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Prevalence, characteristics and outcomes of TB-IRIS among a cohort of PWH and TB

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Introduction/Summary

Tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) occurs in 8-54% of people with HIV (PWH) with TB and is associated with increased mortality, longer hospital stay and longer time to virological control. Among the factors associated to TB-IRIS are low CD4 count and high viral load at diagnosis and timing of ART initiation, while the role of INSTI, especially double-dose DTG has been postulated but not confirmed. Diagnosis of TB-IRIS is challenging and relies on multiple parameters. Current guidelines consider but do not recommend corticosteroid prophylaxis in the presence of specific risk factors. We evaluated the prevalence and clinical characteristics of TB-IRIS in PWH and its associated risk factors.

Methods

Single centre study; retrospectively included all PWH with active TB followed by our HIV Unit from 01/01/2013 to 31/12/2023, stratified by the occurrence of TB-IRIS. We collected data on:

- General characteristics

- TB disease; immunovirological status at TB diagnosis / follow-up

- IRIS diagnosis and management

Corticosteroid prophylaxis for TB-IRIS is not routinely prescribed in our clinic.

Categorical variables: described using absolute number and percentage

Continuous variables: described using the median and interquartile range (IQR), and compared, with $\chi 2$ or Fisher exact test if applicable and Mann-Whitney test.

Correlation analysis: Pearson and Spearman correlations.

Results

In the study period, 21 PWH (n=10 [47.6%] treatment-naïve and n=11 [52.4%] treatment-experienced) were diagnosed with active TB. Among them, 5 cases of TB-IRIS were reported (n=2 unmasking and n=3 paradoxical), with a prevalence of 23.8% overall and 40% among treatment-naïve patients. Mean age was 42.6 years (SD 8.73), 5 (23.8%) were females, 16 (76.2%) were foreign-born, median CD4 count at TB diagnosis was 120 N/mmc (48-339). For 16 TB cases (80% of those with evaluable outcome), treatment success was reached (Table 1). All TB-IRIS cases were successfully managed. Individual characteristics and management of TB-IRIS cases are outlined in Table 2.

Female gender, being foreign born, being treatment-naïve, having disseminated TB and treatment with double-dose DTG were significantly correlated with TB-IRIS. Hospital stay duration was longer in case of TB-IRIS.

Conclusion

We report a high prevalence of TB-IRIS in PWH and TB, with some risk factors compatible to the literature and others specific to our cohort. Multicentric studies addressing prevalence, diagnostics and management of TB-IRIS are warranted to lead to definitive recommendations on prophylaxis and more accurate diagnostics strategies.

References

1. WHO Global Tuberculosis report 2023
2. WHO consiìolidated guidelines on tuberculosis

Table 1. Baseline, immunovirological and TB disease characteristics of the population stratified by the occurrence of IRIS.

	Total, n=21	NON-IRIS, n=16	IRIS, n=5	Univariate analysis, *p*	Matrix correlation, *p*
Age, mean (SD)	42.6 (8.73)	42,1 (9.49)	44.4(6.19)	0.614	
Gender, female, n(%)	5 (23.8)	2 (12.5)	3 (60)	**0.075**	**0.015**
Foreign born, n(%)	16 (76.2)	11 (68.8%)	5 (100)	**0.152**	0.084
Previous TB, n(%)	3 (14.3)	3 (18.8)	0 (0)	0.296	
HIV status at TB diagnosis					
CD4, median (IQR)	120(48-339)	144 (101-460)	48 (43-117)	**0.148**	0.951
CD4<100/mmc, n (%)	7(33.3)	4(25)	3(60)	**0.147**	
VL log10, median (IQR)	5.19 (1.9-6.15)	5.07 (1.90-5.88)	5.75 (2.44-6.15)	0.518	
VL, undetectable, n (%)	6 (28.6)	6 (37.5)	0 (0)	0.262	
Treatment naive n (%)	10 (47.6)	6(37.5)	4 (80)	**0.157**	**0.053**
Treatment experienced, n(%)	11(52.4)	10(62.5)	1(20)	0.310	
Years from HIV diagnosis to TB episode, median (IQR)	10.4(4.5-21)	11.2(3.8-21)	7.2	NA	
On ART at time of TB diagnosis, n (%)	9(42.8)	8(50)	1(20)	0.338	
TB features					
Isolated pulmonary, n(%) Cavitating Miliary	10(47.6) 4(19) 5(23.8)	10(62.5) 4(43.7) 5(25)	0(0)	1.00	
Isolated extrapulmonary, n(%) *lymphonodal	2(9.5)*	2(12.5)	0(0)	1.00	
Disseminated, n(%)	9(42.8)	4(25)	5(100)	**0.003**	**<0.001**
MDR-TB, n(%)	3(14.9)	2(12.5)	1(20)	1.00	
CRP at TB diagnosis, mg/L (cut off 3.5 mg/L), median (IQR)	37(13.6-63.2)	36(7-56)	57.8(26-73.6)	0.298	
ART during TB treatment					
INSTI-based, n(%)	17(80.9)	13(81.2)	4(80)	1.00	
Double dose DTG,n(%) Standard dose RAL, n(%) Double dose RAL, n(%) BIC, n(%)	6(28.8) 3(14.9) 7(33.3) 1(4.8)	3(18.8) 3(14.9) 6(37.5) 1(7.7)	3(60) 0(0) 1(20) 0(0)	**0.075**	**0.041**
NNRTI-based, n(%)	3(14.9)	2(12.5)	1(20)	1.00	
PI-based, n(%)	1(4.8)	1(7.7)	0(0)	NA	
NRTI backbone TDF/FTC, n(%) ABC/3TC, n(%) TAF/FTC, n(%)	 19(90.8) 1(4.8) 1(4.8)	 14(87.5) 1(7.7) 1(7.7)	 5(100) 0(0) 0(0)	 1.00	
Time to ARV initiation after TB treatment start, days mean (SD)	21.8(17.4)	27.9(18)	10.5(9.38)	**0.056**	0.972
Concomitant corticosteroid treatment, n(%)	2(9.5)	2(12.5)	0(0)	1.00	
TB Outcome					
Treatment duration, weeks (median, IQR)* *available for n=15	26.8(25.3-36)	26.7(25.4-31)	36(25.1-60.8)	NA	
Hospital stay duration, days, median (IQR)	32.5(19-38)	31(14-37)	35(33-106)	**0.054**	
Treatment success, n(%)* n=1 ongoing treatment n=4 loss to follow-up	16/20(80)	13/16(81.2)	3/4(75)	1.00	
Immunovirological FU 1-year					
%CD4 increase, mean (SD)* *available for n=13	120(42-166)	91(38-163)	371(245-496)	0.410	
VL, undectectable (<30 cp/ml), n(%)* *available for n=11	11/11(100)	7/7(100)	4/4(100)	NA	

IRIS, immune reconstitution inflammatory syndrome; SD, standard deviation; TB, tuberculosis; Vl, viral load; ART, anti-retroviral treatment; CRP, C reactive protein; IQR, interquartile range; INSTI, integrase strand transfer inhibitor; DTG, dolutegravir; RAL, raltegravir; BIC; bictegravir; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors, NRTI, nucleoside reverse transcriptase inhibitors

Table 2. Individual clinical, laboratory and radiological characteristics of TB-IRIS cases at TB-IRIS diagnosis; TB-IRIS management and outcome

Case	IRIS type	Timing of IRIS onset post ART start	Immunovirological parameters	Radiology	Inflammatory markers	Symptoms	Histology	Treatment	Outcome
#1– 40yo, female treatment-experienced	unmasking	30 days	CD4 count 43/mmc HIV-VL 277 cp/ml	CT scan: new pulmonary infiltrates FDG-PET: lymphonodal tracer uptake	CRP: 71 mg/L Ferritin:1434 mcg/L	Fever, lymphadenopathy, anemia	BM biopsy: histiocytic/macrophagic infiltrates	prednisone 1.5 mg/kg	Symptoms resolution, decrease in inflammatory markers
#2 – 38yo, female treatment-naïve	paradoxical	9 days	CD4: +63% from ART start HIV-VL: -2.37log from ART start	//	CRP: 162 mg/L Ferritin:1335 mcg/L IL-6: 112 ng/L	Fever, lymphadenopathy	Lymph node biopsy: necrotizing lymphadeniis, Ziehl-Nielsen neg	prednisone 1.5 mg/kg	Symptoms resolution, decrease in inflammatory markers
#3 – 45yo, male treatment-naïve	unmasking	22 days	CD4: +96% from ART start HIV-VL: - 0.62log from ART start	CT scan: increased lymphadenopathies and cerebral lesions	//	Fever, confusion	Lymph node biopsy: necrotizing lymphadeniis, Ziehl-Nielsen neg,culture Mtb+	prednisone 0.4 mg/kg	Symptoms resolution, decreased cerebral lesion size
#4 – 45yo, male treatment-naïve	paradoxical	9 days	Baseline CD4 count 31/mmc HIV-VL:-2.32log from ART start	//	CRP: 95 mg/L Ferritin:881 mcg/L IL-6: 68.9 ng/L	Fever	//	prednisone 1.5 mg/kg	Symptoms resolution, decrease in inflammatory markers
#5 – 45yo, female treatment-naïve	paradoxical	17 days	CD4: +92% from ART start HIV-VL: -3.31log from ART start	CT scan: increased lymphadenopathies	Ferritin:799 mcg/L	Fever	Lymph node biopsy: necrotizing lymphadeniis, Ziehl-Nielsen neg	prednisone 1 mg/kg	Symptoms resolution, decrease in inflammatory markers

ART, antiretroviral treatment; VL, viral load; CRP, C-reactive protein; BM, bone marrow