TB-HIV regimens and toxicity

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Co-administration of anti-TB drugs and antiretrovirals

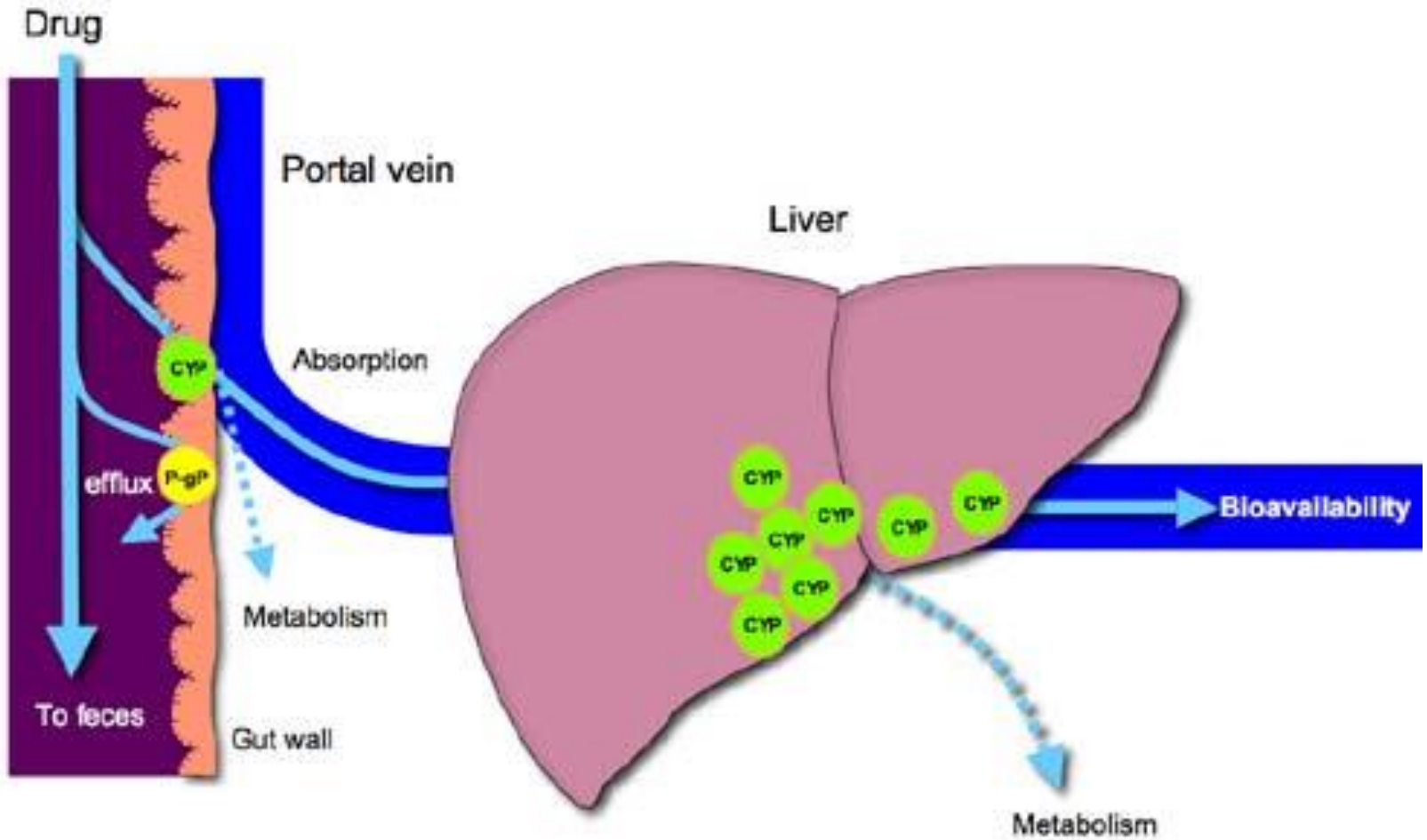
- Access to antiretroviral therapy in Brazil expanded rapidly.
- Rifampicin based TB regimens and ARV are associated with considerable morbidity, even mortality, particularly with drug-induced hepatitis and others adverse reactions
- These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations
- Alternative TB agents are more toxic and less effective, and for that reason have a longer duration to achieve the cure

Pharmacokinetics interactions

(1) the adequacy of drug absorption among patients with advanced HIV disease and

(2) drug-drug interactions

induction of cytochrome P-450 enzymes and P-glycoprotein by rifampin results in reduced concentrations of nonnucleoside reverse transcriptase inhibitors and, particularly, protease inhibitors


Drug
Portal vein
Liver
Absorption
CYP
efflux
P-gP
Metabolism
To feces
Gut wall
Bioavailability
Metabolism

Interaction between PI, NNRTI and rifampicin

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.

Breen et al tórax 2006

HIV+ and negative TB patients were compared
HIV positive patients were more proud to have disseminated TB, Weight loss >10% and 35% had adverse reactions to anti-TB drugs

TABLE 1. Comparison of the Distribution of Baseline and Follow-Up Variables Between HIV-Positive and HIV-Negative Patients

Variable	HIV Positive (n = 106), n (%)	HIV Negative (n = 101), n (%	*P*
White race	56 (53)	43 (43)	0.16
Age ≤40	79 (75)	55 (55)	0.003
Male sex	72 (68)	63 (62)	0.39
Alcohol abuse	21 (20)	20 (20)	0.86
Intravenous drug use	7 (7)	6 (6)	1.0
Use of other illicit drugs	17 (16)	14 (14)	0.46
School education ≥8 yrs	62 (59)	68 (69)	0.14
Monthly income ≤US $500.00	64 (60)	55 (55)	0.66
Psychiatric disease	1 (1)	6 (6)	0.06
Homelessness	5 (5)	2 (2)	0.47
Incarceration	3 (3)	5 (5)	0.49
TB clinical presentation			
Pleural-pulmonary	52 (49)	88 (87)	<0.001
Extrapulmonary, localized	16 (15)	11 (11)	
Disseminated	38 (36)	2 (2)	
Weight loss >10%	67 (70)	37 (40)	<0.001
Positive sputum smear	71 (67)	66 (65)	1.0
Previous antituberculous therapy	15 (14)	12 (12)	0.63
Hemoglobin ≤10 g%	59 (56)	15 (15)	<0.001
Serum albumin ≤3 g%*	37 (41)	24 (26)	0.03
Multidrug resistance	7 (7)	1 (1)	0.07
Severe adverse reaction to anti-TB therapy	37 (35)	10 (10)	<0.001
Susceptible TB infection not treated with rifampicin throughout	14 (13)	3 (3)	0.007
Treatment default	6 (6)	17 (16)	0.014

*Data on baseline albumin available for 90 HIV-positive patients and 92 HIV-negative patients.

Schmaltz et al JAIDS 2009

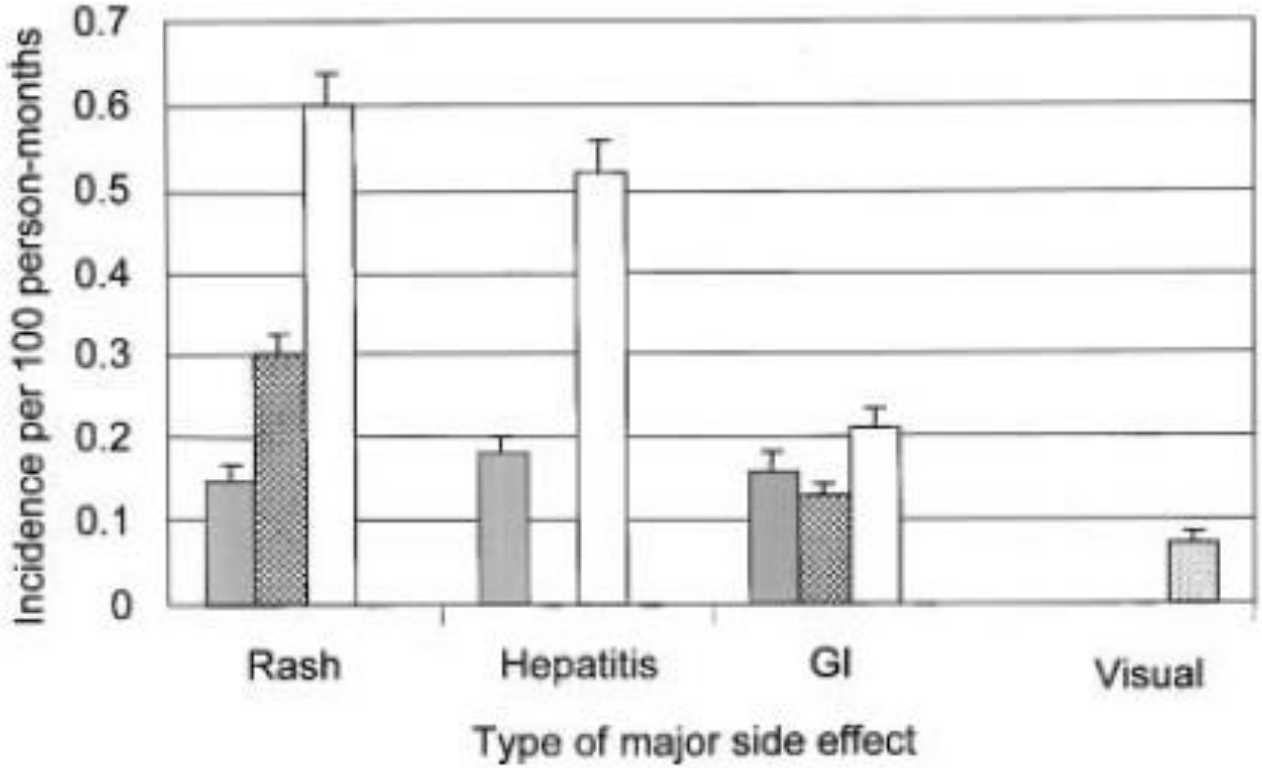


Figure 1. Incidence of serious side effects by type and drug. *Shaded columns*, isoniazid; *cross-hatched columns*, rifampin; *open columns*, pyrazinamide; *dotted columns*, ethambutol.

Yee, Valiquette, Pelletier, et al.: Side Effects of TB Therapy
Am Journ Resp Crit Care 2003

First line antiretrovirals for TB-HIV in Brazil

- **Efavirenz** with a backbone in FDC became the most used ARV wordwide due to the good tolerance and low pill burden
- Patients with CD4 counts <100 cells/mm3 or other severe disease criteria should be treated with **Raltegravir** based regimens due to the increasing incidence of primary resistance to efavirenz in Brazil

Virologic data along the trial

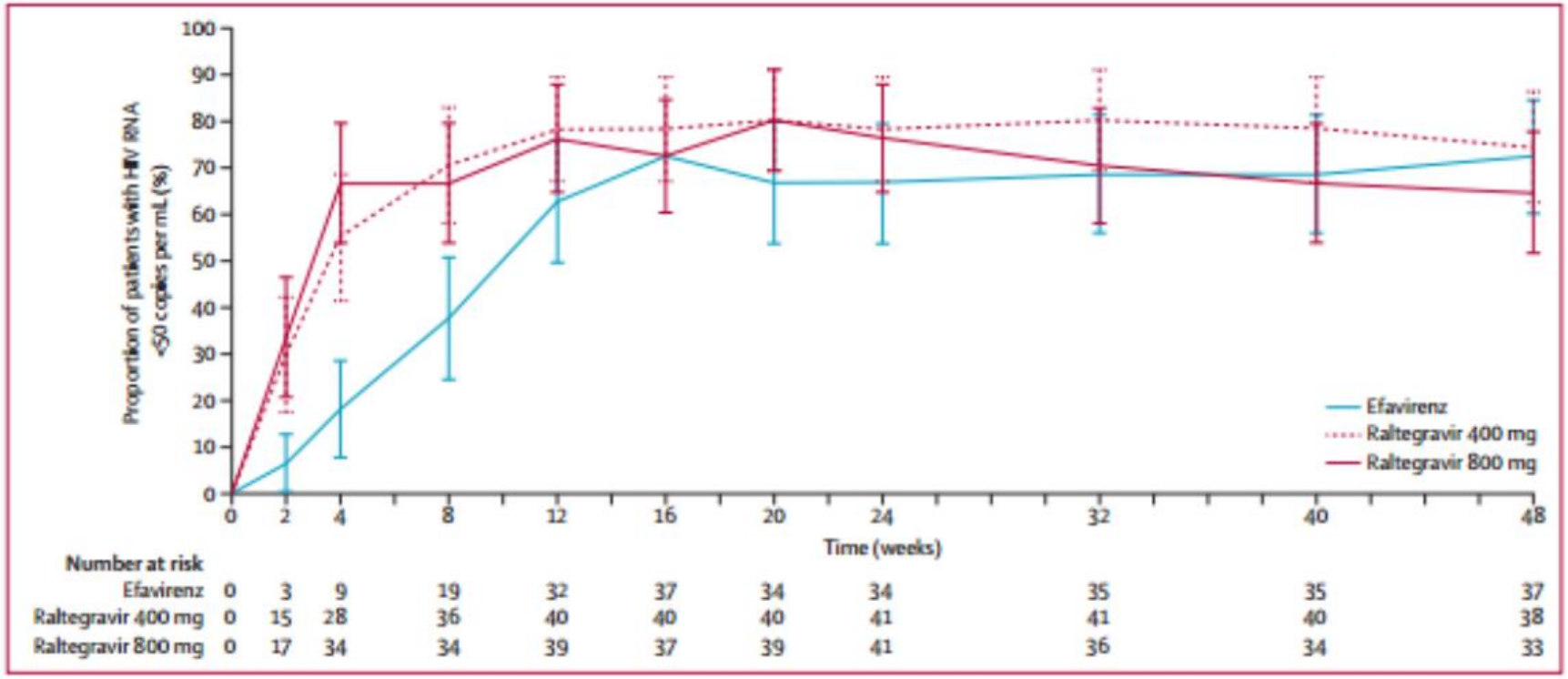
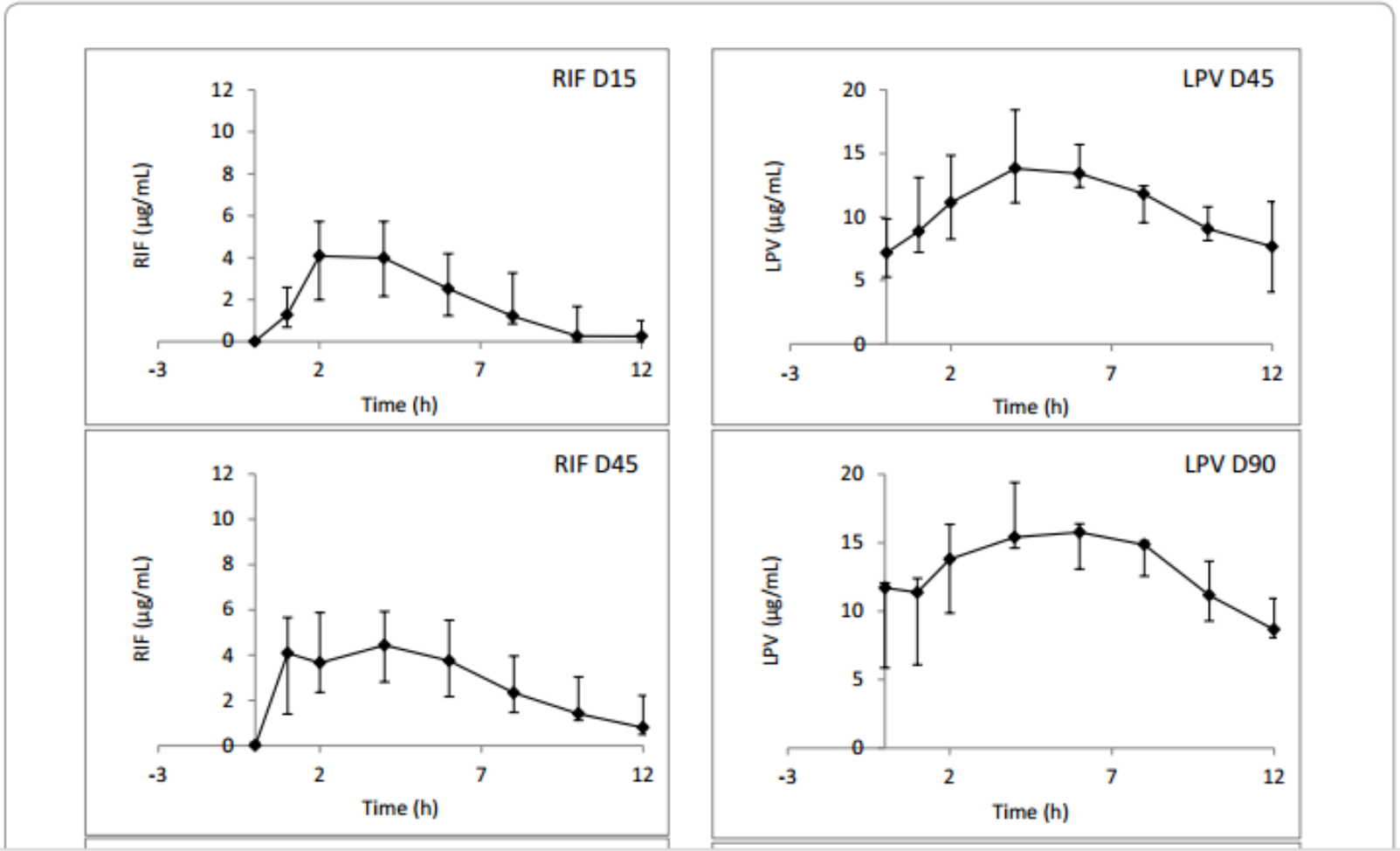


Figure 2: Virological response
Error bars are 95% CIs.

Grinsztejn et al LANCET 2014

HIV infected
Naive patients X ARV experienced

- Tolerance to ARV is better when PIs are not prescribed. To use FDC for TB and kaletra dose can be doubled (800 mg 200mg) or adding 300 mg ritonavir
- No other PI with a good genetic barrier can be used with FDC for TB. Rifabutin is an alternative for those who can “understand” the prescription and be adherent


RIF D15
RIF (µg/mL)
Time (h)
LPV D45
LPV (µg/mL)
Time (h)
RIF D45
RIF (µg/mL)
Time (h)
LPV D90
LPV (µg/mL)
Time (h)

Early X late ARV initiation and adverse reactions

- Early TARV is associated with more adverse reactions (AR) but save lifes in patients with very low CD4 counts (priority for <50 cells/mm3)
- IRIS, another AR due to immune reconstitution, is more proud to occur in patients with low CD4 counts and early ARV therapy

Conclusions

- Toxicity associated with TB and HIV treatments is more frequent than expected
- The use of TB-HIV drugs concomitantly is associated with more toxicity and patients should be monitored carefully
- Regimens associated with less toxicity are urgent to avoid morbidity and hospitalizations
- A less toxic regimen could potentially increase the chance to cure of tuberculosis