Incidence and risk factors for liver enzyme elevation in HIV-1 infected patients treated for tuberculosis: a secondary analysis of the multi-country ANRS 12300 REFLATE TB2 trial

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Introduction

There are limited data describing the incidence and risk factors associated to Liver Enzyme Elevation (LEE) among patients co-infected with HIV and tuberculosis (TB) receiving antiretroviral therapy (ART). This study aimed to describe the incidence, severity and risk factors associated with LEE in patients enrolled in REFLATE TB2 trial.

Methods

ANRS 12300 Reflate TB2 was a multicenter, open-label, phase 3, non-inferiority randomized trial where ART-naïve adult HIV1-infected patients on standard TB treatment received either raltegravir 400 mg BID or efavirenz 600 mg QD both in association with tenofovir and lamivudine[1].
Alanine aminotransferase (ALT) levels were assessed at weeks 0, 2, 4, 8, 12, 24, and 48 after randomization. LEE was defined as any grade 2 or more ALT [≥2.5 upper limit of normal (ULN)] during follow-up visits. Overall incidence of LEE [per 100 persons-year (PY)] over the trial duration and baseline risk factors for LEE were analyzed using univariate and multivariate cox proportional-hazards models [HR (95%CI)] were assessed.

Results

The 453 participants enrolled in the analysis had the following baseline characteristics: median age 35 years (IQR: 29;43), median baseline CD4 count 102/µL (IQR: 38;239), median ALT level 24 IU/L (IQR: 15;38), 31% with disseminated TB. 48/453 participants (10.6%) experienced LEE, corresponding to an incidence of 13.42 per 100 PY (95% CI: 09.89-17.79) and among those, 19 were grade 3 or grade 4 ALT elevations.
Among the 48 participants with LEE, 30 (63%) were male, 28 (58%) were from Vietnam, 31 (65%) were younger than 35 years, 34 (71%) had a baseline Karnofsky ≥ 80%, 32 (67%) declared current or past alcohol consumption, 35 (75%) had baseline CD4 counts ≤100/µL and their median baseline HIV RNA was 5.6 log10 copies/mL, 23 (48%) had ALT≥ 40 IU/L at baseline. 40/48 (83,3%) of the participants with LEE were on TB treatment at the time of LEE occurrence.
In the multivariate analysis, being from Vietnam (HR: 3.159 95% CI: 1.510; 6.611), ALT ≥ 40 IU/L (HR: 2.352 95% CI: 1.265; 4.371) and Neutrophils ≤ 1500 /mm3 (HR: 1.901 95% CI: 1.002; 3.605) at pre-inclusion were associated to LEE (table 2).

Conclusion

- The incidence of LEE was relatively high (13.6% per year) in participants from the Reflate TB 2 trial treated for TB and receiving ART.
- Risk factors for LEE were being from Vietnam, abnormal ALT and low neutrophils at pre-inclusion.
- The type of ART (raltegravir or efavirenz based) was not associated to LEE.
- LEE mechanisms including drug-induced liver injury, hepatic TB lesions and immune reconstitution inflammatory syndrome needs further explorations.

[1] Standard dose raltegravir or efavirenz-based antiretroviral treatment for patients co-infected with HIV and tuberculosis (ANRS 12 300 Reflate TB 2 an open-label, non-inferiority, randomised, phase 3 trial, De Castro, et al. The Lancet Infectious Diseases, Volume 21, Issue 6, 813 - 822

Table 1 : Patient characteristics by occurrence of LEE

	N*	LEE (N=48)	N*	No LEE (N=405)	P-value
Male Sex		30 (62.5%)		242 (59.8%)	0.7133 (K)
Age (year)		30.8 (26.6 - 40.3)		35.8 (29.2 - 43.0)	0.0290 (W)
Country					
Ivory Coast		12 (25.0%)		158 (39.0%)	**< 0.0001 (F)**
Brazil		3 (6.3%)		40 (9.9%)	
Vietnam		28 (58.3%)		83 (20.5%)	
Mozambique		5 (10.4%)		124 (30.6%)	
Tobacco smoking		34 (70.8%)	403	297 (73.7%)	0.3219 (K)
Alcohol consumption		16 (33.3%)	404	177 (43.8%)	0.1653 (K)
BMI (Kg/m²)		18.7 (17.5 - 21.4)	403	19.1 (17.5 - 20.8)	0.5691 (W)
Karnofsky score		90.0 (80.0 - 90.0)		80.0 (80.0 - 90.0)	0.0117 (KW)
ALT (IU/L) at PI		38.5 (26.0 - 72.0)		23.0 (14.0 - 34.0)	**< 0.0001 (W)**
Creatinine clearance at PI (ml/min)		93.5 (79.3 - 115.7)		101.2 (81.5 - 125.3)	0.3708 (W)
Hemoglobin (g/dL) at PI		9.8 (8.8 - 11.8)		9.8 (8.4 - 11.1)	0.2201 (W)
Neutrophils (/mm3) at PI		2085.0 (1425.5 - 3475.0)		2766.6 (1960.0 - 4400.0)	**p = 0.0094 (W)**
Pulmonary tuberculosis		28 (58.3%)		284 (70.1%)	0.1284 (K)
Positive HBsAg at inclusion		8 (16.7%)		36 (8.9%)	0.1159 (F)
Positive HCVAb at inclusion		2 (4.2%)	404	7 (1.7%)	0.2460 (F)
CD4 (/µL) at PI	47	51.0 (20.0 - 115.0)		111.0 (41.0 - 248.0)	**0.0030 (W)**
CD4 (/µL) at W4	46	121.0 (61.0 - 252.0)	391	219.0 (118.0 - 402.0)	**0.0028 (W)**
Log_{10} HIV viral load at W0		5.6 (5.2 - 6.1)	402	5.5 (5.0 - 5.8)	0.0919 (W)
Log_{10} HIV viral load at W4	47	2.7 (2.1 - 3.6)	391	2.6 (2.0 - 3.1)	0.1095 (W)
Antiretroviral treatment					
Raltegravir		30 (62.5)		195 (48.1)	0.0601 (K)
Efavirenz		18 (37.5)		210 (51.9)	

Data are n (%) or median (IQR). *N when missing data W0: Week 0, W4: Week 4, PI : Pre-inclusion, Ag : antigen, Ab: antibodies,
F: Fisher's exact test, K : chi-squared test, KW: Kruskall-Wallis test, W: Wilcoxon test

Table 2 : Multivariate Cox proportional-hazards model

	HR	Lower 95% CI	Upper 95% CI	Pr > Chi-Square
Country				0.0003
Ivory Coast	Ref			
Brazil	0.759	0.205	2.814	
Mozambique	0.597	0.207	1.718	
Vietnam	3.159	1.510	6.611	
ALAT at PI (IU/L)				0.0068
ALT < 40	Ref			
ALT ≥ 40	2.352	1.265	4.371	
Neutrophils at PI (/mm³)				0.0492
Neutrophils > 1500	Ref			
Neutrophils ≤ 1500	1.901	1.002	3.605	

Ref: Reference

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