

OR-02

Incidence and Risk Factors for Tuberculosis Associated Immune Reconstitution Inflammatory Syndrome (TB-IRIS) among HIV-infected Individuals in Europe and Latin America: A Cohort Analysis

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For the TB:HIV Study Group

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Background

- Tuberculosis (TB) is the most common opportunistic infection in HIV-positive people worldwide, often leading to death, especially in patients with advanced disease.
- Antiretroviral therapy (ART) is mandatory in HIV-infected patients with TB;. However, 10-15% of them may experience a worsening of a patient's clinical status due to the recovery of the immune response to viable or nonviable pathogens. This condition is known as paradoxical immune reconstitution inflammatory syndrome (TB-IRIS).
- The characteristics necessary to establish a diagnosis of IRIS are confirmed HIV infection, having started ART with evidence of its effectiveness (e.g., appropriate decrease in plasma HIV RNA levels and recovery of CD4+ T-cell count) and excluding a resistant pathogen (*Lancet Infect Dis. 2008; 8: 516523*).
- The most recognized risk factors for the development of TB-IRIS are a very low CD4+ T-cell count , disseminated infection and earlier initiation of ART after starting anti-TB treatment.

Background: Incidence of TB-IRIS in Clinical Trials

<i>Tuberculosis</i>	
SapIT Trial [35,36]	
Overall	14.2%
Early treatment arm	20.1%
Deferred treatment arm	8.3%
STRIDE trial [37]	
Overall	8%
Early treatment arm	11%
Deferred treatment arm	5%
CAMELIA trial [38]	
Overall	Not analyzed
Early treatment arm [§]	3.76/100 persons/month
Deferred treatment arm [§]	1.53/100 persons/month

Aim & Methods

- The aim of this study was to describe incidence rates, clinical presentation and risk factors for TB-IRIS in Europe and Latin America.
- The TB:HIV collaborative cohort reports cases from 11 European and 2 countries in Latin America.
- The primary risk factor analysis was conducted only for patients with confirmed, fully susceptible TB (by culture and/or by Xpert TB/Rif[®] test) and who started ART during the acute antiTB phase. Patients with multidrug resistant (MDR) TB were excluded.
- A competing risk regression model was used to assess factors independently associated to TBIRIS incidence. In this analysis, the event of interest was IRIS, and death was regarded as the competing event.

Results

- Globally, TBIRIS was diagnosed in 88 cases among 1359 TB diagnosis (6%), being the proportion higher in Western/Southern Europe (12%) than in Eastern Europe and Latin America (5%). Nine people died (crude mortality rate 5%).
- In most cases (35%) TB-IRIS manifested as lymphadenitis; 47% received steroids and 9% needed surgery.
- Most cases were diagnosed within the first month after starting ART (Median time [IQR] to TB-IRIS was 18.9 [14.7-23.1] days).
- For a primary risk factor analysis, only individuals having started ART during anti-TB treatment and with a fully susceptible TB were considered (197 cases followed a median [IQR] of 1.2 [0.5-2.1] years). In this population, 10 cases of IRIS were diagnosed and the incidence rate (95% CI) was 9.36 (5.04-17.28) *per* 100 persons/year.

Results: Global Population Characteristics

Table 1 : Baseline (BL) Demographic and Clinical data.

Variable		IRIS		Total (N= 1359)	p-value
		No (N=1271)	Yes (N=88)		
Gender ¹	male	915 (72%)	66 (75%)	981 (72%)	0.5423 ²
Age (years) at TB diagnosis ³		38 (9)	37 (9)	38 (9)	0.7465 ⁴
Ethnicity ¹	White	864 (71%)	58 (67%)	922 (70%)	0.7012 ²
Region ¹	Southern Europe	139 (11%)	22 (25%)	161 (12%)	0.0001 ²
	Western Europe	138 (11%)	15 (17%)	153 (11%)	
	Eastern Europe	767 (60%)	35 (40%)	802 (59%)	
	Latin America	227 (18%)	16 (18%)	243 (18%)	
Route of Transmission ¹	MSM	121 (10%)	16 (19%)	137 (10%)	0.0058 ²
	IDU	544 (45%)	26 (31%)	570 (44%)	
	HET	415 (34%)	31 (37%)	446 (34%)	
	Other	142 (11%)	10 (11%)	145 (11%)	
BL CD4+ (cells/ μ L) ³		136 (38; 328)	77 (37; 197)	128 (38;312)	0.0086 ⁴
BL Log RNA-HIV (cp/mL) ³		5 (3; 6)	5 (2; 6)	5 (3;6)	0.7178 ⁴
TB type	Pulmonary	417 (33%)	11 (13%)	428 (31%)	0.0001 ²
	Extrapulmonary	179 (14%)	21 (24%)	200 (15%)	
	Disseminated	675 (53%)	56 (64%)	731 (54%)	

Table 2: Clinical presentation of IRIS (N=88)

TB-IRIS cases	88 (100%)
Worsening of radiological features of TB*	46 (52%)
TB-inflammatory lymphadenitis	31 (35%)
Cold Abscesses or TB Arthritis	28 (32%)
TB-Inflammatory Syndrome	22 (25%)
TB-CNS	10 (11%)
Serositis	8 (9%)

* Found by chest radiography, abdominal US, CT, or MRI

Results: Risk factors analysis

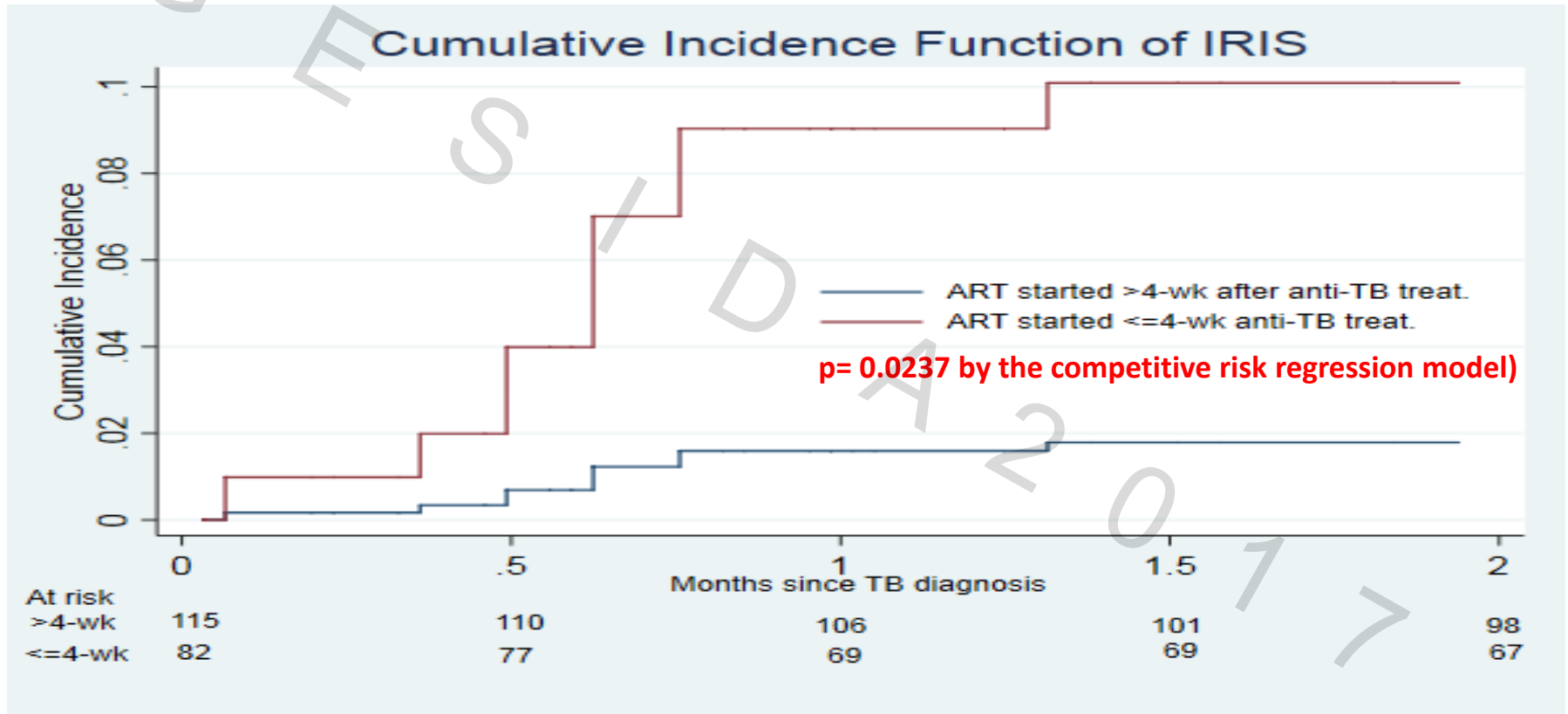
In the final competing risk regression model, the only factor associated to TB-IRIS incidence was early ART (within 4 weeks, uHR= 5.9 [1.27-26.94], p=0.024).

Variable		U-Hazard Ratio	(95% Conf. Interval)	p-value
Gender (<i>n</i> = 197)	male	1		0.1504
	female	2.52	(0.72; 8.89)	
Age (years) at TB diagnosis ¹ (<i>n</i> = 197)		0.99	(0.94; 1.05)	0.7506
Region (<i>n</i> = 197)	South E	1		0.1667
	West E	1.58	(0.38; 6.53)	
	East E	0.17	(0.02; 1.61)	
	Latin America	0.41	(0.04; 4.02)	
Weight baseline ¹ (<i>n</i> = 171)		0.98	(0.95; 1.01)	0.1561
Mode Infection: IDU (<i>n</i> = 197)	non IDU	1		0.1325
	IDU	0.20	(0.03; 1.62)	
CD4 >=50 baseline ² (<i>n</i> = 121)		0.46	(0.10; 2.08)	0.3155
log RNA-HIV (baseline) ¹ (<i>n</i> = 94)		1.92	(0.84; 4.38)	0.1215
ART started <=4w TB treatment (<i>n</i> = 197)	no (>4wk)	1		0.0237
	yes (<=4wk)	5.84	(1.27; 26.94)	
TB disseminated (<i>n</i> = 197)	no	1		0.5116
	yes	1.57	(0.41; 6.04)	
Num. active drugs (<i>n</i> = 182)	<3	1		0.6298
	>=3	1.46	(0.31; 6.81)	

1: Unadjusted Hazard Ratio per unit increase. 2: Unadjusted Hazard Ratio for >=50 vs. <50

Table 2: Selected competing risk regression model.

Survival analysis for early vs. deferred ART



Conclusions

- Overall, the proportion of TB-IRIS in Europe/Latin America was lower than that found in clinical trials conducted in Sub-Saharan Africa (6% vs. 14.2% in the integrated arms of the SAPIT Trial*)
- However, TB-IRIS rates were higher in Western/Southern Europe (12%) than in Eastern Europe and Latin America (5%). Reasons for this differences might be explored.
- Data from our cohort confirm that early ART initiation (≤ 4 weeks) was an independent risk factor for TB-IRIS.
- Further analyses are on-going to better characterize TB-IRIS in the HIV:TB cohort.

*Abdool Karim SS et al. N Engl J Med. 2010;362:697-706.

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