Integrase inhibitor-based antiretroviral treatment does not increase the risk of TB-IRIS in people with HIV treated for tuberculosis: findings from the Reflate TB2 randomized trial

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Introduction

- Antiretroviral therapy (ART) initiation in people with HIV (PWH) and tuberculosis (TB) may be complicated due to the occurrence of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS).
- **Integrase inhibitors (INSTIs)**, by providing a faster HIV-RNA decline than efavirenz, **could increase the risk for TB-IRIS**
- We assessed the incidence and determinants of TB-IRIS in PWH with TB on raltegravir or efavirenz-based ART.

Methods

- Secondary analysis of the **ANRS 12300 Reflate TB 2 multicenter, phase 3 trial**, that randomized ART-naive PWH on standard TB treatment, to receive raltegravir or efavirenz-based ART.
- TB-IRIS was defined according to the International Network for the Study of HIV-associated IRIS (INSHI) criteria (Meintjes, 2008).
- **Incidence rates** (IR) were estimated by 100 persons-year (PY).
- Stratified Kaplan-Meier curves (log-rank test) and cox regression models were used to assess **determinants of TB-IRIS**.

Results

- Of 460 trial participants, **453 participants** from Brazil, Côte d'Ivoire, Mozambique and Vietnam **were included** in this analysis.
- Median age was 35 years (IQR: 29-43), 40% were female, 69% had pulmonary TB only, median CD4 was 102 (IQR 38-239) cells/µL and median HIV RNA 5.5 (IQR 5.0-5.8) Log_{10} copies/mL.
- 48 participants developed TB-IRIS (**IR = 24.7/100 PY**), 19 cases in the raltegravir arm and 29 in the efavirenz arm (log-rank test: p=0.123) (Figure).
- Factors associated with TB-IRIS were: **CD4 count ≤100 cells/µL**, **HIV RNA ≥500,000 copies/mL**, **extra-pulmonary/disseminated TB** (Table).

Figure. TB-IRIS free survival probabilities by ART treatment arm.

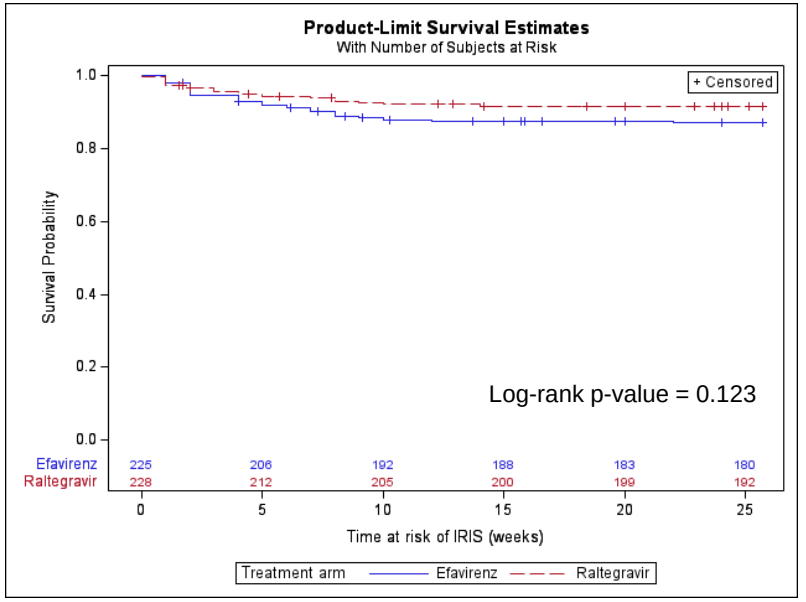

Table. Factors associated with TB-IRIS incidence.

	Total, N	TB-IRIS, n(%)	Univariate analysis cHR	Univariate analysis 95% CI	Multivariate analysis aHR	Multivariate analysis 95% CI
Country						
Brazil	43	5 (11.6%)	1			
Ivory Coast	170	17 (10.0%)	0.84	0.31-2.29		
Mozambique	129	6 (4.7%)	0.39	0.12-1.28		
Vietnam	111	20 (18.0%)	1.65	0.62-4.40		
CD4+ T cell counts (cells/mm³)						
>100	228	12 (5.3%)	1			
≤ 100	224	36 (16%)	3.17	1.65-6.12	**2.48**	**1.27-4.85**
HIV-1 RNA (copies/mL)						
< 500,000	294	17 (5.8%)	1			
≥ 500,000	156	30 (19.2%)	3.65	2.01-6.62	**2.92**	**1.59-5.36**
TB anatomical site at baseline						
Pulmonary only	312	25 (8%)	1			
Extrapulmonary*	141	23 (16%)	2.22	1.25-3.93	**2.17**	**1.23-3.85**

* With or without concomitant pulmonary TB

Conclusion

- Early introduction of **INSTI-based ART** in PWH treated for TB **did not result in an increased risk of TB IRIS**, compared to efavirenz-based regimens.
- **Advanced HIV disease**, marked by pre-ART low CD4+ T cell counts and high HIV-1 RNA, as well as extrapulmonary and disseminated TB were the **major risk factors for TB-IRIS**.

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