Paradoxical Immune Reconstitution Inflammatory Syndrome associated with *Talaromyces marneffei* Infection among ART-Naïve Population

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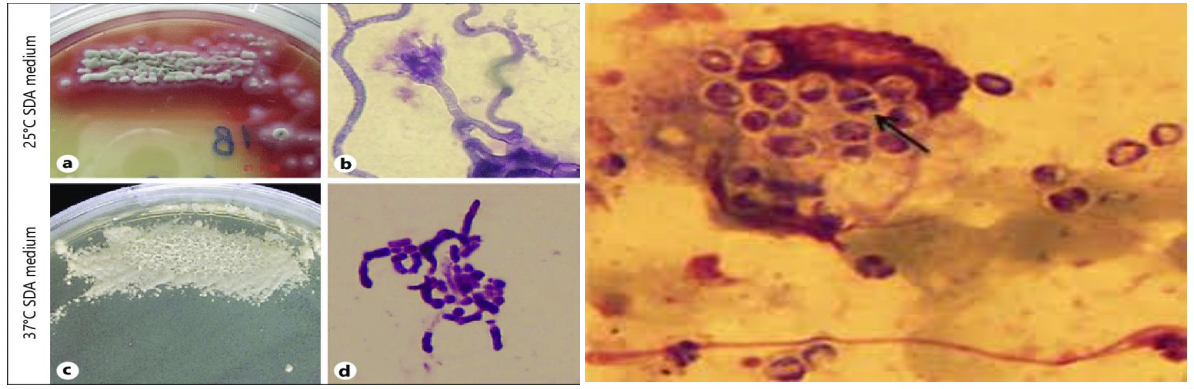
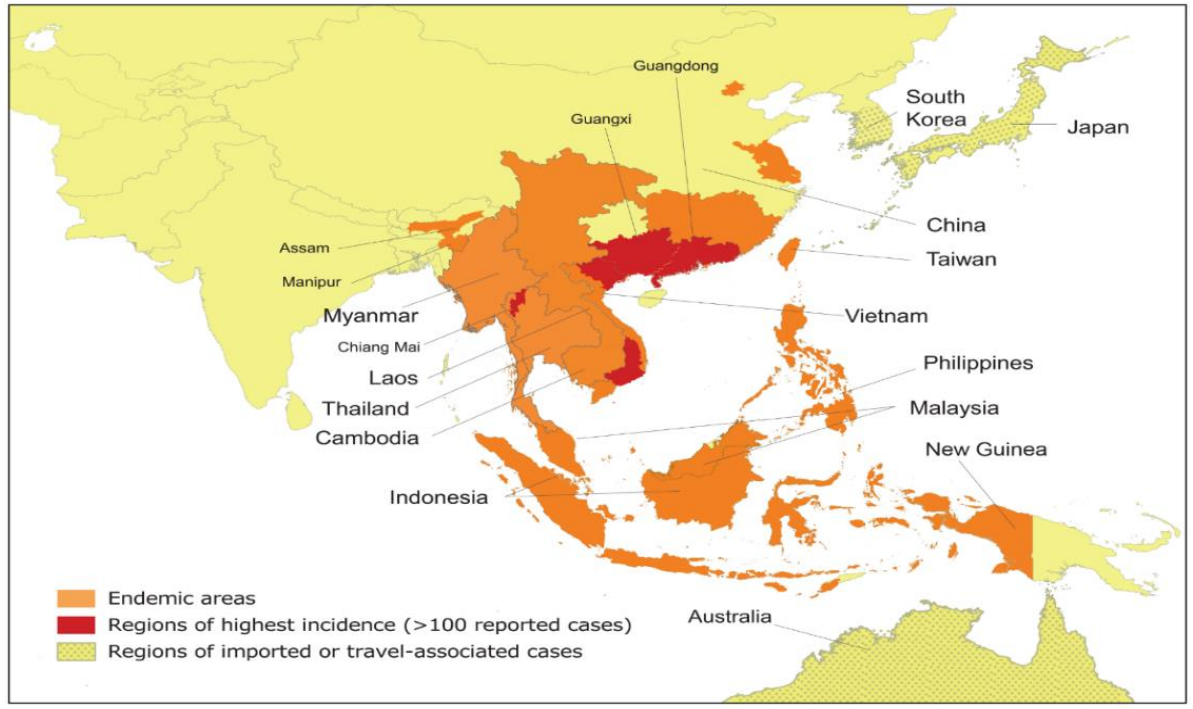
There is no conflict of interest

Talaromycosis (formerly termed Penicilliosis)

- A systemic fungal infection caused by the dimorphic fungus *Talaromyces marneffei (Tm).*
- Endemic in Southeast Asia, Southern China and Eastern India.
- Patients with advanced HIV disease and disseminated Tm infection are known to develop immune reconstitution syndrome (IRIS) as they initiate ART.



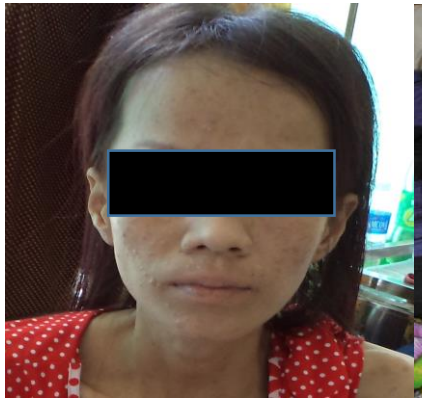


Hunters Tropical Medicine, 10th Edition, in 2019.

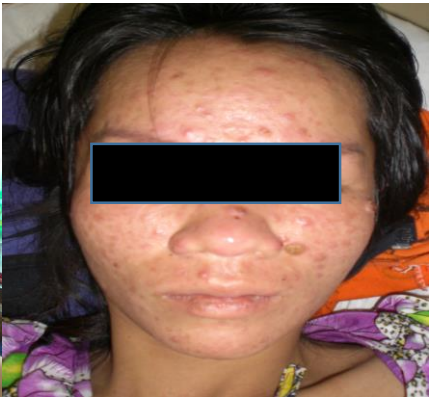
Talaromycosis-IRIS

- Tm IRIS might present in one of two forms:
  - ✓ **Paradoxical IRIS:** A ‘paradoxical’ worsening of a treated or under treatment of the fungal infection
  - ✓ **Unmasking IRIS:** The uncovering of previously ‘occult’ or subclinical infections
- To date, data on incidence and outcomes of Tm IRIS are lacking. In addition, it is clinically difficult to differentiate between Tm IRIS and relapse.

Paradoxical Tm-IRIS *



At IVAP trial enrollment for Tm infection



At Tm IRIS 5 months after ART initiation

**Le T et al. A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis. N Engl J Med 2017.*

Study objectives

- To investigate the incidence, clinical characteristics and outcomes of paradoxical Tm IRIS
- To identify clinical predictors of Tm IRIS
- To identify clinical factors that can distinguish between Tm IRIS and relapse

Study methods

- We conducted a prospective Tm IRIS sub-study within the **IVAP trial***- "Itraconazole versus Amphotericin B for HIV-associated Talaromycosis".

5 study sites in Vietnam

Hanoi
Hai Phong
Uong Bi
Viet Tiep

Ho Chi Minh City

IVAP

N=440 Tm patients

Study enrolment

2012 Followed-up for 6 months **2016**

Outcomes
- **Death**
- **Tm IRIS**
- **Tm relapse**

- Patients were evaluated monthly for the development of IRIS and relapse events, which were independently adjudicated by a clinician expert panel.

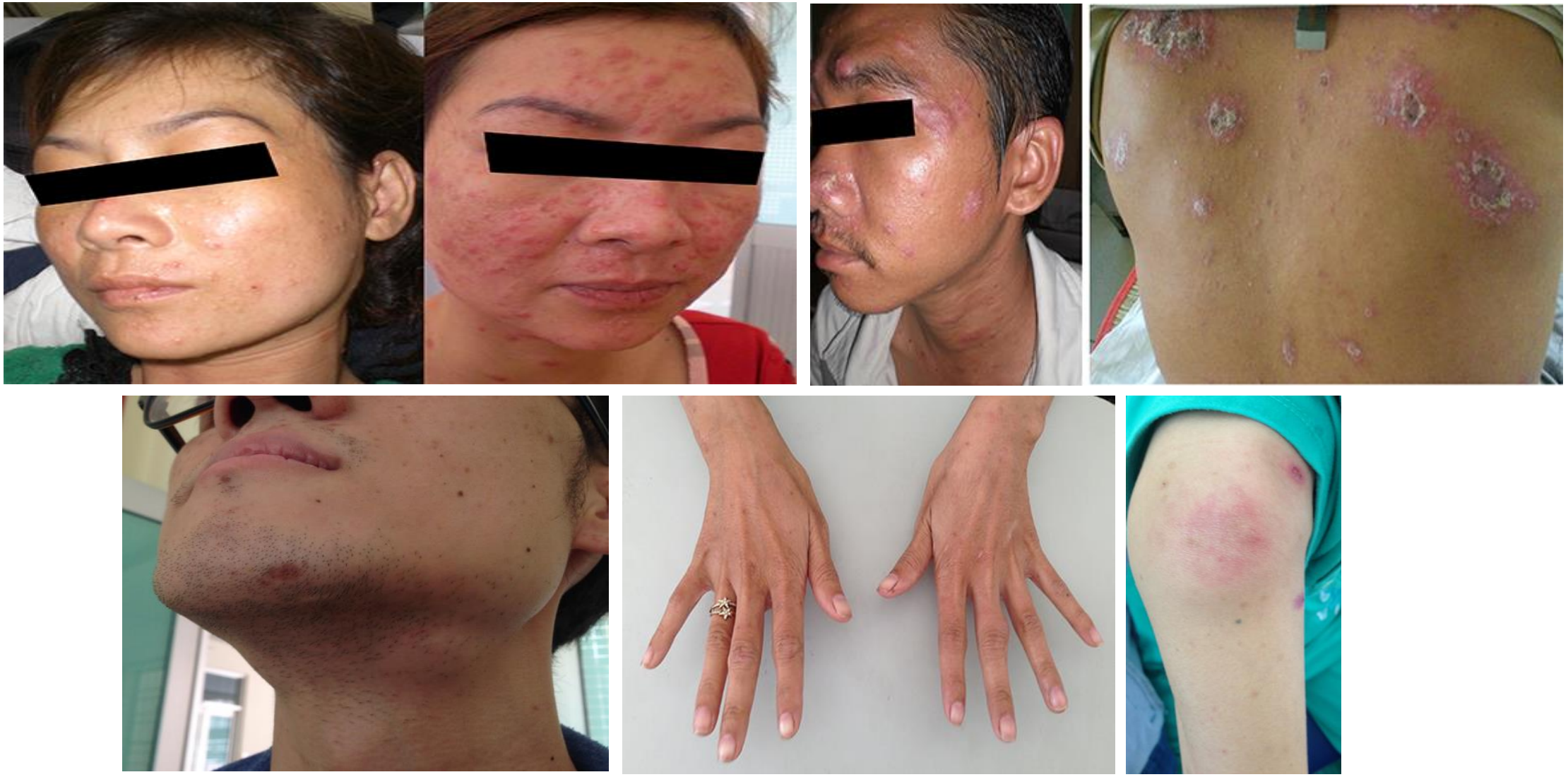
**Le T et al. A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis. N Engl J Med 2017.*

Statistical analysis

Multivariable joint model of longitudinal and survival data were used to identify predictors of paradoxical Tm IRIS:

- **Time-to-event** was the time from primary Tm diagnosis to IRIS development.
- Death before IRIS event as a right-censored event-time.
- **Pre-defined covariates** included: age, baseline CD4 count, time from Tm diagnosis to ART initiation, type of induction therapy (itraconazole/amphotericin B), baseline blood fungal count and the number of fungal count (CFU) decline.
- Repeated blood fungal count (CFUs) at baseline and the number of fungal count decline (fungicidal activity) were treated as **time-varying covariates.**

Clinical presentations of Tm IRIS



Study results

- Median age was 33 years old (IQR: 28-35)
- Median time from ART initiation to Tm IRIS: 3 months (IQR: 02-4.8)
- **Paradoxical Tm IRIS:** 23/215 (10.7%) ART-naïve patients. Incidence rate was 10.3 cases per 1,000 person-months (IQR: 6.5-15.4).
- **Unmasking Tm IRIS:** 16/225 (7.1%) ART-treated patients at enrollments
- **Tm relapse:** 18/440 (4.1%) Tm patients. Incidence rate was 8 cases per 1,000 person-months (IQR: 4.7-12.5).
- Management of paradoxical Tm IRIS:
  - ✓ 13/23 (56.5%) received re-Induction Therapy with Amphotericin B
  - ✓ 11/23 (43.5%) continued Itraconazole maintenance therapy
- **Outcome:**
  - ✓ All 23 (100%) paradoxical Tm IRIS patients survived
  - ✓ 6/18 (33.4%) patients with Tm relapse died

Survival submodel of the joint model

Risk factor	Coefficient (95% CI)	HR (95% CI)	SE	P value
Age (+10 years)	-0.544 (-0.619 to -0.469)	0.58 (0.54 - 0.63)	0.0384	0.170
Baseline CD4 count (+10 cells/µL)	-0.541 (-0.591 to -0.491)	0.58 (0.55 - 0.61)	0.0255	0.128
Time from T.m diagnosis to ART initiation (months)	-0.377 (-0.415 to -0.339)	0.69 (0.66 - 0.71)	0.0193	0.277
Induction therapy with Itraconazole compared to Amphotericin B	3.161 (2.977 to 3.344)	23.58 (19.63 - 28.34)	0.0937	< 0.001
Baseline blood fungal count (1 log_{10} CFU/ml)	0.133 (0.103 to 0.162)	1.14 (1.11 - 1.18)	0.015	0.592
Number of CFU decline (1 log_{10} CFU/ml)	-0.001 (-0.003 to 0.001)	1.00 (0.99 - 1.00)	0.0011	0.938

Note: HR, Hazard ratio was calculated from Exp (Coefficient); SE, Standard error

Differentiation between Tm IRIS and Tm relapse

Factors	Tm IRIS (N=23)	Tm Relapse (N=18)	Primary Tm (N = 399)	ANOVA P [a]	P [b]	P [c]	P [d]
Baseline CD4 count (cells/µL)	09 (04 - 14)	09 (05 - 19)	10 (05 - 22)	0.34	0.54	0.54	0.12
WBC (K cells/µL)	5.0 (4.4 - 8.3)	5.1 (3.2 - 9.2)	3.7 (2.4 - 5.8)	0.20	0.70	0.18	< 0.01
Hemoglobin (g/dL)	11.2 (10.3 - 12.6)	8.7 (8.0 - 9.1)	8.8 (7.7 - 10.1)	< 0.001	0.004	0.81	< 0.001
Platelet (K cells/µL)	286 (232 - 341)	263 (40 - 343)	112 (50 - 125)	< 0.001	0.40	0.26	< 0.001
AST (IQR) (U/L)	39 (25 - 55)	169 (62 - 308)	122 (73 - 209)	< 0.001	0.02	0.61	< 0.001
ALT (IQR) (U/L)	27 (22 - 44)	54 (25 - 134)	48 (30 - 79)	0.13	0.25	0.89	0.02

Note: Tm, *Talaromyces marneffei*, P value[a] from ANOVA test, P value[b,c,d] from Wilcoxon rank sum tests for paired comparisons among Tm IRIS, Tm relapse and Primary Tm infection, respectively

Conclusions

- Paradoxical Tm IRIS occurs between 2-5 months after ART initiation
- Incidence is driven by suboptimal induction therapy with itraconazole
- Characterized by inflammatory clinical features, with a CD4 count rise of ~100 cells/μL, and normalized laboratory values (Hemoglobin, platelet, and AST)
- The survival is close to 100% in Tm IRIS; in contrast, mortality is > 30% in Tm relapse

We would like to thank all patients, physicians and nurses and for their participation and contribution in the study.

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