Virologic efficacy of raltegravir vs. efavirenz based antiretroviral treatment in HIV1-infected adults with tuberculosis

W48 results of the ANRS 12300 Reflate TB2 trial

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Disclosures

- Grant research from Gilead not related to the present study (Voice program 2015)

Alternatives to efavirenz in HIV/TB co-infection

- Alternatives to Efavirenz (EFV)-based regimens are needed for patients co-infected with HIV and tuberculosis (HIV/TB) : CNS tolerance and drug resistance to NNRTIs
- Integrase inhibitors (INSTIs) have been assessed as alternatives
- Dolutegravir (DTG) and raltegravir (RAL) PK show interaction with rifampin (RIF) is compensated when double dose of INSTI is used

- INSPIRING study : phase 3b non comparative, randomized, open-label trial evaluating DTG 50mg bid vs EFV 600mg qd

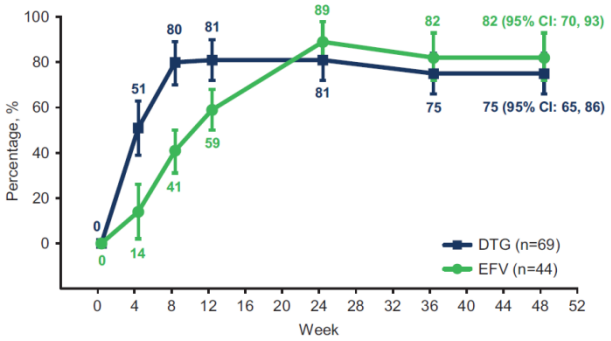

Figure 2. Proportion of participants in the ITT-E population with Snapshot HIV-1 RNA ≤50 copies/mL, by week following initiation of antiretroviral therapy with DTG or EFV. Abbreviations: CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; HIV-1, human immunodeficiency virus–1; ITT-E, intent-to-treat exposed.

Dooley KE *et al*. CID 2019

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What is the appropriate dose of raltegravir?

- Phase II: ANRS 12180 REFLATE TB

  Evaluate efficacy and safety of RAL 400 mg bid, RAL 800 mg bid, or EFV 600 mg qd in TB/HIV patients on RIF containing TB treatment

- Choice of the RAL dose: 400mg bid vs. 800mg bid
  - Similar proportion of patients with HIV RNA<50 copies/mL at W48
  - Drug-drug interaction (DDI) lower than that observed in healthy volunteers
  - Better tolerance profile : 2 patients experienced grade 3-4 hepatotoxicity in the RAL 800 mg bid
  - Pill burden and cost

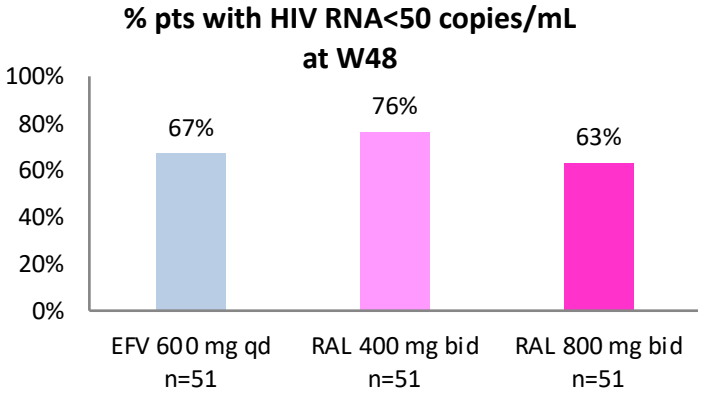

Table 2. Comparison of Plasma Raltegravir Pharmacokinetics Following Administration of Raltegravir 400 mg Twice Daily (Arm 1), With and Without Rifampicin

Pharmacokinetic Parameter	Period 1 (on RIF) Geometric Mean, Median (Range)	Period 2 (off RIF) Geometric Mean, Median (Range)	Period 1/Period 2 GMR (90% CI)	*P* Value
C_{max}, ng/mL	2929 3322 (228–7920)	2966 3572 (184–11 632)	0.99 (.67–1.45)	.18
T_{max}, h	. . . 4 (0–12)	. . . 2 (0–8)	. . .	. . .
C_0, ng/mL	165 205 (5–4395)	368 414 (10–2065)	[illegible]	.96
C_{12}, ng/mL	138 142 (10–1642)	199 260 (24–5732)	0.69 (.42–1.13)	.69
$AUC_{0\text{-}12}$, ng × h/mL	9278 10 300 (740–21 835)	9910 14 814 (672–34 437)	[illegible] (.64–1.37)	.24

Grinsztejn *et al.* Lancet HIV 2014
Taburet *et al.* CID 2015

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Study design

Phase III open label randomized non-inferiority multicenter trial

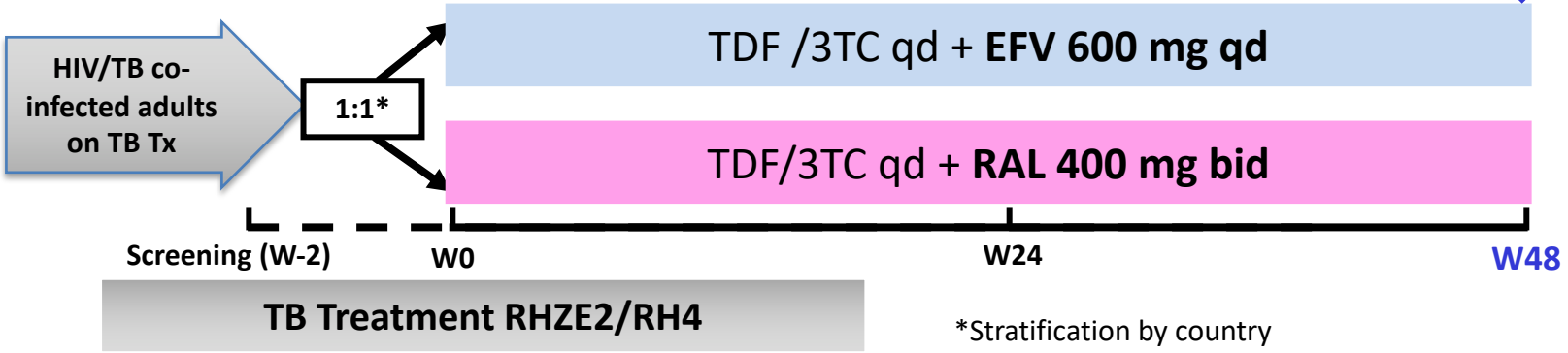
Brazil, Côte d'Ivoire, France, Mozambique, Vietnam

230 patients/arm (*80% power, non-inf. margin -12%, one-sided α=2.5%)*

Inclusion criteria
- HIV1 infection
- ART naïve
- Confirmed or probable TB
- Standard TB Tx ≤8 weeks

Exclusion criteria
- HIV2 infection
- TB meningitis
- ALT >5ULN, Hb <6.5g/dL, Creat cl. <60mL/min
- Pregnancy/breastfeeding

Primary endpoint
FDA snapshot
HIV-1 RNA < 50 copies/mL



*Stratification by country

Study flow chart

625 Screened

162 Not eligible

3 Eligible but not randomized
- 1 Death before randomisation
- 1 Withdrawal
- 1 Creat. clear. <60 ml/min

460 Randomized

230 EFV arm

1 HIV-1 RNA<50 copies/mL
2 HIV-2

227 ITT set
230 Safety set

Study completed	203(88%)
Early termination of study	27 (12%)
- Death	14 (6%)
- LFU	10 (4%)
- Withdrawal	1 (0%)
- Transfer out	2 (1%)

230 RAL arm

2 HIV-1 RNA<50 copies/mL
1 ART not initiated

228 ITT set
229 Safety set

Study completed	201 (87%)
Early termination of study	29 (13%)
- Death	12 (5%)
- LFU	10 (4%)
- Withdrawal	1 (0%)
- Transfer out	6 (3%)

Baseline characteristics (1)

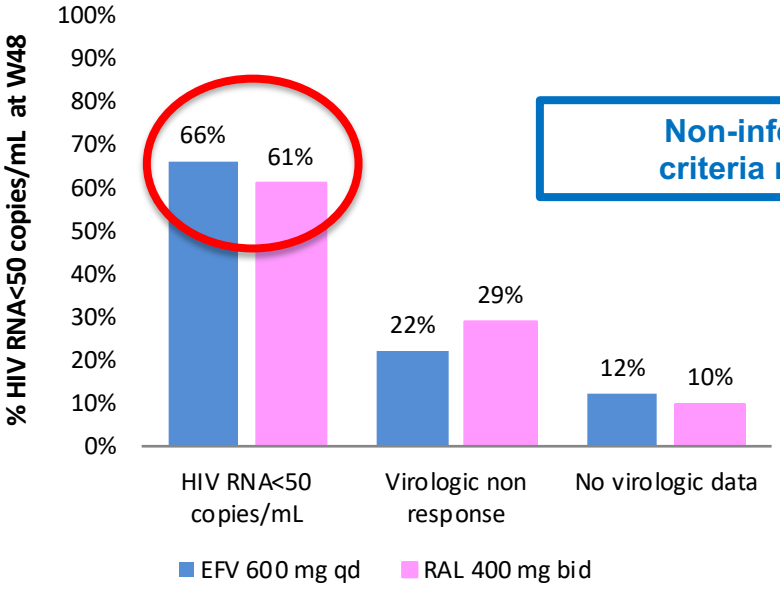
Data are n(%) or median (IQR)	EFV arm (n=227)	RAL arm (n=228)
Age (year)	37 (30 - 43)	34 (28 - 42)
BMI (Kg/m2)	19.1 (17.5 - 20.8)	19.1 (17.6 - 21.2)
Gender female	90 (40%)	90 (39%)
CD4 (cells/mm^3)	108 (35 - 238)	98 (39 - 242)
CD4 $\leq$ 50/mm^3	77 (34%)	75 (33%)
HIV RNA (Log10 copies/mL)	5.5 (5.0 - 5.9)	5.5 (5.0 - 5.8)
HIV RNA ≥100,000 copies/mL)	164 (72%)	172 (75%)
Time on TB treatment at enrolment	20 (15 – 27)	20 (15 – 28)
Cotrimoxazole prophylaxis	201 (89%)	199 (87%)
ALT (UI/L)	23 (15 - 37)	24 (15 - 39)
Creatinine clearance (mL/min)	98 (77 - 118)	103 (85 - 132)
Hemoglobin (g/dL)	9.9 (8.2 - 11.4)	9.8 (8.7 - 11.2)
HBs Ag positive	21 (9%)	24 (11%)
HCV Ab positive	7 (3%)	2 (1%)

Baseline characteristics (2)

Data are n(%) or median (IQR)	EFV arm (n=227)	RAL arm (n=228)
Previous tuberculosis disease treated	3 (1%)	3 (1%)
Time on TB Tx at enrolment	20 (15 – 27)	20 (15 – 28)
Tuberculosis site of disease		
Pulmonary	159 (70%)	152 (67%)
Extra-pulmonary	43 (19%)	44 (19%)
Pulmonary + extra-pulmonary	25 (11%)	32 (14%)
Bacteriological confirmation	159 (70%)	149 (65%)
Smear positive	113 (50%)	93 (41%)
Xpert MTB positive	132 (58%)	132 (58%)
MTB culture positive	114 (50%)	112 (49%)
Probable tuberculosis	66 (29%)	76 (33%)
LAM positive	18 (8%)	15 (7%)
Bacteriological confirmations or LAM+	177 (78%)	164 (72%)
No bacteriological data	2 (1%)	3 (1%)

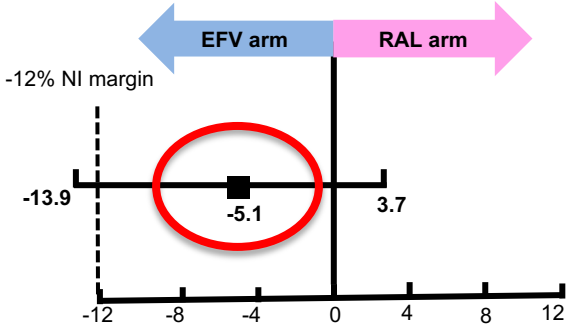
Efficacy outcome – W48

Primary endpoint ITT : HIV RNA<50 copies/mL at W48 (FDA snapshot)



Non-inferiority criteria not met

Treatment Difference (95% CI): RAL - EFV



	EFV arm (n=227)	RAL arm (n=228)
Virologic success (HIV-1 RNA<50 c/mL)	**150 (66%)**	**139 (61%)**
Virologic failure	**50 (22%)**	**66 (29%)**
HIV-1 RNA ≥ 50 copies per mL in the window	31	45
Discontinued Due to Lack of Efficacy	9	13
Discontinued Due to Other Reasons and Last HIV-1 RNA ≥ 50 c/mL	10	8
No data in the W48 window	**27 (12%)**	**23 (10%)**
Discontinued study/study drug due to AE or death*	18	12
Discontinued study/study drug for other reasons	7	11
On study but missing data in window	2	0

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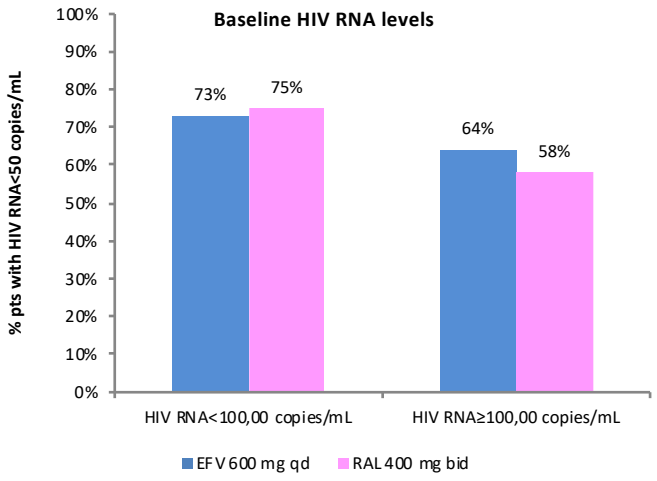
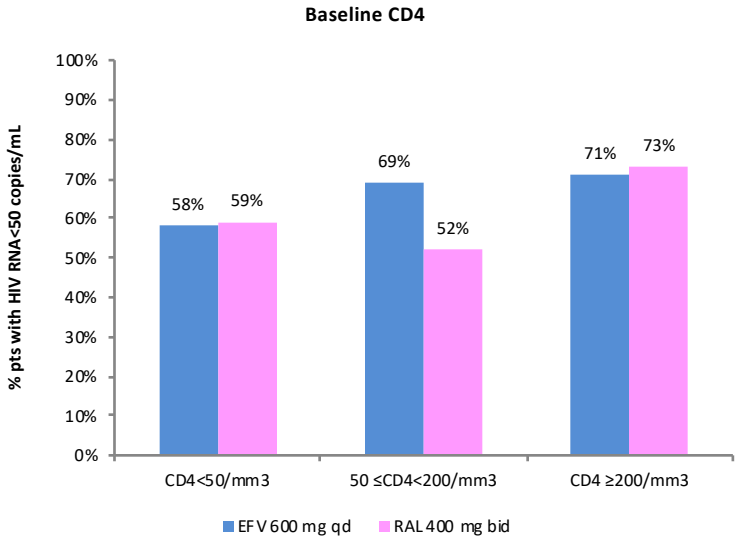
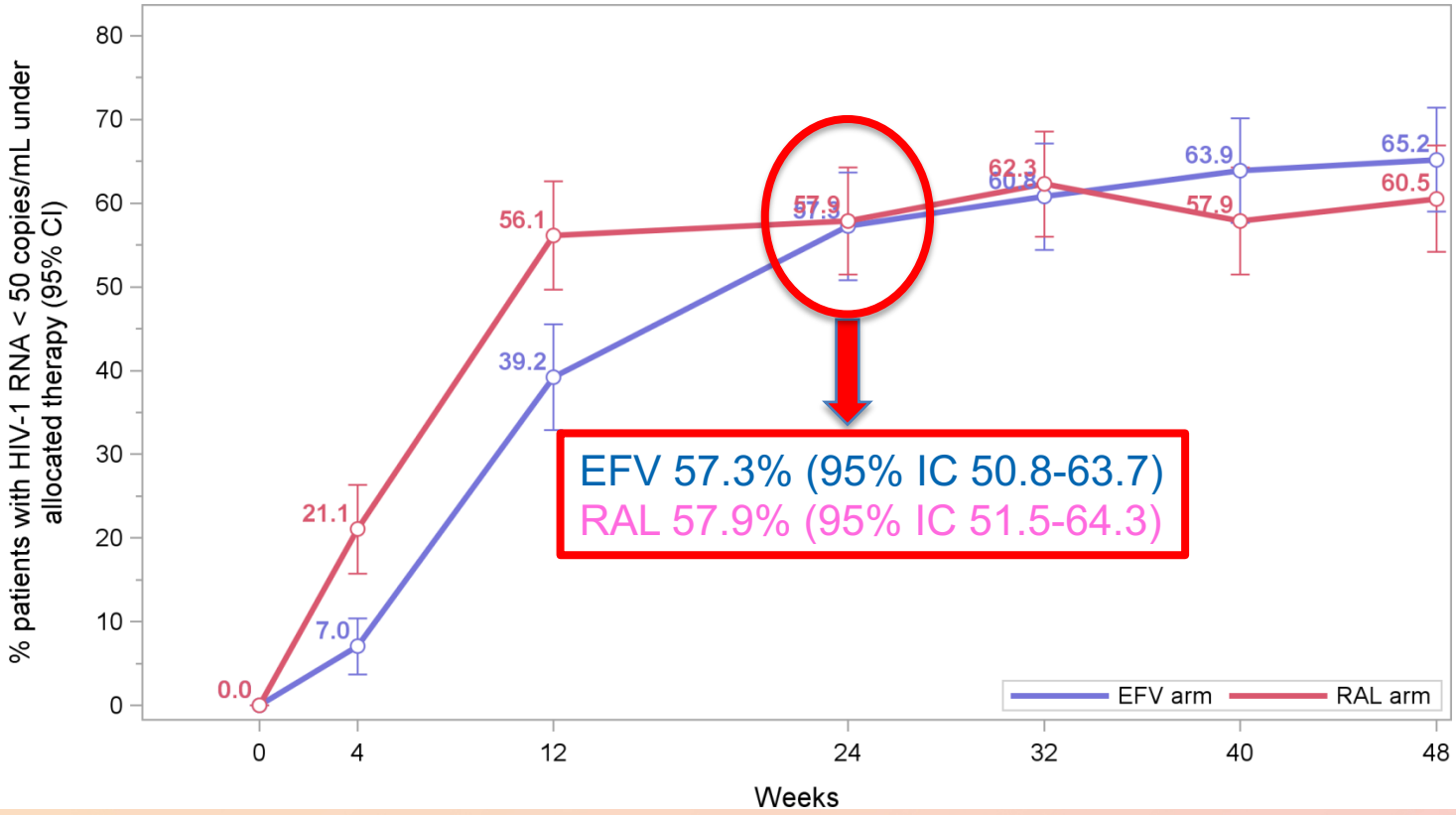
Efficacy outcome by baseline characteristics – W48

Primary endpoint ITT : HIV RNA<50 copies/mL at W48 (FDA snapshot)





HIV RNA<50 copies/mL under allocated therapy - ITT



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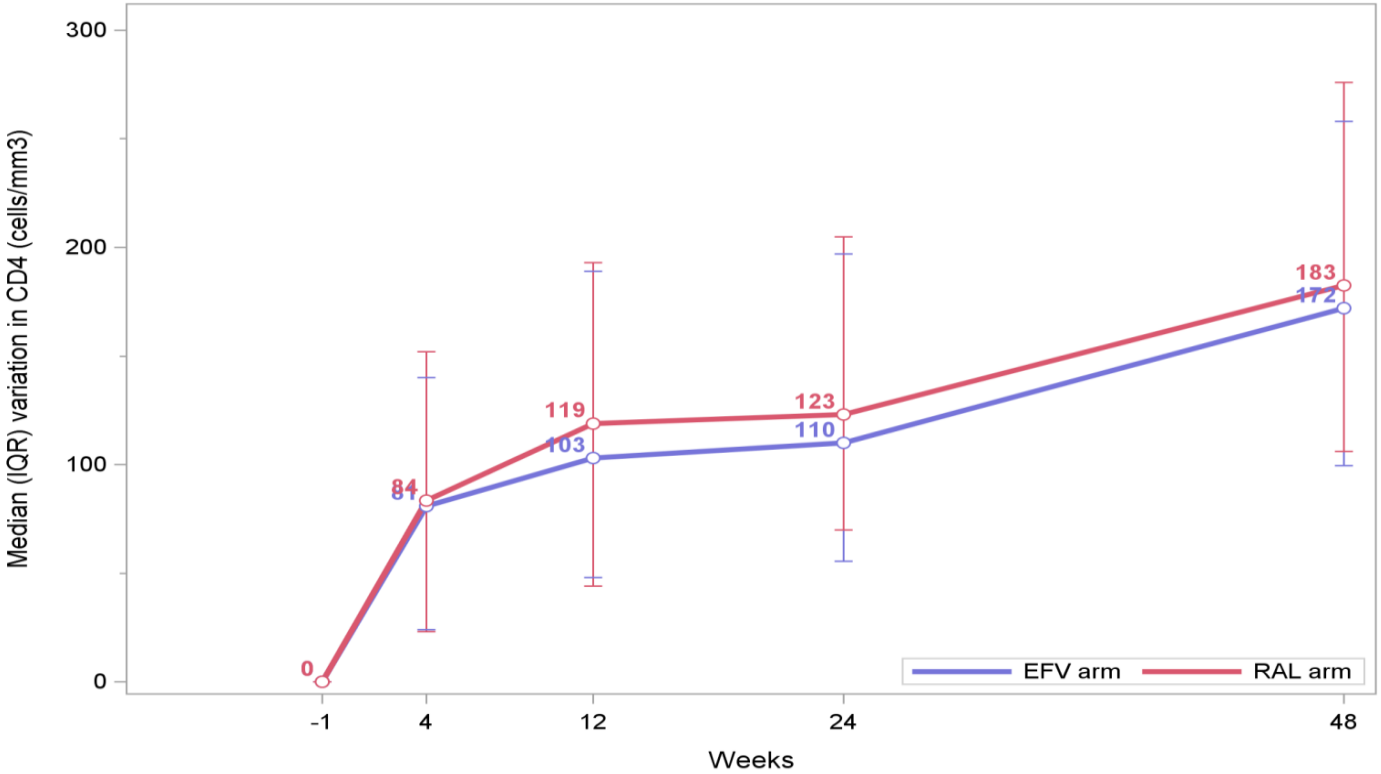
Median CD4 counts gain - ITT



EFV arm	227	216	209	200	196
RAL arm	228	222	213	208	198

Adverse events through W48

	Efavirenz (N=230)		Raltegravir (N=229)	
Any AE, *N AE*, n patient (%)	*1038*	208 (90%)	*950*	207 (90%)
Grade 3 or 4 AEs, *N AE*, n patient (%)	***90***	**68 (30%)**	***70***	**62 (27%)**
Grade 3	*57*	41 (18%)	*50*	42 (18%)
Grade 4	*33*	27 (12%)	*20*	20 (9%)
Type of grade 3-4 AE, *N AE,* n patient (%)				
Drug-related AE	*26*	22 (10%)	*25*	25 (11%)
ART discontinuation due to drug-related AE	*3*	3(<1%)	*1*	1 (<1%)
IRIS	*13*	13 (6%)	*10*	10 (4%)
Hepatotoxicity	*9*	9 (4%)	*9*	9 (4%)
Hypersensitivity	*1*	1 (1%)	*1*	1 (<1%)
Renal failure	*4*	4 (2%)	*0*	0 (0%)

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Conclusion

- This study is the first large phase III randomized trial comparing efavirenz to INSTI-based ART in the context of HIV-TB co-infection
- Despite promising virological and PK data from our previous phase II study we failed to demonstrate the non-inferiority of raltegravir 400 mg bid when compared to efavirenz 600mg qd at W48
- Risk factors for virological failure are being analyzed
- Based on these results, efavirenz should still be considered as the preferred first line therapy for HIV/TB co-infected patients
- Raltegravir 400 mg bid may represent an alternative in selected patients

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