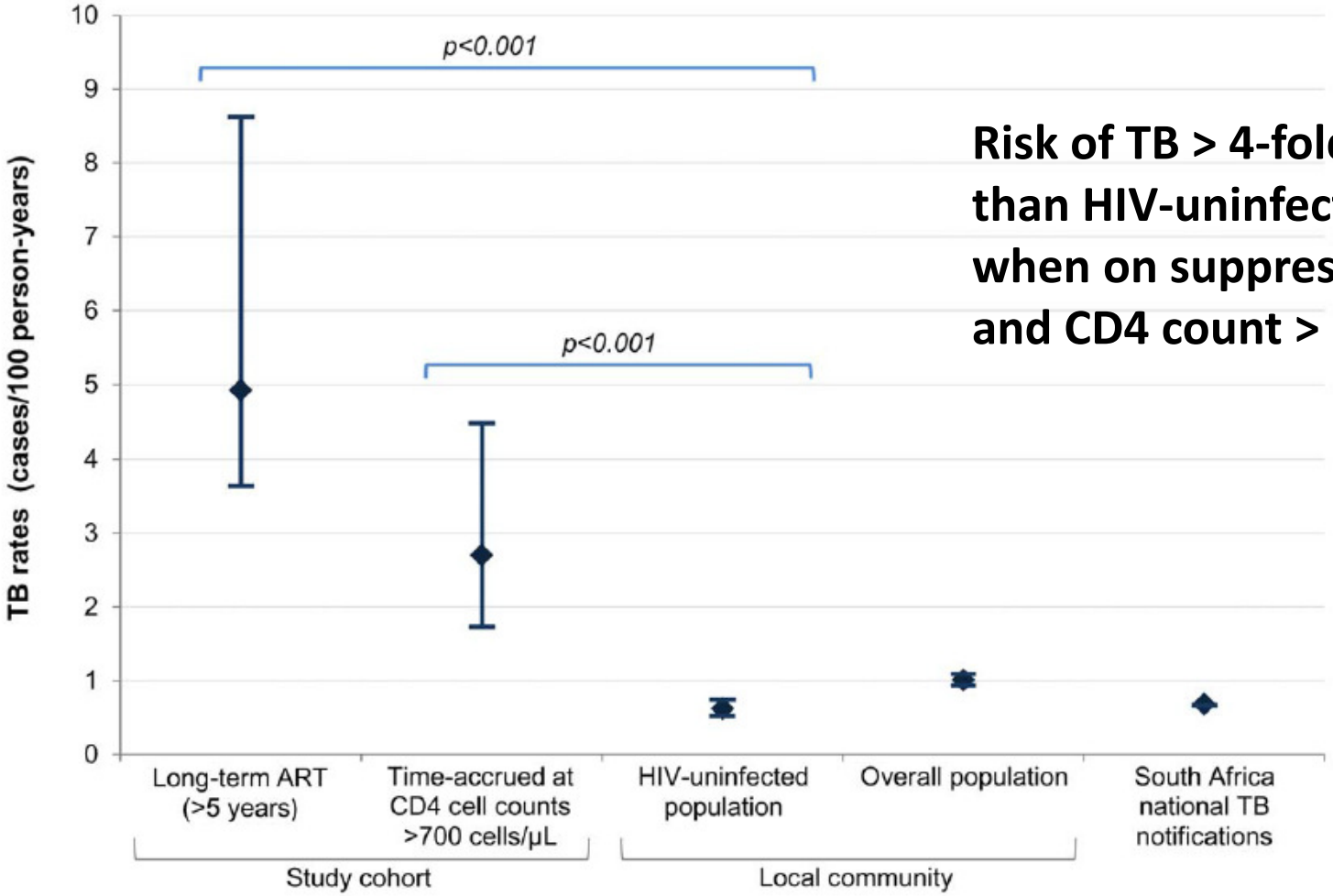
Department:
Health
REPUBLIC OF SOUTH AFRICA

ART coverage associated with reduced TB incidence



Nanoo LID 2015

ART not fully protective



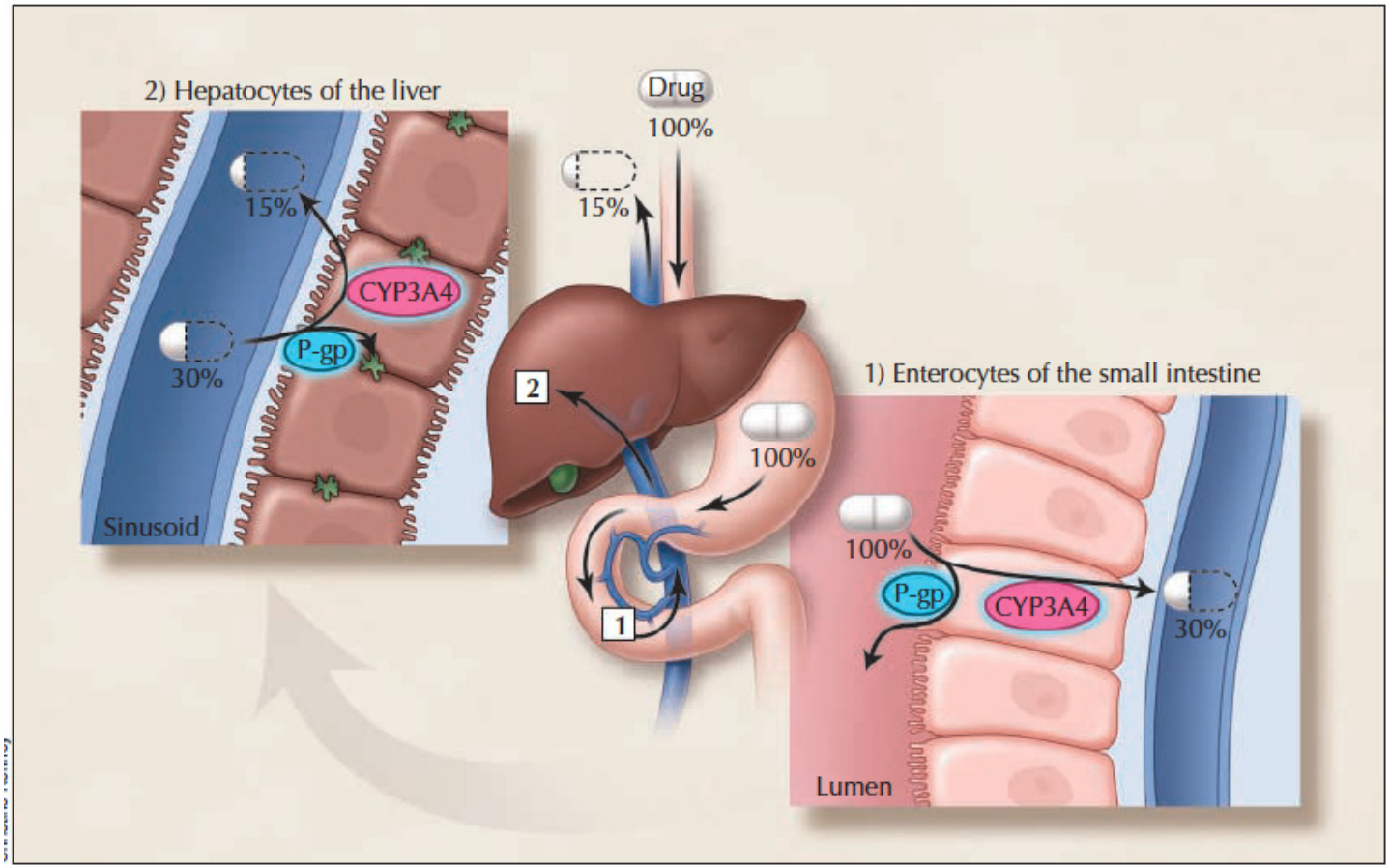
Risk of TB > 4-fold higher than HIV-uninfected even when on suppressive ART and CD4 count > 700

Gupta PloS ONE 2012

Many people will be on TB treatment and ART

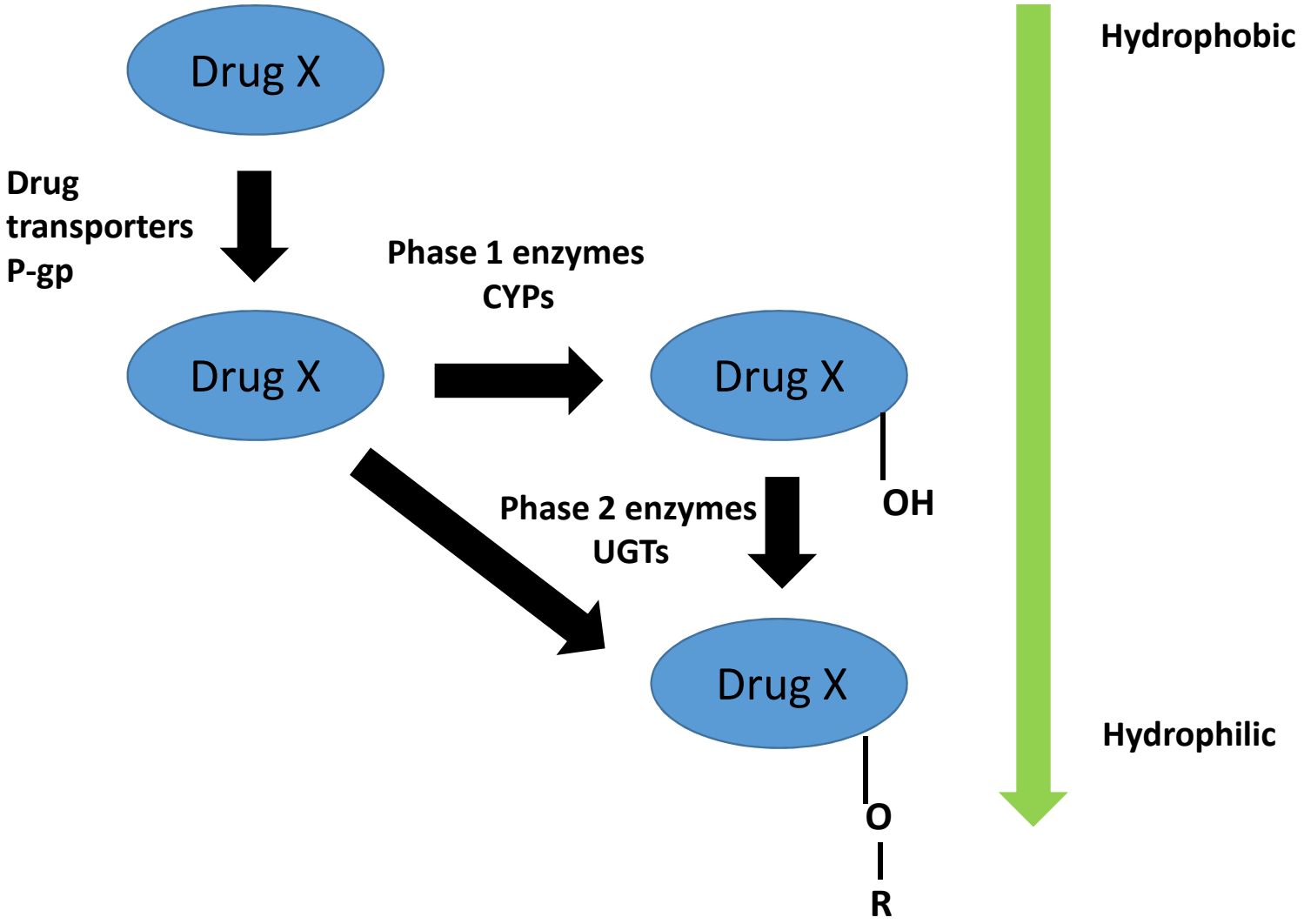
- Important to understand co-prescribing in HIV/TB
- Consequences of DDIs:
  - Reduced treatment efficacy due to low exposures (in both directions)
  - Increased risk of toxicity due to increased concentrations
- Identify and manage shared toxicities

Bioavailability influenced by drug transporters and metabolizing enzymes

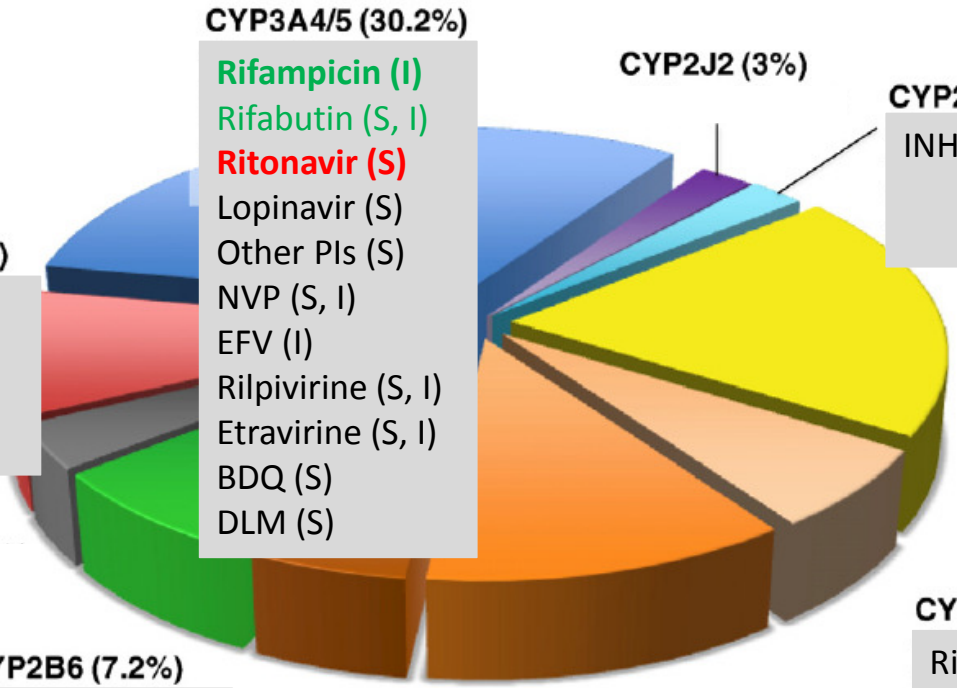


Induced by rifampicin
Inhibited by ritonavir

Bailey CMAJ 2004


Drug X
Drug transporters P-gp
Drug X
Phase 1 enzymes CYPs
Drug X
OH
Phase 2 enzymes UGTs
Drug X
O
R
Hydrophobic
Hydrophilic

CYPs major metabolic pathway for TB drugs and ARVs



CYP3A4/5 (30.2%)
Rifampicin (I)
Rifabutin (S, I)
Ritonavir (S)
Lopinavir (S)
Other PIs (S)
NVP (S, I)
EFV (I)
Rilpivirine (S, I)
Etravirine (S, I)
BDQ (S)
DLM (S)

CYP2J2 (3%)

CYP2E1 (3%)
INH (I)

CYP2D6 (20%)

CYP2C19 (6.8%)
Rifampicin (I)
EFV (I)
Etravirine (S)

CYP2C9 (12.8%)
Rifampicin (I)
Ritonavir (I)
Etravirine (S)

CYP2C8 (4.7%)
Rifampicin (I)
Ritonavir (I)

CYP2B6 (7.2%)
Rifampicin (I)
EFV (S, I)
NVP (S, I)

CYP2A6 (3.4%)
Rifampicin (I)
[EFV] (S)
INH (In)

CYP1A2 (8.9%)
Rifampicin (I)
Ritonavir (I)

Source of PK and PD variability and DDIs

Zanger Pharmacology and Therapeutics 2013

Treatment for DS-TB same in HIV on ART

- **Rifampicin**
- Isoniazid
- Ethambutol
- Pyrazinamide

2 months

Weight-based dosing

30 - 37 kg:	2 RHZE
38 - 54 kg:	3 RHZE
55 - 70 kg:	4 RHZE
> 70 kg:	5 RHZE

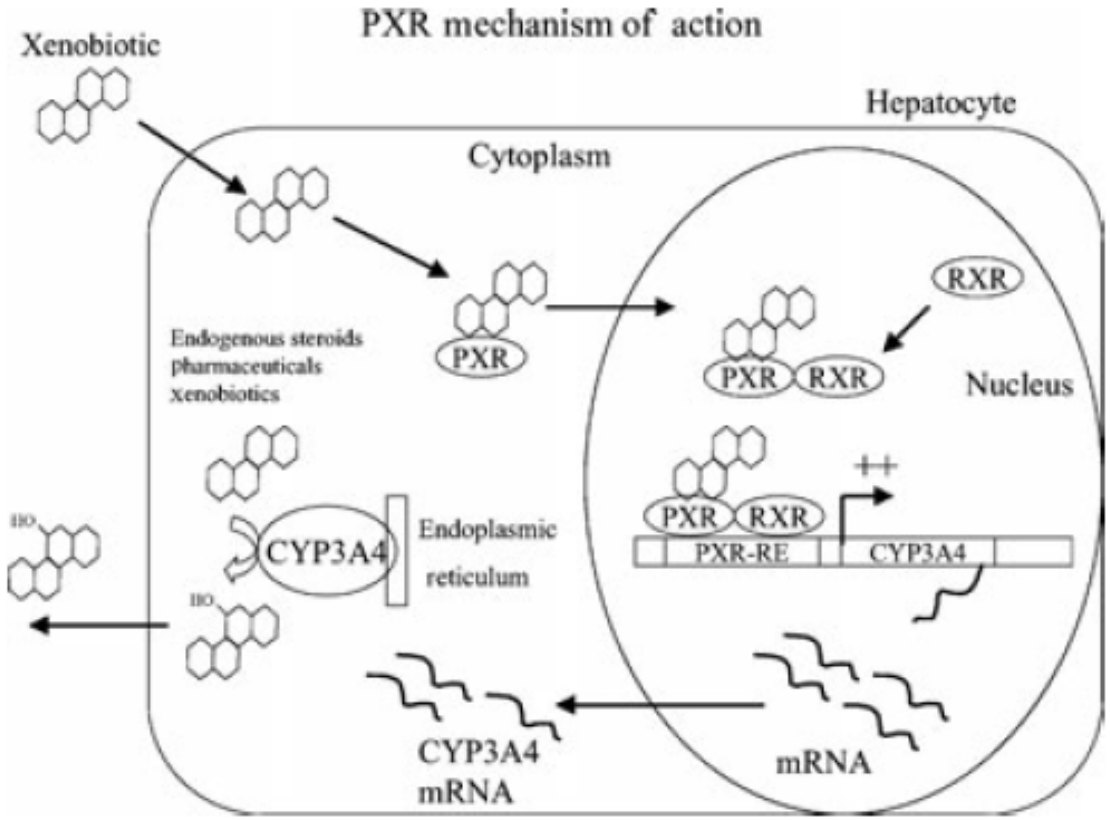
- **Rifampicin**
- Isoniazid

4 months

30 - 37 kg:	2 RH (150/75)
38 - 54 kg:	3 RH (150/75)
55 - 70 kg:	2 RH (300/150)
> 70 kg:	2 RH (300/150)

Give daily

Rifampicin leads to increased transcription of CYP3A4



Tompkins J Biochem Mol Toxicol 2007

Rifampicin is a potent inducer of multiple enzyme/transporters: DDIs

Enzyme/transporter	ARV substrate
CYP3A4 CYP2B6	PIs, NVP EFV, NVP
P-glycoprotein	PIs TAF
BCRP	TAF
UGT1A1	Raltegravir Dolutegravir

Rifampicin and EFV

- Package insert reports reduced EFV exposure and recommends dose increase to 800 mg daily with rifampicin if weight > 60kg
- But **no difference in exposure or impact on clinical outcomes when EFV 600 mg used with rifampicin**
- **Conclusion: No dose adjustment for regimen 1 ART on standard TB treatment**

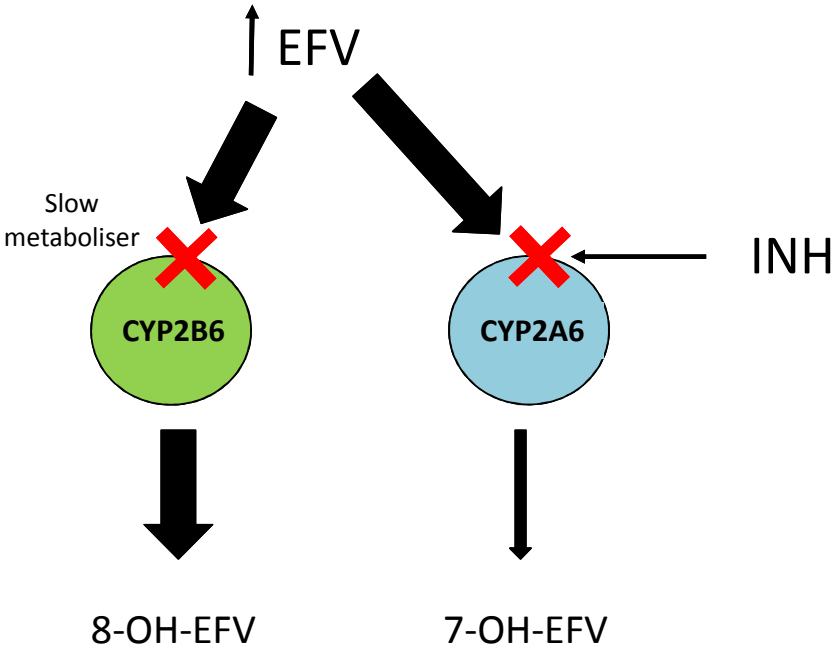
Cohen Antivir Ther 2009
Friedland JAC 2006
Manosuthi AIDS 2005

Paradoxically EFV exposure increased in some patients on TB treatment

- SAPIT study: 30% reduction in EFV clearance during TB treatment (‘slow metabolizers')
- EFV concentrations higher in patients with slow metabolizer *CYP2B6* genotypes on TB Rx
- Prevalence of slow metaboliser genotypes ~20% in black South Africans

Gengiah Eur J Cin Pharm 2012
Luetkemeyer CID 2013

Increased EFV concentrations during TB treatment in patients with slow metaboliser genotypes may be explained by INH inhibition of CYP2A6



This may lead to increased risk of EFV-neurotoxicity

Consider EFV toxicity in all HIV/TB patients with unexplained encephalopathy

BJCP British Journal of Clinical Pharmacology

Letter to the Editors

Severe efavirenz-induced vacuolar axonopathy complicated by fatal aspiration pneumonia

Chris Kenyon,[1] Sipho Mfolozi,[2] Roland Croxford,[3] Robert Colebunders[5] & Karen Cohen[4]

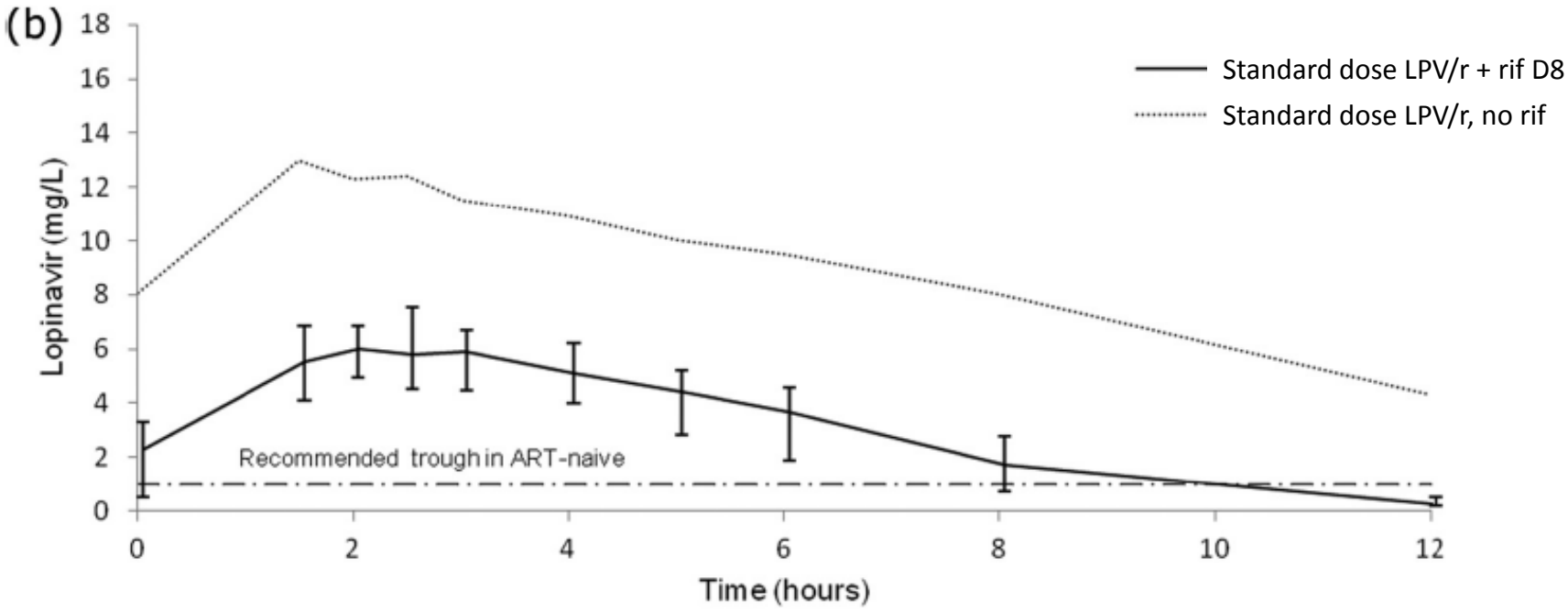
J Acquir Immune Defic Syndr. 2017 May 17. doi: 10.1097/QAI.0000000000001451. [Epub ahead of print]

Late efavirenz-induced ataxia and encephalopathy: a case series.

Variava E[1], Sigauke FR, Norman J, Rakgokong M, Muchichwa P, Mochan A, Maartens G, Martinson NA.

Rifampicin and LPV/r

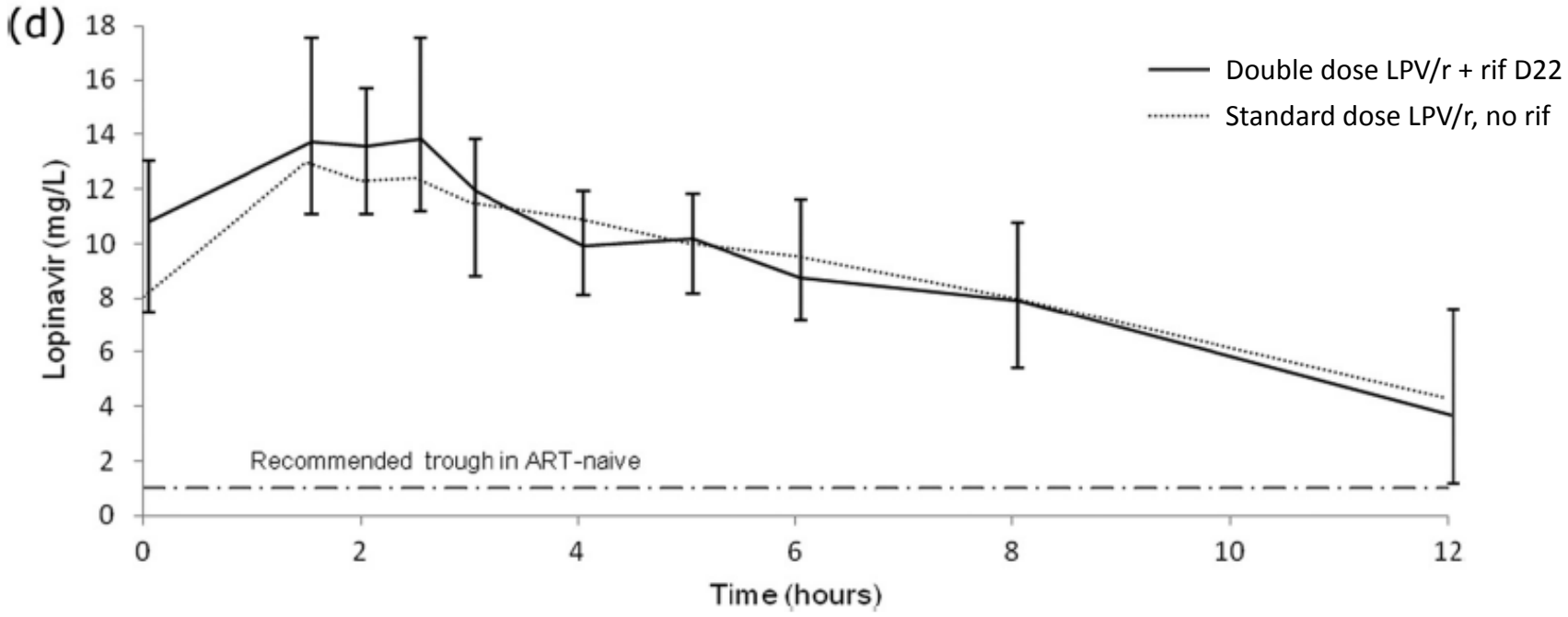
- PIs substrates of CYP3A4 and P-gp
- Rifampicin reduces LPV/r exposure by 75%



Decloedt AAC 2011

Double dose of LPV/r overcomes induction by rifampicin

- Although limited hepatotoxicity and few discontinuations in study, poorly-tolerated in practice



Decloedt AAC 2011

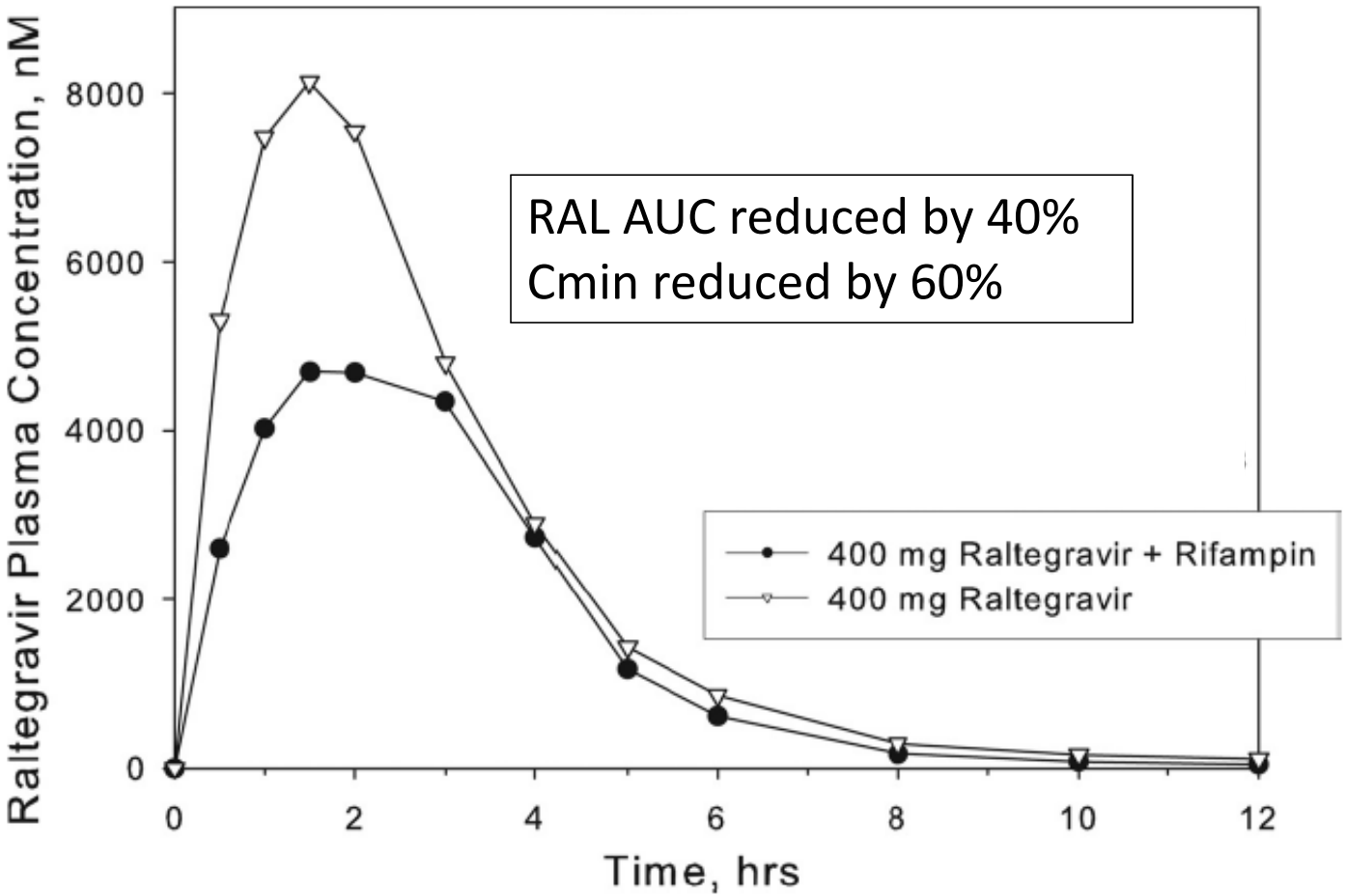
Rifampicin reduces exposure of all PIs

- ATV 95%: don't co-administer
- DRV 57%: don't co-administer
  - Modelling study found potential doses to overcome induction:

Dose	Mean DRV AUC_{0-24} (90% CI)	Mean reduction in AUC_{0-24}
800/100 OD	69.4 (68.0–70.8)	Ref
800/100 OD + RIF	29.7 (29.0–30.4)	57%
1200/200 OD +RIF	51.4 (50.3–52.6)	26%
1600/200 OD + RIF	68.5 (67.0–70.1)	1.3%
800/100 BD + RIF	58.7 (57.6–59.8)	15%

Dickinson JAC 2016

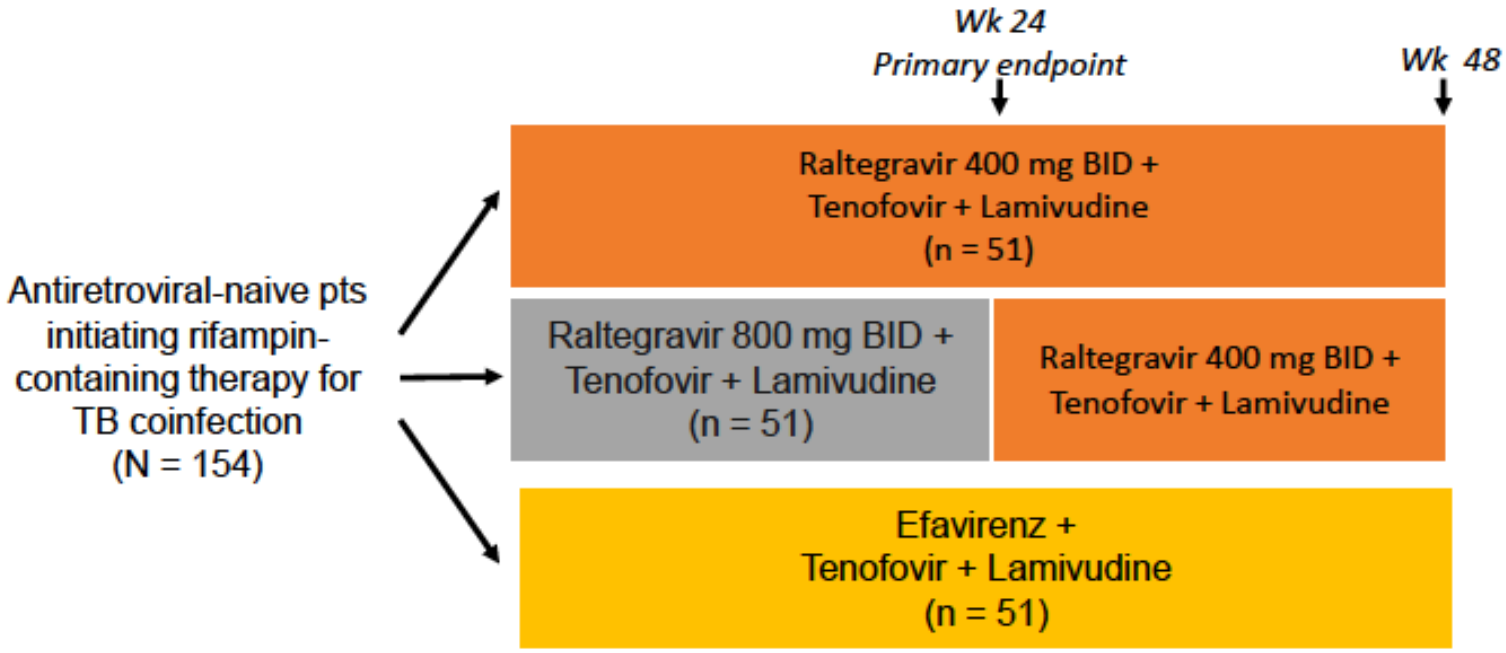
Rifampicin reduces RAL exposure in healthy volunteers



Wenning AAC 2009

But what is the PK and clinical impact in HIV/TB patients?

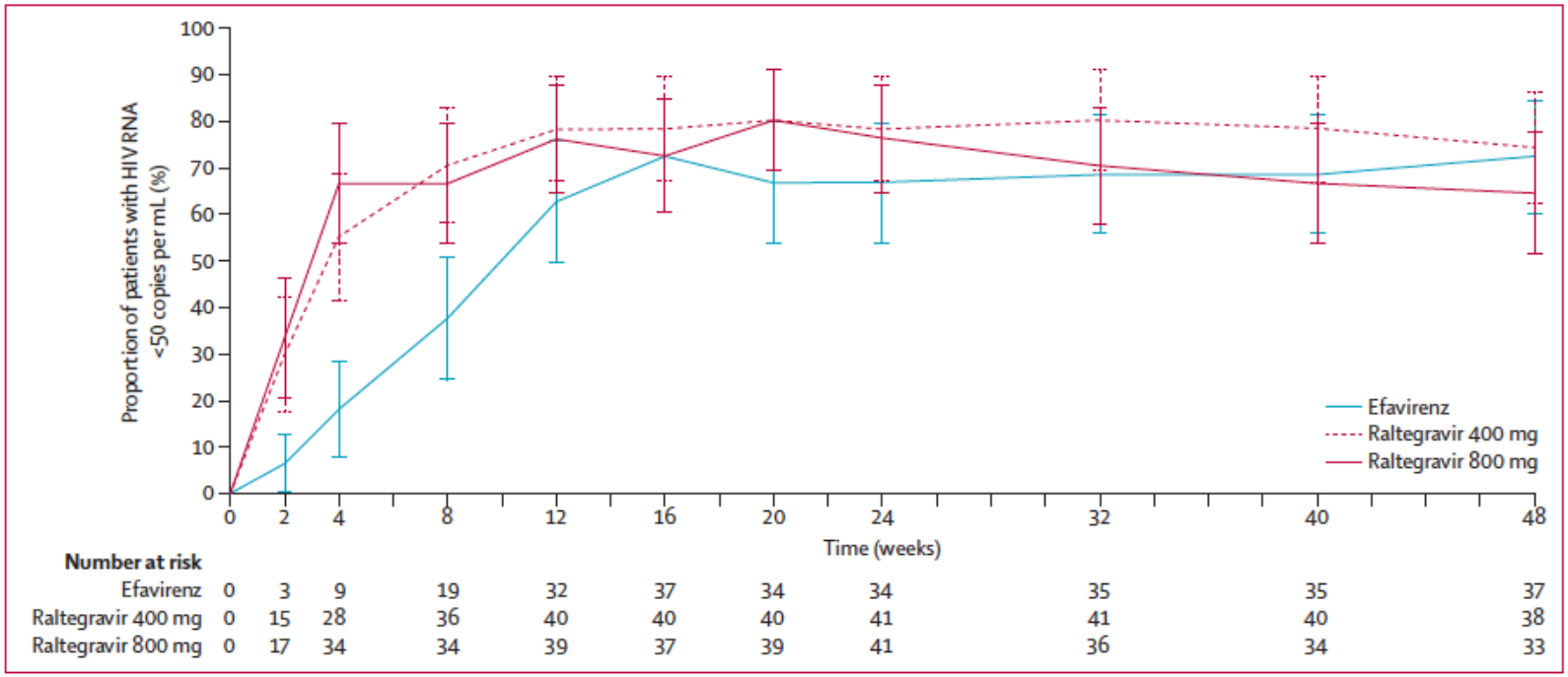
- ANRS-REFLATE trial: Phase II open label RCT
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24



Grinsztejn LID 2014

Clinical impact of standard RAL dose in HIV/TB: similar rates of virological suppression

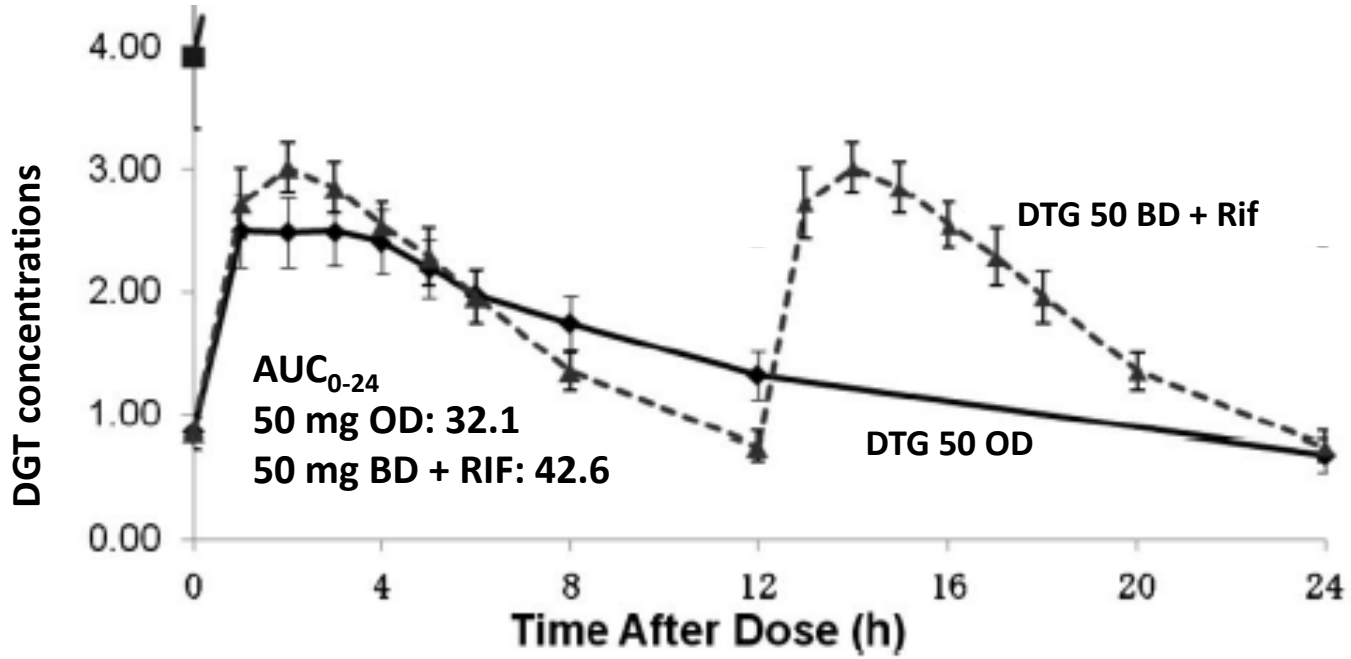
Requires Phase III trial, but based on these limited PK and clinical data
RAL 400 recommended for patients on TB treatment (IAS-USA)



Grinsztejn LID 2014
Günthard JAMA 2016

RIF reduces DTG exposure: (over)compensated by BD dosing

- Healthy volunteers:
  - Increased clearance with rif, but Cmin still above IC50 theshold with BD dosing
  - DTG 50 mg BD + RIF has higher exposures (33%) than DTG 50 mg OD alone



Dooley JAIDS 2013

Recommended dose 50 mg BD with TB Rx, but important questions:

- Does it translate into similar efficacy compared with EFV?
- Emerging concerns about neuropsychiatric AEs on DTG
  - Meta-analysis of clinical trials: uncommon compared to EFV
- UGT1A1 polymorphisms
  - Higher exposures and toxicity?
- Higher pill burden than FDC
  - Adherence?
- More potent than EFV
  - More IRIS?
- Pregnant women?

van den Berk CROI 2016
De Boer AIDS 2016
Menard AIDS 2017
Viswanathan CROI 2017

Rifampicin and TAF

- Much higher intracellular concentration of active drug than TDF, and much lower plasma concentration of tenofovir
  - Less toxicity
  - Lower doses required
- TAF substrate of P-gp and other transporters: levels reduced by rifampicin
- **No PK studies with rifampicin, but co-administration not recommended** (package insert)

Sax Lancet 2015

Rifabutin and ARVs

- Rifabutin is a weak inducer, and a substrate, of CYP3A4
  - Minimal effect on PI exposure: used in TB treatment with PIs
  - PIs inhibit RBT metabolism, thus increasing exposure and necessitating dose reduction of the rifabutin

Rifabutin and PIs

- Dosing with PIs:
  - **RBT 150 mg daily with PIs results in similar exposure to standard dose (300 mg daily) without PI**
  - **Recommendation: Halve the dose in the setting of PI co-administration**

Hennig JAC 2016

In Practise…

- Lopinavir based ART
  - Continue rifampicin based TB regimen
  - Double the dose of LPV/r
- Patients requiring Atazanavir because of LPV intolerance
- OR patients requiring Darunavir because of resistance (ie Regimen 3)
  - Use a Rifabutin based regimen
  - Dose adjust to 150mg Rifabutin daily

Rifabutin and NNRTIs

- Rilpivirine
  - RPV exposure reduced by 42% with RBT: increase RPV dose 50 mg daily (US guidelines: avoid)

Summary of important DDIs in DS-TB

Antiretroviral	Rifampicin	Other DS-TB Rx
Efavirenz	• Does not require dose adjustment	INH in slow metabolizers may increase EFV toxicity
Nevirapine	• Do not coadminister	• Worse outcomes with TB Rx
Rilpivirine/etravirine	• Do not coadminister	• Incr RVP dose with RBT
Lopinavir/ritonavir	• Requires double dose with 4 tablets (800/200 mg) BD • Increase the dose gradually	• Can use with RBT (adjust RBT dose to half)
Atazanavir/ritonavir	• Do not coadminister	
Darunavir/ritonavir	• Do not coadminister	
Raltegravir	• Standard dose	• No adjustment with RBT
Dolutegravir	• Double dose 50 mg BD	
TAF	• Do not coadminister	

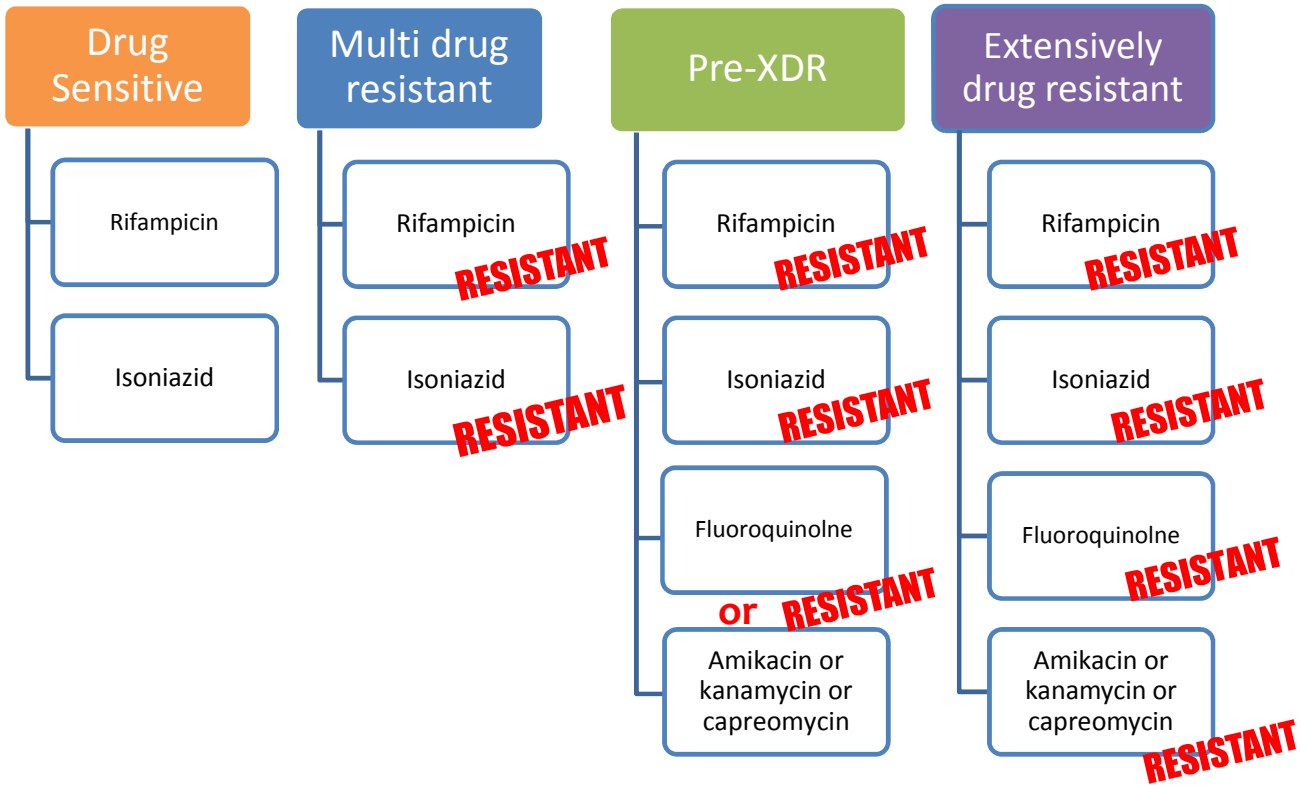
Preferred regimens in TB co-infection

- **First Line ART**
  - **WHO and NDoH: TDF + 3TC/FTC + EFV (600)**
- **For Second line**
  - **AZT/3TC or TDF/FTC + double dose LPV/r**
  - **ATV/r use rifabutin**
- **For Third line**
  - **DRV/r use rifabutin instead of rifampicin**

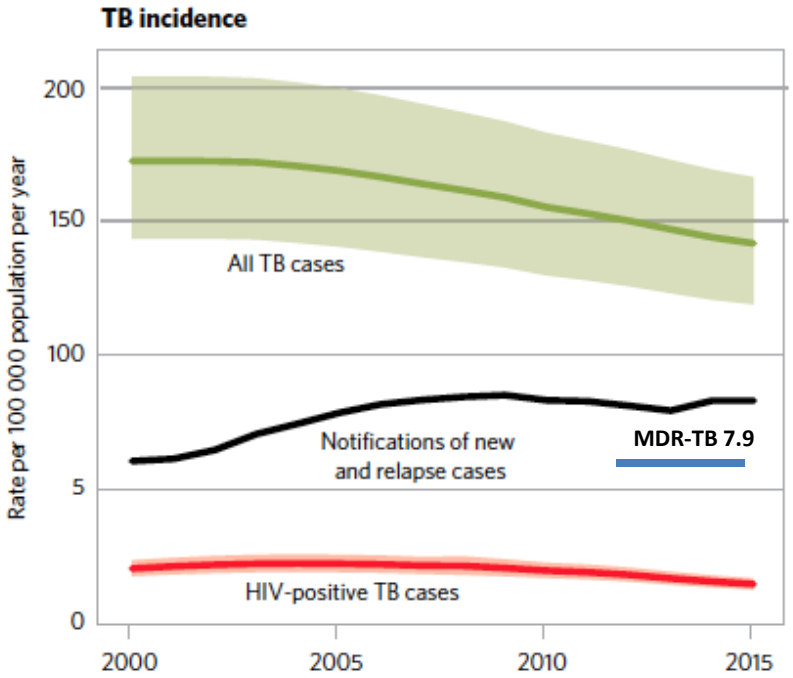
- **(IAS-USA: EFV, DTG, RTG (boosted PI only if INSTI not an option)**

Bonnet LID 2013

Definitions of TB Drug Resistance



DR-TB is a big problem

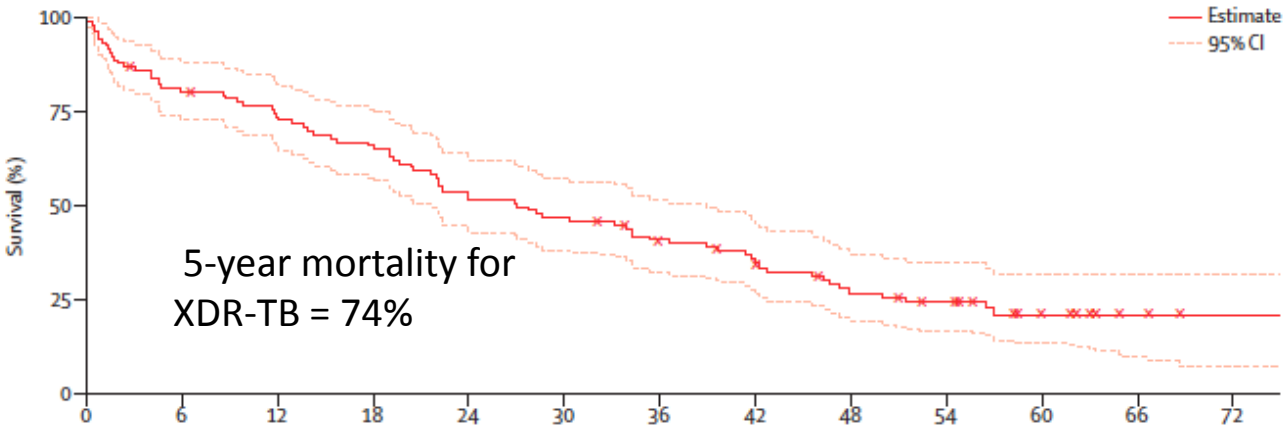


- Incidence of MDR-TB unchanged or declining less slowly
- Around 600,000 cases of MDR in 2015
- Quarter of a million deaths
- 9.5% of MDR have XDR-TB

WHO Global Report 2016

DR-TB is a big problem

- < 50% treatment success in high burden countries
- XDR mortality in 2013: 27%
- XDR treatment success: 28%



WHO Global Report 2015/6
Pietersen Lancet 2014

Standard Rx for MDR-TB: no major DDIs with ART

Conventional

Mfx/Km/Eto/Tzd/PZA +- hdINH/Emb

18 – 24 months

Shortened

Mfx/Km/Cfz/PZA/Emb/Eto (+- hdINH)

9-12 months

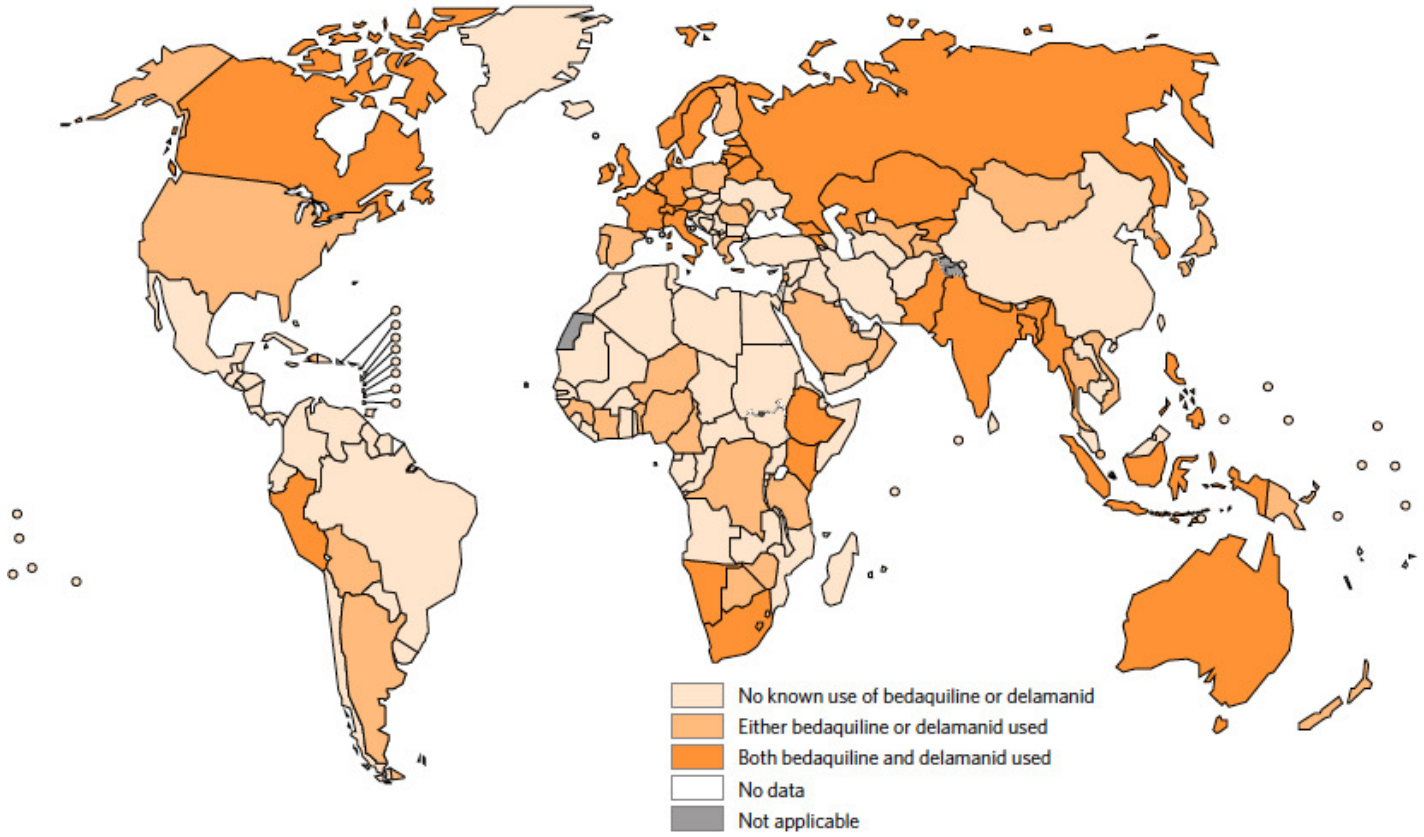
BDQ and DLM are being rolled out

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interim policy guidance

The use of delamanid in the treatment of multidrug-resistant tuberculosis

Interim policy guidance



WHO Global Report 2016

Multiple trials of new DR-TB regimens

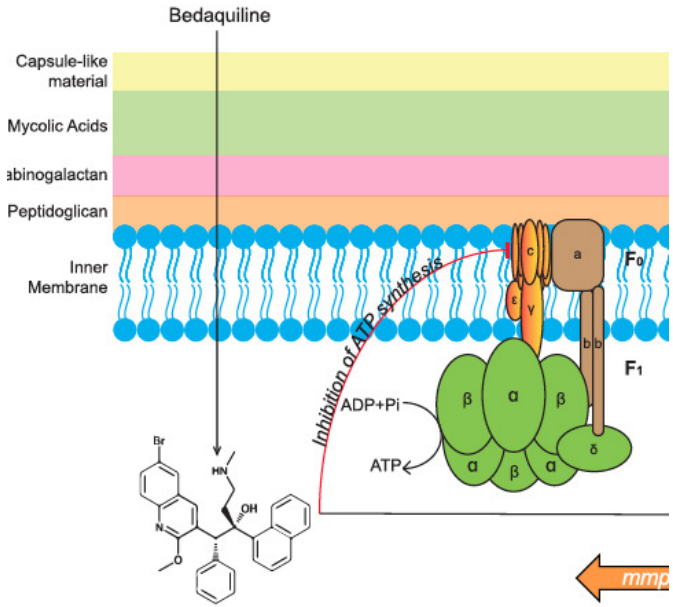
Trial	Phase	Patients	Design	Primary end point
NExT (NCT02454205)	Phase 2 to 3	MDR-TB, adults *n* = 300	Open-label RCT of an injection-free regimen including linezolid[a] and bedaquiline (plus standard drugs without kanamycin) for 6–9 months compared with WHO standard regimen	Favorable outcome at 24 months
Nix-TB (NCT02333799)	Phase 3	MDR- and XDR-TB, adults *n* = 200	Open-label, single-arm evaluation of bedaquiline and pretomanid plus linezolid[b] for 6–9 months	Bacteriologic or clinical failure at 24 months
endTB (NCT02754765)	Phase 3	MDR-TB, adults *n* = 750	Open-label RCT of five all-oral experimental regimens compared with standard of care. Experimental regimens contain bedaquiline and/or delamanid together with four companion drugs, including linezolid[c]	Favorable outcome at 18 months
TB-PRACTECAL (NCT02589782)	Phase 2 to 3	MDR-TB, adults *n* = 630	Open-label RCT comparing three novel regimens including bedaquiline, pretomanid, and linezolid[d], plus moxifloxacin or clofazimine for 6 months with WHO standard of care	Culture conversion and discontinuation/death at 8 weeks, unfavorable outcome at 72 weeks
MDR-END (NCT02619994)	Phase 3	MDR-TB, adults *n* = 238	Open-label RCT comparing a 9–12-month regimen of delamanid, linezolid[e], levofloxacin, and pyrazinamide with WHO standard or care	Treatment success at 24 months

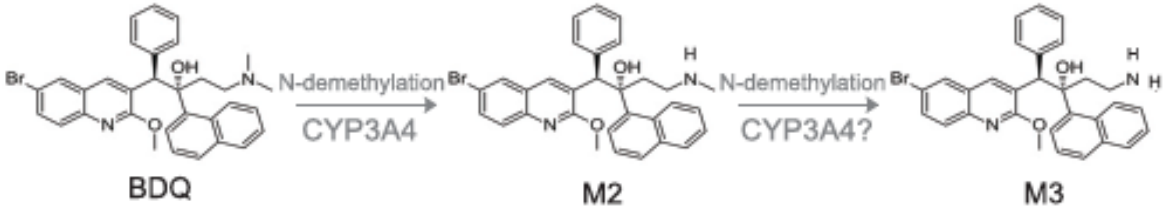
Key New MDR Drugs

- Bedaquiline
- Delamanid/Pretomanid
- Linezolid
- Clofazimine

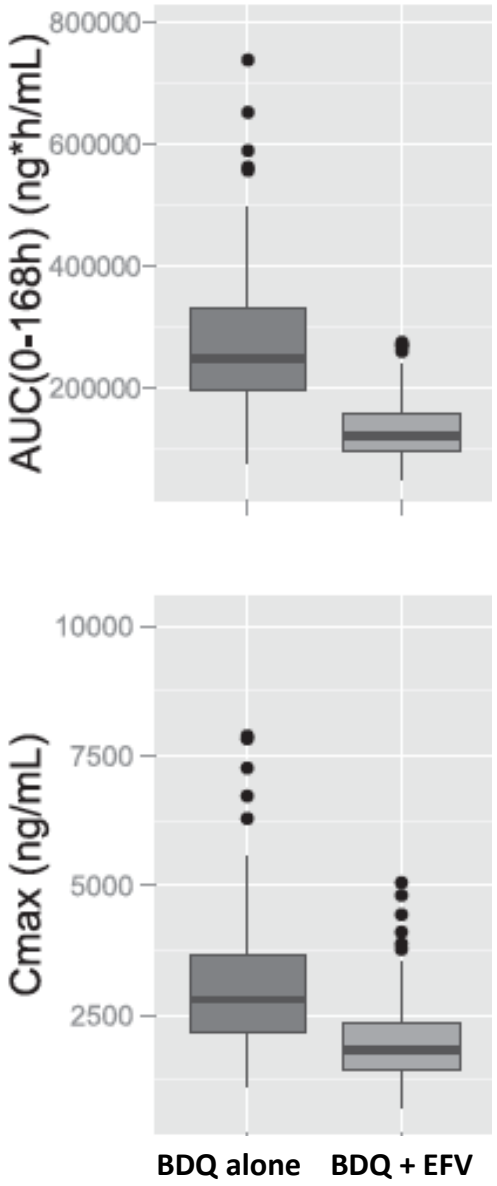
Bedaquiline

- Diarylquinoline, novel MoA: potent against MTB
- Accumulates in tissues: extremely long half life ~6 months
- Metabolised by CYP3A4 to M2 metabolite (less active, more toxic); no influence on CYP or transporters





AEs include QT prolongation and hepatitis: related to dose?



BDQ DDIs: NNRTIs

- EFV reduces steady state concentrations of bedaquiline(modelling study): do not coadminister
- NVP has no significant effect on BDQ bioavailability in models and clinical study
  - Can be used
- Rilpivirine: not studied, unlikely to have an effect on BDQ concentrations

Pandie JAC 2016
Svensson AAC 2013

BDQ DDIs: Aluvia

- Model: reduces BDQ clearance by 35%, M2 clearance by 58% (2- and 3-fold increase in steady state concentrations)
- Patients: 62% increase in AUC
- Clinical consequences unclear: monitor ECG closely
- We are using this combination at standard doses

Pandie JAC 2016
Svensson AAC 2014

Delamanid

- Nitroimidazole
- Metabolised by albumin, smaller contribution by CYP3A4
- Associated QT prolongation
- Delamanid has No impact on EFV or LPV/r exposure
- Higher DLM concentrations with LPV/r: clinical impact?
- We are using it at standard doses

Mallikaarjun AAC 2016
Sasahara Drug Metab Dispos 2015

Other new/repurposed drugs

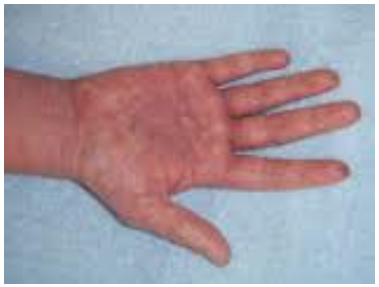
- Pretomanid (PA-824)
  - Metabolised by CYP3A4
  - Phase I study: reduced exposure with EFV - avoid
- Clofazimine
  - Substrate of P-gp: effect of PIs?
- Linezolid
  - May be a P-gp and/or CYP substrate: effect of PIs?

Dooley AAC 2014

Summary of important DDIs in DR-TB

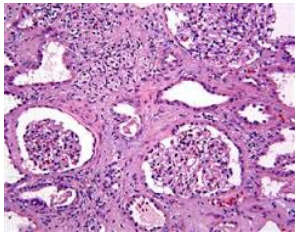
Antiretroviral	Bedaquiline	Delaminid
Efavirenz	• Do not coadminister	• No interaction
Nevirapine	• No dose adjustment	• Not expected
Rilpivirine	• Not expected	• Not expected
Lopinavir/ritonavir	• Increases BDQ exposure: may lead to toxicity?	• Increased DLM exposure: clinical relevance?
Atazanavir/ritonavir		
Darunavir/ritonavir		
Raltegravir	• No interaction expected	• Not studied, no interaction expected
Dolutegravir		

Shared toxicities



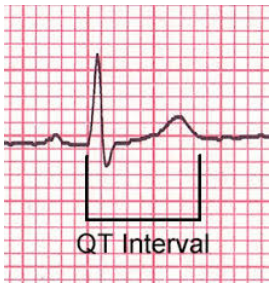
All TB drugs
NNRTIs
Cotrimoxazole

RHZ, RBT, FQs, BDQ, PMD, DLM
NNRTIs, PIs
Cotrimoxazole



SLIs, Rif
TDF

LZD
AZT



FQs, BDQ, DLM, CFZ

INH, TZD, LZD
d4T, ddI

INH, TZD
EFV, DTG

Conclusions

- Many people on HIV and TB treatment
- Clinical consequences of DDIs and shared toxicity
- Many potential DDIs, particularly with rifampicin
- Key new HIV and TB drugs have important DDIs