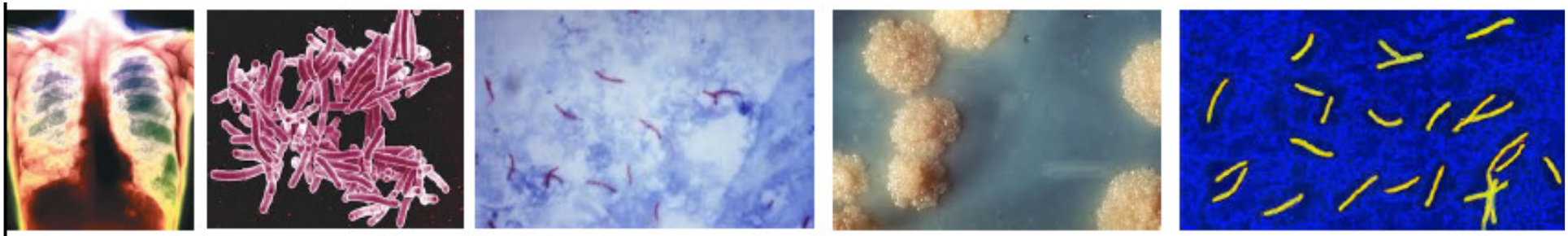
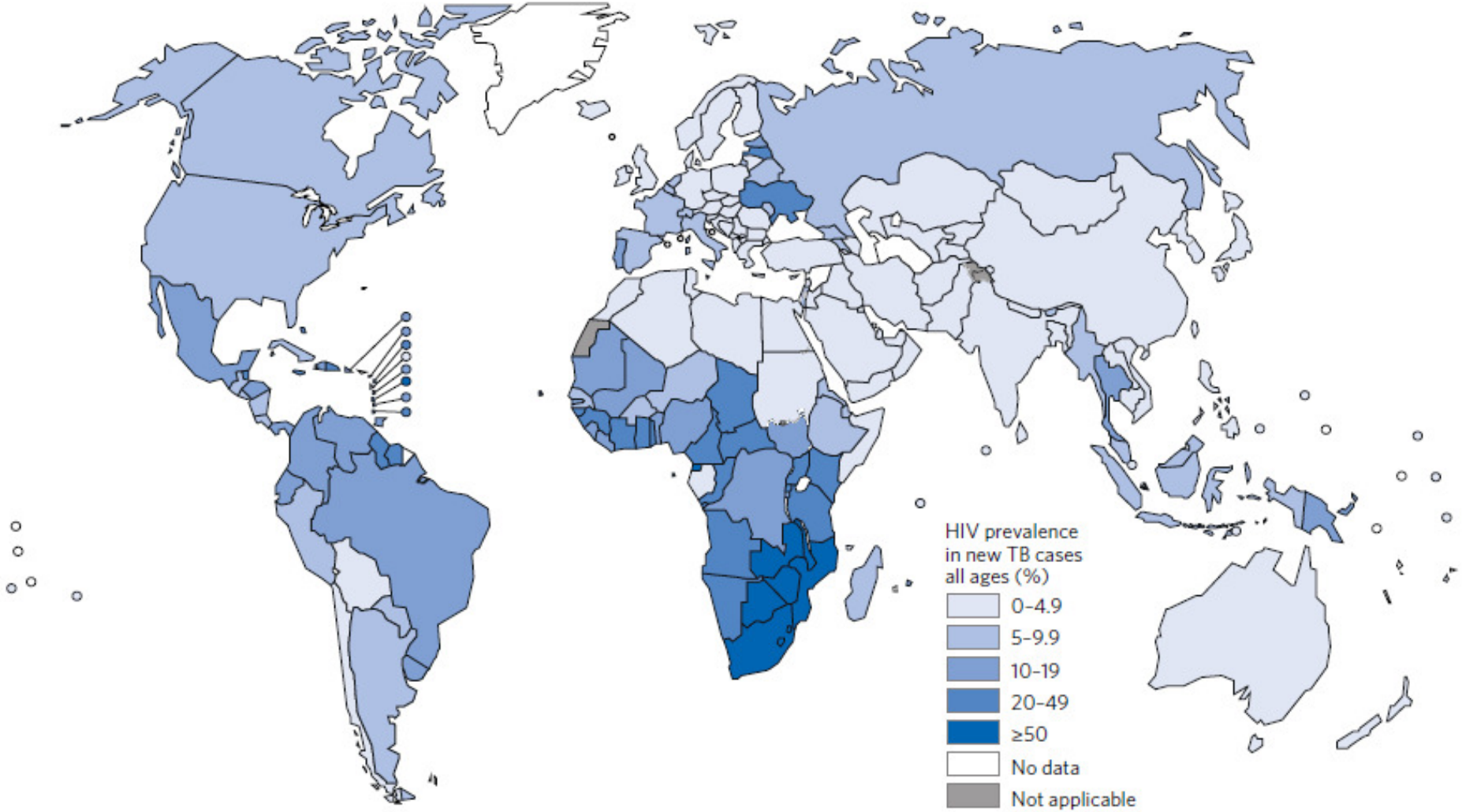


Using new antiretroviral agents and dosing with TB treatment

John Black

With many acknowledgments

Estimated HIV prevalence in new and relapse TB cases, 2015

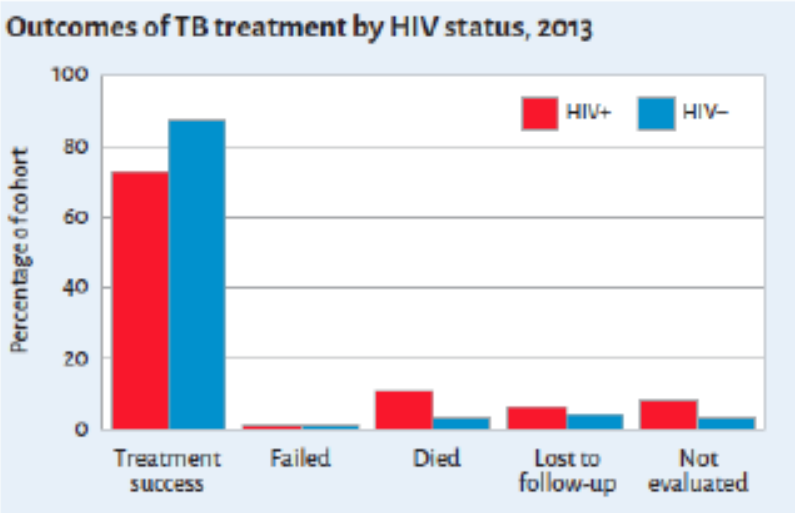


:: TABLE 3.3

Estimated epidemiological burden of TB in 2015 for 30 high TB burden countries, WHO regions and globally. Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval. Rates per 100 000 population except where indicated.[a]

	HIV-NEGATIVE TB MORTALITY		HIV-POSITIVE TB MORTALITY		TOTAL TB INCIDENCE		HIV PREVALENCE IN INCIDENT TB %	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL
Angola	45	27–67	29	6.5–67	370	240–529	30	24–36
Bangladesh[b]	45	27–68	0.14	0.12–0.18	225	146–321	0.18	0.14–0.21
Brazil	2.7	2.5–2.8	1.1	0.56–1.7	41	35–47	15	14–16
Cambodia	55	39–74	2.8	1.2–5.0	380	246–543	2.4	2.2–2.7
Central African Republic	45	26–70	55	20–107	391	253–558	45	36–54
China	2.6	2.5–2.7	0.19	0.09–0.33	67	57–77	1.7	1.4–2.0
Congo	49	29–75	53	44–63	379	246–542	36	29–44
DPR Korea	61	40–87	0.15	0.07–0.26	561	432–706	0.31	0.26–0.38
DR Congo	66	39–99	21	17–26	324	210–463	15	13–19
Ethiopia	26	15–38	4.0	1.6–7.4	192	142–250	8.3	7.6–9.1
India[c]	32	29–35	2.8	1.6–4.3	217	112–355	4.0	3.6–4.4
Indonesia	40	26–57	10	7.6–13	395	255–564	7.7	6.2–9.3
Kenya	20	13–27	16	1.5–45	233	189–281	33	32–35
Lesotho	55	29–89	223	139–328	788	510–1125	72	63–80
Liberia	70	41–107	19	16–22	308	199–440	13	11–15
Mozambique	74	43–115	120	73–178	551	356–787	52	45–58
Myanmar	49	30–74	9.0	6.4–12	365	267–479	8.9	7.9–9.8
Namibia	32	21–45	36	2.5–112	489	376–616	41	39–43
Nigeria	99	53–160	31	24–40	322	189–488	17	14–20
Pakistan	23	4.9–56	0.83	0.60–1.1	270	175–386	1.7	1.4–2.1
Papua New Guinea	41	24–61	8.8	5.2–13	432	352–521	15	12–18
Philippines	13	8.7–19	0.44	0.24–0.70	322	277–370	1.3	1.1–1.6
Russian Federation	11	10–11	1.0	0–5.2	80	69–92	9.9	8.8–11
Sierra Leone	51	30–76	13	6.2–21	307	198–438	13.3	12–15
South Africa	44	39–50	133	50–256	834	539–1190	57	52–61
Thailand	12	10–15	8.0	4.9–12	172	102–259	13	12–14
UR Tanzania	56	25–99	47	31–66	306	146–525	35	31–40
Viet Nam	17	12–23	1.1	0.21–2.8	137	110–166	4.3	4.0–4.6
Zambia	31	18–47	77	42–121	391	253–558	60	54–66
Zimbabwe	11	6.3–16	40	14–81	242	179–314	69	64–74

HIV-associated TB has worse outcomes



Estimated case fatality ratios (CFRs) in the absence of treatment

CATEGORY OF TB CASE	CFR (95% UNCERTAINTY INTERVAL)
HIV-negative, not on TB treatment	0.43 (0.28–0.53)
HIV-positive, not on TB treatment or ART	0.78 (0.65–0.94)

WHO Global report 2015

Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy

N Engl J Med 2010;362:697-706.

Abdool Karim et al

Table 2. Death Rates and Hazard Ratios, Stratified According to CD4+ Cell Count.

CD4+ Count	Integrated Therapy				Sequential Therapy				Hazard Ratio (95% CI)*	P Value
	No. of Patients	No. of Person-Yr	No. of Deaths	Death Rate/ 100 Person-Yr (95% CI)	No. of Patients	No. of Person-Yr	No. of Deaths	Death Rate/ 100 Person-Yr (95% CI)		
All patients	429	467	25	5.4 (3.5–7.9)	213	223	27	12.1 (8.0–17.7)	0.44 (0.25–0.79)	0.003
≤200 cells/mm³	273	281	23	8.2 (5.2–12.3)	138	137	21	15.3 (9.6–23.5)	0.54 (0.30–0.98)	0.04
>200 cells/mm³	156	186	2	1.1 (0.1–3.9)	75	86	6	7.0 (2.6–15.3)	0.16 (0.03–0.79)	0.02

* Hazard ratios are for the integrated-therapy group, as compared with the sequential-therapy group.

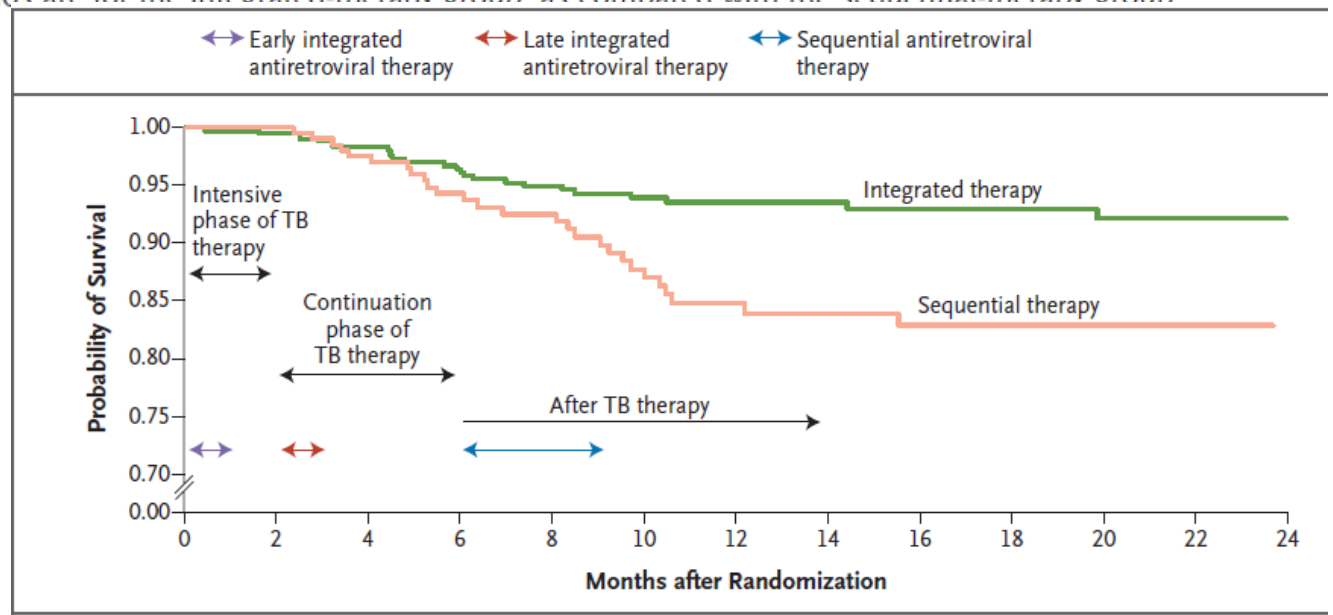
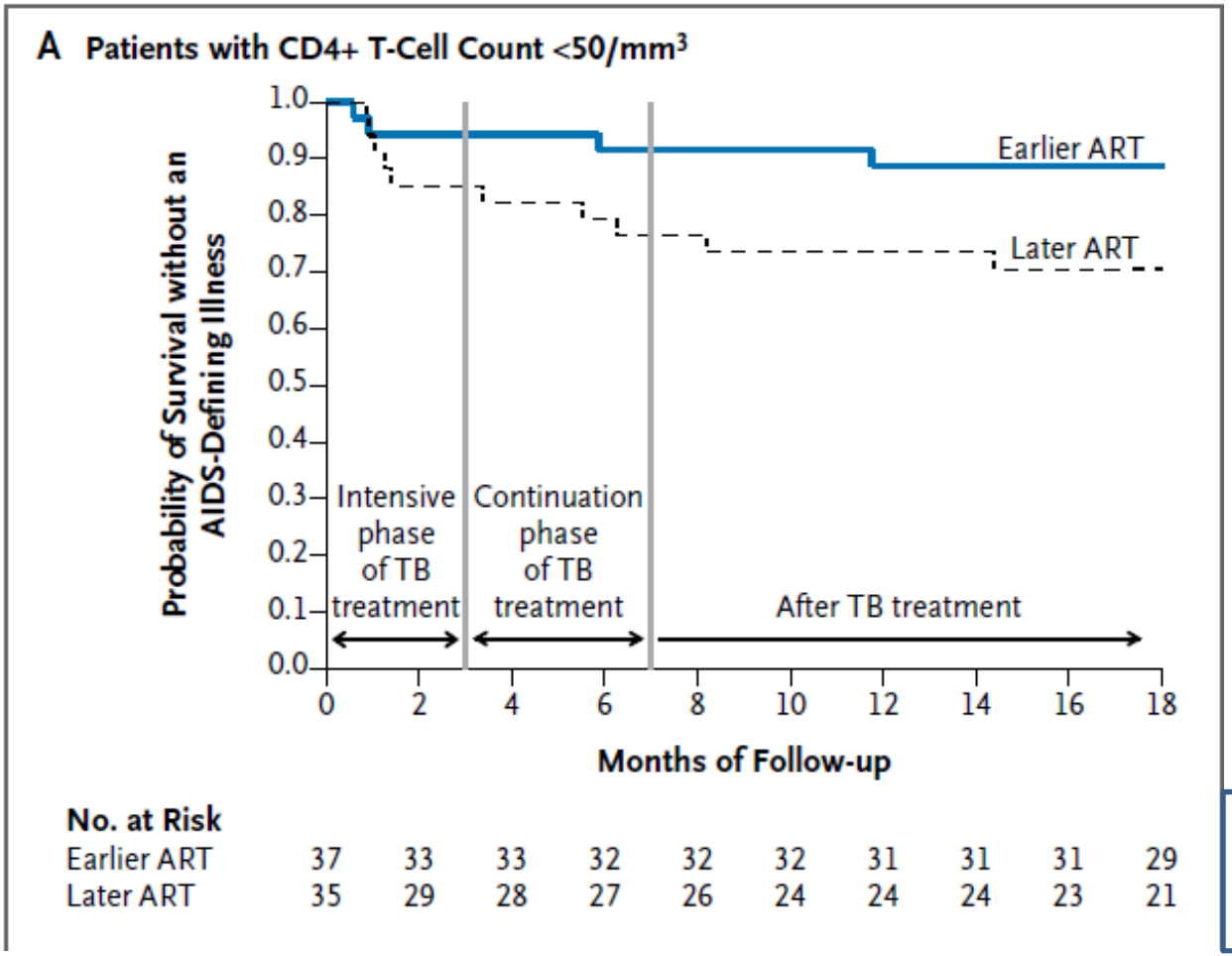


Figure 2. Kaplan–Meier Survival Curves.

Integration of Antiretroviral Therapy with Tuberculosis Treatment

Abdool Karim et al

N Engl J Med 2011;365:1492-501.



(incidence-rate ratio, 0.32; 95% CI, 0.07 to 1.13; P = 0.06).

Vs CAMELIA (median CD4 = 25)

- Mortality 18% vs 27%

HR 0.62 95% CI; 0.44 to 0.86; P = 0.006

Vs ACTG (CD4 <50 subgroup)

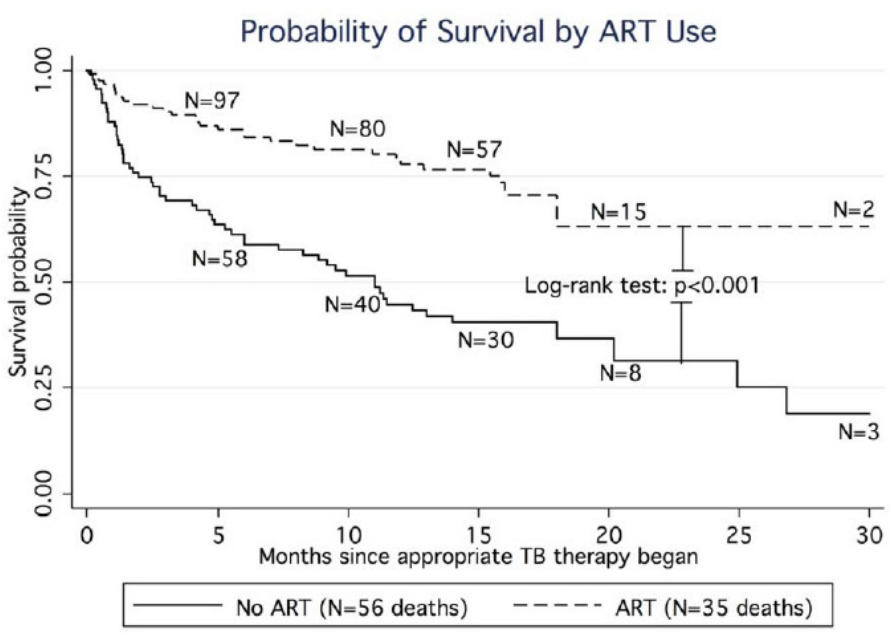
- Mortality 15.5% vs 26.6%
  (95% CI, 1.5 to 20.5; P = 0.02)

Regardless of disease 25% of those with CD4<50 die if delay ART by 2/12

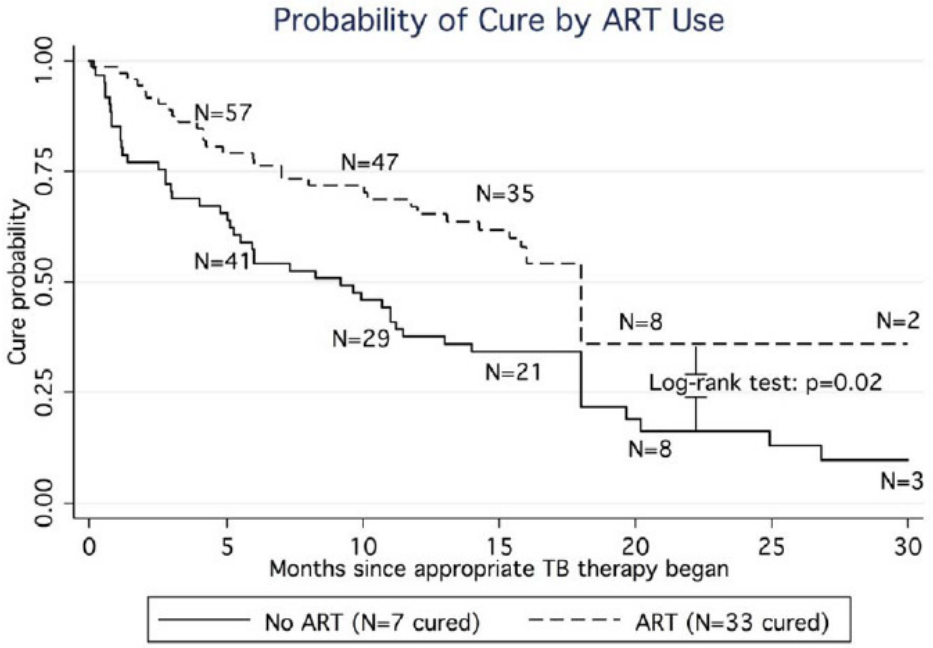
Use of Anti-Retroviral Therapy in Tuberculosis Patients on Second-Line Anti-TB Regimens: A Systematic Review

Matthew Arentz[1]*, Patricia Pavlinac[1], Michael E. Kimerling[2], David J. Horne[1], Dennis Falzon[3], Holger J. Schünemann[4], Sarah Royce[5], Keertan Dheda[6,7,8], Judd L. Walson[1], for the ART/DR-TB study group[¶]

PLoS ONE 7(11): e47370. doi:10.1371/journal.pone.0047370



(HR 0.4, 95% CI 0.3–0.6)



(HR 3.4, 95% CI 1.6–7.4)

10.4.2 TB treatment in HIV

Table 38: ART for adults with concomitant TB

TB develops while on ART	TB diagnosed before starting ART
Continue ARV therapy throughout TB treatment First-line regimen: Patient can remain on the regimen they are taking (unless they are on NVP) Second-line regimen: The Lopinavir/Ritonavir (LPv/r) dose should be doubled (increase gradually from 2 tablets 12 hourly to 4 tablets 12 hourly) while the patient is on Rifampicin-based TB treatment Monitor ALT monthly Reduce Lopinavir/Ritonavir to standard dose 2 weeks after TB treatment is completed	In TB/HIV co-infection not on ART Start with TB treatment first, followed by ART as soon as possible and within 8 weeks If CD4 <50 cells/µl initiate ART within 2 weeks of starting TB treatment, when the patient's symptoms are improving and TB treatment is tolerated If CD4 >50 cells/µl initiate ART within 2-8 weeks of starting TB treatment First line ART regimen: » Tenofovir 300mg daily » Lamivudine 300mg or Emtricitabine 200mg daily » Efavirenz 600mg at night

NOTE: HIV positive TB patients qualify for lifelong ART regardless of CD4 cell count.

Complete 2 to 8 weeks maximum, of TB therapy before commencing ART **(and as soon as possible if CD4 count is less than 50 cells/µl)**.In general, ART should be initiated as soon as the patient is tolerating their TB therapy; this is usually within 2-4 weeks.

EFV-based regimens are generally preferred in patients with active TB; however, other regimens are also effective. Dose adjustment of PI may be required. Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. Monitor and investigate appropriately for hepatotoxicity symptoms. Continue these changes to Lopinavir/Ritonavir until two weeks after completion of TB treatment.

High Co-Infection Rate- Many patients 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

SA guidelines

First line:

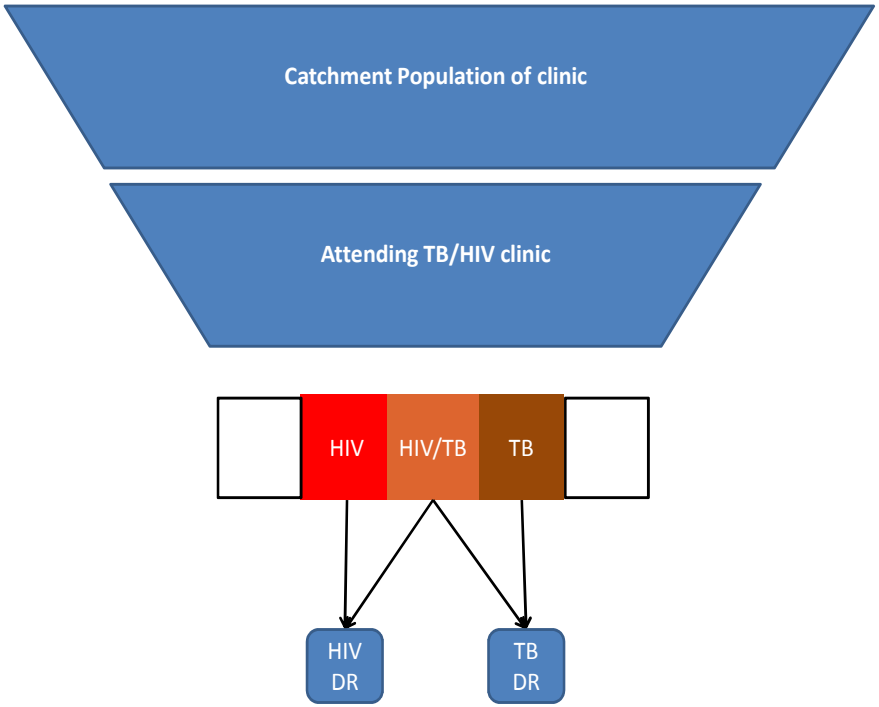
- Tenofovir
  - Low barrier
  - Renal and bone
  - Hep b cover
- Emtricitabine
  - Low barrier
  - Low toxicity
- Efavirenz
  - Low barrier
  - Neuropsych and liver toxicity
  - Drug interactions
- FDC and good potency

Second line:

- Zidovudine
  - High barrier
  - Significant toxicity
- Lamivudine
  - Crippling effect
- Lopinavir/ritonavir
  - High barrier
  - Significant toxicity
  - Significant drug interactions
- No FDC

Prospective Sentinel Surveillance of Tuberculosis and Human Immunodeficiency Virus in South Africa and Related Drug Resistance: Study design

- Sentinel site surveillance using the GERMS platform
  - 1 clinic per province
- To measure levels of HIV + TB DR at initiation of therapy
- MP, NW, EC, GP, KZN (Nov '14 – May '17)



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

GERMS SOUTH AFRICA

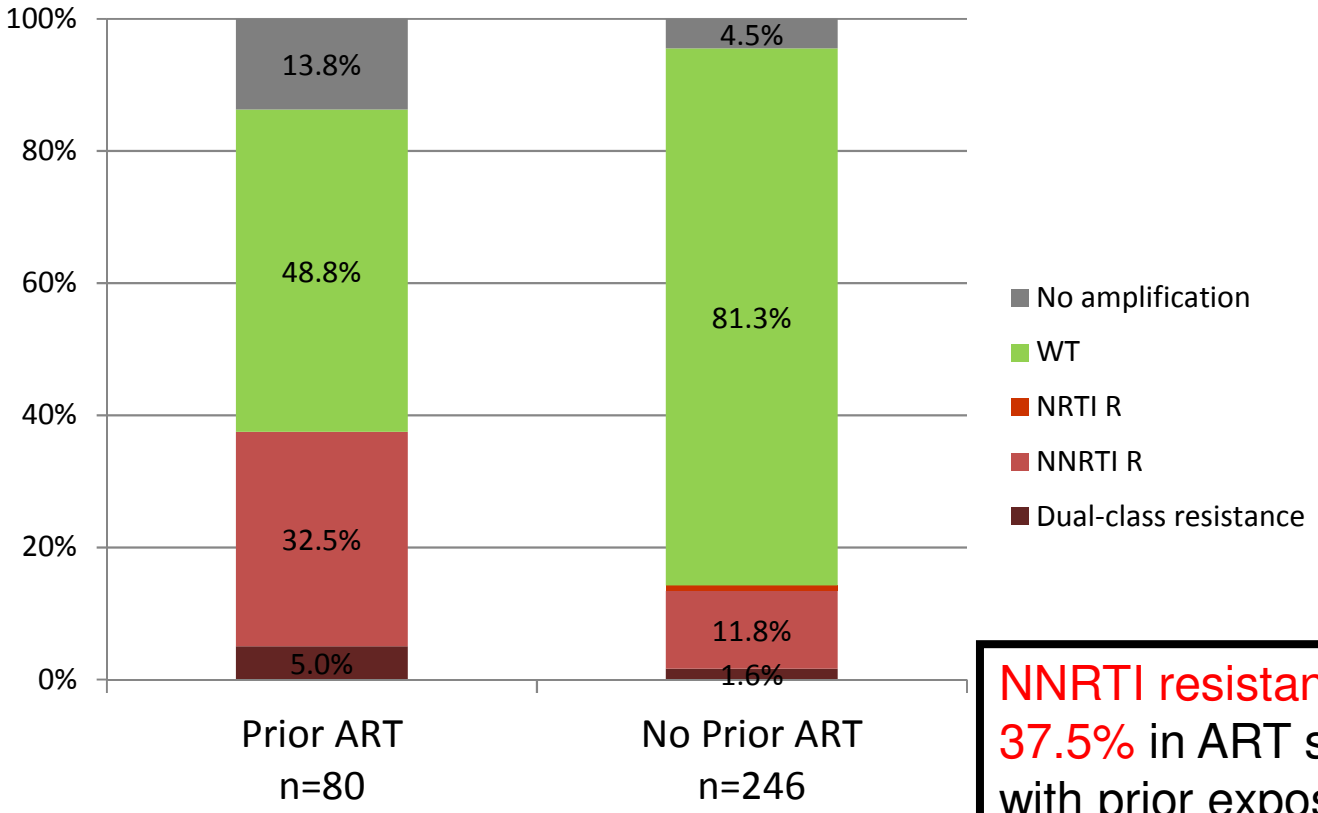
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Preliminary Data

Demographics:

- To date, n=1,139 specimens collected and tested for HIVDR
- 340 questionnaires were captured:
  - 71% of enrolled participants were female
  - median age of all participants is 32 years (IQR 26 - 40 years)
  - median recent CD4 count at time of cART initiation was 257 cells/µl (IQR 160 – 389 cells/µl).
- Prior exposure to ART (as PMTCT and/or previous cART) was reported in 80/326 (24.5%) participants
  - 14 (17.5%) reported receiving PMTCT
  - 47 (58.8%) had previously received standardized cART for clinical management
  - 19 (23.7%) participants reported receiving both PMTCT and cART.

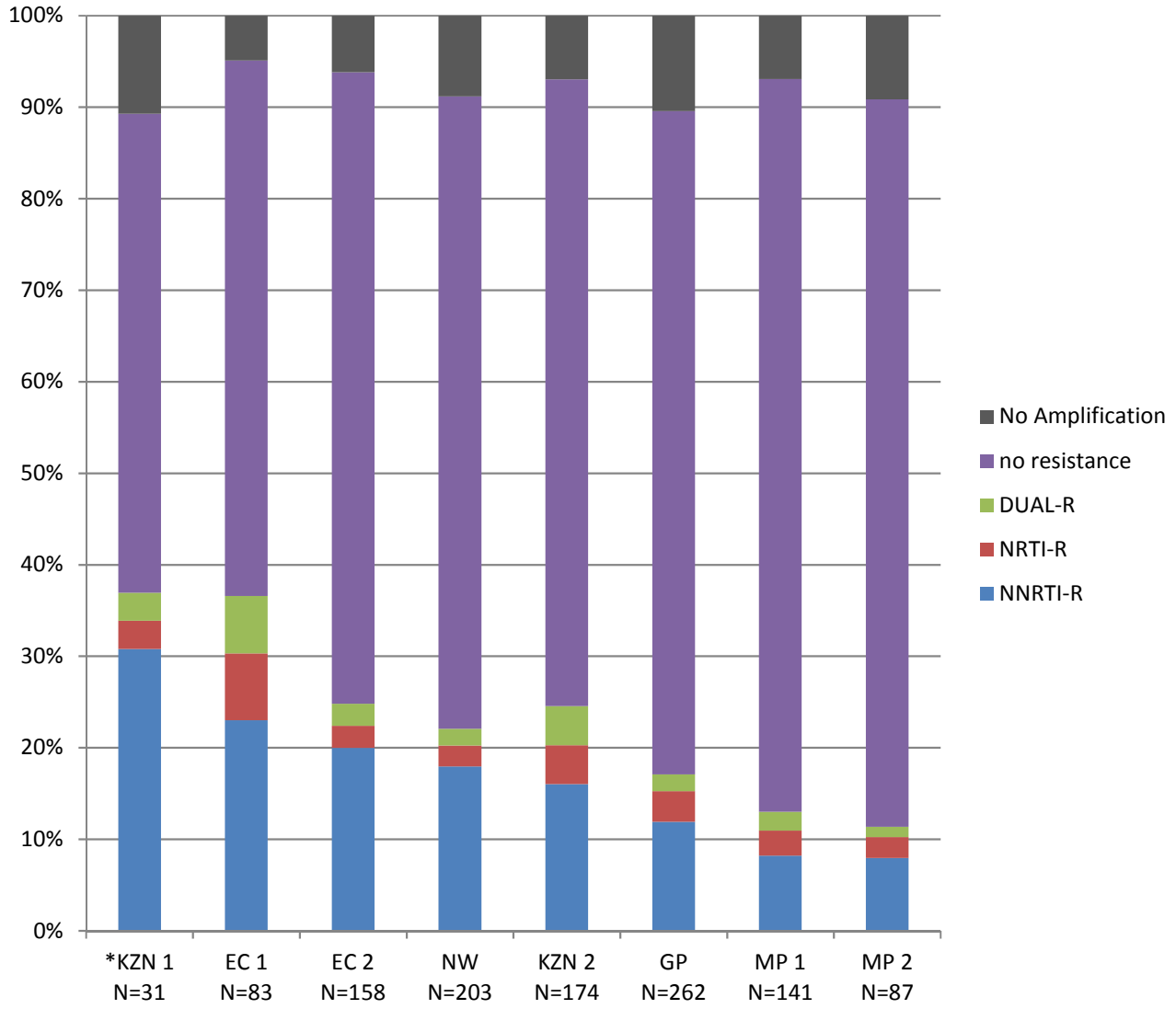
Levels of NNRTI and dual-class resistance detected amongst patients enrolled into study according to self-reported prior ART exposure



NNRTI resistance:
37.5% in ART starters with prior exposure to ARVs

13.4% in ARV-naive

Levels of NNRTI and dual-class resistance detected amongst patients enrolled into study in 8 clinics across SA (N=1,032)



- SA will need to change first and second line regimens
- Ideal drugs:
  - High barrier to resistance
  - High potency/efficacy
  - Low toxicity
  - Low DDI potential
  - Fixed dose combination
  - Once a day dosing

Recommended ART Regimens for Treatment-Naive Pts

Regimen	DHHS[1]	IAS-USA[2]	BHIVA[3]	EACS[4]	GeSIDA[5]
DTG/3TC/ABC	Recommended	Recommended	Alternative	Recommended	Recommended
DTG + FTC/TDF	Recommended	Alternative	Recommended	Recommended	Recommended
DTG + FTC/TAF	Recommended	Recommended	Recommended	Recommended	Not included
EVG/COBI/FTC/TDF	Recommended	Alternative	Recommended	Recommended	Alternative
EVG/COBI/FTC/TAF	Recommended	Recommended	Recommended	Recommended	Recommended
RAL + FTC/TDF	Recommended	Alternative	Recommended	Recommended	Recommended
RAL + FTC/TAF	Recommended	Recommended	Recommended	Recommended	Not included
ATV/RTV + FTC/TDF	Alternative	Not included	Recommended	Alternative	Alternative
ATV/RTV + FTC/TAF	Alternative	Not included	Recommended	Alternative	Alternative
DRV/RTV* + FTC/TDF	Recommended	Alternative	Recommended	Recommended	Alternative
DRV/RTV* + FTC/TAF	Recommended	Alternative	Recommended	Recommended	Not included
RPV/FTC/TDF	Alternative	Alternative	Recommended	Recommended	Alternative
RPV/FTC/TAF	Alternative	Alternative	Recommended	Recommended	Not included

Recommended Alternative Not included

References in slidenotes.

Slide credit: clinicaloptions.com

Drug Interactions

Medication	Potential for interactions
Darunavir	Substrate/Inhibitor: CYP3A4, P-gp; Inducer: 2C9
Ritonavir	Substrate: CYP3A4, 2D6, P-gp; Inhibitor: CYP3A4, 2D6, P-gp; Inducer: CYP1A2, 2C8, 2C9, 2C19
Cobicistat	Substrate/Inhibitor: CYP3A4, 2D6, P-gp (inhibit)
Elvitegravir	Substrate: CYP3A4; Inducer: CYP2C9
Tenofovir	Substrate: P-gp
Dolutegravir	Substrate: CYP3A4, P-gp
Raltegravir	No involvement in P-gp or CYP450

P-gp: P- glycoprotein.

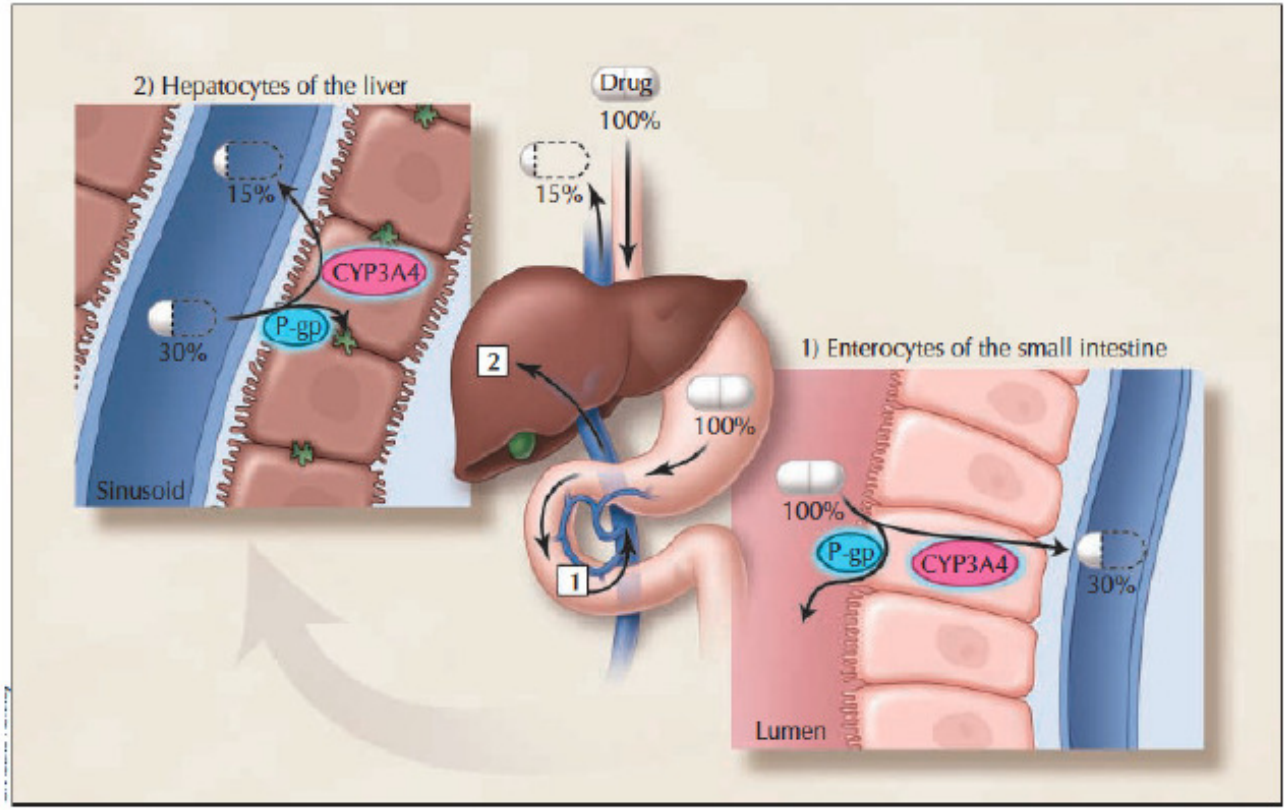
Drugs That Should Not Be Used With Antiretroviral Agents

ARV	Drugs That Should Not Be Used Concomitantly
DTG[1]	Dofetilide, rifapentine, St John's wort
EFV[1]	St John's wort, dasabuvir, ombitasvir, paritaprevir, simeprevir, elbasvir/grazoprevir
EVG/COBI[1]	Ranolazine, eplerenone, ivabradine, lovastatin, simvastatin, rifampin, rifapentine, carbamazepine, phenobarbital, phenytoin, lurasidone, pimozide, midazolam, triazolam, St John's wort, dasabuvir, elbasvir/grazoprevir, ledipasvir, ombitasvir, paritaprevir, simeprevir, alfuzosin, cisapride, ergot derivatives, flibanserin, **salmeterol**, sildenafil for PAH
RPV[1]	Rifampin, rifapentine, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, St John's wort, dasabuvir, ombitasvir, paritaprevir, **PPIs (eg, omeprazole)**
TAF/FTC[1,2]	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St John's wort
TDF/FTC[2]	Nephrotoxic drugs

1. DHHS guidelines. July 2016.
2. TAF/FTC [package insert]. 2016.
3. TDF/FTC [package insert]. 2016.

Slide credit: clinicaloptions.com

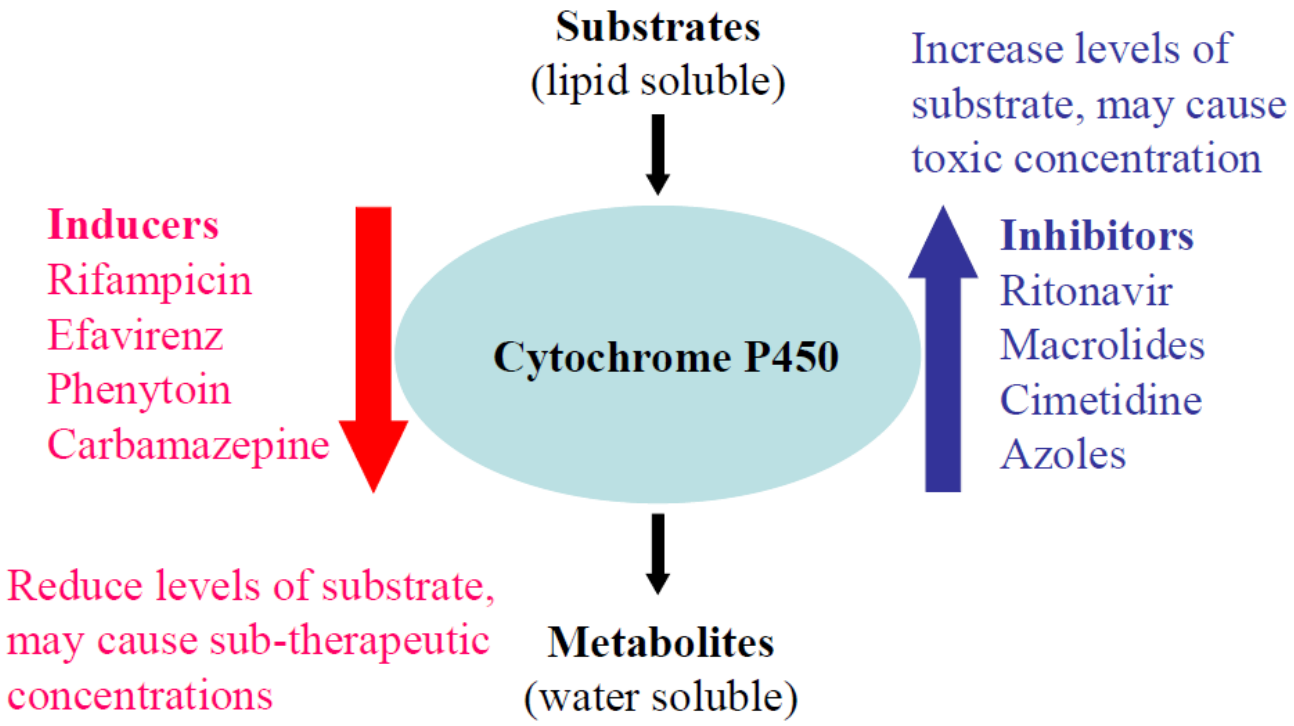
Bioavailability influenced by drug transporters and metabolising enzymes



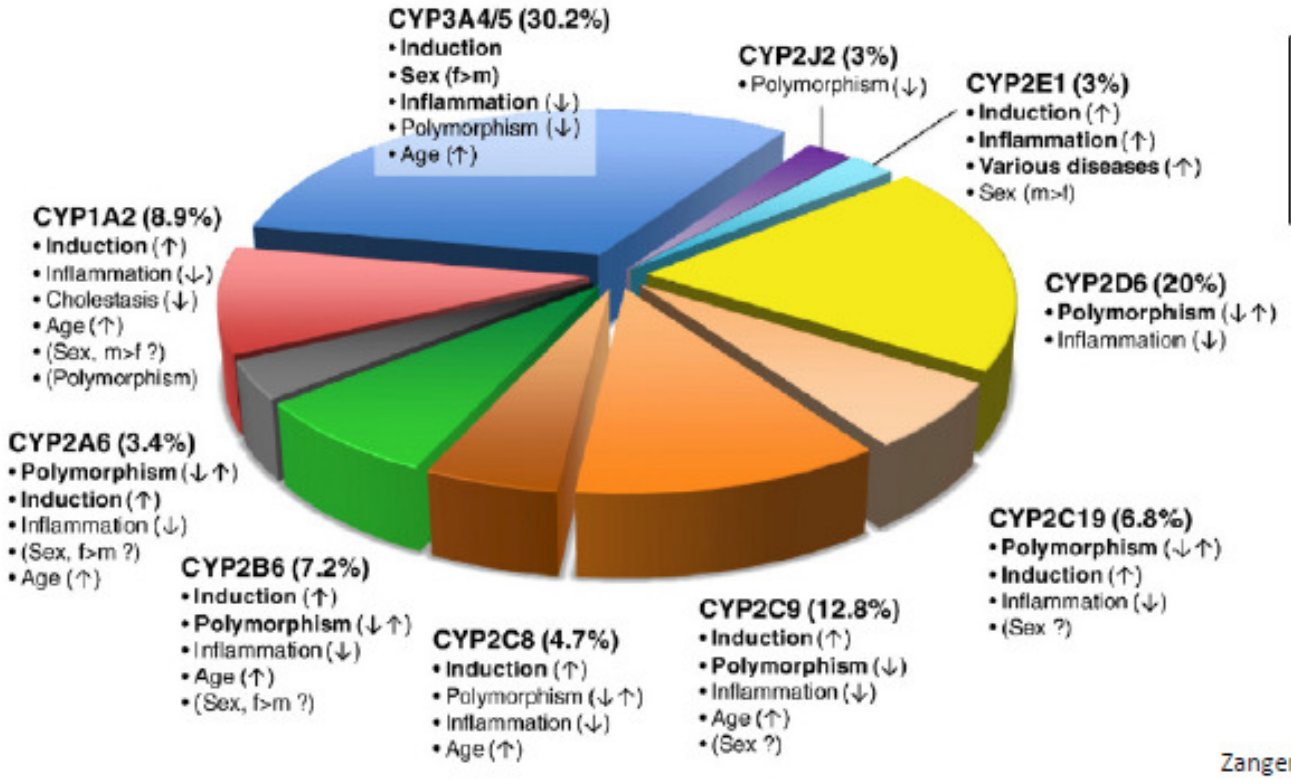
Induced by rifampicin
Inhibited by ritonovir

Bailey CMAJ 2004

Metabolism:
CYP450 drug interactions



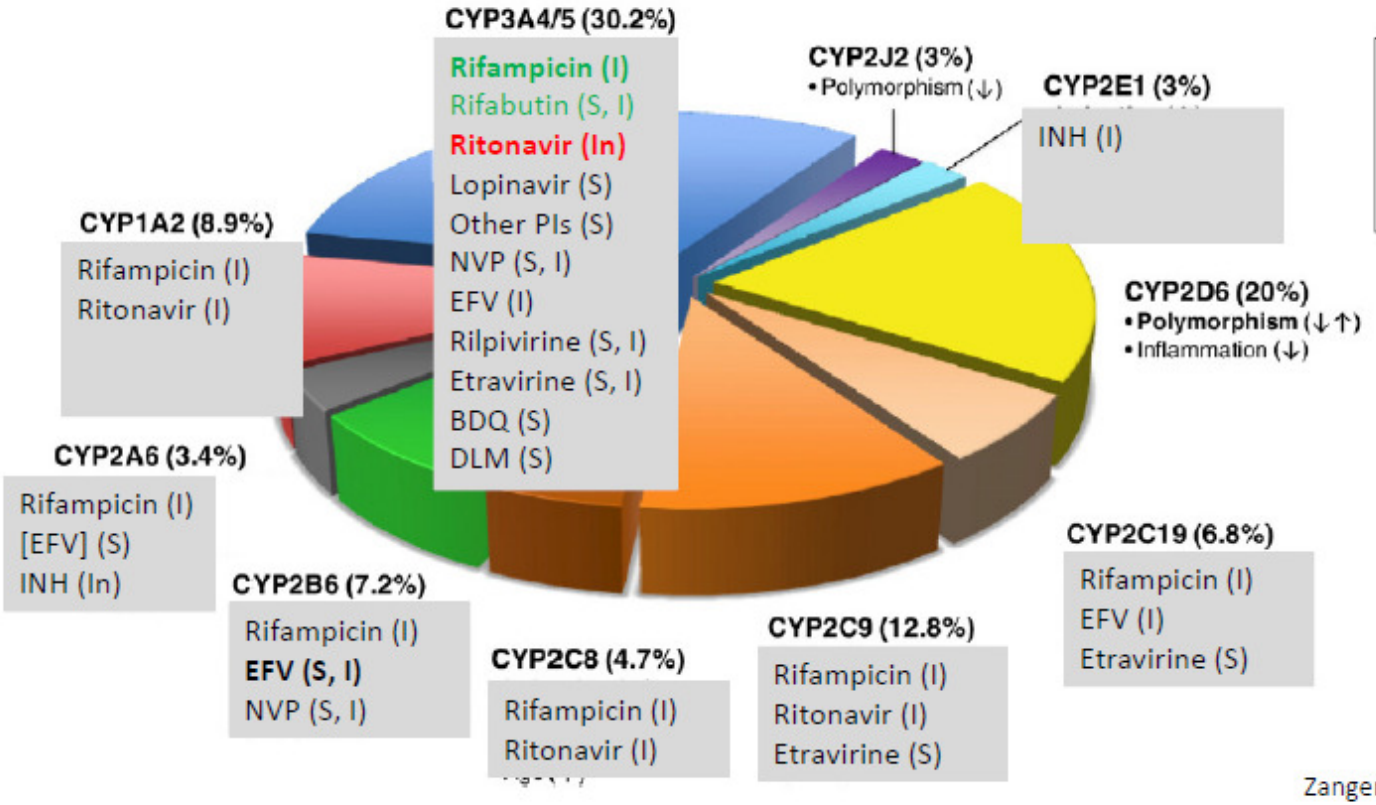
CYPs major metabolic pathway for TB drugs and ARVs



Source of PK and PD variability and DDIs

Zanger Pharmacology and Therapeutics 2013

CYPs major metabolic pathway for TB drugs and ARVs



Source of PK and PD variability and DDIs

Zanger Pharmacology and Therapeutics 2013

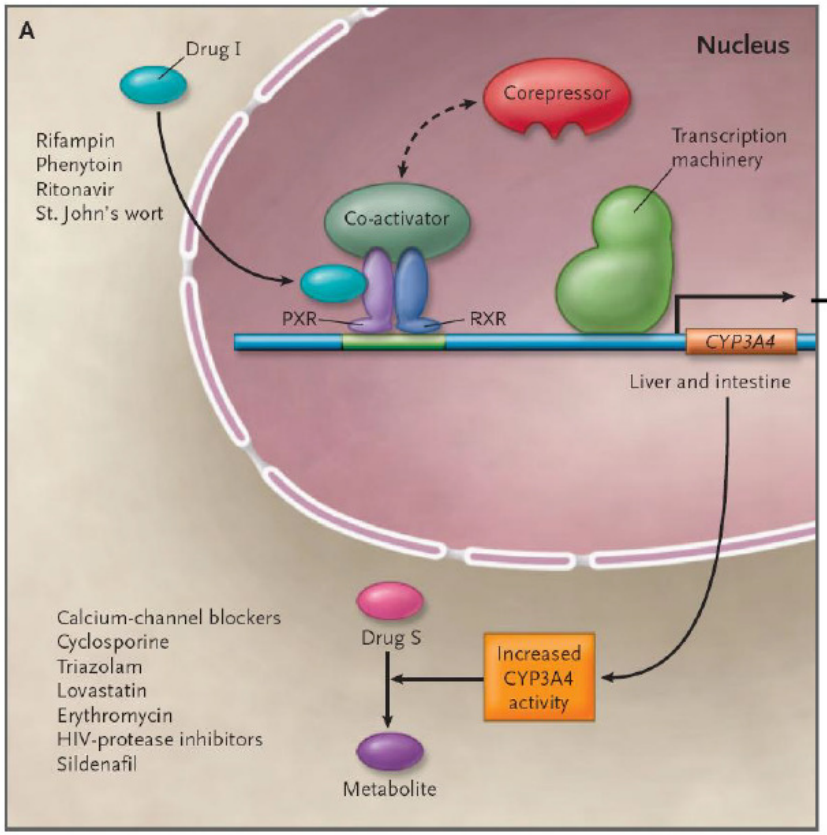
Inhibition of CYP450

- Inhibition may be reversible or irreversible
- Irreversible inhibitors (e.g. ritonavir):
  - Reactive intermediate metabolite binds irreversibly to enzyme causing inactivation
  - More potent inhibition than reversible
  - Duration of inhibition is longer (5-10 days compared with about 48 hours after stopping) as new enzyme needs to be synthesised
- Severe toxicity may occur if a P450 substrate is co-administered

Induction of metabolism

- Many drugs & exogenous substances (eg smoking, grilled food, garlic) can induce
- Several (2 main) pathways to turn on regulatory gene that affects MANY downstream genes that have the net effect of reducing exposure to a xenobiotic/drug

PXR-RXR mechanism of enzyme induction



OTHERS ↑

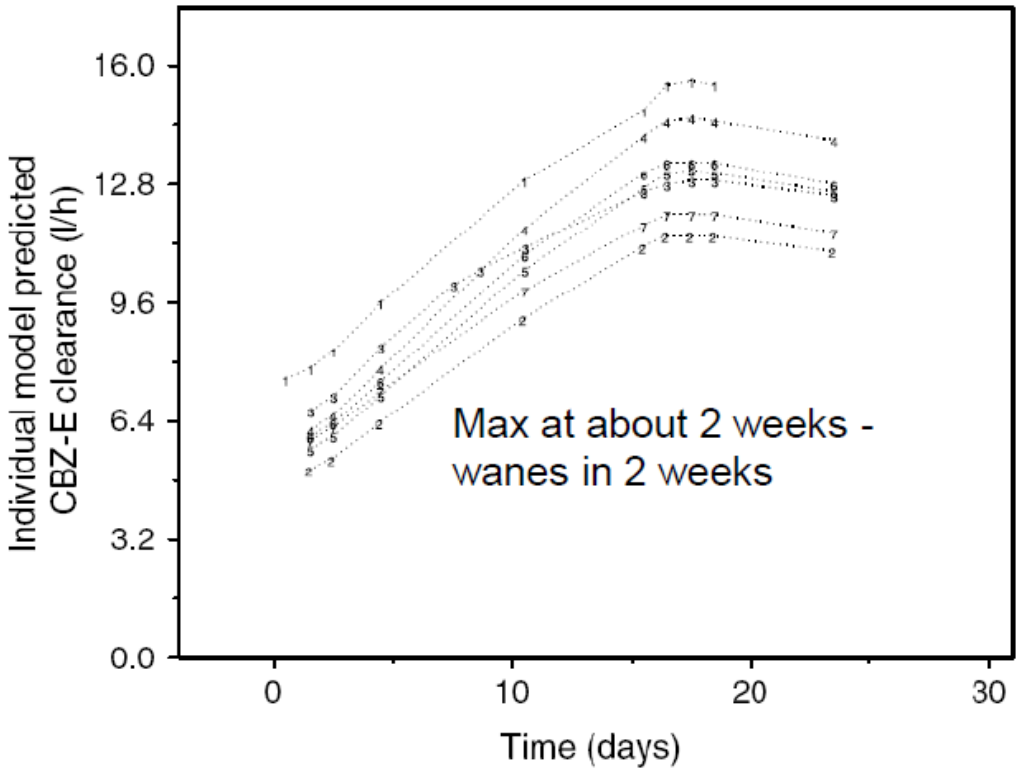
Phase I
CYP2B6
CYP2C8/9

Phase II
UGT
GST

Transporters
P-glycoprotein

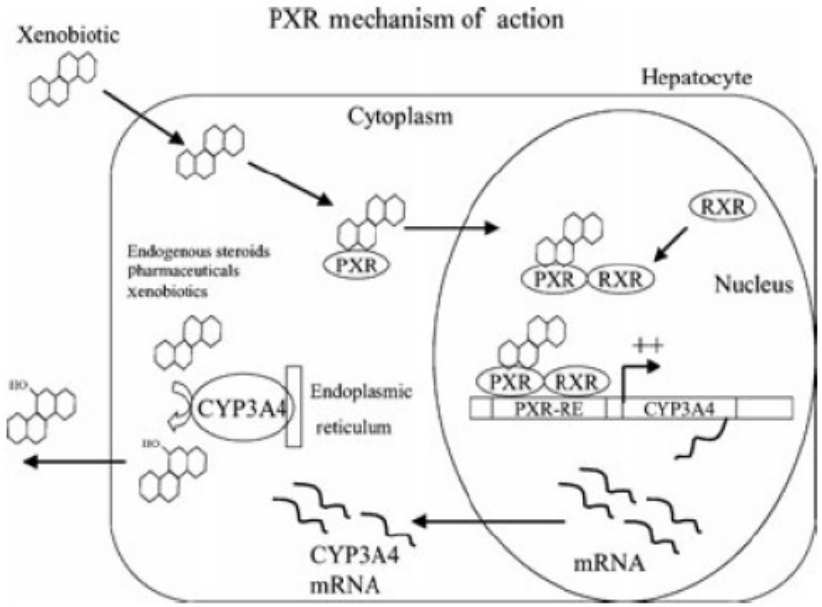
NEJM 2005;352:2211
Chen 2006

Time course of induction



Magnusson Clin Pharm Ther doi:10.1038/sj.clpt.6100431

Rifampicin leads to increased transcription of CYP3A4



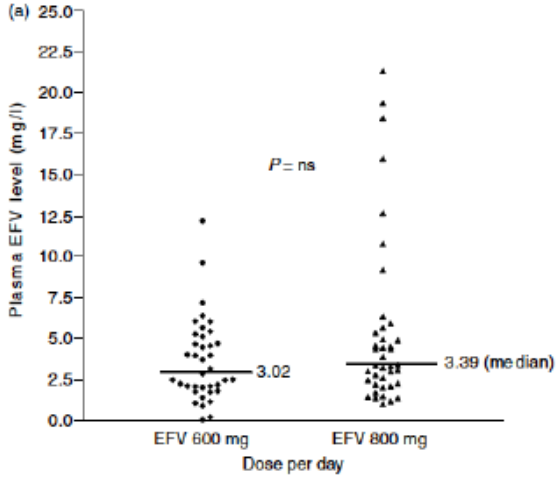
Tompkins J Biochem Mol Toxicol 2007

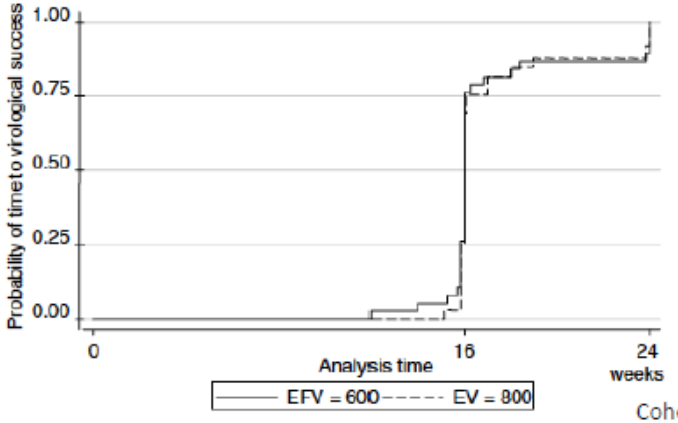
Rifampicin is a potent inducer of multiple enzyme/transporters: DDIs

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

Rifampicin and EFV

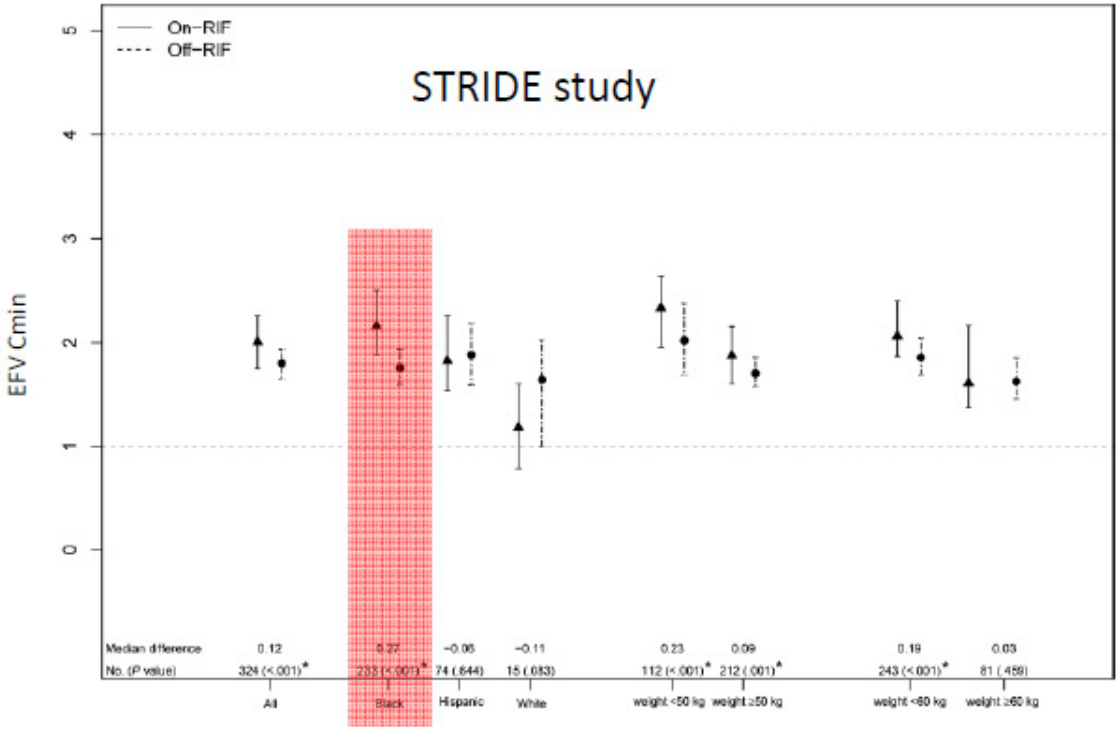
- Package insert reports reduced EFV exposure and recommends dose increase to 800 mg daily with rifampicin if weight > 60kg
- But **no difference in exposure or impact on clinical outcomes when EFV 600 mg used with rifampicin**





Cohen Antivir Ther 2009
Friedland JAC 2006
Manosuthi AIDS 2005

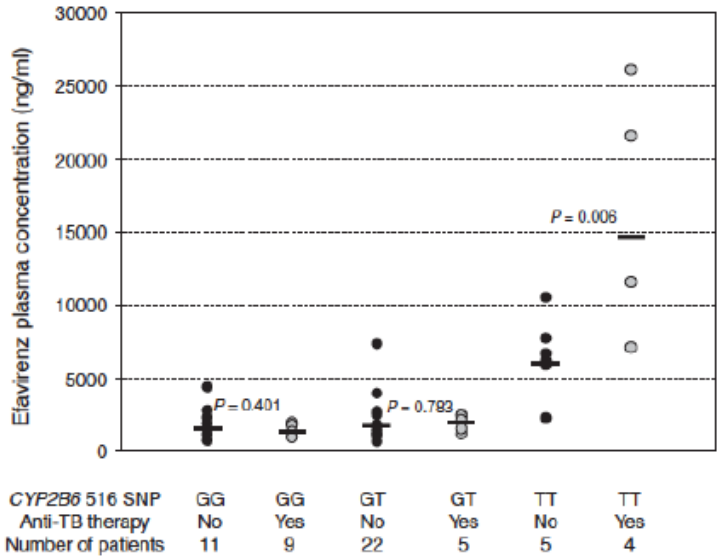
Paradoxically EFV exposure increased in some patients on TB treatment



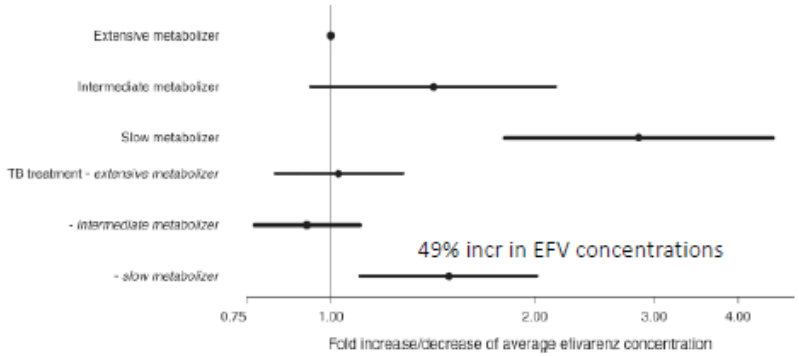
SAPIT study: 30% reduction in EFV clearance during TB treatment (20% 'slow metabolisers')

Gengiah Eur J Cin Pharm 2012
Luetkemeyer CID 2013

EFV concentrations higher in patients with slow metaboliser *CYP2B6* genotypes on TB Rx

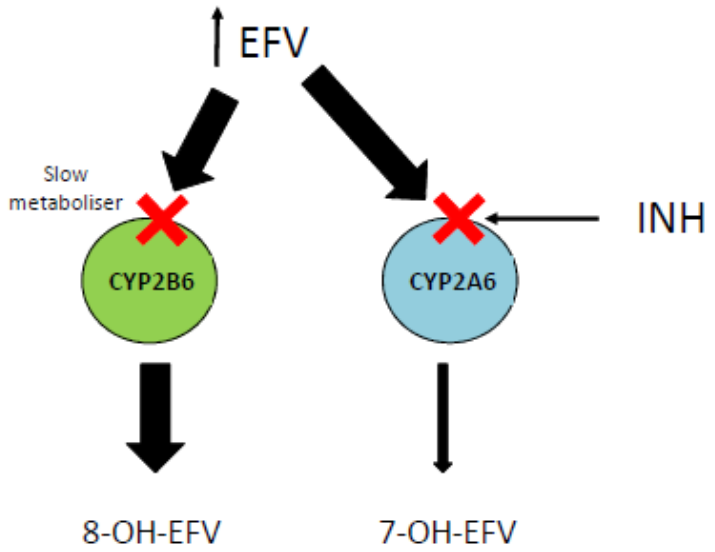


Prevalence of slow metaboliser genotypes
~20% in black South Africans



McIlleron AIDS 2013
Kwara AIDS 2011

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.

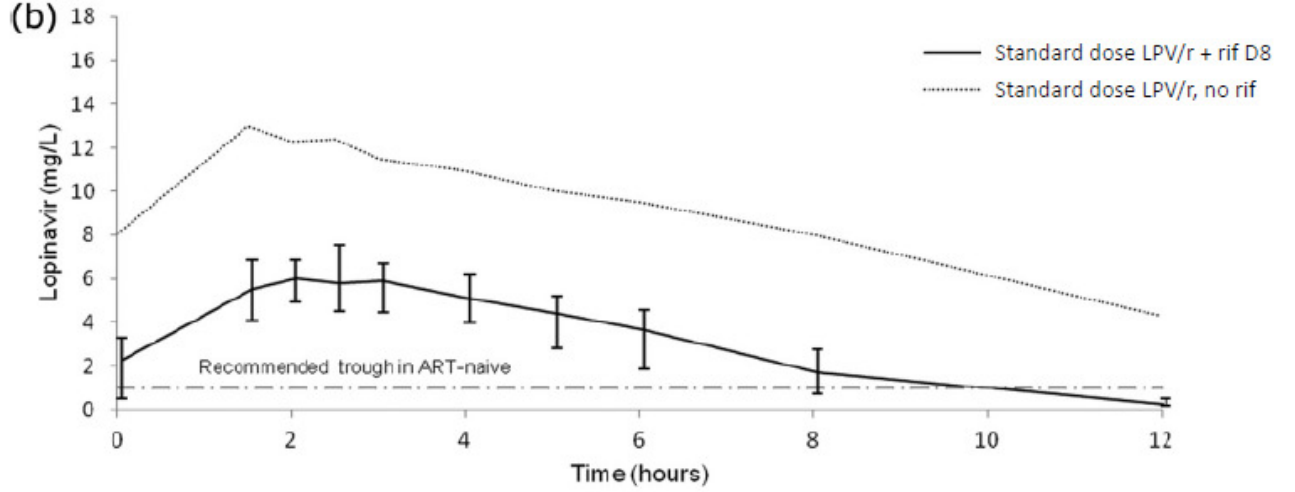
Adjusted dose PIs & rifampicin: healthy volunteers

- Very high rates of hepatitis reported in 3 healthy volunteer studies (Saquinavir, Atazanavir, Lopinavir); all stopped early due to toxicity
- ?relevant to HIV+ patients: e.g. rif + PZA for LTBI well tolerated in HIV+, but not in HIV-

Arch Drug Inf. 2009 Mar;2(1):8-16
AIDS 2008;22:931-5
JAIDS 2009;50:290-3
CID 2004;39:561

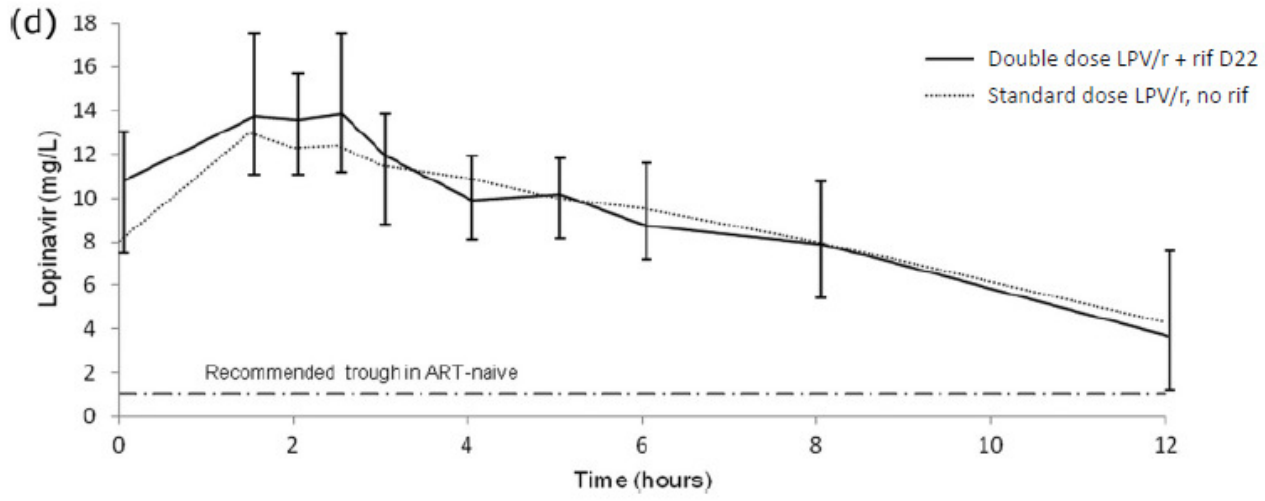
Rifampicin and LPV/r

- PIs substrates of CTP3A4 and P-gp
- Rifampicin reduces LPV/r exposure by 75%



Decloedt AAC 2011

Double dose of LPV/r overcomes induction by rifampicin



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

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 increasing exposure and necessitating dose reduction

Interaction	Rifampicin	Rifabutin
Major metabolic pathway	Deacetylation, hydrolysis to formyl derivatives	CYP3A-mediated hydroxylation, deacetylation
Serum half-life (h)	2-5	32-67
Effect on CYP3A	Pronounced	Weak
Auto-induction	Yes	Yes
Example of CYP3A induction: effect on indinavir AUC	92% decrease	34% decrease
Change in AUC when given with a CYP3A inhibitor[a]	No effect	293% increase

Complications of Antiretroviral Therapy in Patients with Tuberculosis: Drug Interactions, Toxicity, and Immune Reconstitution Inflammatory Syndrome

Helen McIlleron,[1] Graeme Meintjes,[2] William J. Burman,[3] and Gary Maartens[1]

[1]Division of Clinical Pharmacology and [2]Department of Medicine, University of Cape Town, Cape Town, South Africa; [3]Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver

Table 1. Pharmacokinetic drug interactions between rifampin (RIF), rifabutin (RIB), protease inhibitors (PIs), and nonnucleoside reverse-transcriptase inhibitors (NNRTIs).

Drug	Interaction with RIF	Recommendation for concurrent ARV use with RIF[a]	Interaction with RIB	Recommendation for concurrent ARV use with RIB	RIB dose adjustment
PIs					
RTV	RTV ↓ 35%	No dose adjustment	RIB ↑ 435%	No dose adjustment	150 mg 3× per week
IDV	IDV ↓ 89%	Avoid	IDV ↓ 32%; RIB ↑ 204%	IDV 1000 mg t.i.d.	150 mg daily or 300 mg 3× per week
SQV	SQV ↓ 84%	Avoid SQV (400 mg) + RTV (400 mg) b.i.d.; may be effective but is hepatotoxic in healthy volunteers; monitor liver function closely	SQV ↓ 40%	Avoid unboosted SQV	
NFV	NFV ↓ 82%	Avoid	NFV (1250 mg b.i.d.[b]) ↔; RIB ↑ 207%	NFV 1250 mg b.i.d.	150 mg daily or 300 mg 3× per week
APV, f-APV	APV ↓ 82%	Avoid	APV ↓ 15%; RIB ↑ 193%	No dose adjustment	150 mg daily or 300 mg 3× per week
ATV	Predicted significant ATV ↓	Avoid	RIB ↑ 250%	No dose adjustment	150 mg daily or 150 mg 3× per week
RTV-boosted[c]		Avoid		No dose adjustment	150 mg 3× per week
RTV-boosted LPV (Kaletra)	LPV ↓ 75%	Avoid LPV/rtv + RTV (300 mg b.i.d.): monitor liver function closely	RIB ↑ 303%	No dose adjustment	150 mg 3× per week
NNRTIs					
NVP	NVP ↓ 20%–55%	No dose adjustment; safety and efficacy not established; monitor liver function closely	NVP ↓ 16%	No dose adjustment	No dose adjustment
EFV	EFV ↓ 25%	Consider EFV ↑ to 800 mg daily in patients >60 kg	EFV ↔; RIB ↓ 35%	No dose adjustment	450–600 mg daily or 600 mg 3× per week
DLV	DLV ↓ 96%	Avoid	DLV ↓ 80%; RIB ↑ 100%	Avoid	

NOTE. Adapted from [10]. Percentage values are changes in area under the concentration-time curve: ↑, increase; ↓, decrease; ↔, no change. APV, amprenavir; ARV, antiretroviral; ATV, atazanavir; b.i.d., twice daily; DLV, delavirdine; EFV, efavirenz; f-APV, fosamprenavir; IDV, indinavir; LPV, lopinavir; LPV/rtv, ritonavir-boosted LPV; NFV, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir, t.i.d., 3 times daily.

[a] Rifampin levels are not significantly affected by PI or NNRTI coadministration; therefore, no rifampin dose adjustment is required.

[b] NFV (750 mg t.i.d.) should not be used with RIB.

[c] SQV, APV/f-APV, IDV, or ATV.

Population pharmacokinetic drug–drug interaction pooled analysis of existing data for rifabutin and HIV PIs

Stefanie Hennig[1,2*], Elin M. Svensson[2], Ronald Niebecker[2], P. Bernard Fourie[3], Marc H. Weiner[4], Stefano Bonora[5], Charles A. Peloquin[6], Keith Gallicano[7], Charles Flexner[8], Alex Pym[9], Peter Vis[10†], Piero L. Olliaro[11], Helen McIlleron[12] and Mats O. Karlsson[2]

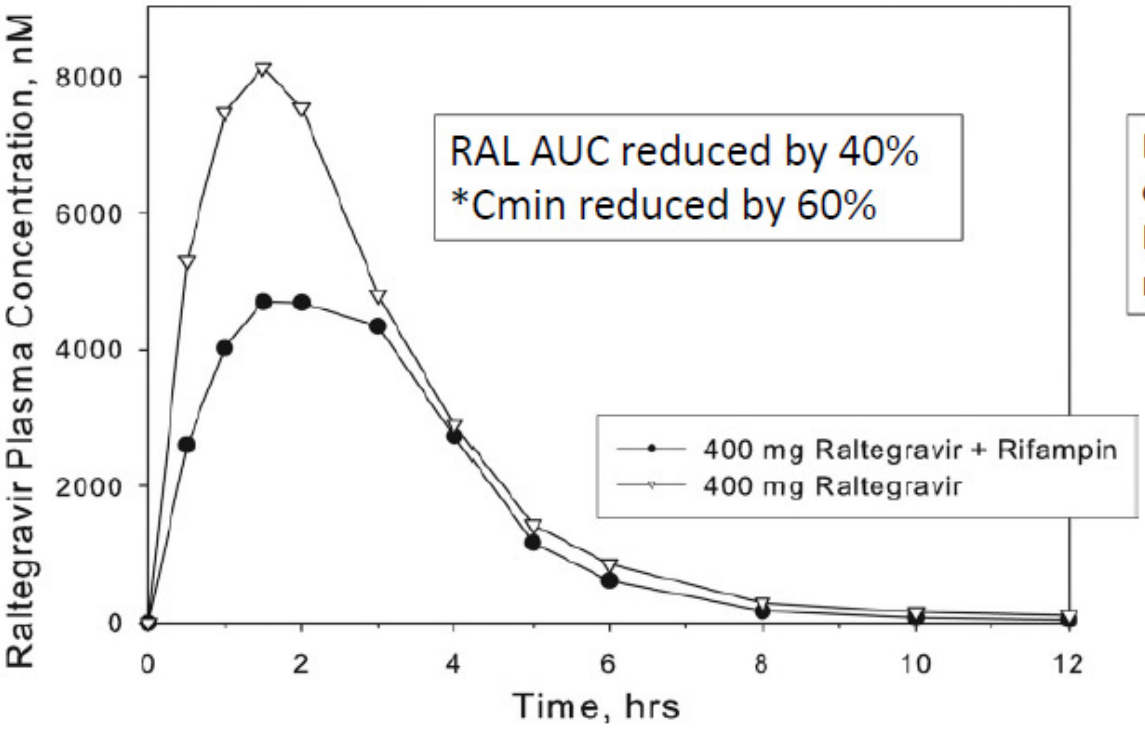
Conclusions: Given together with non-boosted or ritonavir-boosted PIs, rifabutin at 150 mg once daily results in similar or higher exposure compared with rifabutin at 300 mg once daily without concomitant PIs and may achieve peak concentrations within an acceptable therapeutic range. Although 300 mg of rifabutin every 3 days with boosted PI achieves an average equivalent exposure, intermittent doses of rifamycins are not supported by current guidelines.

Rifabutin recommendations:

- 300mg od with no interacting drugs
- 150mg od preferred with PI based regimens
  - Concerns about failure risk with intermittent dosing and poor PI adherence
- 600mg od with EFV
- Monitor for toxicity (WCC, eyes)

J Antimicrob Chemother 2016; **71**: 1330–1340

NOW TO THE NEW:
Rifampicin reduces RAL exposure in healthy volunteers

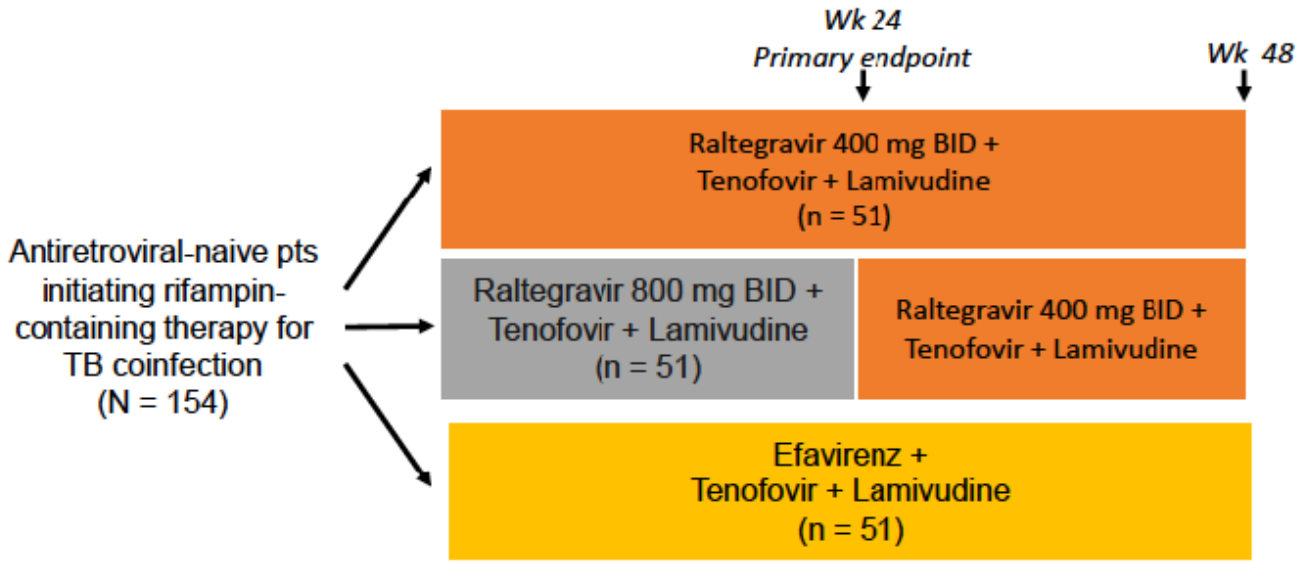


Effect on AUC overcome by RAL 800 (but not Cmin)

Wenning AAC 2009

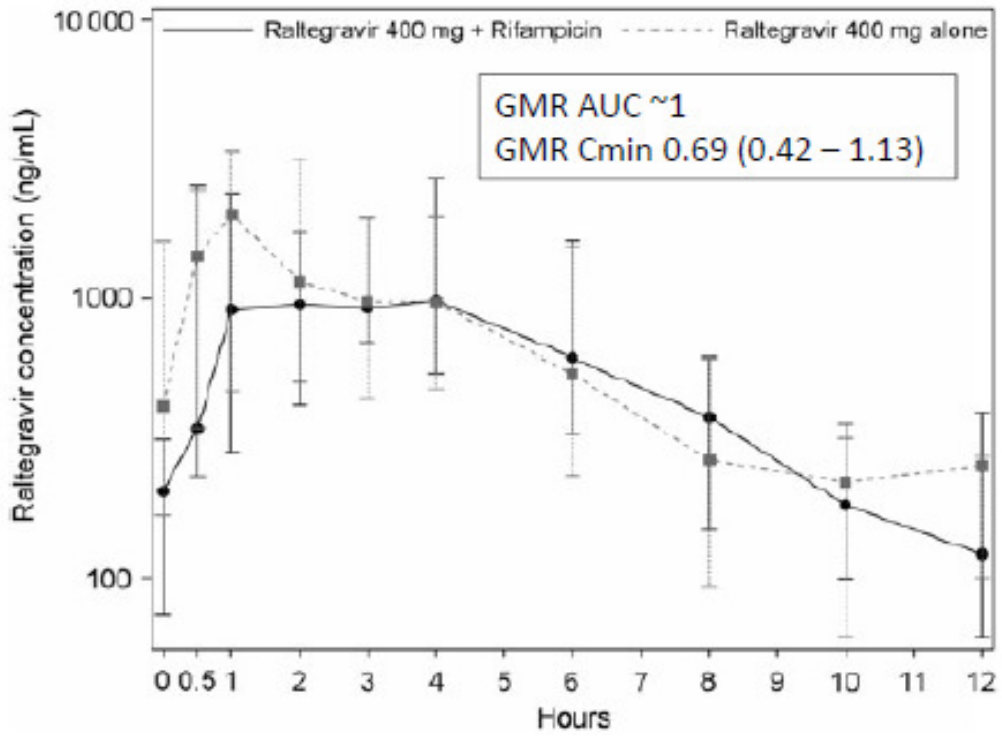
But what is the PK and clinical impact in HIV/TB patients?

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



Grinsztejn LID 2014

Lower trough with RAL 400 + RIF but not significant



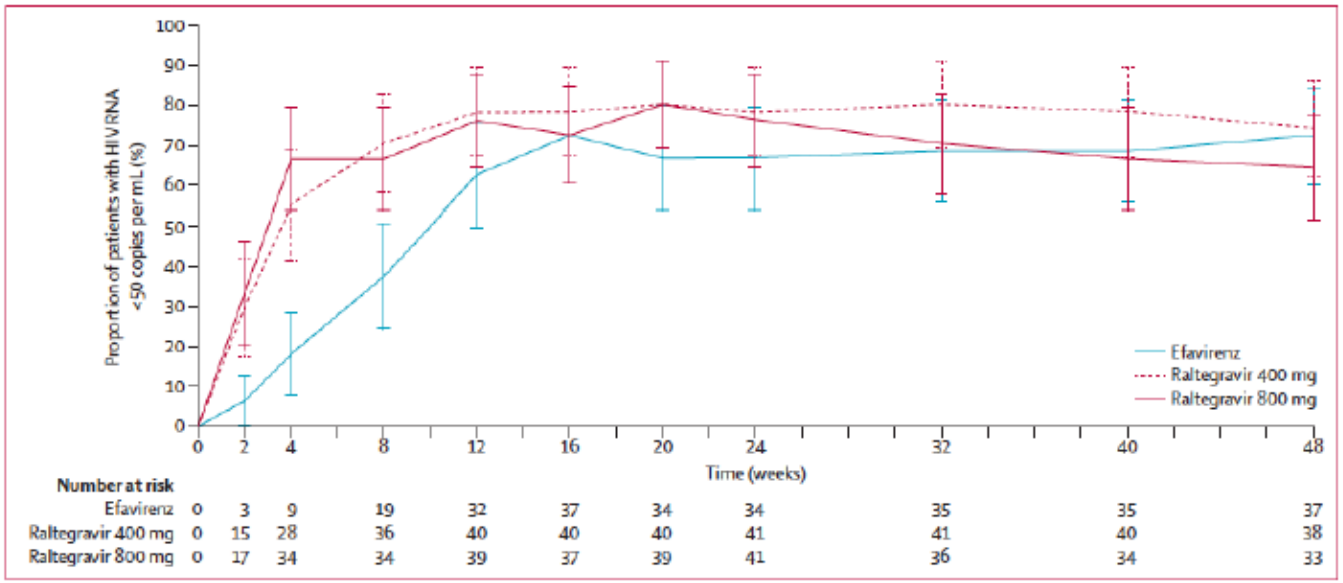
Only a single Cmin < 14 ng/L (IC_{50} for RAL)

RAL 800 resulted in 68% higher Cmin

Taburet CID 2015

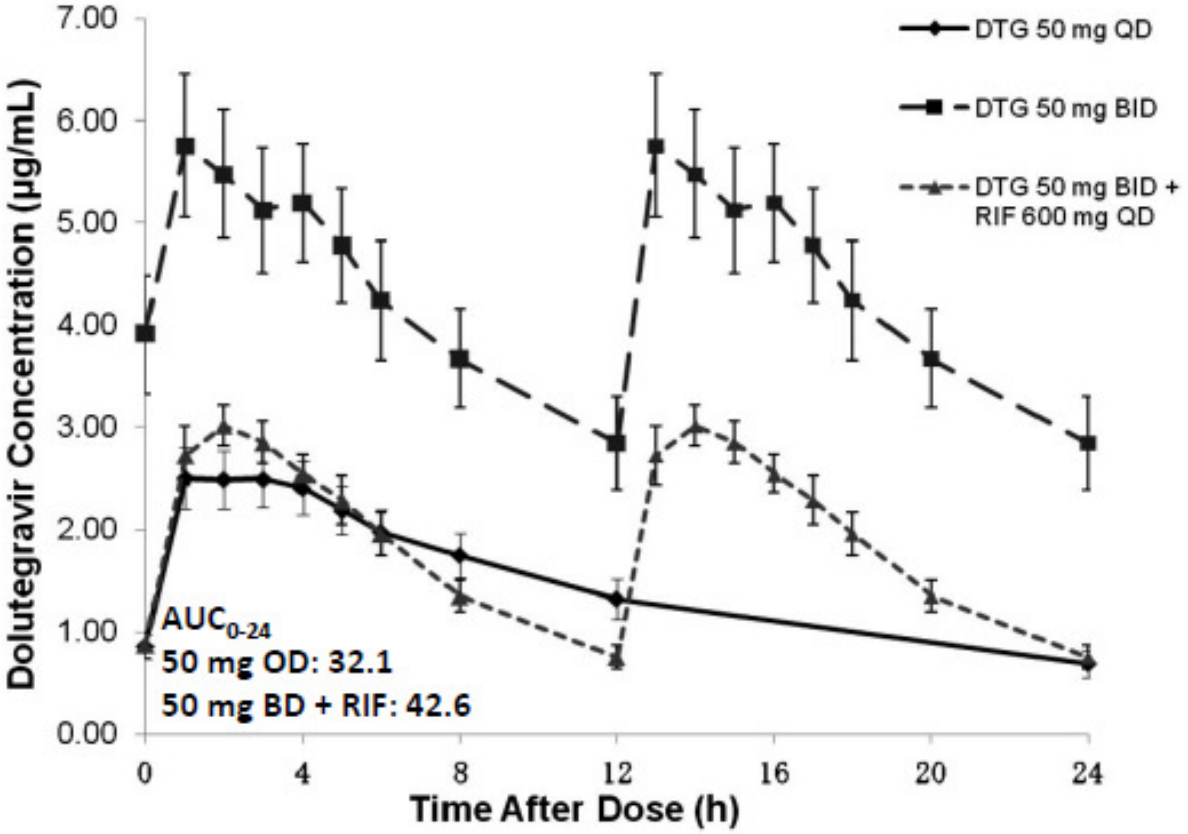
Clinical impact of standard RAL dose in HIV/TB: similar rates of virological suppression

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 IC_{50} threshold with BD dosing
  - DTG 50 mg BD + RIF has higher exposures (33%) than DTG 50 mg OD alone

Dooley JAIDS 2013

Dolutegravir adjusted doses in TB

- Absorption is saturable, so doubling the daily dose is not an option
- Clearance is increased and estimated C_{min} is about the same as IC90
- Therefore 12 hourly dosing is likely to be necessary
- INSPIRING study will assess PK of DTG 12 hourly in patients with TB & evaluate efficacy (not powered versus comparator though)
- Need an adequately powered RCT of virologic efficacy of DTG 12 hourly (plus 2 NRTI) against the current standard of care (EFV, TDF, FTC) in patients with TB

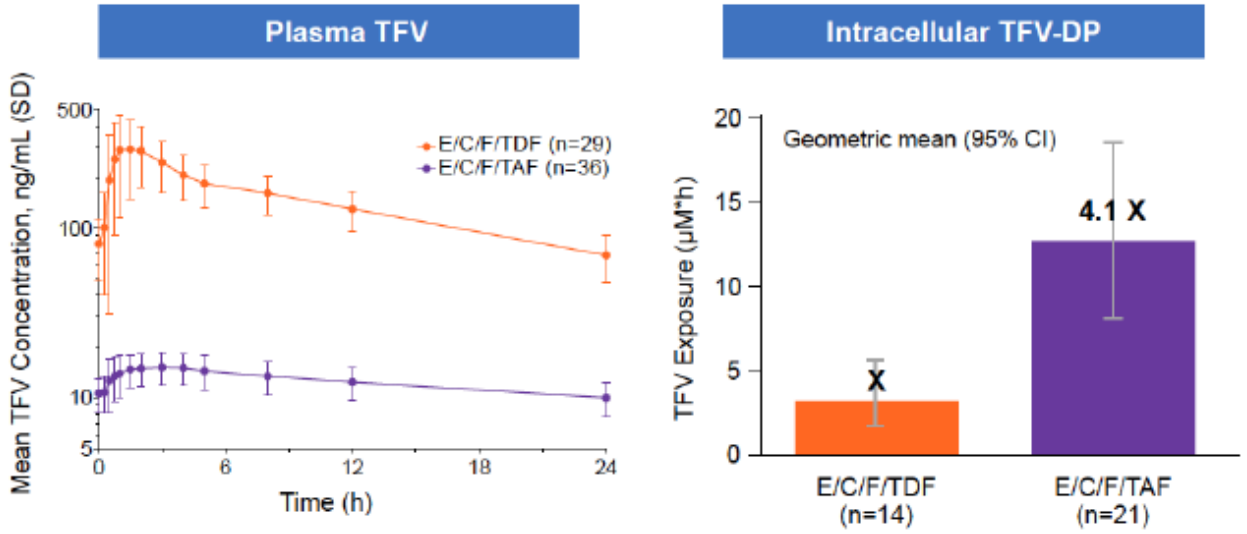
Recommended dose 50 mg BD with TB Rx, but important questions:

- Does it translate into similar efficacy compared with EFV?
- Emerging concerns about neuropsychiatric AEs on DTG
  - Meta-analysis of clinical trials: uncommon but similar frequency to EFV
  - Discontinuation due to intolerability ~14% in European cohorts (NP-AEs most common reason)
- UGT1A1 polymorphisms
  - Higher exposures and toxicity?
- Higher pill burden than FDC
  - Adherence?
- More potent than EFV
  - More IRIS?

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

Rifampicin and TAF

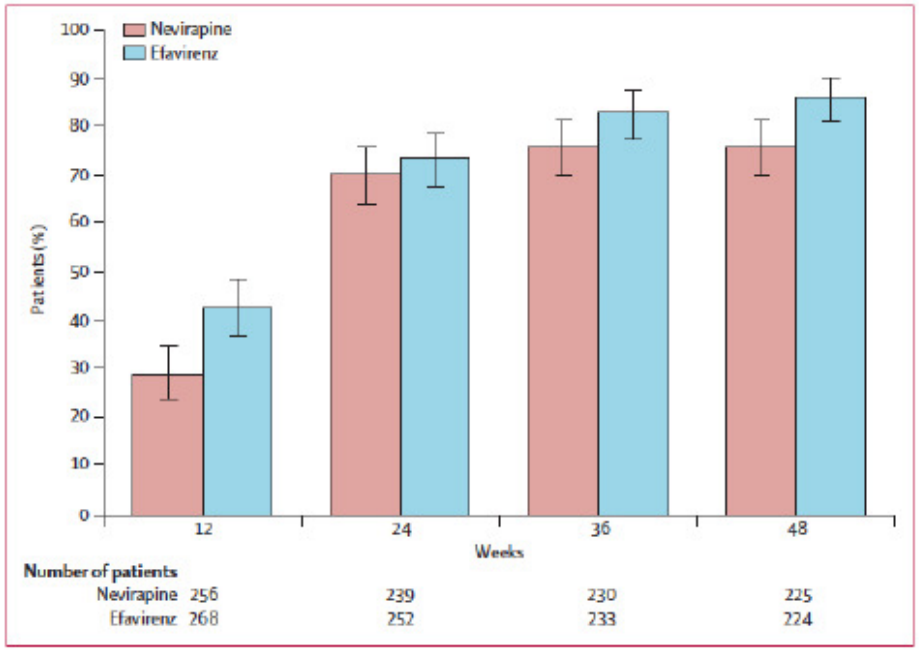
- Much higher intracellular concentration of active drug than TDF, and much lower plasma concentration of TFV
  - Less toxicity
  - Lower doses required
- TAF substrate of P-gp and other transporters: inhibited by RTV, cobicistat, induced by rifampicin
- **No PK studies with rif, but co-administration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



Sax Lancet 2015

Preferred regimens in TB co-infection

- **WHO and NDoH: TDF + 3TC/FTC + EFV (600)**
- **IAS-USA: EFV, DTG, RTG (boosted PI only if INSTI not an option)**



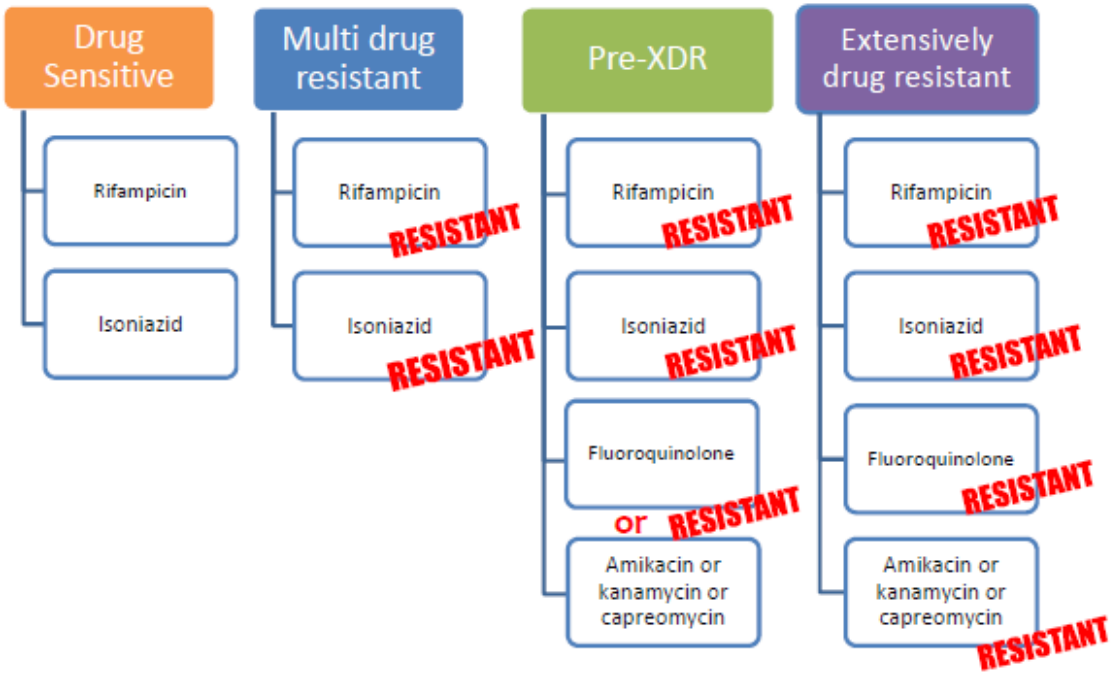
NVP failed to demonstrate non-inferiority to EFV in patients with TB (CARINEMO trial)

Bonnet LID 2013

Summary of important DDIs in DS-TB

Antiretroviral	Rifampicin	Other DS-TB Rx
Efavirenz	• Does not require dose adjustment	• Caution with INH • Incr RBT dose
Nevirapine	• Omit 200 mg daily lead-in dose	• 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)
Atazanavir/ritonavir	• Do not coadminister	
Darunavir/ritonavir	• Do not coadminister	
Raltegravir	• Standard dose	• No adjustment with RBT
Dolutegravir	• Double dose 50 mg BD	
Elvitegravir	• Do not coadminister	
TAF	• Do not coadminister	

Definitions of TB Drug Resistance



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

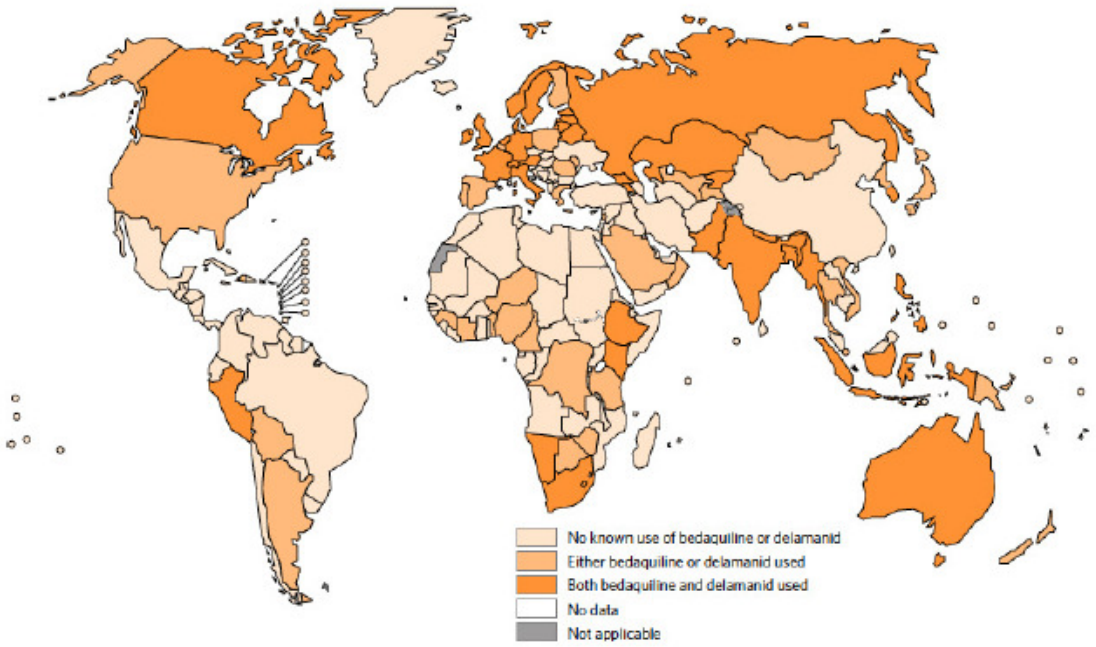
BDQ and DLM are being rolled out

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



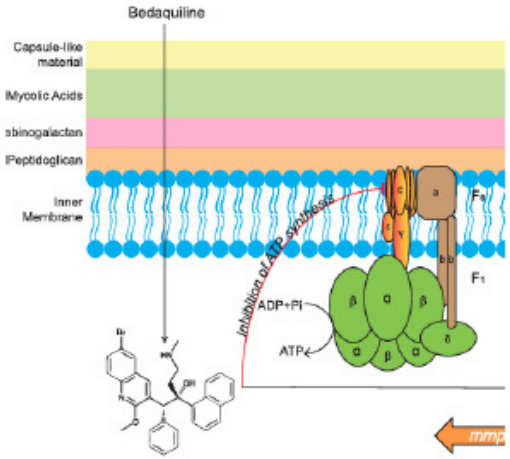
WHO Global Report 2016

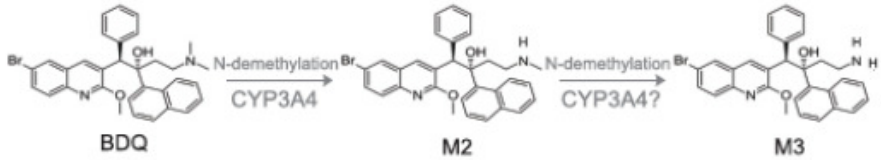
Multiple trials of new DR-TB regimens

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

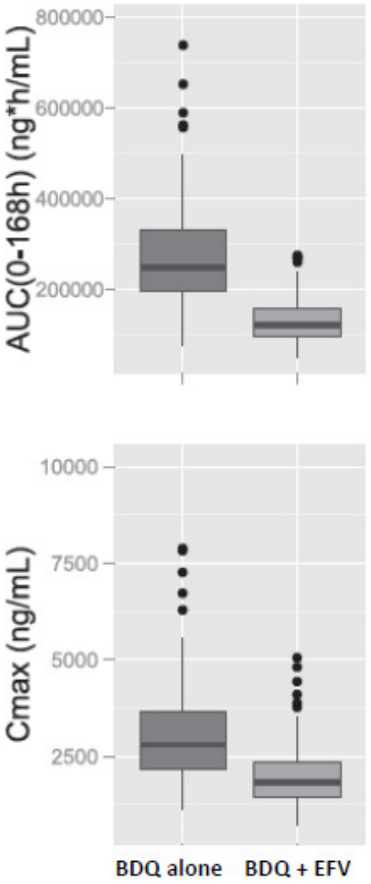
Bedaquiline

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





AEs include QT prolongation and hepatitis: related to dose?



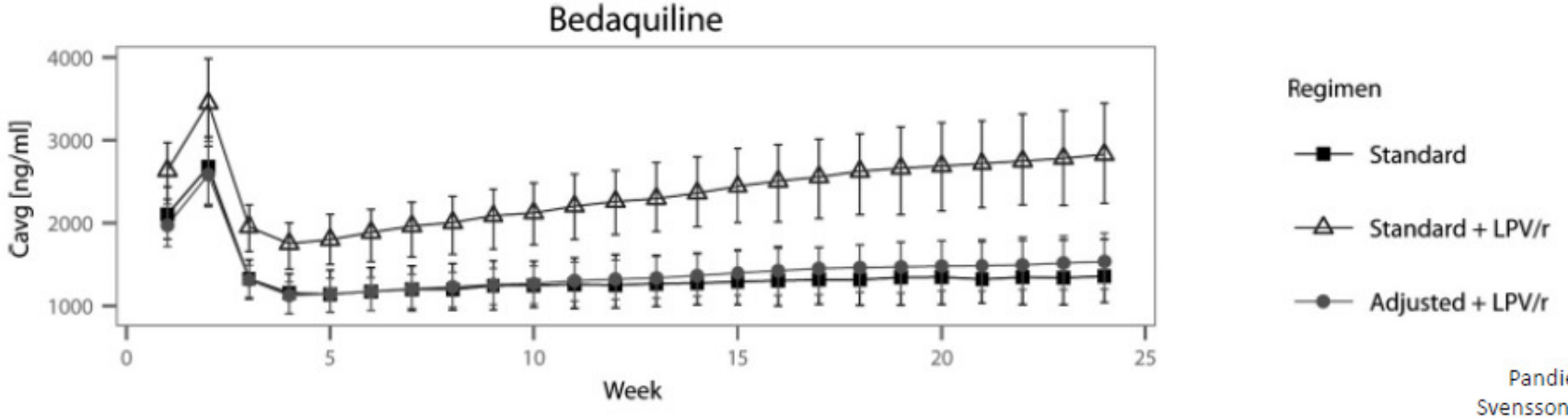
BDQ DDIs: NNRTIs

- EFV steady state concentrations reduced by 52% (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

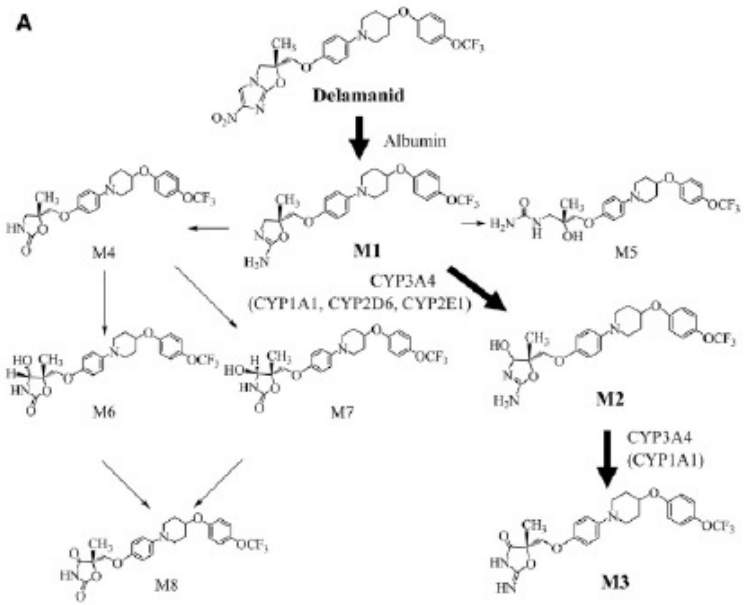
- Model: reduces BDQ clearance by 35%, M2 clearance by 58% (2- and 3-fold increase in steady state concentrations)
- Patients: 62% increase in AUC
- Clinical consequences unclear: monitor ECG closely



Pandie JAC 2016
Svensson AAC 2014

Delamanid

- Nitroimidazole
- Metabolised by albumin, smaller contribution by CYP3A4
- Associated QT prolongation
- No impact on EFV or LPV/r exposure
- Higher DLM concentrations with LPV/r: clinical impact?



Mallikaarjun AAC 2016
Sasahara Drug Metab Dispos 2015

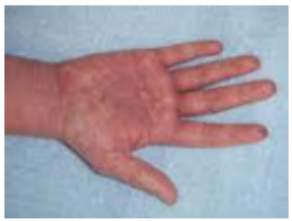
Other new/repurposed drugs

- 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?

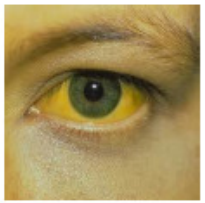
Summary of important DDIs in DR-TB

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

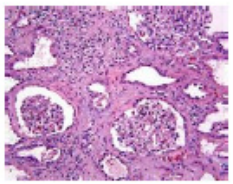
Shared toxicities



All TB drugs
NNRTIs
Cotrimoxazole

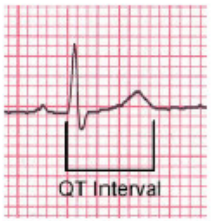


RHZ, RBT, FQs, BDQ, PMD, DLM
NNRTIs, PIs
Cotrimoxazole



SLIs, Rif
TDF

LZD
AZT



FQs, BDQ, DLM, CFZ

INH, TZD, LZD
d4T, ddI

INH, TZD
EFV, DTG

Conclusions

- Many co-infected patients on HIV and TB treatment
- TB is a real and present danger in South Africa
- Rifampicin remains a core drug for DS TB
- Many potential DDIs particularly with rifampicin
- Key new HIV and TB drugs also have important DDIs
- Ongoing PCV and close monitoring required