

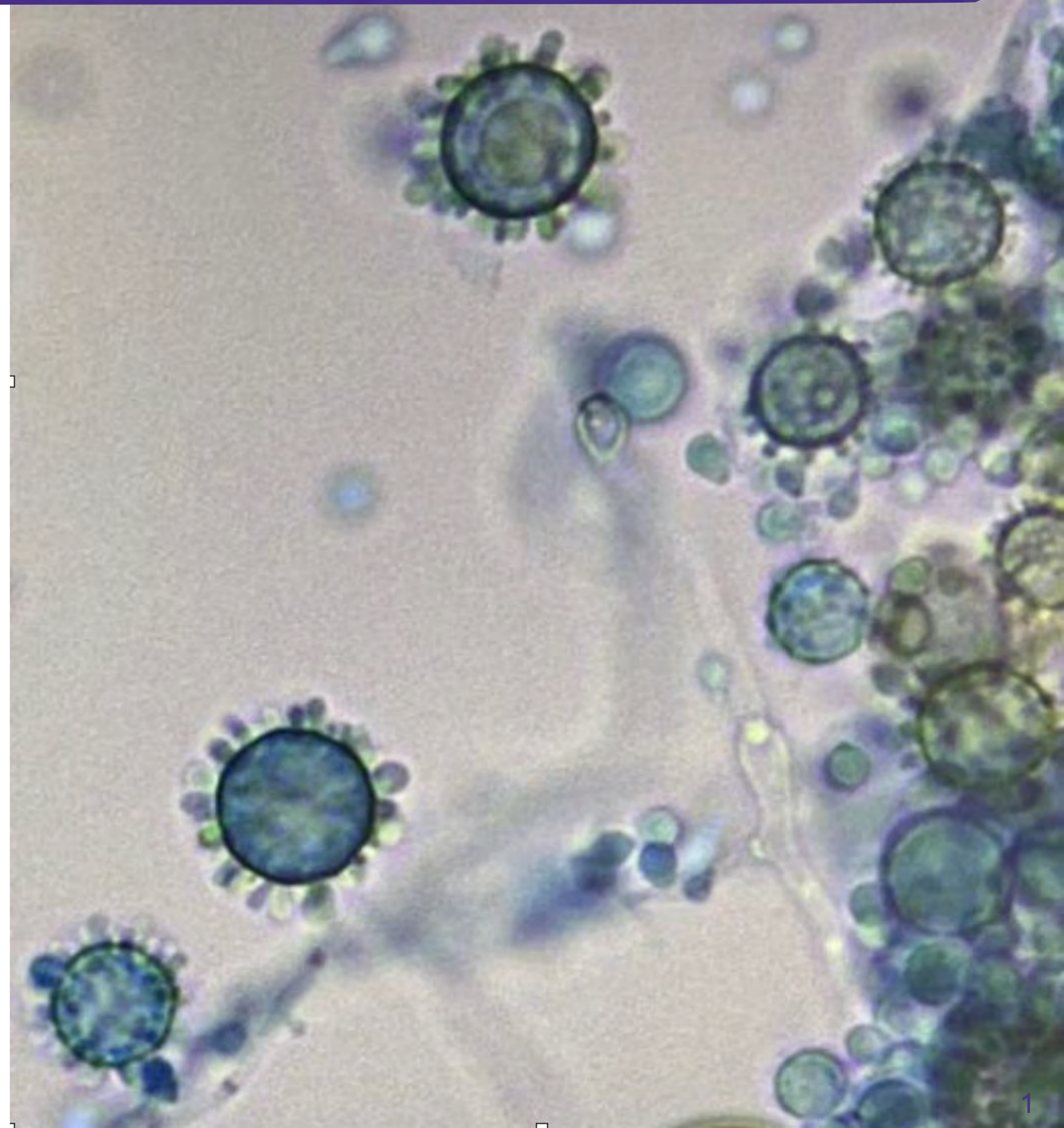


Avancées diagnostiques et pronostiques de l'histoplasmosse disséminée

Session thématique Tropiques caraïbo-latino-
américaines : nouvelles menaces infectieuses

Ugo FRANÇOISE

MIT — Hôpital Saint-Antoine
APHP / Sorbonne Université





Déclaration de liens d'intérêt avec les industriels de santé
en rapport avec le thème de la présentation (loi du 04/03/2002) :

L'orateur ne
souhaite
pas répondre

☐

- **Intervenant** : Ugo FRANÇOISE
- **Titre** : Avancées diagnostiques et pronostiques de l'histoplasmosse disséminée
- Consultant ou membre d'un conseil scientifique
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations
- Investigateur principal d'une recherche ou d'une étude clinique

☐ OUI

☒ NON

☐ OUI

☒ NON

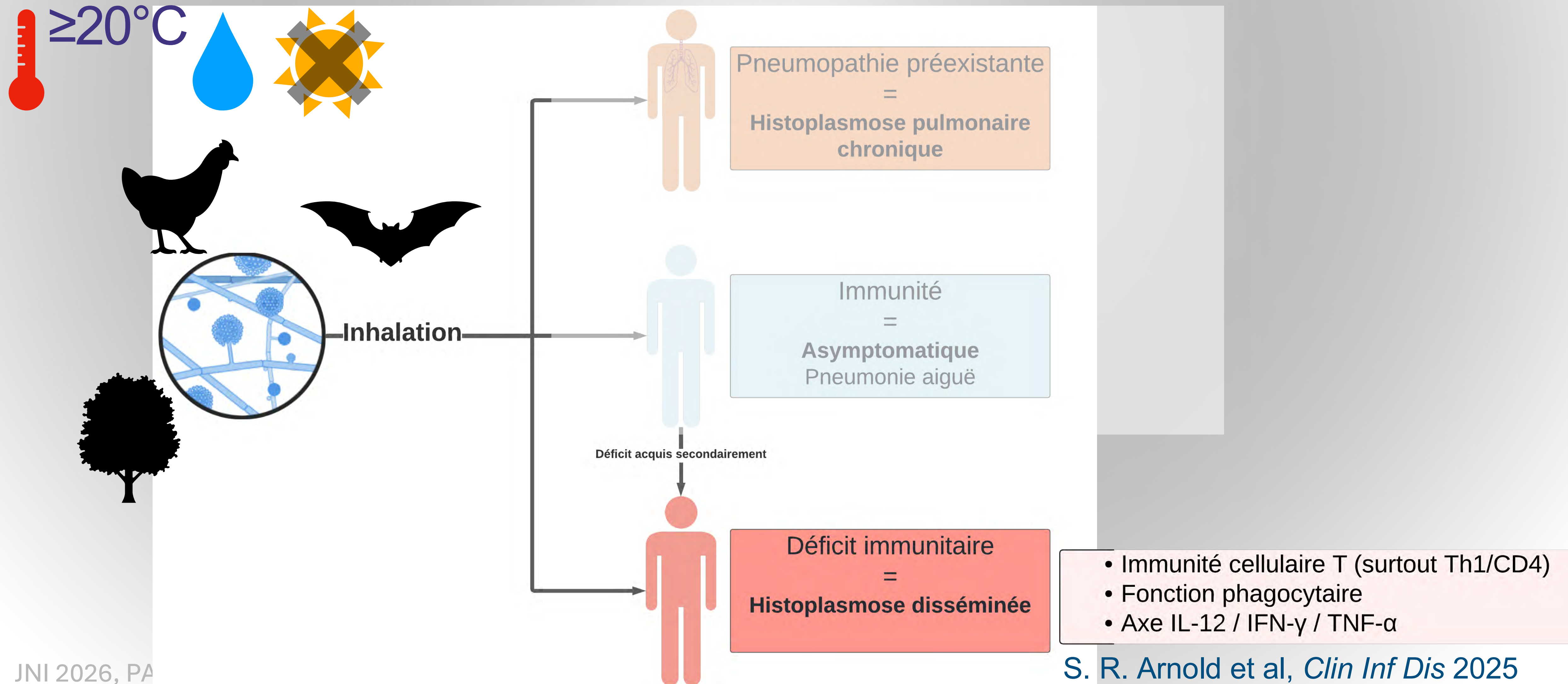
☐ OUI

☒ NON

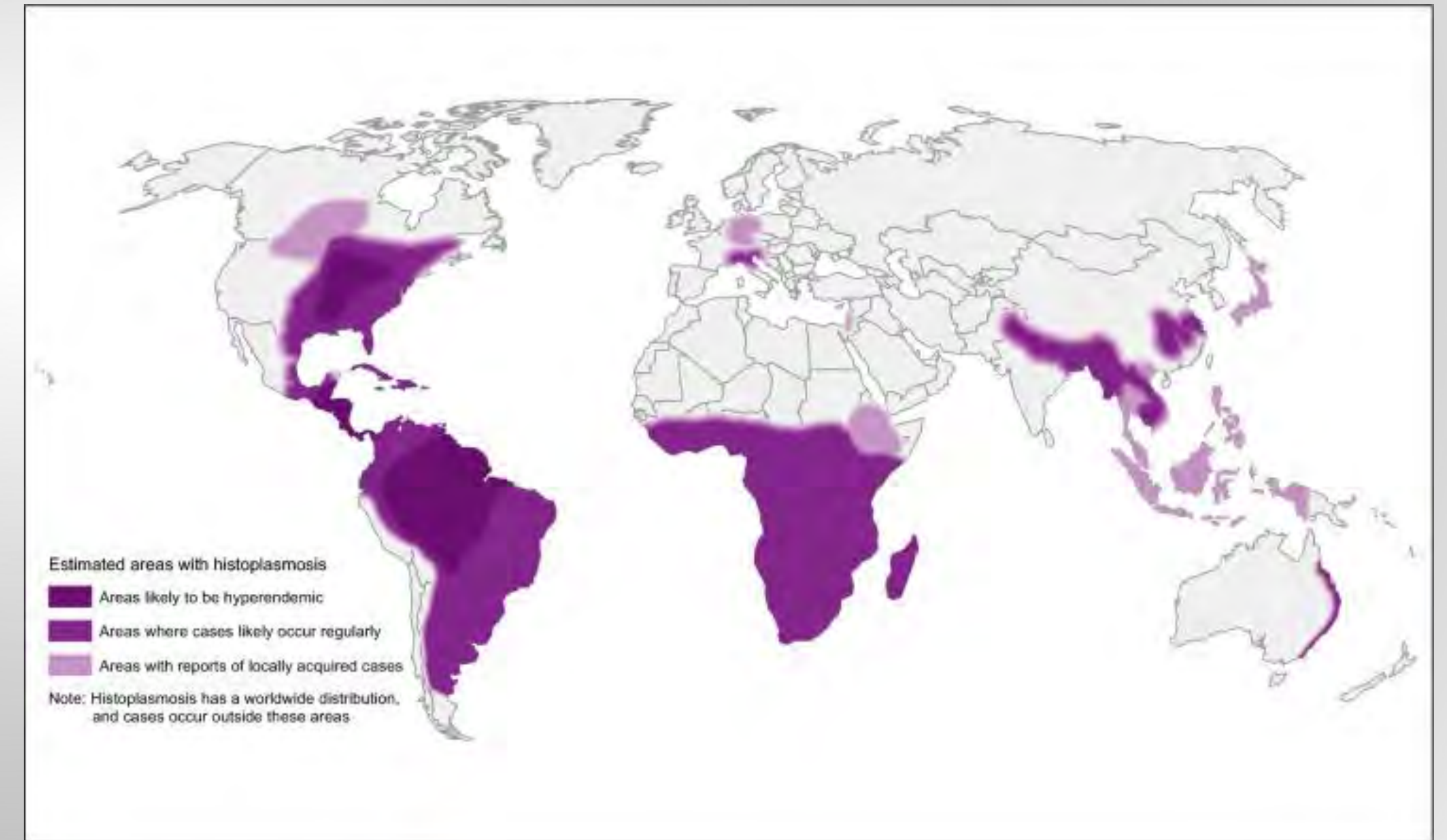
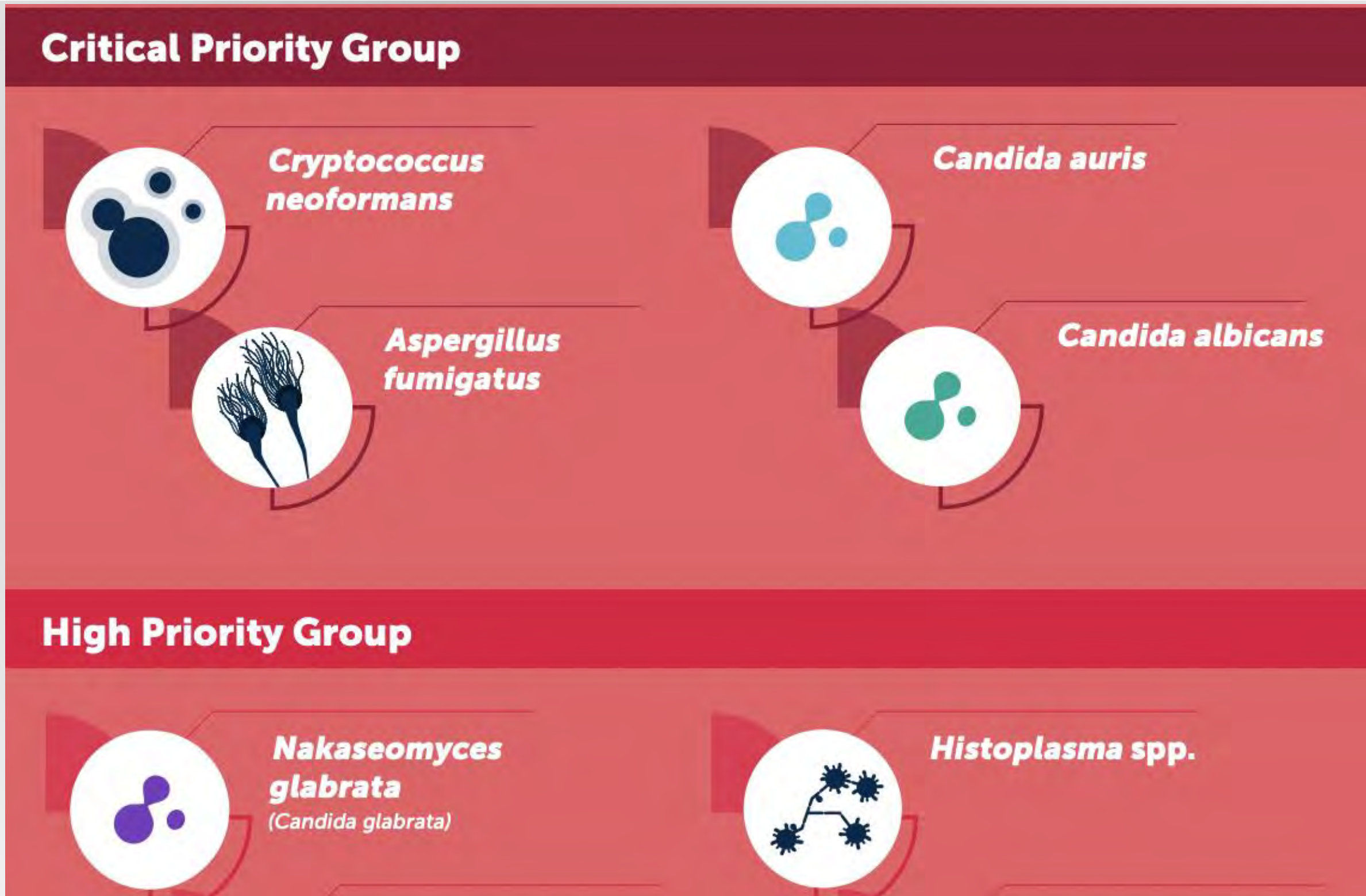
☐ OUI

☒ NON

Qui développe une histoplasmosse disséminée ?



Quand évoquer une histoplasmosse disséminée ?



N. Ashraf et al, *Mycopathologia* 2020

WHO fungal priority pathogens list 2022

Comment

Histoplasmosis dethrones tuberculosis in Latin America



A Pasqualotto et F. Quieroz-Telles *Lancet Inf Dis* 2018

Quand évoquer une histoplasmosse disséminée ?

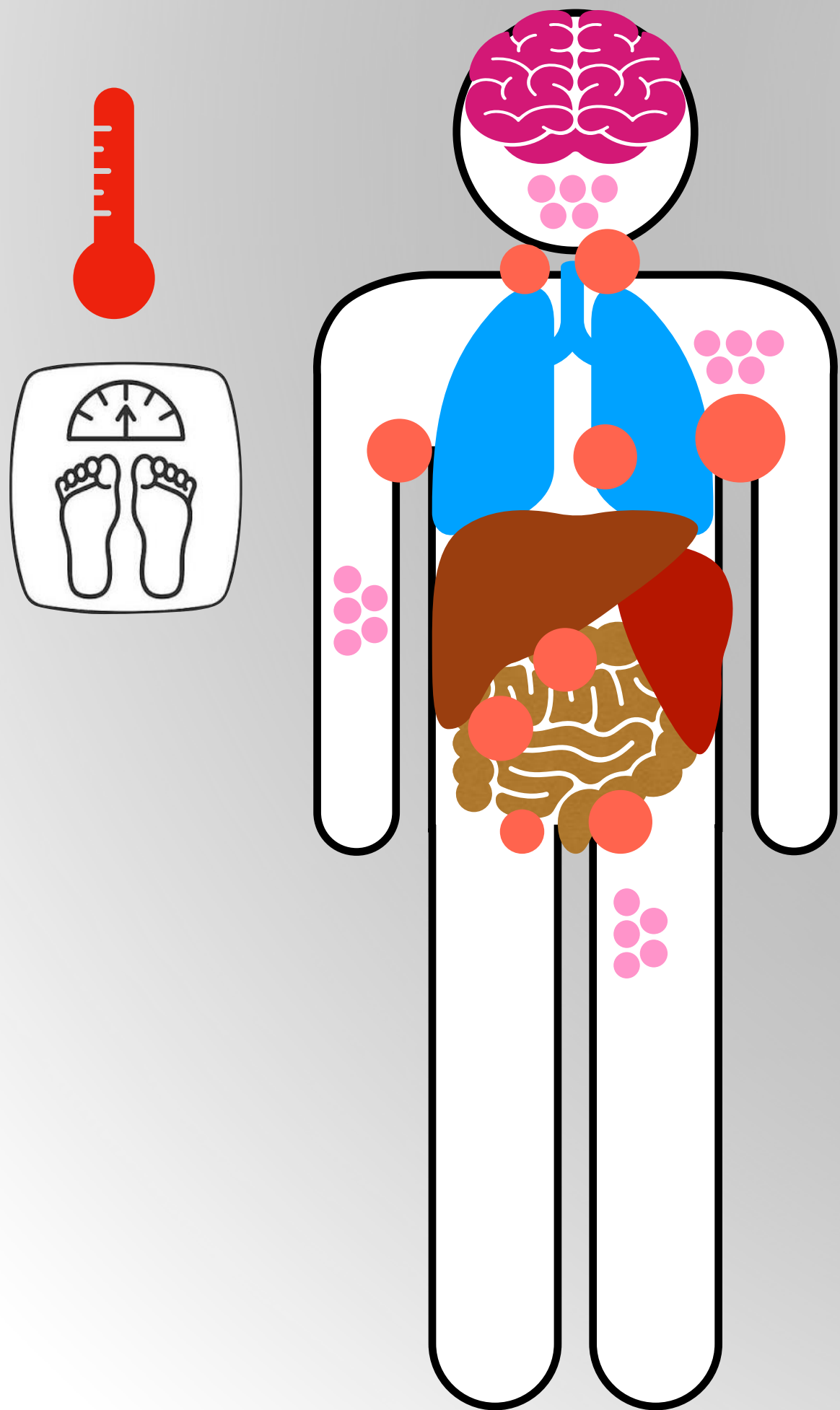
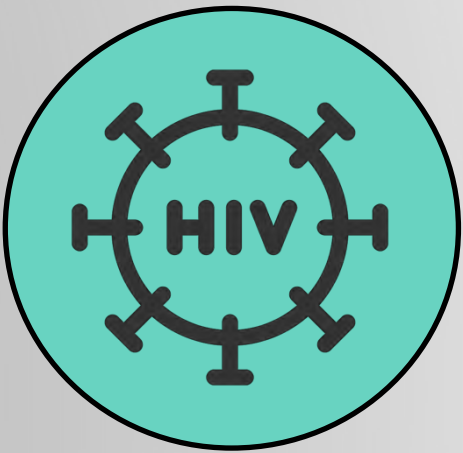
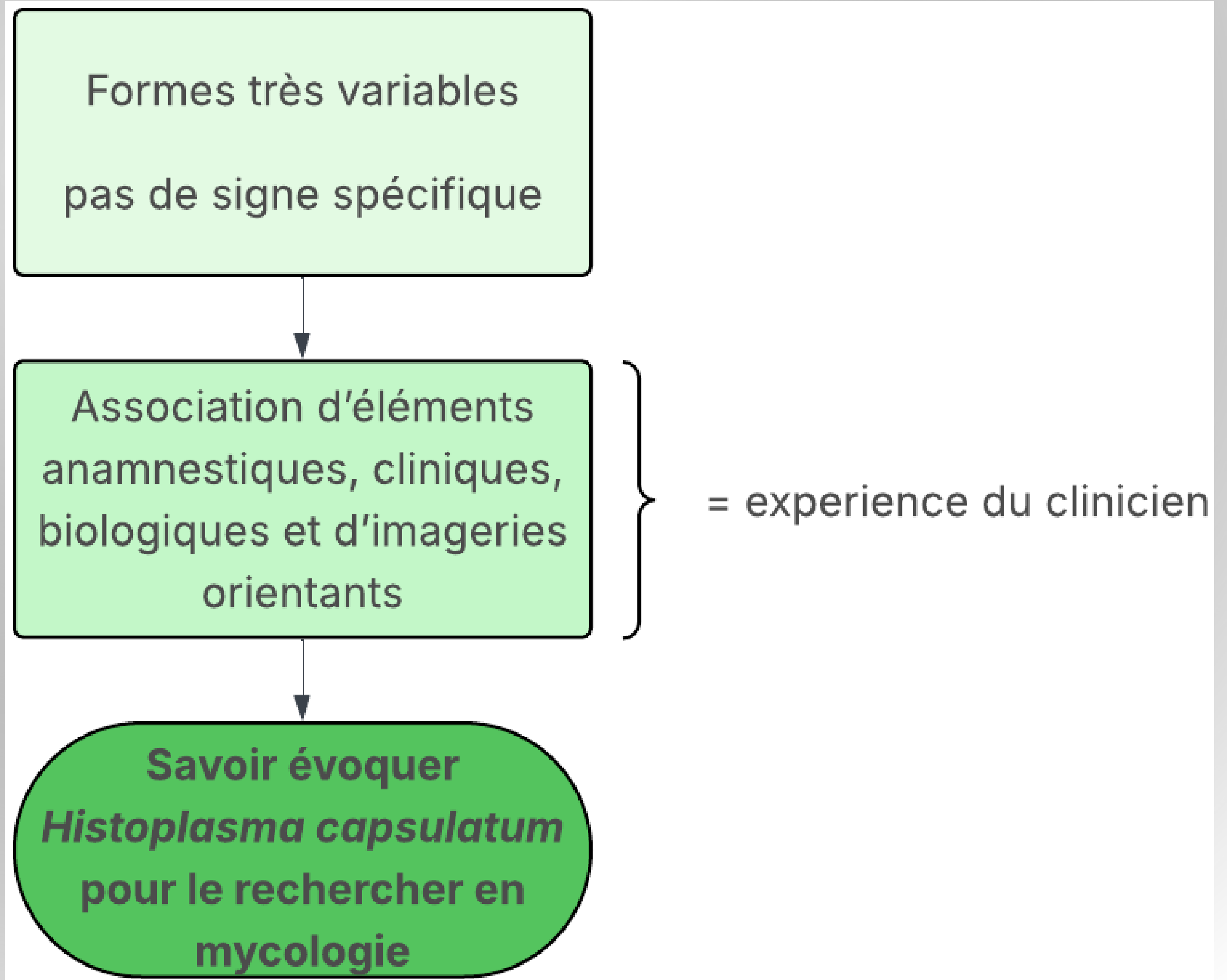


Table 1. Frequency of different signs and symptoms and sites sampled to try to identify the pathogen.

Variable	N	Proportion (%)	Standard Deviation
Signs and Symptoms			
Fever	348	89	31
Weigh loss	158	83	37
Digestive	348	70	45
Lymph node	348	48	50
Pulmonary	348	47	50
Neurological	348	20	40
Cutaneous	348	6	25
Oral	348	5	22
Ocular	348	0.28	5
Sampling Sites			
Bone marrow	349	61	48
Alveolobronchial	349	28	45
Blood	349	26	43
Liver	349	24	43
Lymph node	349	20	40
Lower digestive	349	19	39
Cerebro-spinal fluid	349	17	38
Cutaneomucous	349	11	31
Upper digestive	349	8	28
Urine	349	5	23



Quand évoquer une histoplasmosse disséminée ?



Partie I

Le diagnostic

Diagnostic de l'histoplasmosse disséminée **prouvée**

❖ Histoplasmosse **prouvée** = méthodes « conventionnelles »

JP Donnelly et al, *Clin Inf Dis* 2020

Diagnostic de l'histoplasmosse disséminée prouvée

❖ Examen direct mycologique



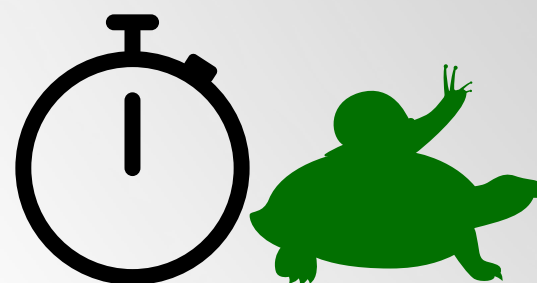
❖ MGG

❖ Histologie



❖ Grocott

❖ Culture



❖ 25-37°C

❖ P3

Scheel CM, Gómez BL, *Curr Trop Med Rep*, 2014

	Prouvée		
	Examen direct	Histologie	Culture
Rapide			
Peu coûteuse			
Non invasive			
Sûre			
Reproductible			
Sensible			
Spécifique			

Diagnostic de l'histoplasmose disséminée probable

Histoplasmose probable

=

exposition environnementale + maladie compatible +
test antigénique *Histoplasma* positif

JP Donnelly et al, *Clin Inf Dis* 2020

Companie	ELISA	LFA
	X	
	X	X
		X

Les différents tests antigéniques spécifiques

❖ ELISA

Clarus *Histoplasma* GM

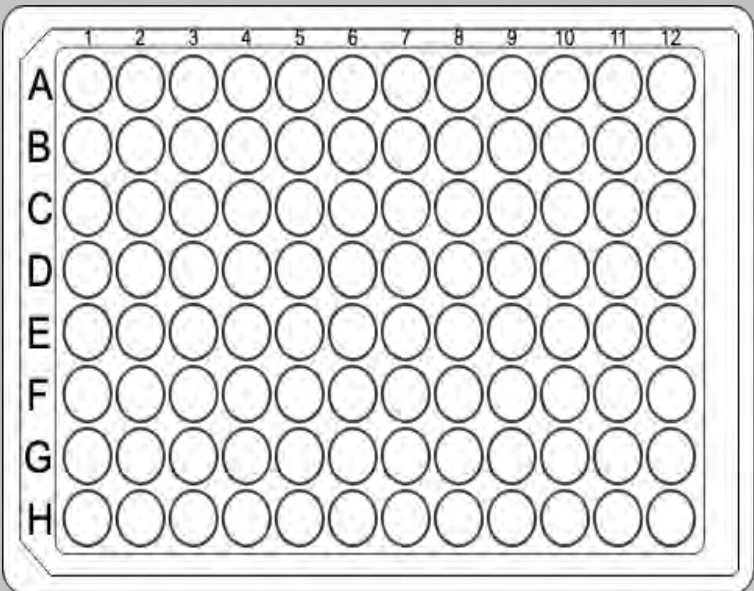


Urines



LFA

En développement



Test quantitatif
96 échantillons
⌚ 2h

Les différents tests antigéniques spécifiques

❖ ELISA



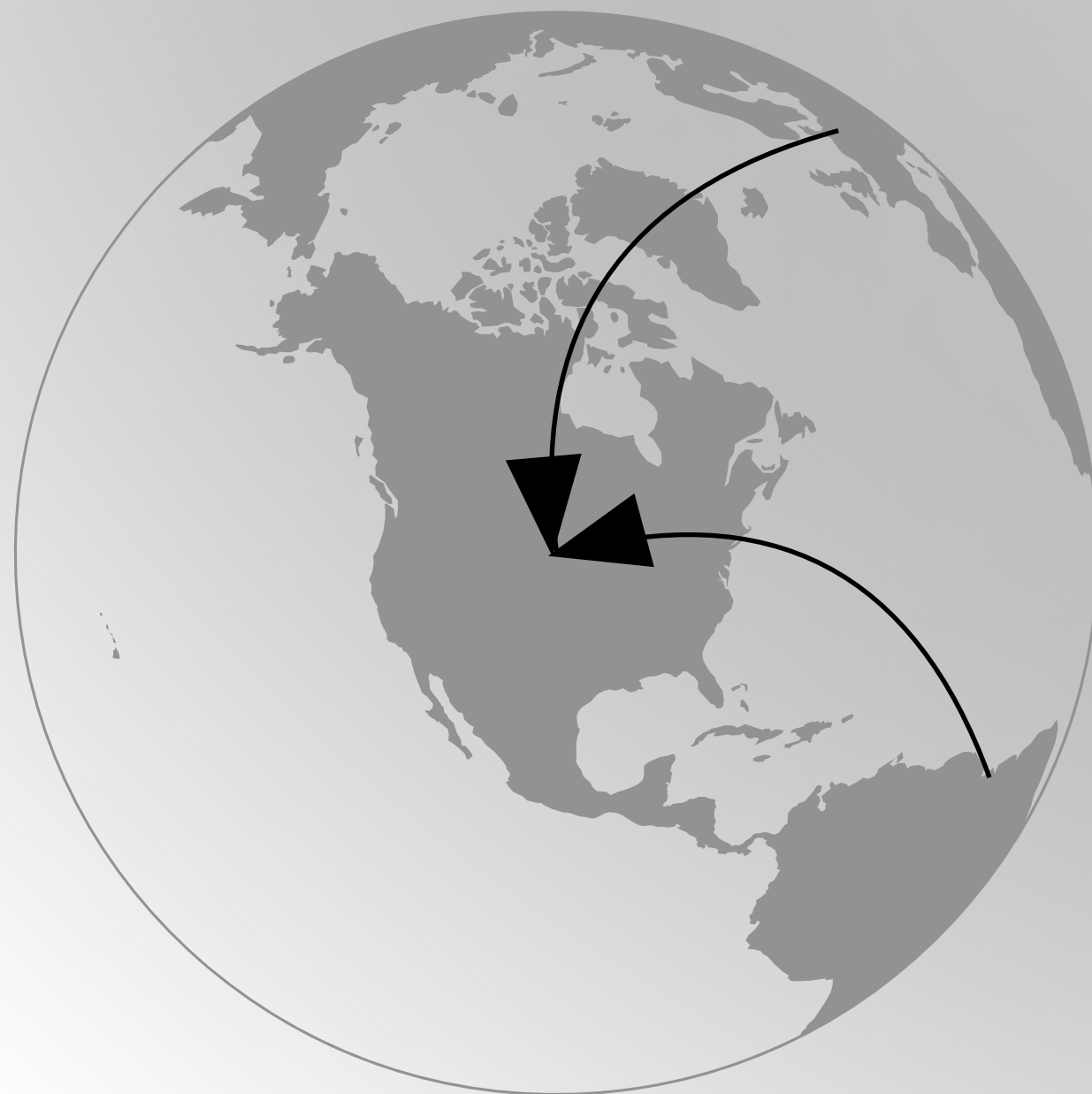
❖ LFA



Prélèvements à envoyer à Indianapolis
Urine, Serum, Plasma, LCS, LBA

Histoplasma Urine Antigen LFA

Test qualitatif ⌚ 40 min



JNI 2026, PARIS

The Process

① Dilute



② Mix



③ Pipette



④ Read



A non-invasive, accurate CE marked* test that can be performed in low complexity settings.
This test is the answer to rapid histoplasmosis diagnoses.

*Not FDA cleared. Not available in the U.S.

Les différents tests antigéniques spécifiques

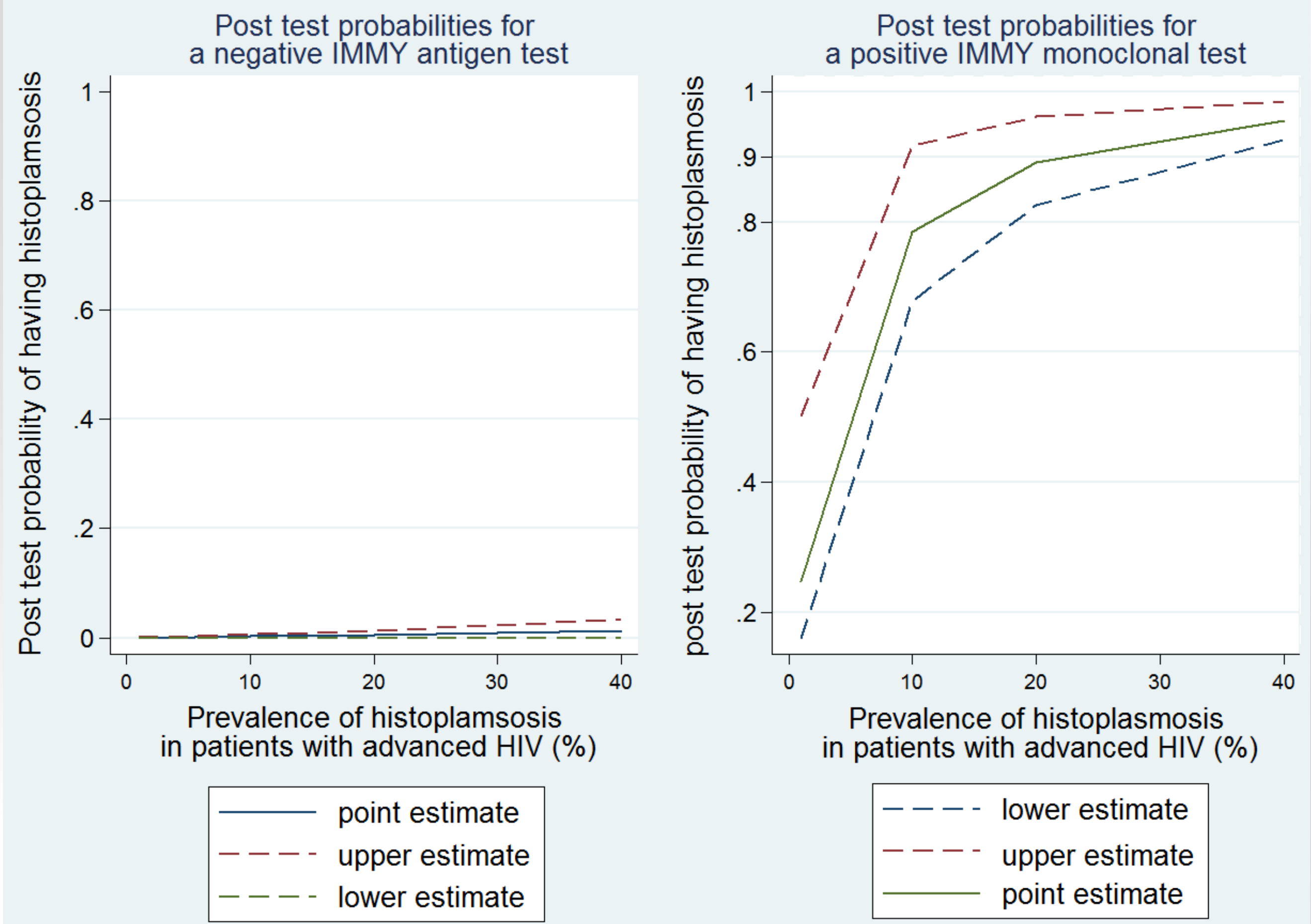


❖ LFA



⌚ 15min

Les différents tests antigéniques spécifiques

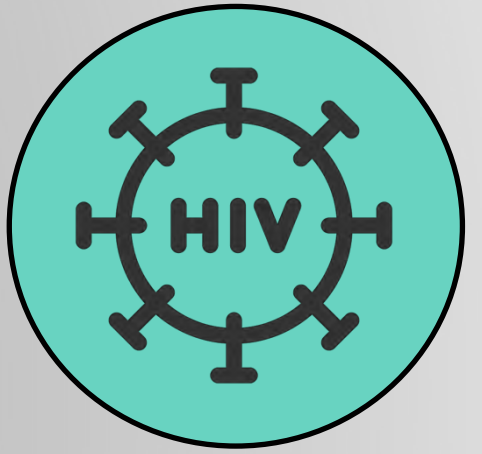


Culture		
LFA	+	-
	25	3
	+	-
	1	71

Sensitivity	96% (80-100)
Specificity	96% (89-99)
Accuracy	96% (90-99)
Positive predictive value	89% (73-96)
Negative predictive value	99% (91-100)

DH Caceres et al, *J fungi* 2021

Les différents tests antigéniques spécifiques



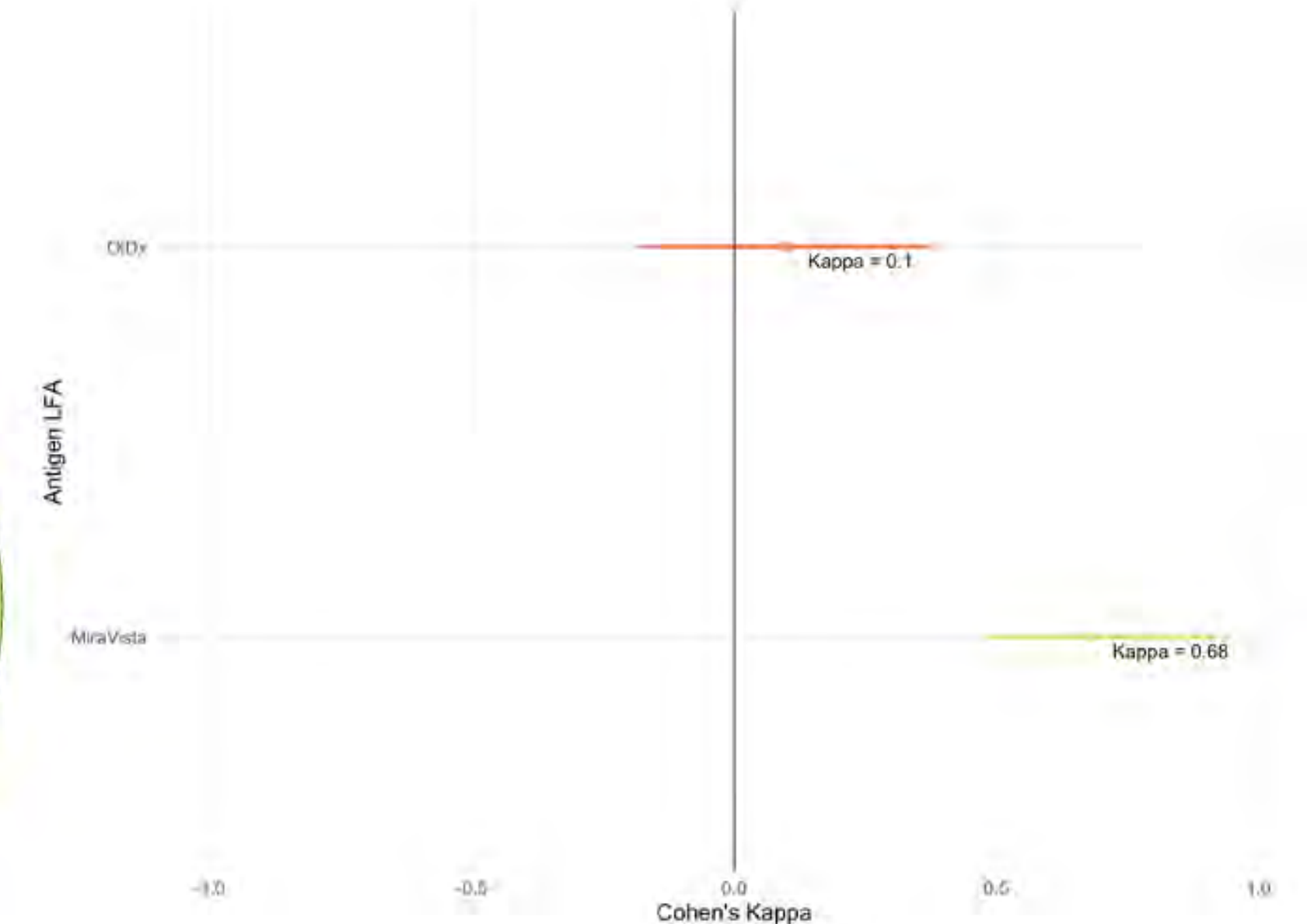
❖ Étude de performance Colombie

Se : 92% (95% CI 74%–99%)

Spe : 32% (95% CI 20%–46%)

DH Caceres et al, Mycopathologia 2022

❖ Étude de performance Côte d'Ivoire



A. Surny-Leclère et al, *Clin Inf Dis* 2025

Figure S2.a. Euler diagram of the distribution of patients with positive *Histoplasma* antigen tests (EIA, Miravista LFA, OIDx LFA) b. Cohen's kappa coefficients between the LFA (Miravista and OIDx) and *Histoplasma* EIA (IMMY) results, with 95% confidence intervals

Les différents tests antigéniques spécifiques

⚠ Faux Positifs

- ❖ Réactions croisées avec d'autres dimorphiques
- ❖ Défaut de sensibilité des méthodes conventionnelles

⚠ Faux Négatifs

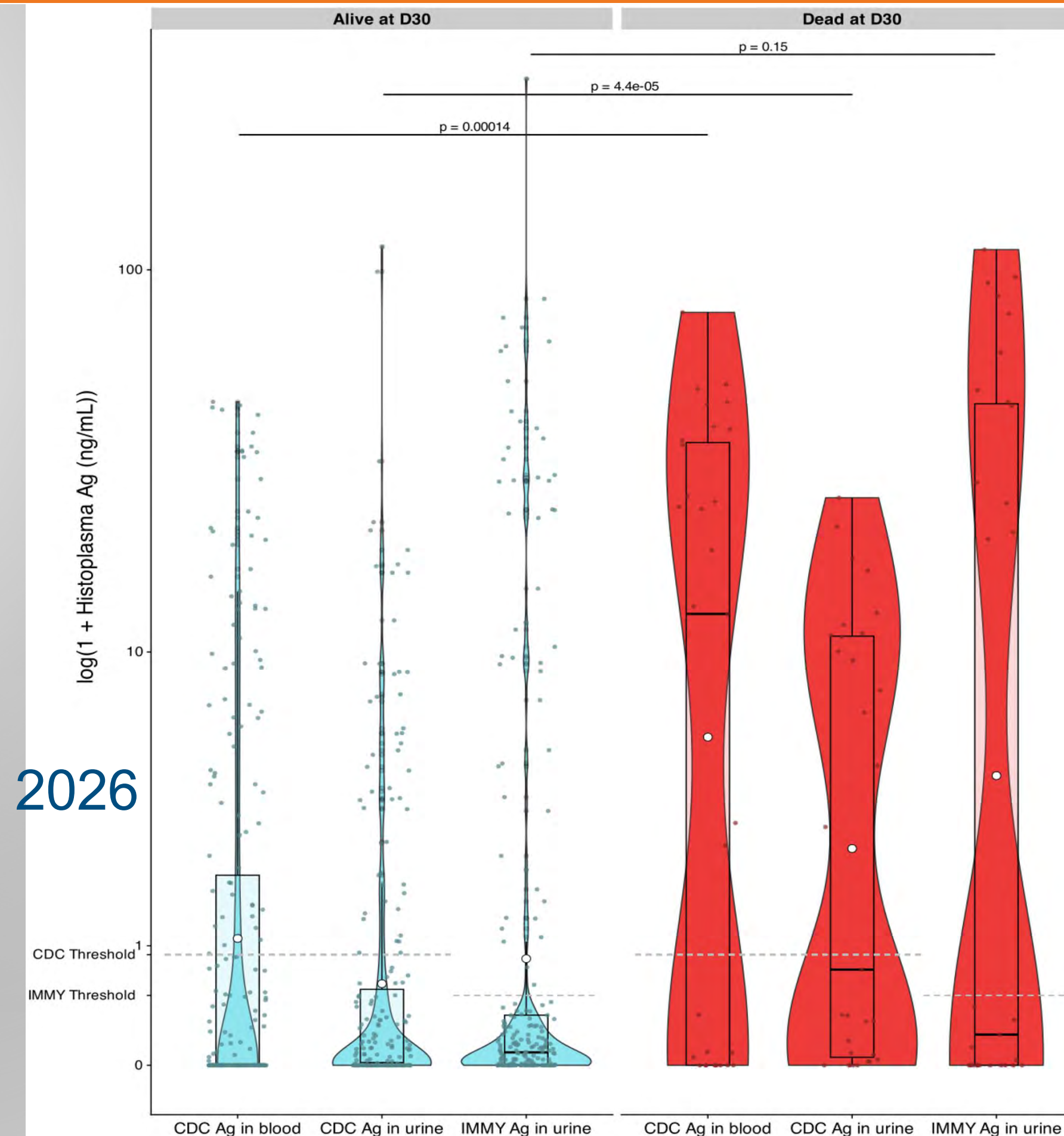
- ❖ Dilution de l'antigène urinaire

M Dzombo et al, Microbiol. Spectr. 2024 U. Françoise et al. *Int J Inf Dis* 2026

- ❖ Effet post zone Ten Have et al, *Med Mycol* 2026

⚠ Significativité d'un test positif isolé

- ❖ Antigénurie sans symptôme = survie possible sans traitement antifongique



L'impact des tests antigéniques *Histoplasma*

HIV-associated histoplasmosis in patients living on the the Guiana Shield:

a prospective prevalence study

PLHIV hospitalized for altered general condition, fever, or symptoms suggestive of an infectious syndrome

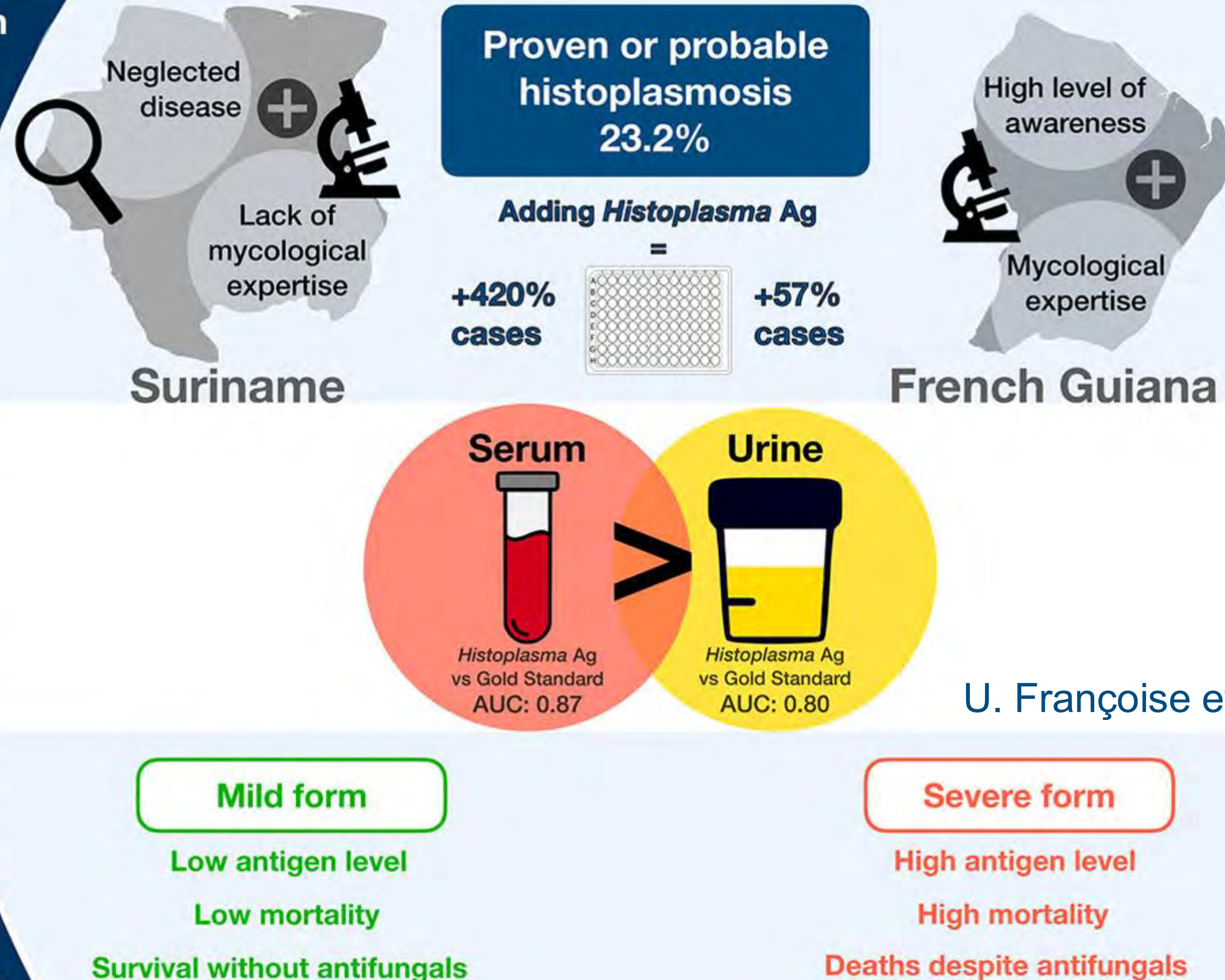
► **High prevalences** in Suriname and French Guiana

► **Antigen testing increased** histoplasmosis diagnosis

► **Serum antigen detection** outperformed urine testing

► **Higher antigen levels** associated with severe disease and mortality

Ugo Françoise, Mathieu Nacher, Sigrid Mac Donald, Marja Van Eer, Christina Scheel, Tom Chiller, Diego H Caceres, Beatriz L Gomez, Denis Blanchet, Christine Aznar, Pierre Couppié, Stephen Vreden, Antoine Adenis



U. Françoise et al. *Int J Inf Dis* 2026

Diagnostic chez l'immunodéprimé non VIH

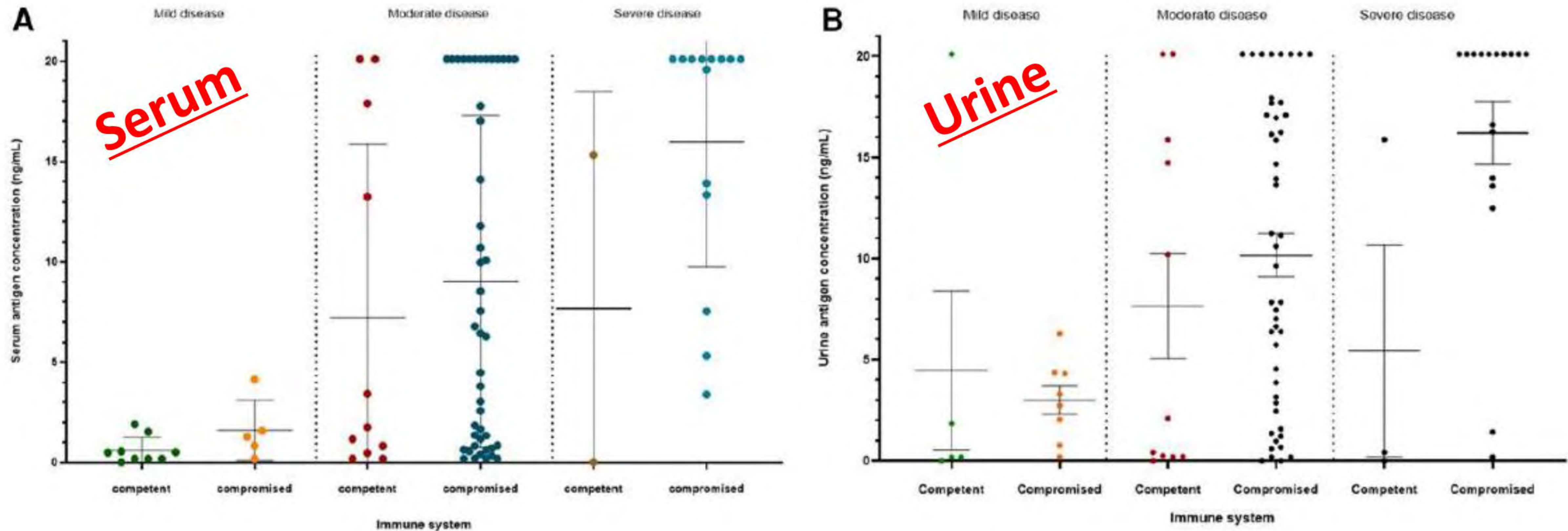


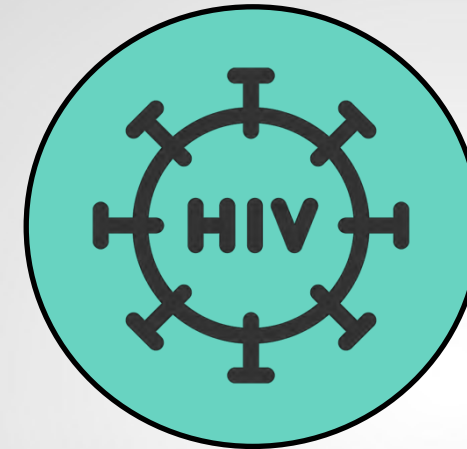
Figure 1. Antigen concentration by disease severity and immune status. *A*, Serum antigen concentrations by EIA. *B*, Urine antigen concentrations by EIA.

Disponibilité des tests antigéniques

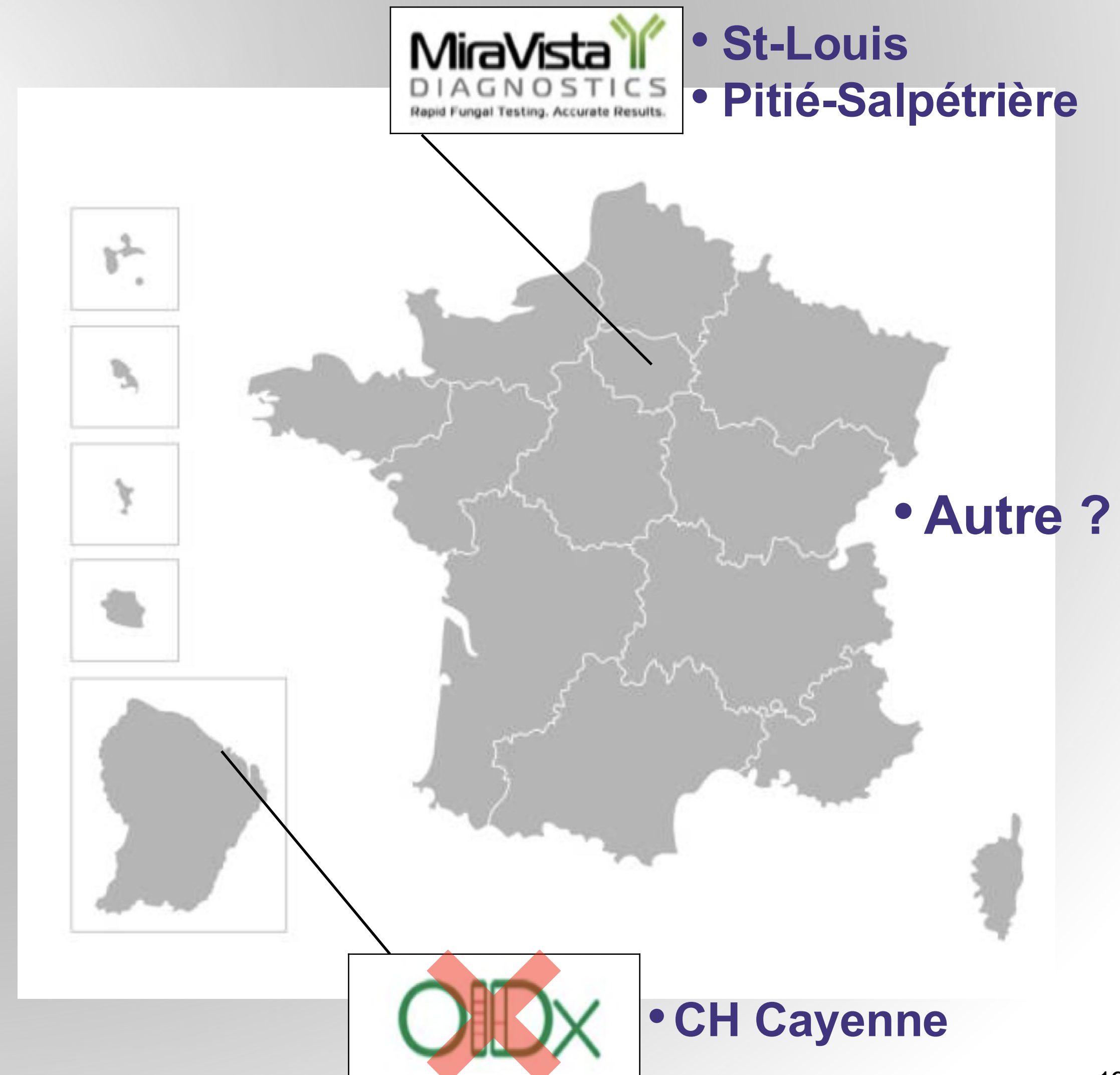
RECOMMANDATIONS
DE PRISE EN CHARGE DU VIH,
DES HÉPATITES VIRALES ET DES IST
RAPPORT D'EXPERTS
Sous la direction du Pr Pierre Delobel

CNS
Conseil national du sida
et des hépatites virales

anrs
MALADIES INFECTIEUSES
ÉMERGENTES **Inserm**



- ❖ La disponibilité des tests antigéniques d'*Histoplasma* nécessiterait d'être plus large en France.



Tests antigéniques « classiques » : β -D-glucane & GM

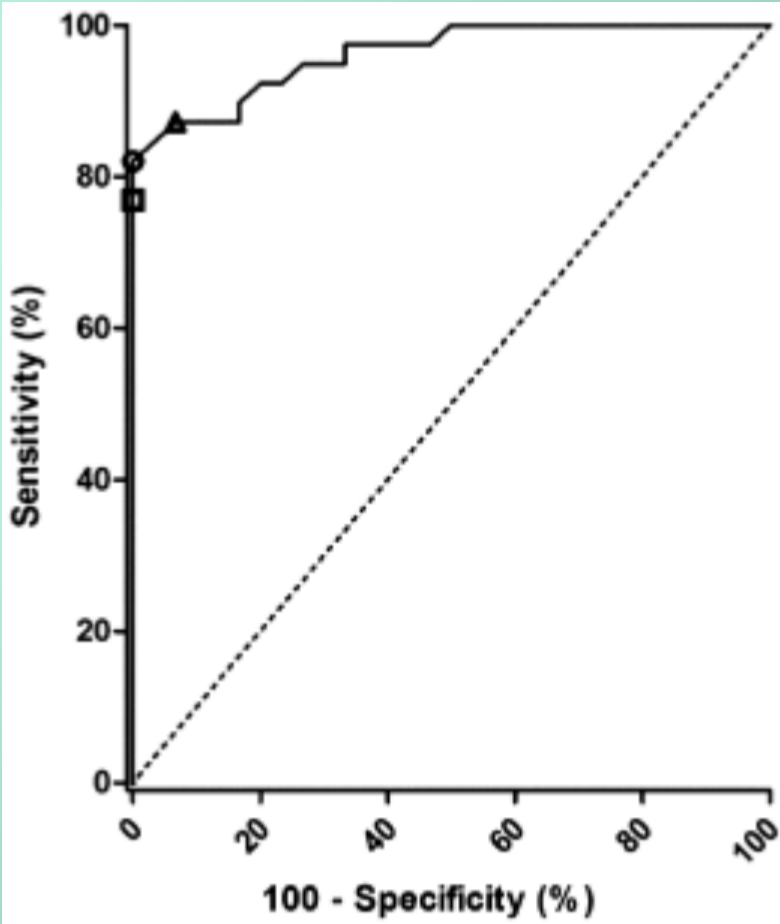
❖ β -D-glucane

Table 1. Results of (1 $\rightarrow$ 3)- β -d-Glucan Testing by Diagnosis

(1 $\rightarrow$ 3)- β -D-Glucan Level	All PDH (n = 36)	PDH With Respiratory Symptoms (n = 31)	PCP (n = 41)
Mean ($\pm$ SD), pg/mL	339.5 ($\pm$ 185.4)	333.6 ($\pm$ 185.9)	440.3 ($\pm$ 134.3)
Min, max, pg/mL	42, 500	42, 500	30, 500
Median (Q1, Q3), pg/mL	475.0 (118, 500)	465 (116, 500)	500 (489, 500)
Positive ($\geq$ 80 pg/mL)	33 (91.7)	29 (93.6)	40 (97.5)
Indeterminate (60–79 pg/mL)	1 (2.7)	1 (3.2)	0
Negative (<60 pg/mL)	2 (5.6)	1 (3.2)	1 (2.4)
$\geq$ 500 pg/mL	17 (47.2)	14 (45.2)	31 (75.6)

M Saccente et G Krishnan, Clin Inf Dis 2021

❖ Galactomannane



Histo prouvée : 39/69

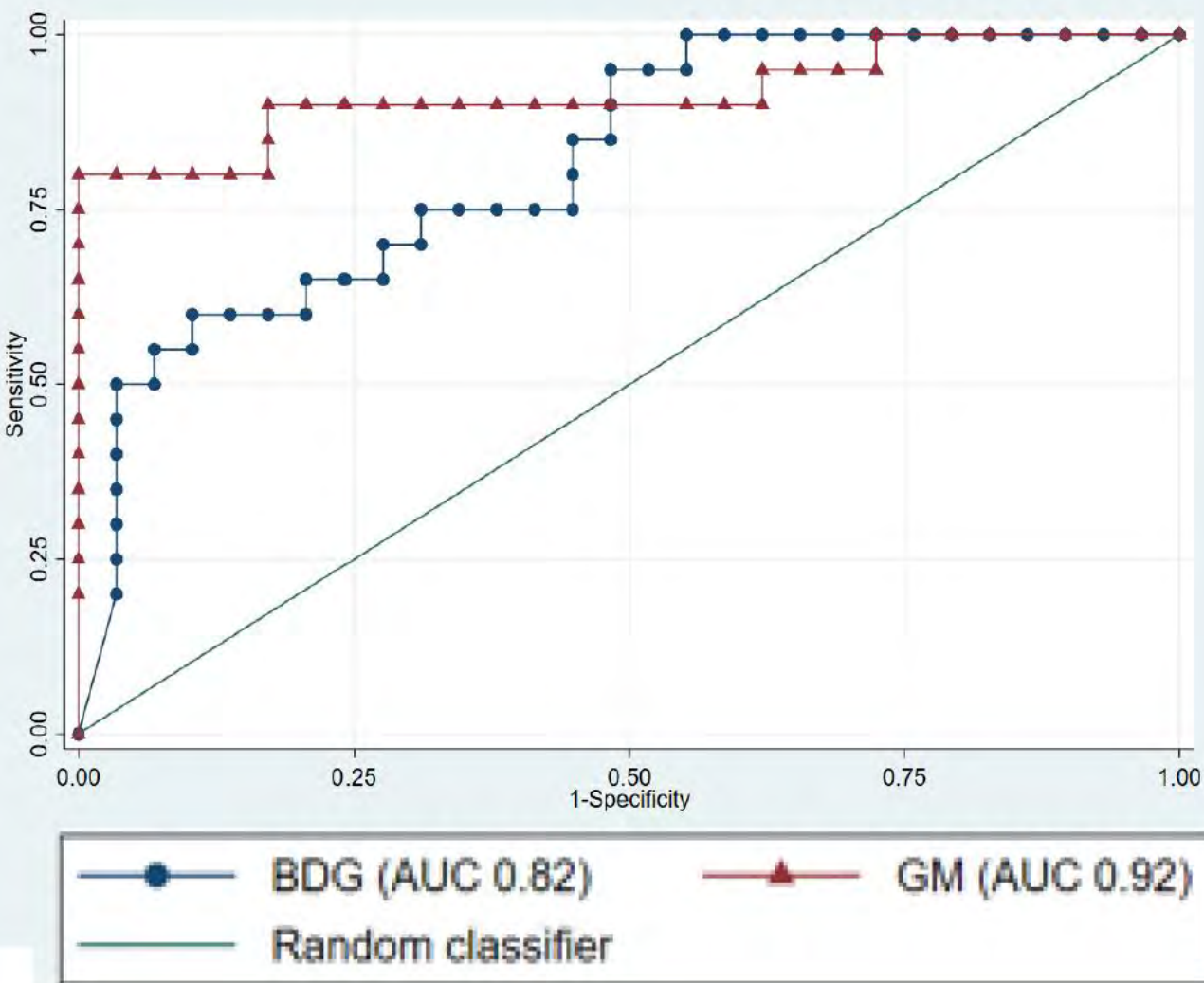
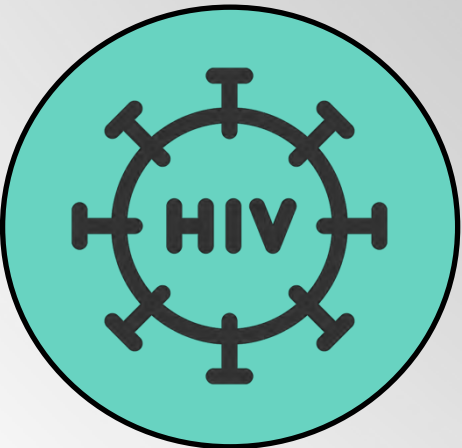
❖ 0.5

Se 77% (IC95%: 60-88)
Spe 100% (IC95%: 86-100)

❖ 0.4

Se 82% (IC95%: 66-92)
Spe 100% (IC95%: 86-100)

X. Iriart et al, Int J Med Microbiol 2014



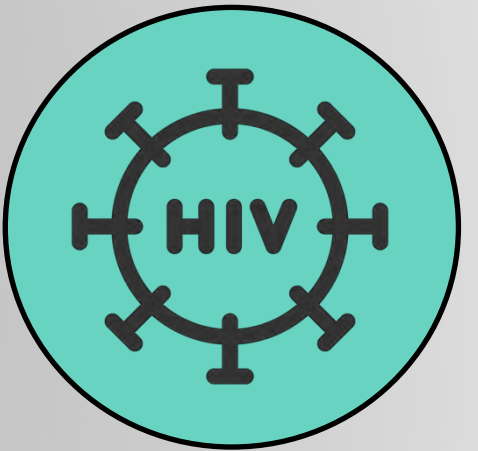
	BDG (150 pg/mL)	GM (0.5)
Sensitivity	95% [85-100]	90% [77-100]
Specificity	52% [34-70]	83% [69-97]
Positive LR	2 [1.4-3.0]	5.3 [2.4-12.0]
Negative LR	0.1 [0.01-0.7]	0.12 [0.03-0.45]

Optimal thresholds :

	BDG (288 pg/mL)	GM (1.29)
Sensitivity	60%	80%
Specificity	89.7%	100%
Positive LR	5.8	-
Negative LR	0.45	0.2
Exactitude	77.6%	92%

A. Moussiegt et al, Int J Inf Dis 2025

Tests antigéniques « classiques » : β -D-glucane & GM



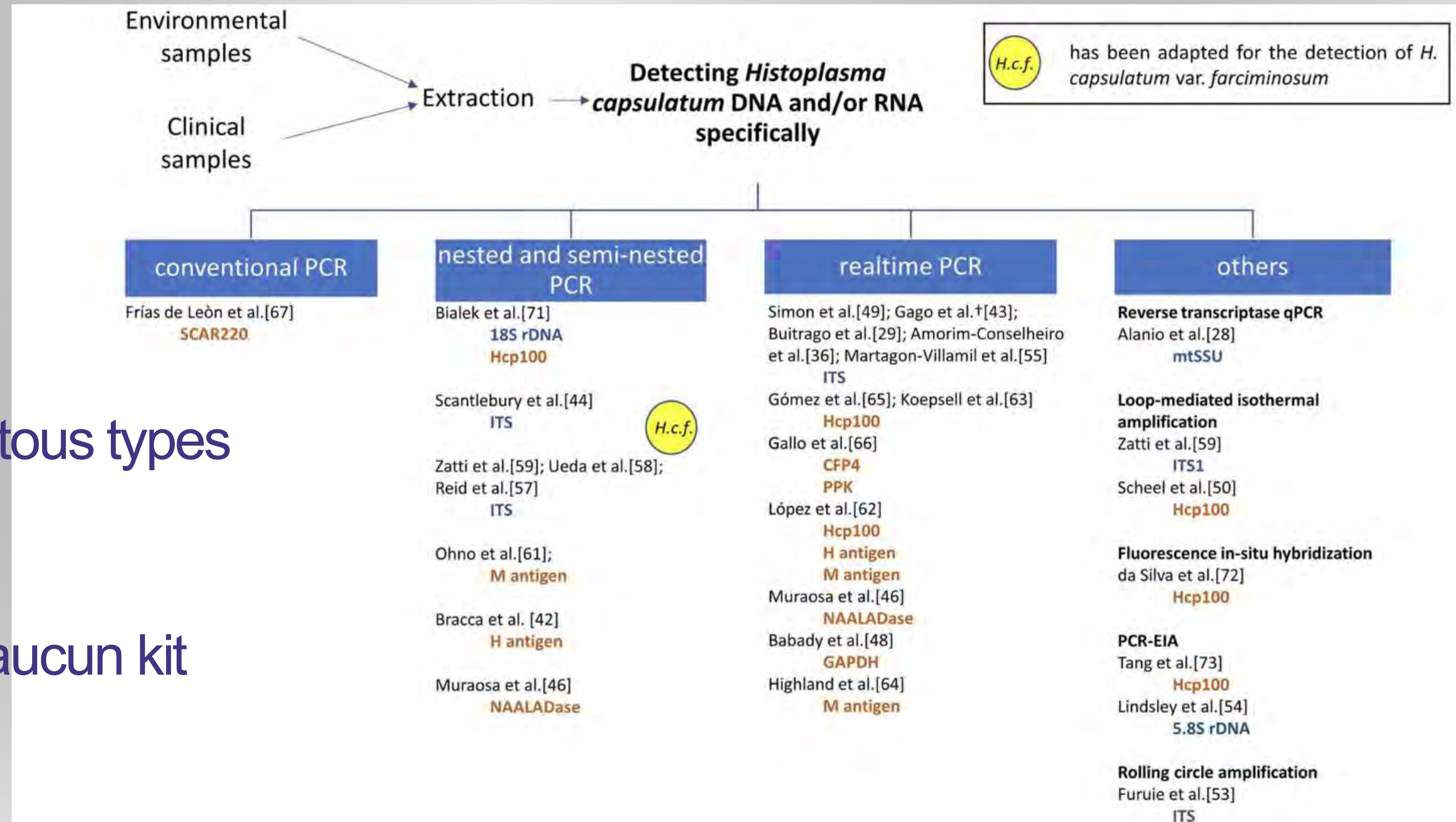
❖ En pratique :

- ❖ β -D-glucane **indéetectable** = pas d'histoplasmosse disséminée ?
- ❖ β -D-glucane augmenté + CTMX = **penser** à l'histoplasmosse
- ❖ GM sérique $<0,5$ = **n'élimine pas** le diagnostic
- ❖ GM sérique $\geq 0,5$ = savoir **évoquer** l'histoplasmosse si terrain compatible

PCR *Histoplasma*

❖ Réalisable sur tous types d'échantillons

❖ PCR-maison, aucun kit commercialisé



PCR *Histoplasma*

❖ RT-qPCR prometteuse { Se 97,7%
Spe 99%

A. Alanio et al. *J Mol Diagn* 2021

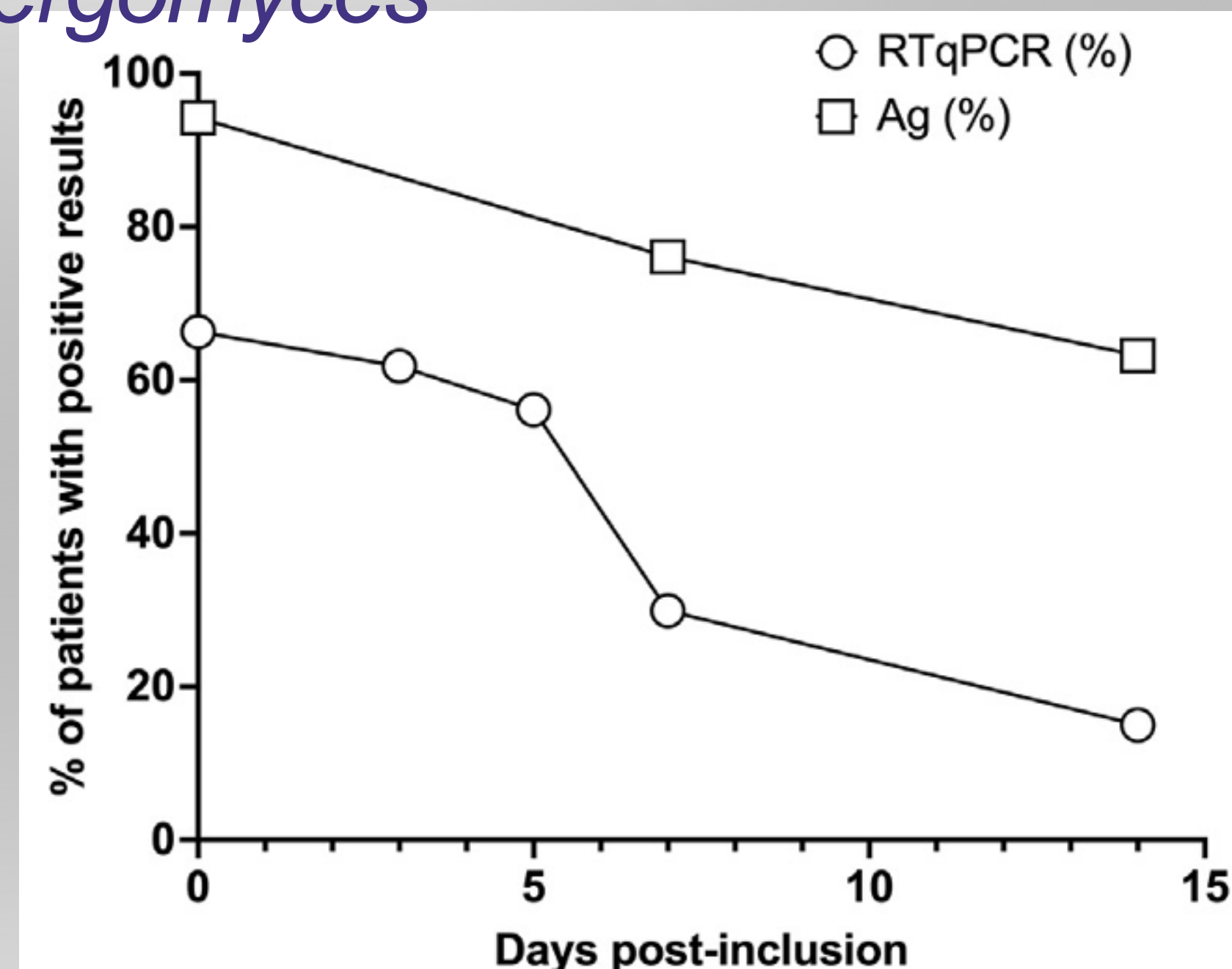
❖ Validation externe multicentrique :

D. Wilmes et al. *Mycoses* 2023

❖ faux positifs *Blastomyces* et *Emergomyces*

❖ Intérêt pour le suivi

A. Sturny-Leclère et al. *Clin Microbiol Infect* 2025



Diagnostic de l'histoplasmosse disséminée

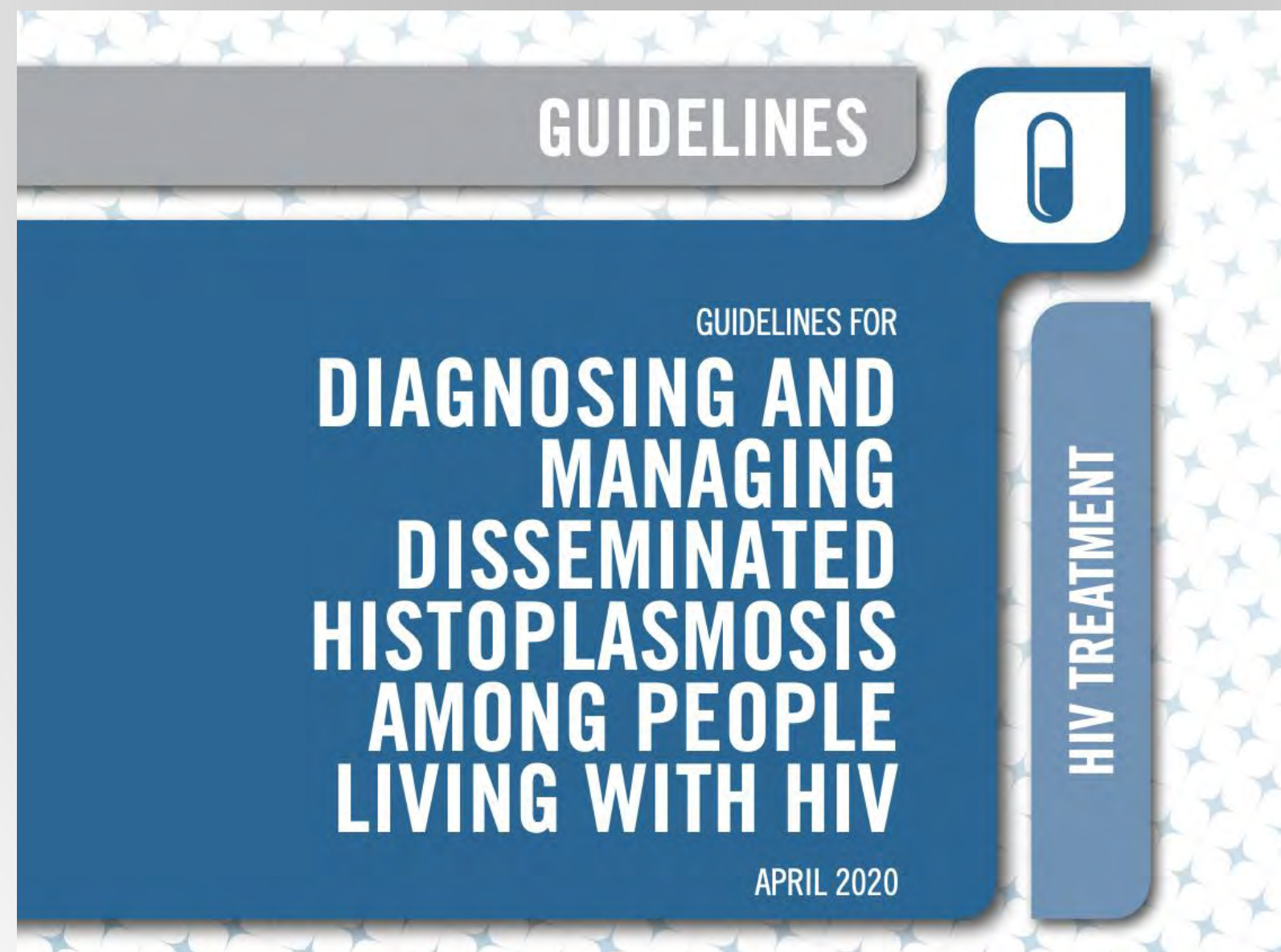
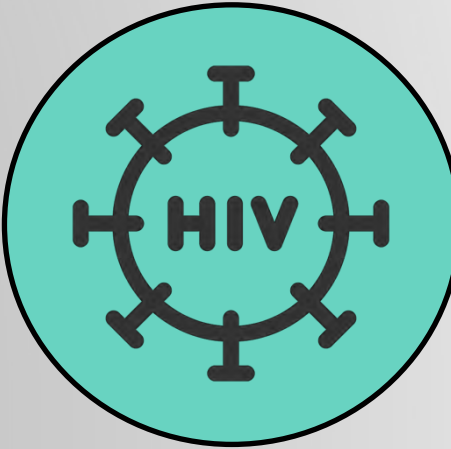
	Prouvée			Probable	Hors recos
	Examen direct	Histologie	Culture	Antigène <i>Histoplasma</i>	(RT-q)PCR
Rapide					
Peu coûteuse					
Non invasive					
Sûre					
Reproductible					
Sensible					
Spécifique					

Partie II

Traitement et pronostic

Traitement de l'histoplasmosse disséminée

❖ Recommandations mondiales — européennes — françaises



PAHO-WHO Guidelines 2020



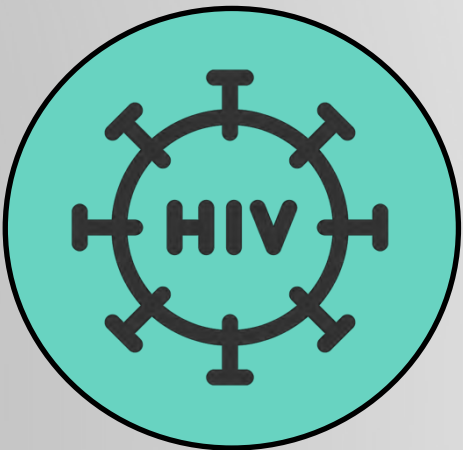
EACS 13.0 2025



Rapport d'experts CNS 2024

Traitement de l'histoplasmosse disséminée

❖ Résumé des recommandations



	Attaque	Entretien	Grade
Non grave	Itraconazole 12 mois (3-6 mois)		A-B
Grave	L-AmB 3mg/kg 1-2 semaines	Itraconazole 12 mois (3-6 mois)	A-B
Neuroméningée	L-AmB 5 mg/kg 4-6 semaines	Itraconazole > 12 mois	C

Dosage Itraconazole : Taux résiduel > 1 mg/L & < 3-4 mg/L

Traitement de l'histoplasmosse disséminée

❖ Recommandations autres immunodéprimés

Table 2. Categories of Immunocompromise and Risk for Disseminated/Severe Histoplasmosis
Categories of immunocompromise represent a continuum rather than distinct categories. Conditions are categorized here as a guide; given limited evidence, this table is not exhaustive or exact.

High	Moderate	Low ^a
Receiving corticosteroids: [11] ≥2 mg/kg/d of prednisone (or equivalent) for persons ≤10 kg or ≥20 mg/d of prednisone (or equivalent) for persons >10 kg for at least 2 wks	Receiving corticosteroids: [11] 0.5–2 mg/kg/d of prednisone (or equivalent) for persons <10 kg or 5–20 mg/d of prednisone (or equivalent) for persons >10 kg for at least 4 wks	Receiving corticosteroids: [11] <0.5 mg/kg/d of prednisone (or equivalent) for persons <10 kg or ≤5 mg/d of prednisone (or equivalent) for persons >10 kg for at least 4 wks
Primary cellular immunodeficiency (eg, SCID, autosomal dominant hyperIgE syndrome [AD HIES], interferon-gamma receptor/IL-12 pathway defects)	Primary immunodeficiency (eg, common variable immunodeficiency, Nuclear factor-kappaB Essential Modulator [NEMO] deficiency, chronic mucocutaneous candidiasis, X-linked hyper IgM syndrome, autosomal recessive HIES)	
Advanced or untreated HIV/AIDS (CD4 <200 cells/mm ³) ^b [8]	HIV (CD4 200–300 cells/mm ³) [8, 12–21]	HIV (CD4 ≥300 cells/mm ³); VL undetectable [8]
Hematopoietic stem cell transplant within 100 d or receiving immunosuppressive therapy for graft versus host disease	Hematopoietic stem cell transplant >100 d prior and no evidence of graft versus host disease	
	Hematologic malignancy	
Chimeric antigen receptor (CAR) T-cell therapy within 90 d [22]	CAR T-cell therapy >90 d and resolved cytopenias [22]	
Solid organ transplant and treatment of rejection ^c	Solid organ transplant recipient on maintenance immunosuppressive regimen ^c	
Autoimmune and rheumatic diseases requiring treatment with biologic agents ^d , especially those that interfere with T-cell function and granuloma formation [18, 23–28]		Autoimmune and rheumatic diseases not requiring treatment
		General medical frailty, including but not limited to: Liver, kidney, lung disease, diabetes, malnutrition

Abbreviations: HIV, human immunodeficiency virus; IgE, immunoglobulin E; IL, interleukin; NF, nuclear factor; SCID, severe combined immunodeficiency; VL, viral load.
^aThe following conditions confer no known increased risk: sickle cell disease and other asplenia syndromes; antibody, complement, or neutrophil deficiencies.
^bSevere immunocompromise in children ≤5 y of age is defined as CD4+ T lymphocyte [CD4+] percentage <15%, and in individuals ≥6 y, CD4+ percentage <15% and CD4+ >200 lymphocytes/mm³ [11].
^cCarefully consider drug-drug interactions (eg, tacrolimus for graft-vs-host disease prophylaxis).
^dThere are a variety of biologic agents with varying levels of immunosuppression. Serious infections have happened in patients receiving biologic response modifiers, including tuberculosis and disseminated infections caused by viruses, fungi, or bacteria. Frequently reported biologics associated with disseminated/severe histoplasmosis include: Tumor necrosis factor-alpha inhibitors (TNF-alpha inhibitors [eg, infliximab, etanercept, adalimumab]); IL-12/IL-23 blockade (ustekinumab, risankizumab, guselkumab).

2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on Histoplasmosis: Treatment of Mild or Moderate Acute Pulmonary Histoplasmosis in Adults, Children, and Pregnant People

Peter Pappas,^{1,2} Robert J. Lentz,^{2,4} Kayla R. Stover,^{3,5} Nathan P. Wiederhold,^{4,6} Monica I. Ardura,^{5,6} John W. Baddley,⁷ Nevert Badreldin,⁸ Nathan C. Bahr,^{9,10} Karen Bloch,¹¹ Carol A. Kauffman,¹² Rachel A. Miller,¹³ Satish Mocherla,¹⁴ Michael Saccoccia,¹⁵ Ilan Schwartz,¹² Joshua Wolf,^{16,17} Jennifer Loveless,^{17,18} Andrej Spec,^{16,19} and Sandra R. Arnold^{14,20,19}

- ❖ Histoplasmosse pulmonaire aiguë
- ❖ Stratification du risque de dissémination

Risque de dissémination	Élevé	Modéré	Faible
Nodule asymptomatique	Discuter itraconazole		Pas de traitement
Histoplasmosse pulmonaire aiguë non grave	Itraconazole		Pas de traitement
Histoplasmosse pulmonaire aiguë grave	Itraconazole		

Évaluation de la gravité

❖ **Grave**



❖ **L-AmB**

❖ **Non grave**



❖ **Itraconazole**

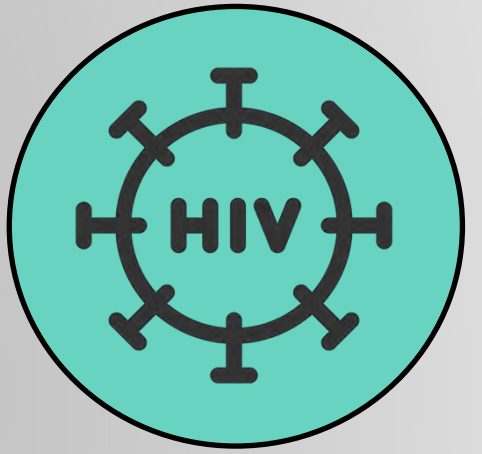
Options
thérapeutiques

« Facile »

L'histoplasmose disséminée grave

❖ Gravité « évidente »

❖ Atteinte neuroméningée



« may require extending induction therapy or increasing dosage »

« ART as soon as possible CNS involvement is not suspected or proven »

« The efficacy and duration of the required maintenance therapy is less clear »

PAHO-WHO Guidelines 2020



❖ Syndrome d'activation lymphohistiocytaire

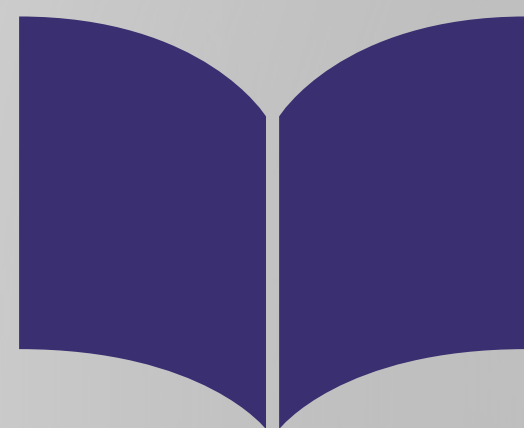
❖ Histoplasmose = 1° cause chez le PVVIH

Duc Nguyen et al., *Front. Cell. Infect. Microbio* 2020

❖ **L-AmB**

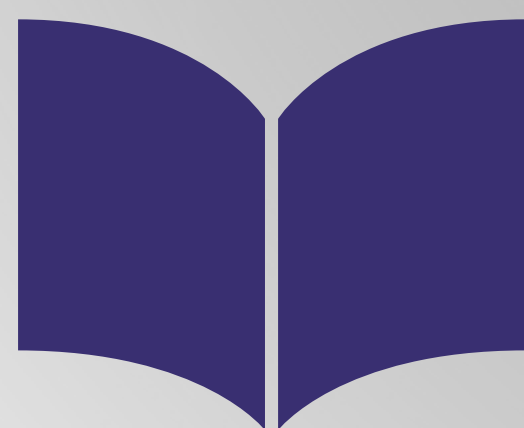


Évaluation de la gravité



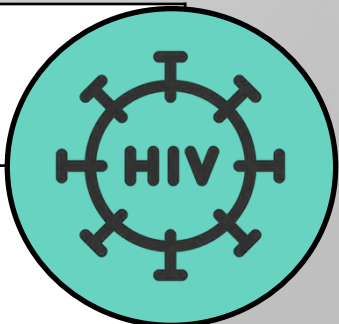
CDC-NIH-HIVMA-IDSA

C. Benson et al, *MMWR Recomm Rep* 2004



PAHO-WHO
2020

Grave	
• Fièvre >39°C • PAS <90 mmHg • PO2 <70 mmHg • Amaigrissement >5% • Karnofsky <70 • Albumine < 35g/L • Coagulopathie • Hb <10g/dL	• PNN <1G/L • Plaquettes <100 G/L • ASAT >2,5 N • Bilirubinémie >2 N • Créatininémie >2N • Autre défaillance d'organe • Méningite
Modérément grave/grave	
• Insuffisance respiratoire ou circulatoire • Signes neurologiques • Défaillance rénale • Anomalies de la coagulation • Performance status OMS >2	
Légère / Modérée	
Aucun signe précédent	



❖ Peu pratiques

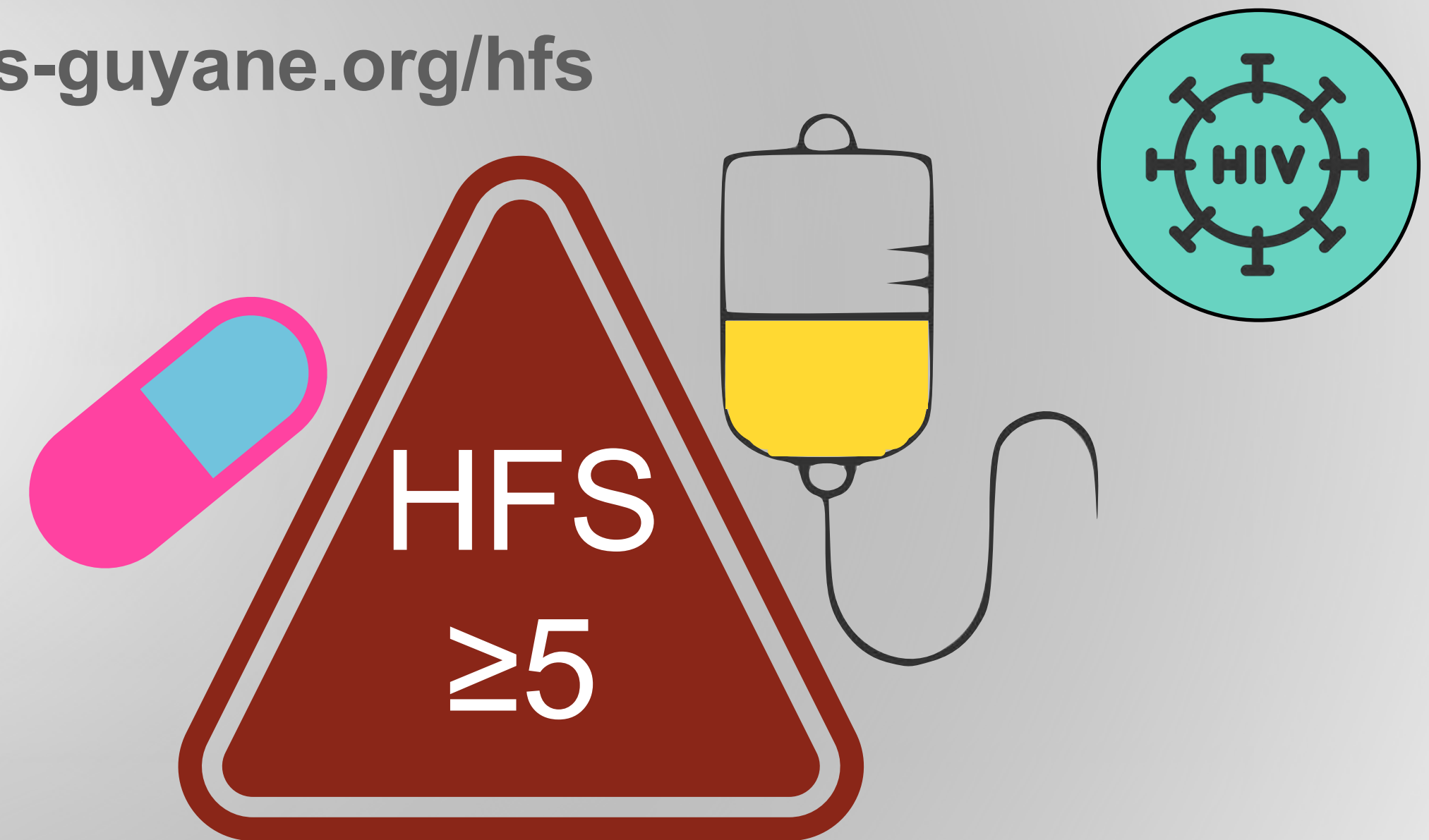
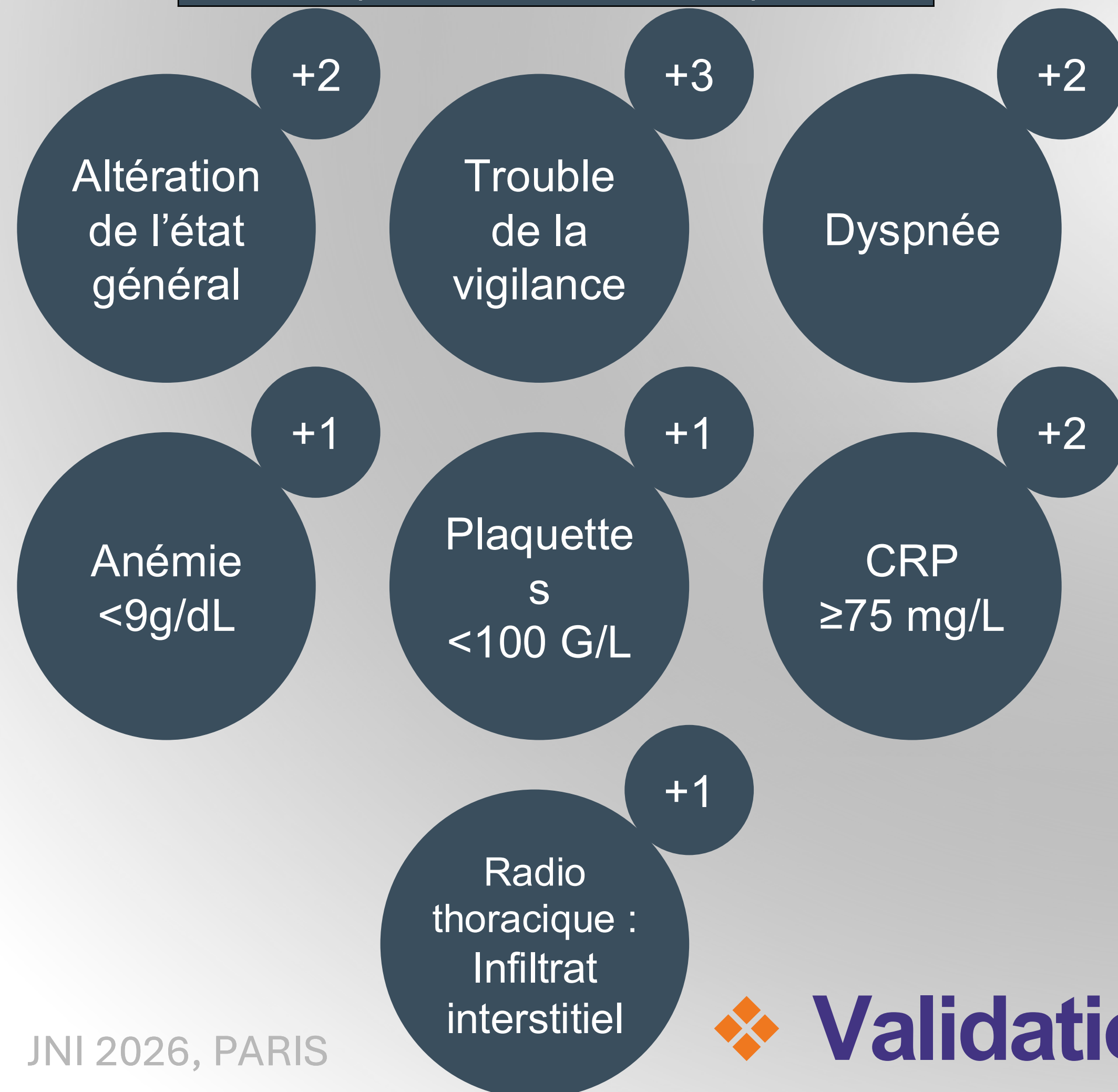
❖ Pas validées

❖ Peu reproductibles

Histoplasmosis case-Fatality Score

AUC 0,91
(IC95% : 0,88-0,94)

<https://cicec-antilles-guyane.org/hfs>



Se 84% (95%CI: 73-93)

Spe 81% (95%CI: 76-84)

PPV 40% (95%CI: 33-49)

NPV 97% (95%CI: 95-99)

U. Françoise et al. *Int J Inf Dis* 2023

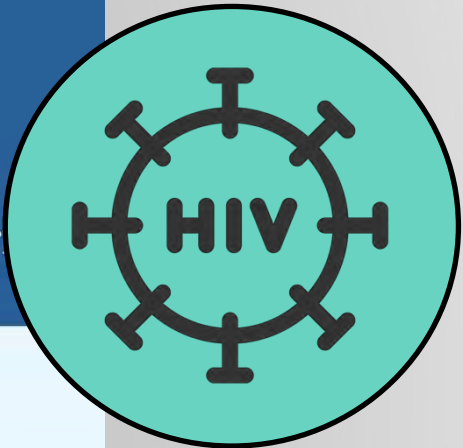


Validation externe en cours

Monodose d'Amphotéricine B Liposomale

Single High-dose of Liposomal Amphotericin B in HIV/AIDS-related Disseminated Histoplasmosis: a Randomized Trial

Pasqualotto et al., 2023 | *Clinical Infectious Diseases*



Liposomal amphotericin is the drug of choice for disseminated histoplasmosis, but access is limited due to the high costs of the conventional long regimens.

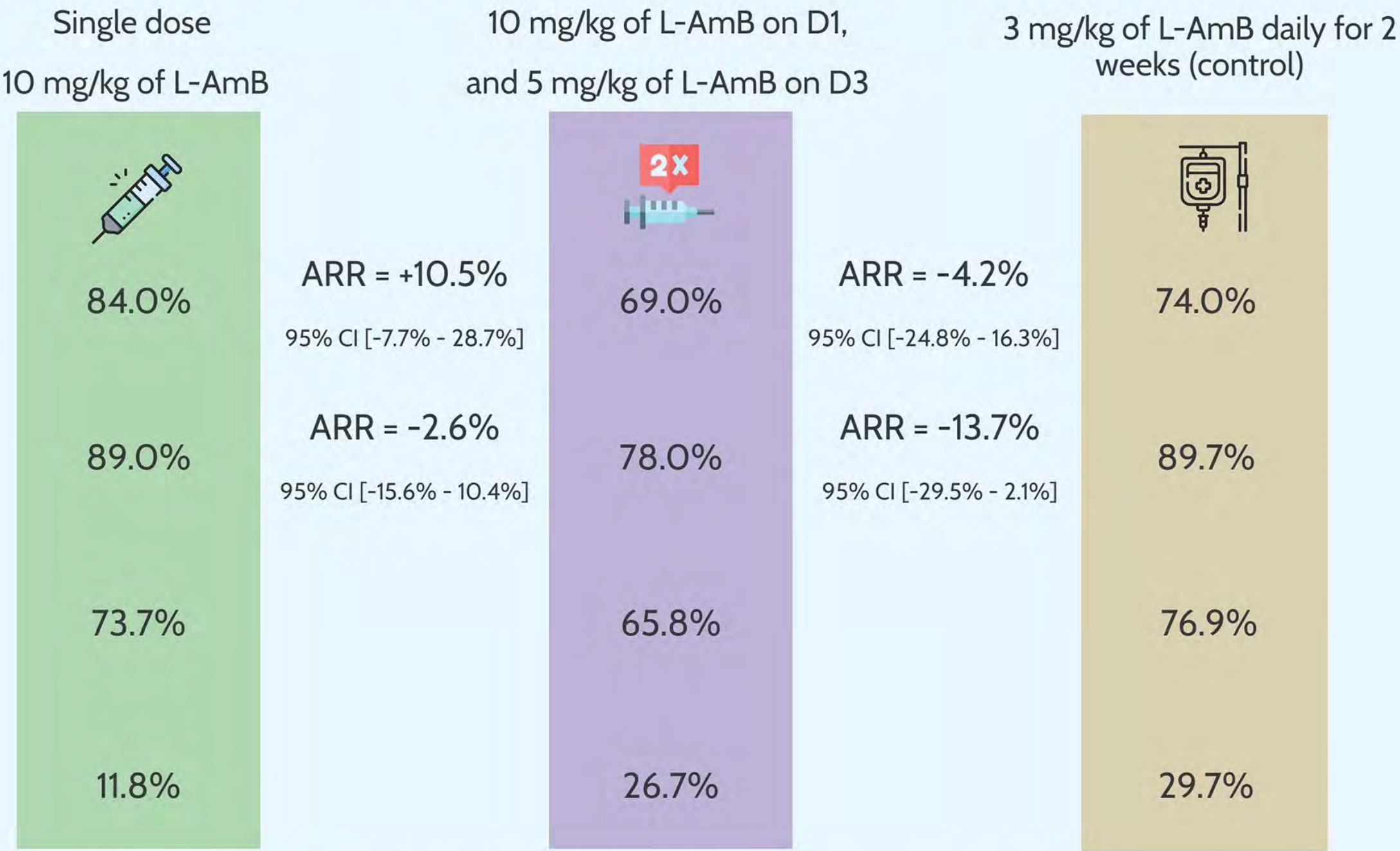


PARTICIPANTS: Adult people living with HIV, hospitalized and diagnosed with disseminated histoplasmosis, in six Brazilian tertiary medical centers.

METHODS

Prospective randomized multicenter open-label trial. Interventions: One or two-dose induction L-AmB therapy versus control (three arms), all followed by oral itraconazole therapy.

-  Clinical response at day 14
-  Overall survival at day 14
-  1-year overall survival
-  Nephrotoxicity at day 14 (any AKI criteria)



One day induction therapy with 10 mg/kg of L-AmB in AIDS-related histoplasmosis was safe. A phase III clinical trial is needed to confirm clinical response. A single-dose regimen would markedly reduce drug-acquisition costs and shorten and simplify treatment, which are key points in terms of increased access.

Importance de la restauration immunitaire

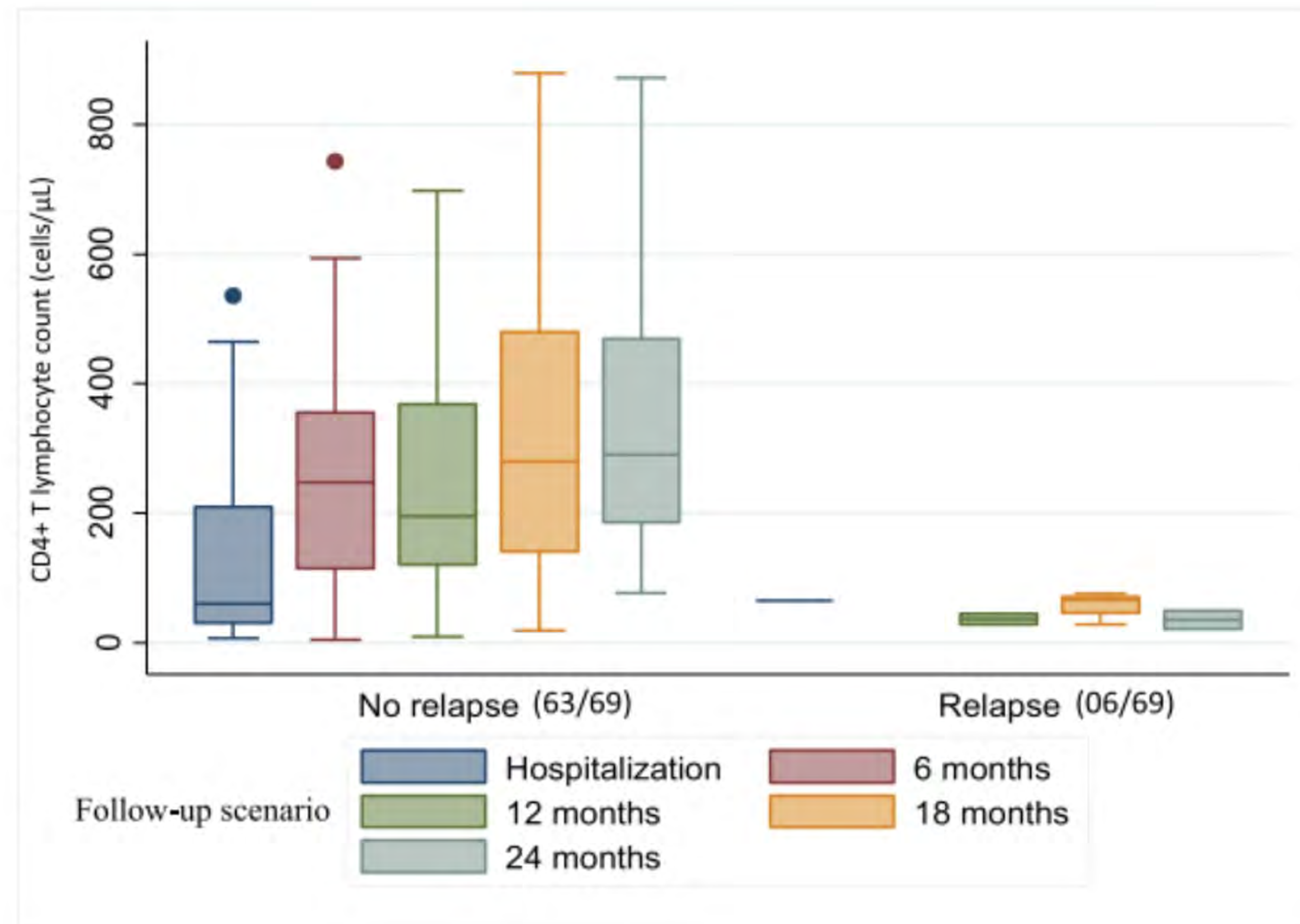
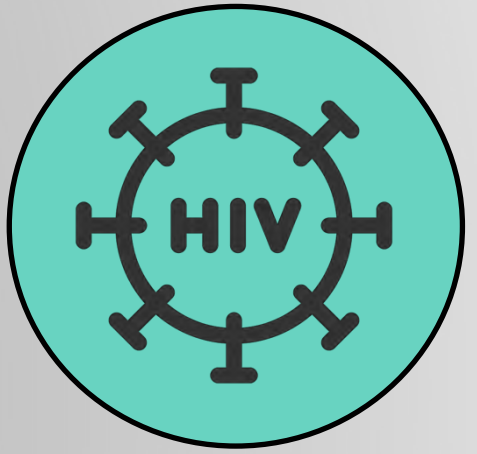


Fig. 2. Immune recovery versus fungal relapse in patients with disseminated histoplasmosis/AIDS coinfection followed up at the São José Hospital outpatient clinic during antifungal consolidation therapy, 2010–2015, Fortaleza/Ceará, Brazil.

Avancées diagnostiques et pronostiques de l'histoplasmosse disséminée

Les clés diagnostiques Les clés thérapeutiques

- Y penser
- Bien prélever / Tout prélever
- Sensibiliser les biologistes
- Demander l'Ag *Histoplasma*

- Y penser
- Évaluer la gravité
- Traiter sans attendre
- Restaurer l'immunité

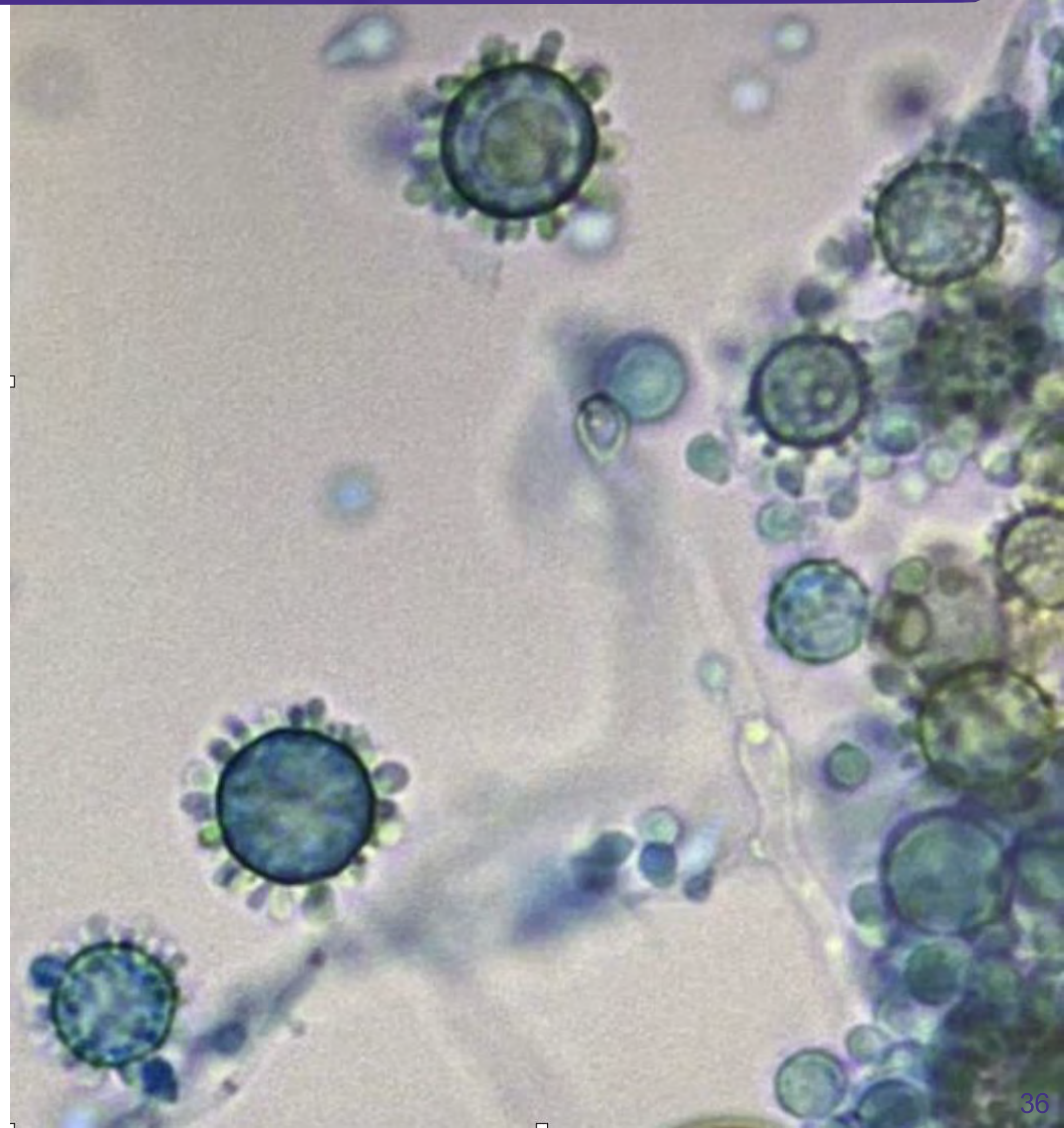


Merci pour votre attention

Session thématique Tropiques caraïbo-latino-
américaines : nouvelles menaces infectieuses

Ugo FRANÇOISE

MIT — Hôpital Saint-Antoine
APHP / Sorbonne Université



Méthodes diagnostiques conventionnelles

❖ Examen anatomopathologique



+ <7 jours ouvrés

+ Peu coûteux

- Prélèvements invasifs

- Qualité/quantité de prélèvement

- Colorations complexes/toxiques

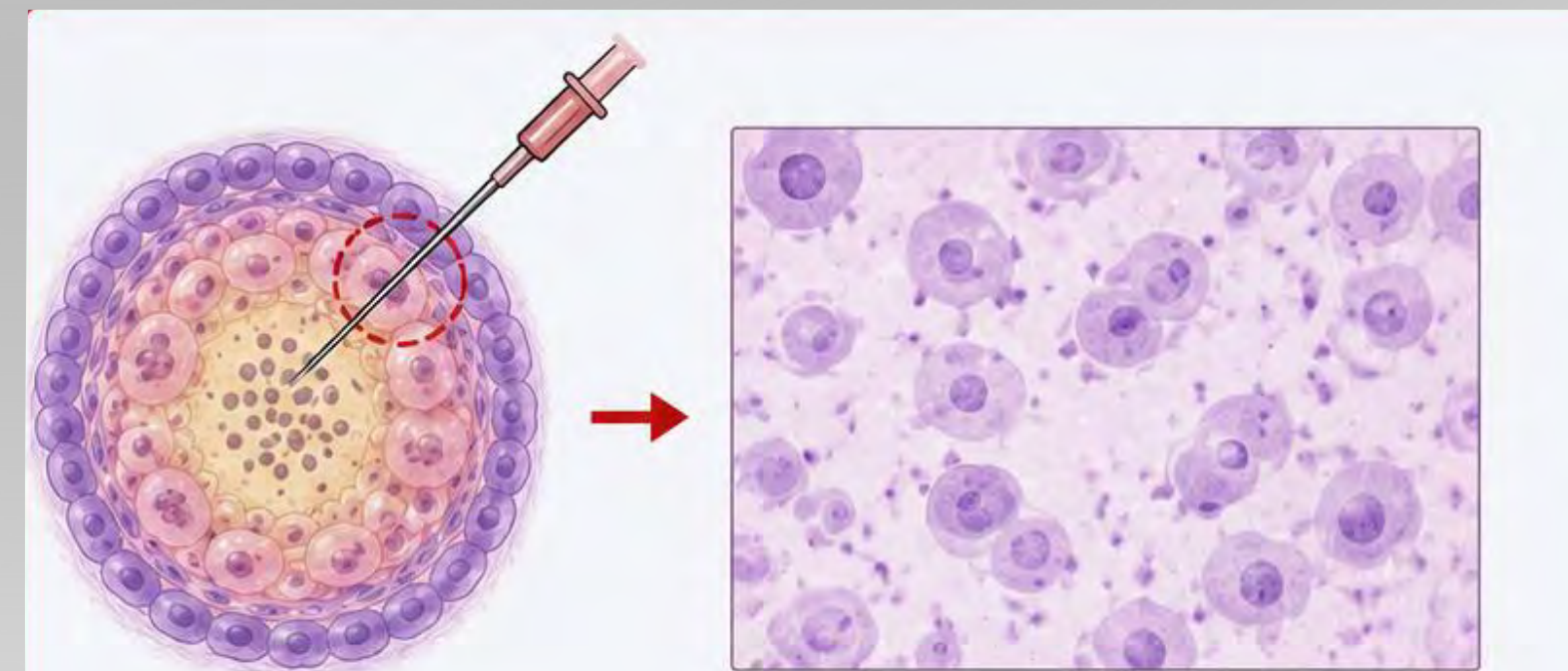
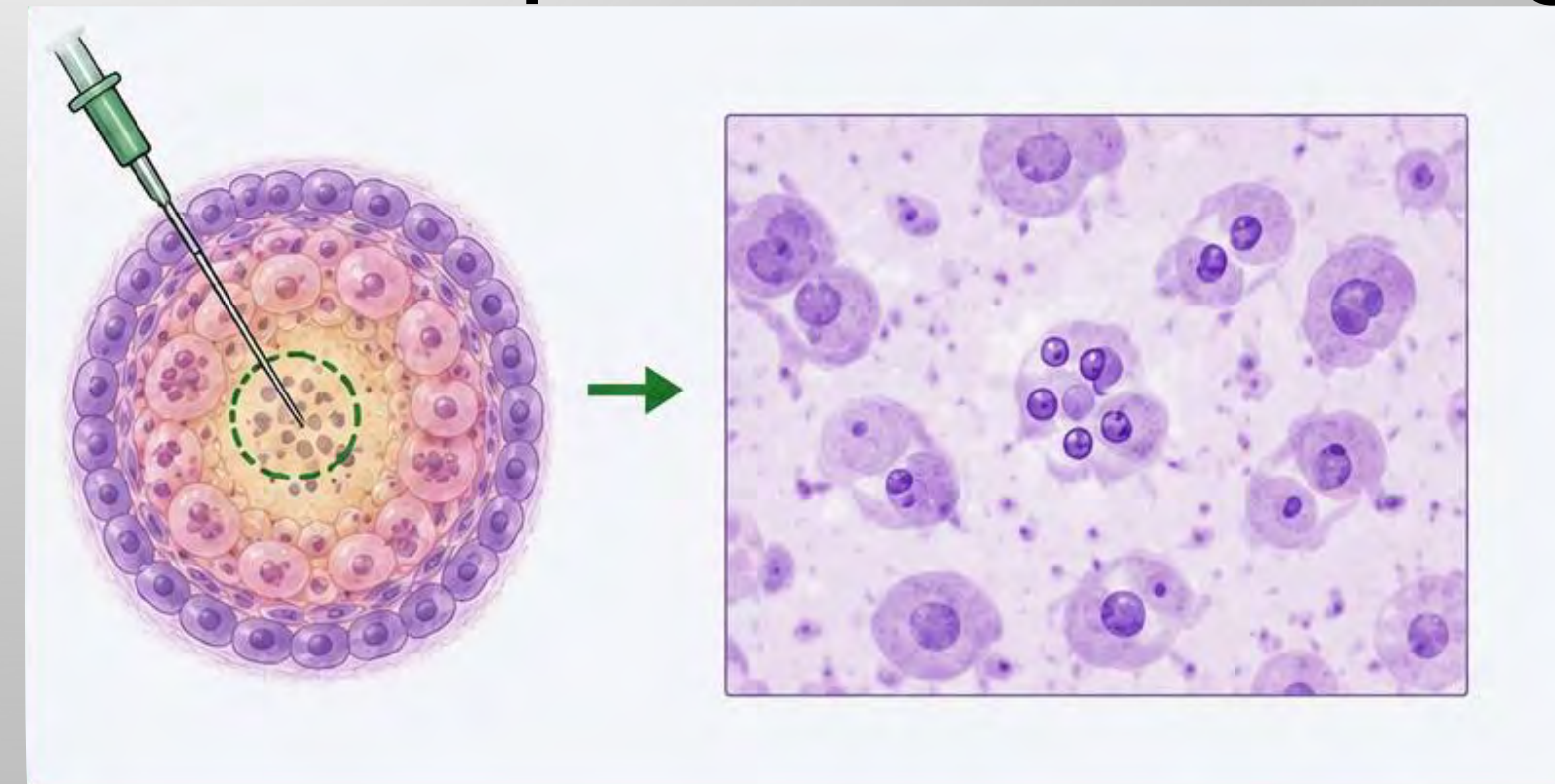
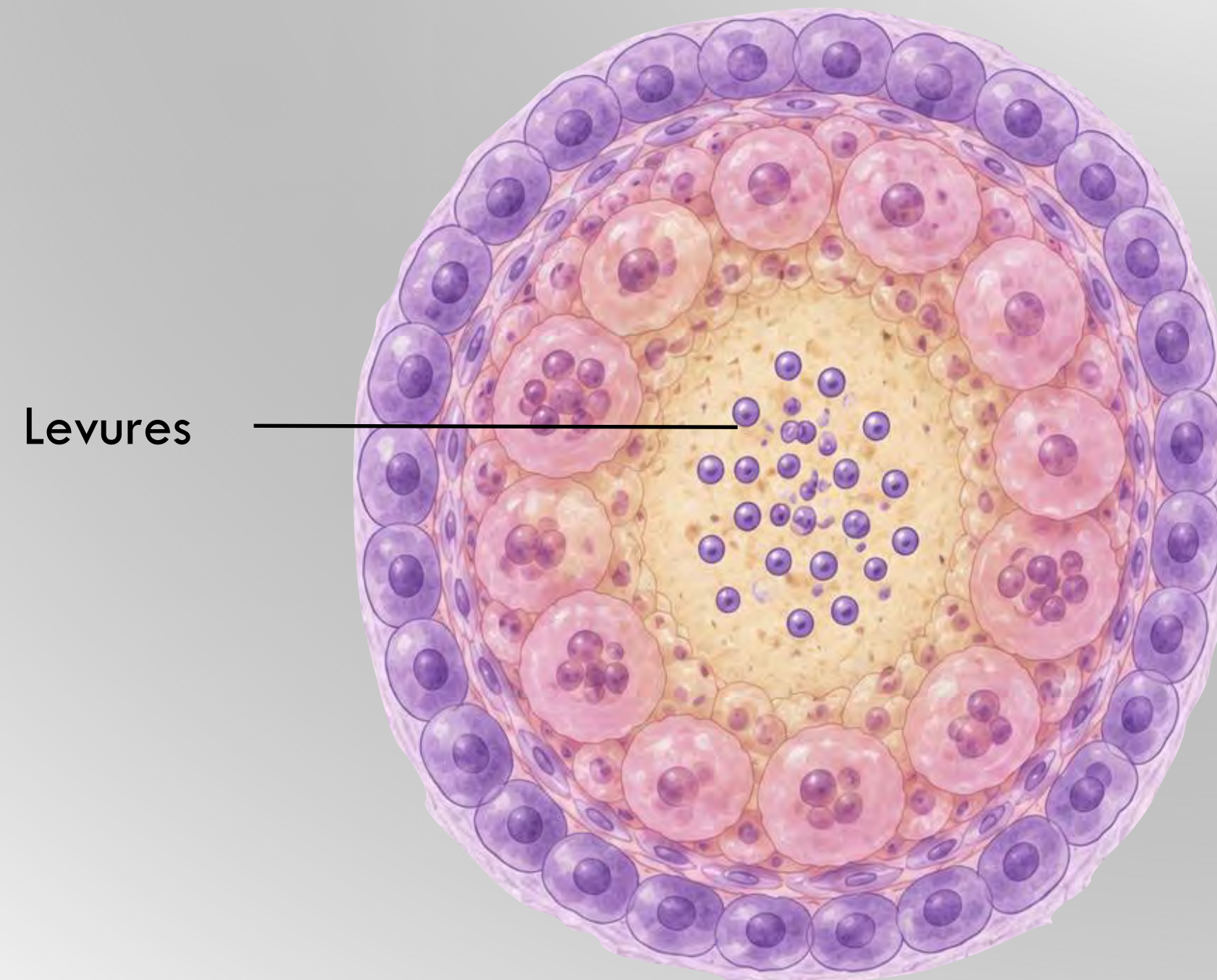
- Expérience du biologiste

Méthodes diagnostiques conventionnelles



❖ Examen direct mycologique

- + Rapide <24h (jours ouvrés)
- + Peu coûteux
- Prélèvements invasifs
- Qualité/quantité de prélèvement
- Expérience du biologiste



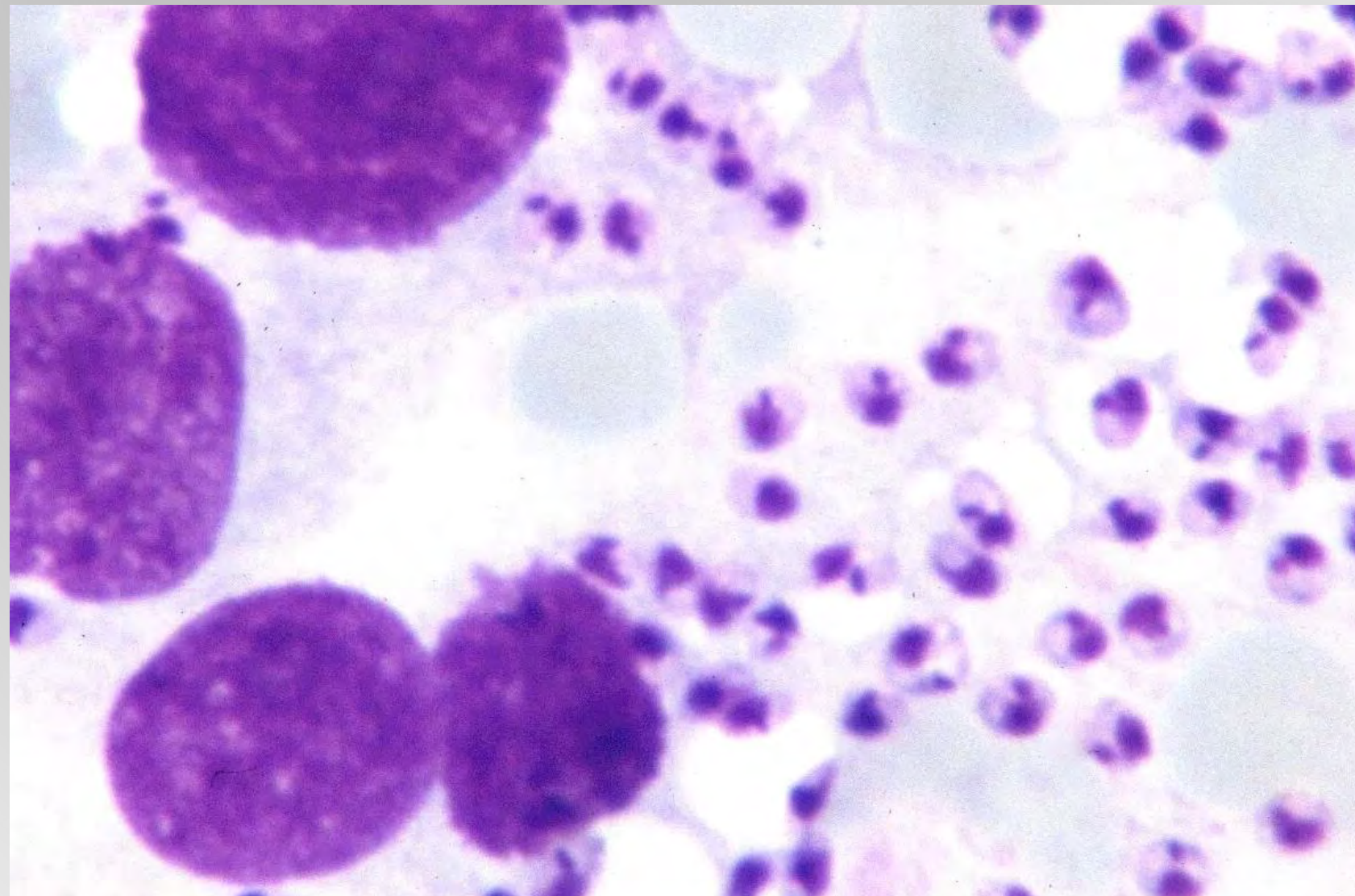
⚠ Faux négatifs

Méthodes diagnostiques conventionnelles

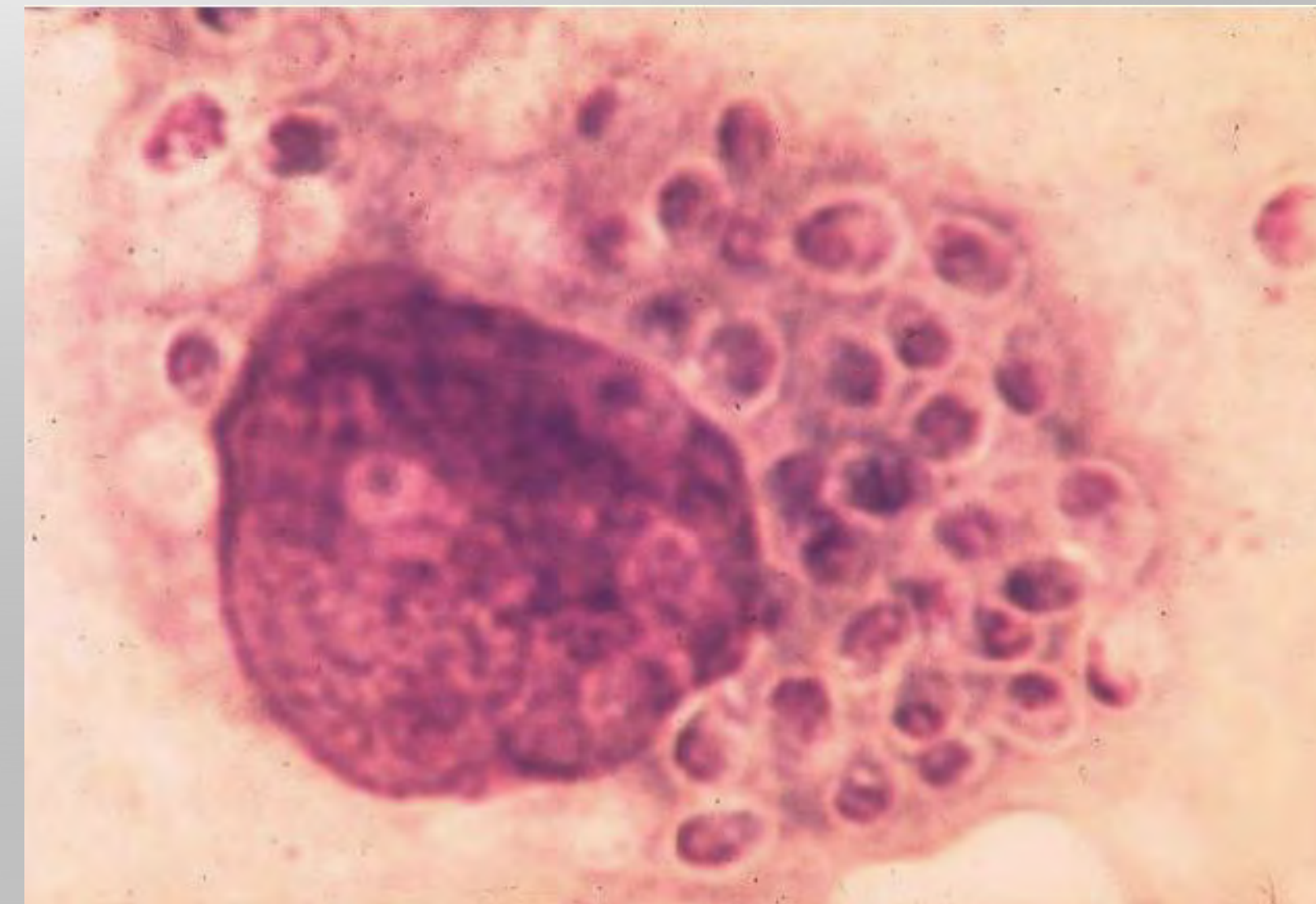


❖ Examen direct mycologique

- + Rapide <24h (jours ouvrés)
- + Peu coûteux
- Prélèvements invasifs
- Qualité/quantité de prélèvement
- Expérience du biologiste



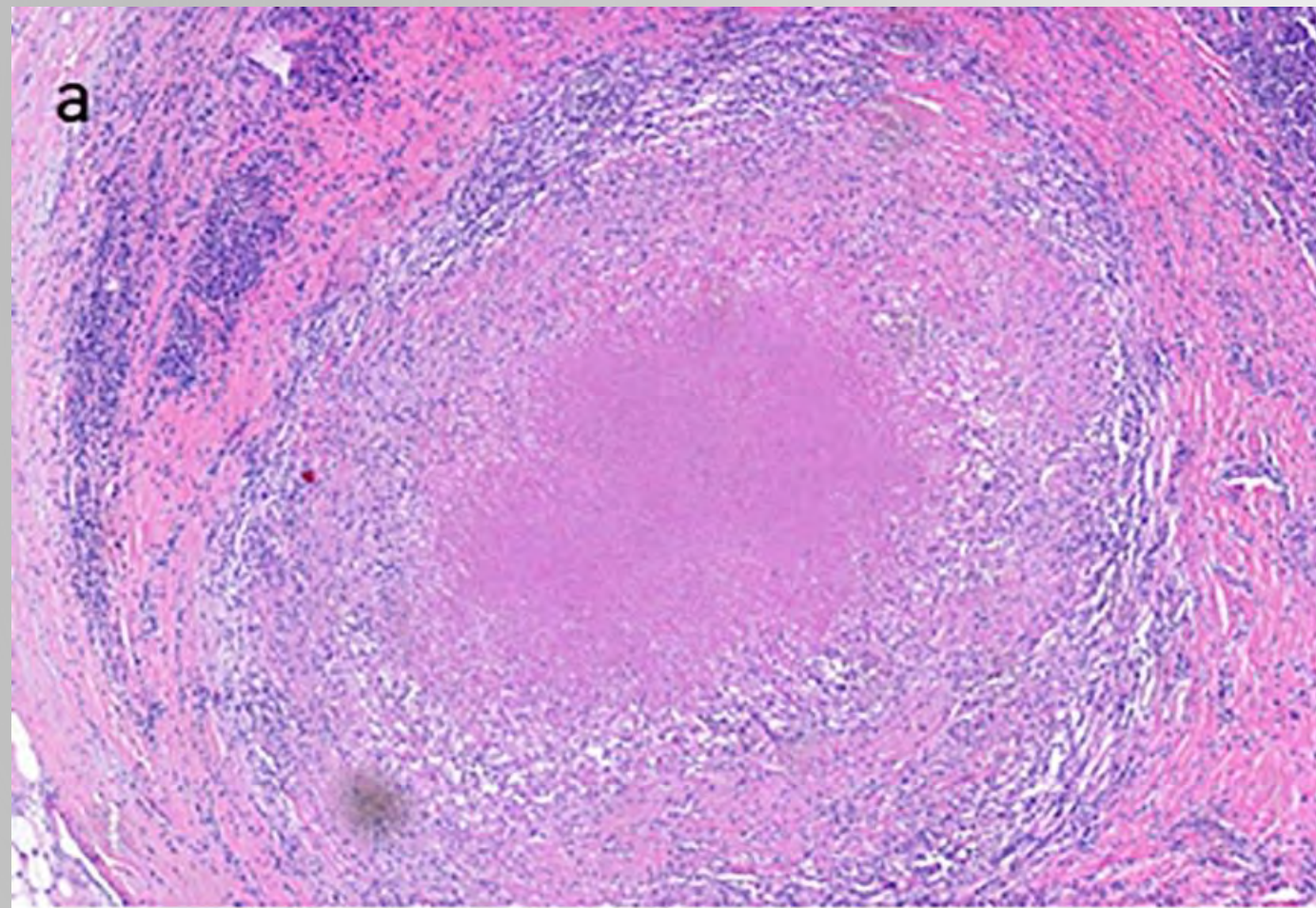
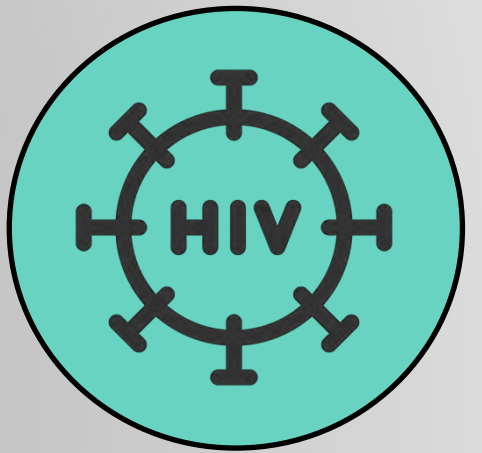
Leshmania



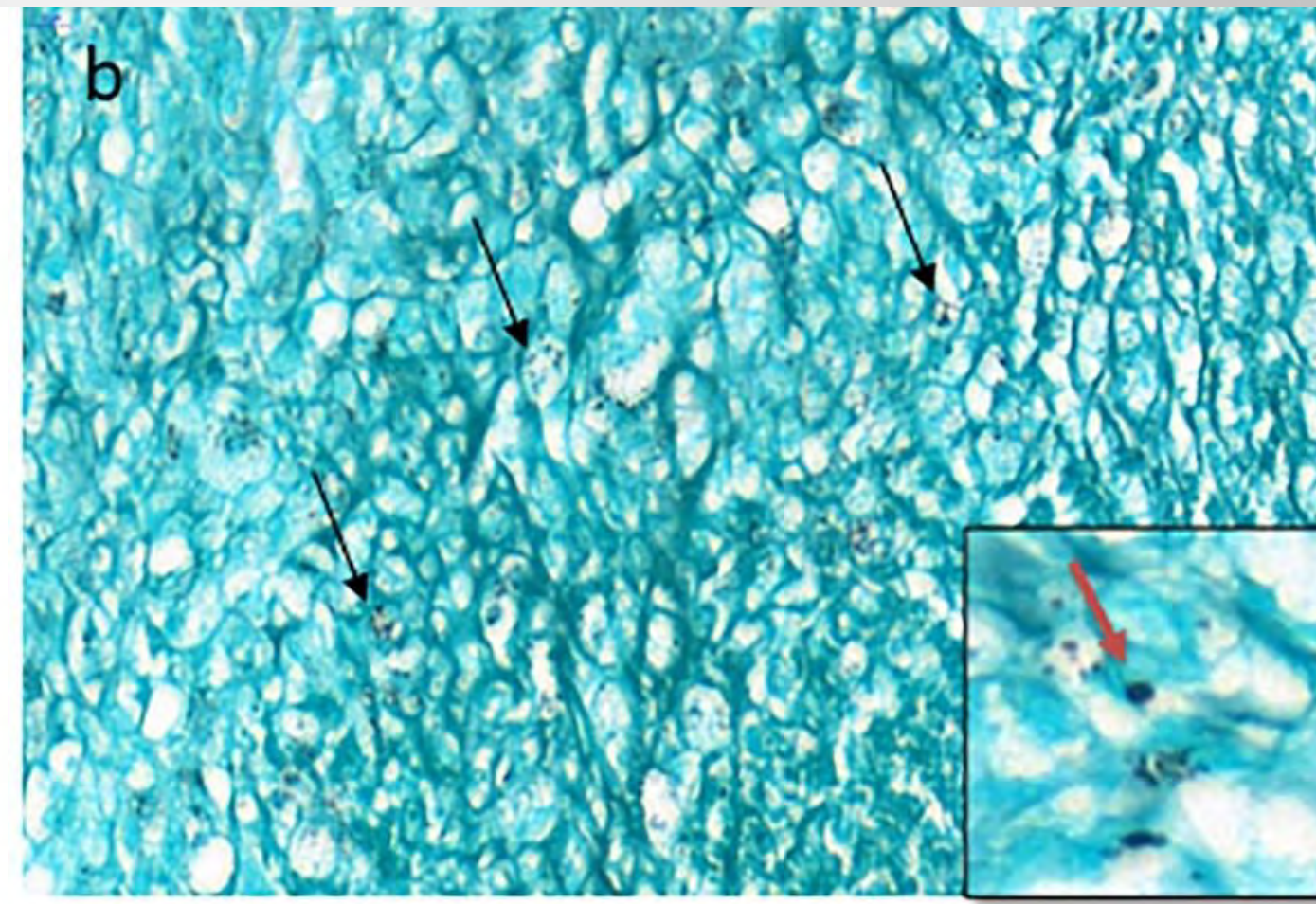
Histoplasma

Méthodes diagnostiques conventionnelles

❖ Examen anatomopathologique



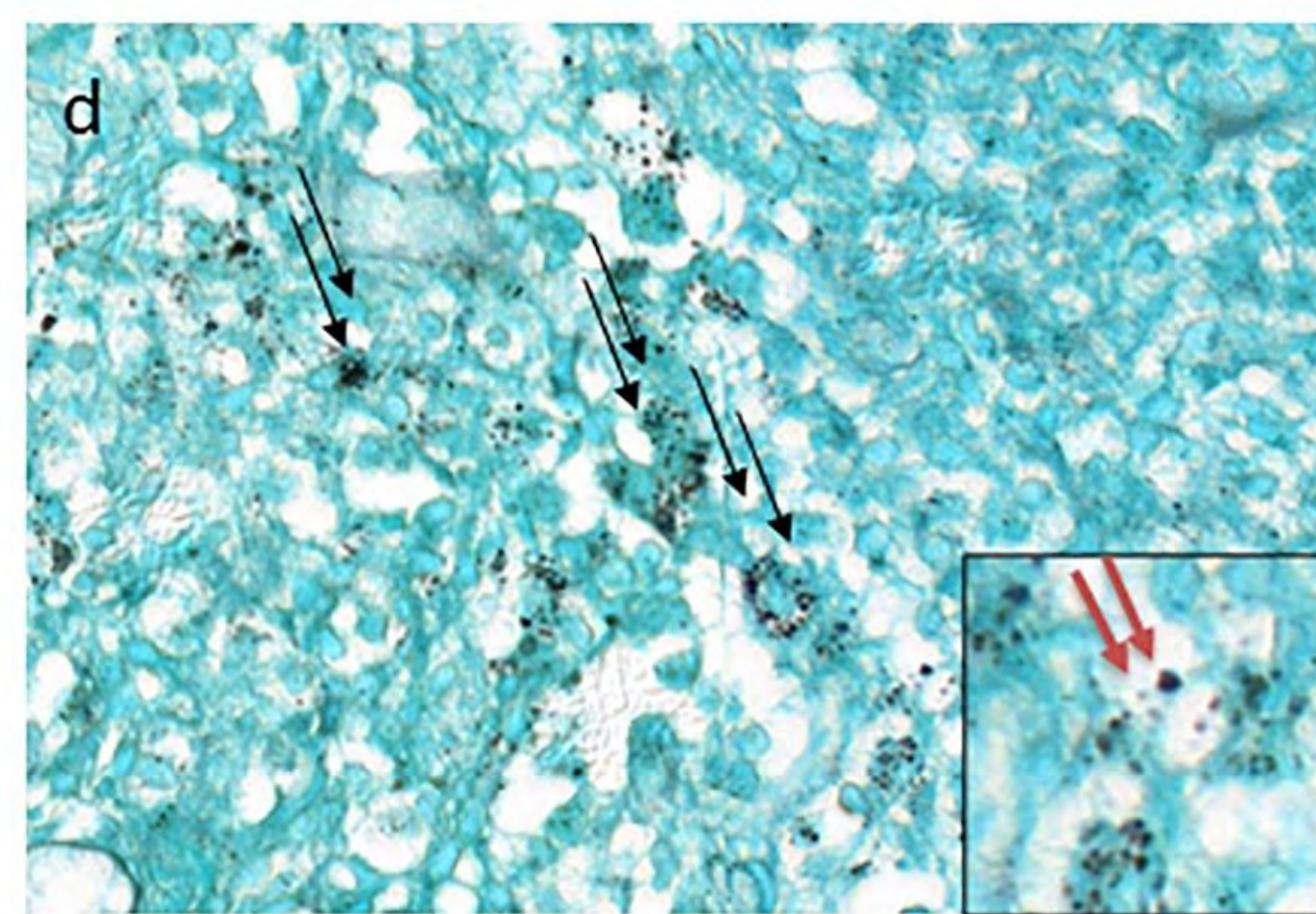
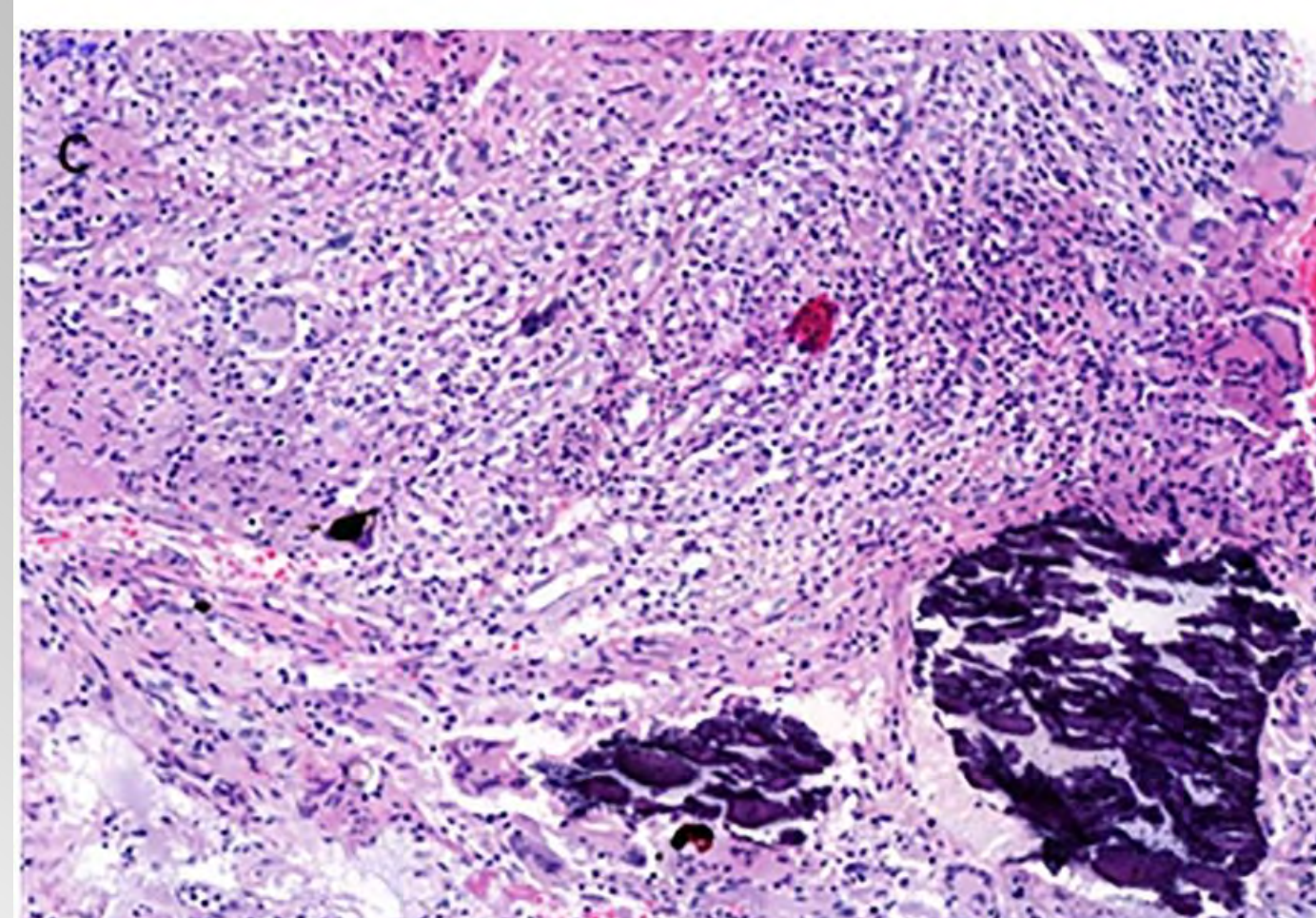
HES



Grocott

(a) Granulome ganglionnaire avec nécrose caséeuse

(b) Rares levures intracellulaires en périphérie



(c) Granulome bronchique non nécrotique

(d) Rares levures intracellulaires focales

Méthodes diagnostiques conventionnelles

❖ Culture mycologique

+ Plus sensible

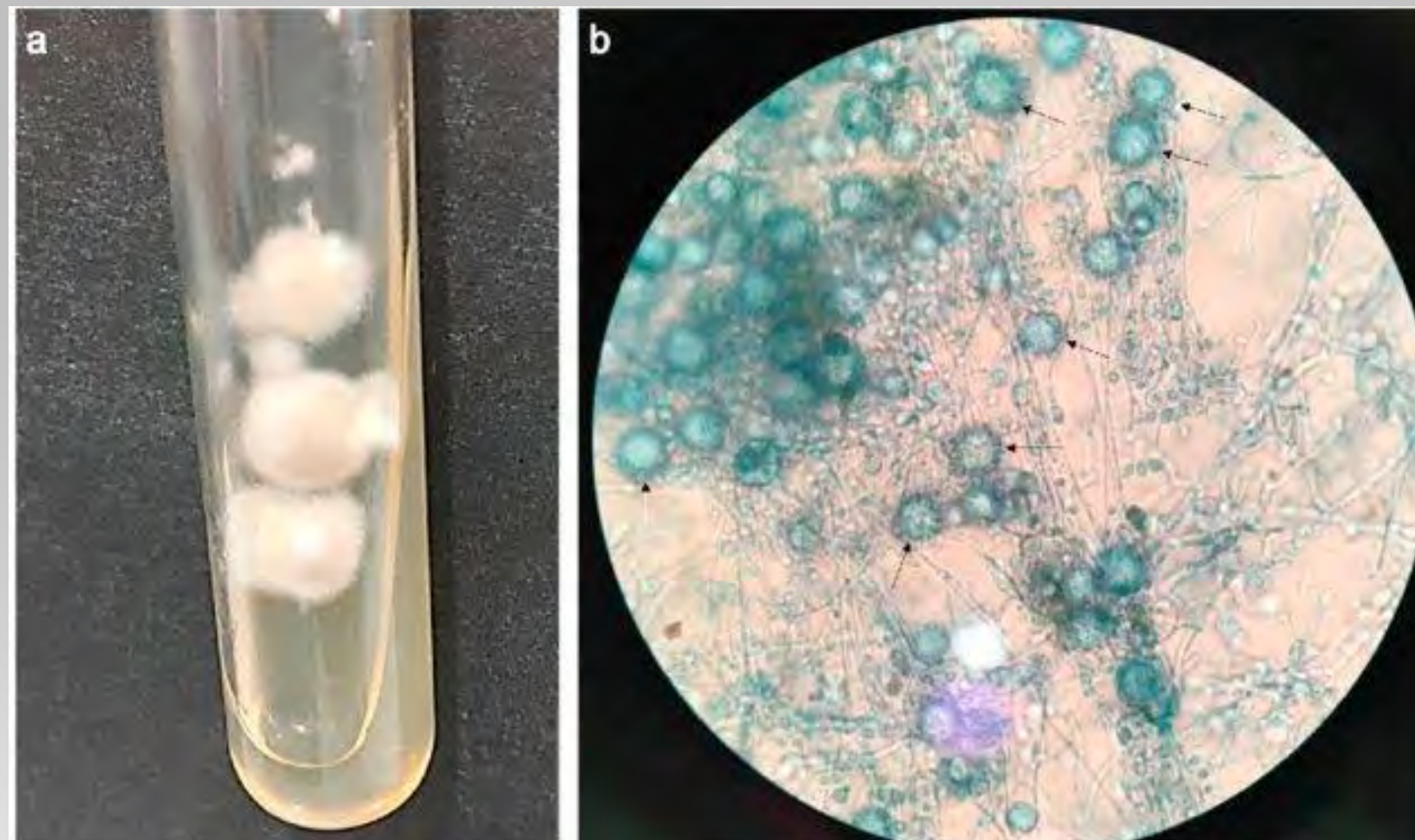
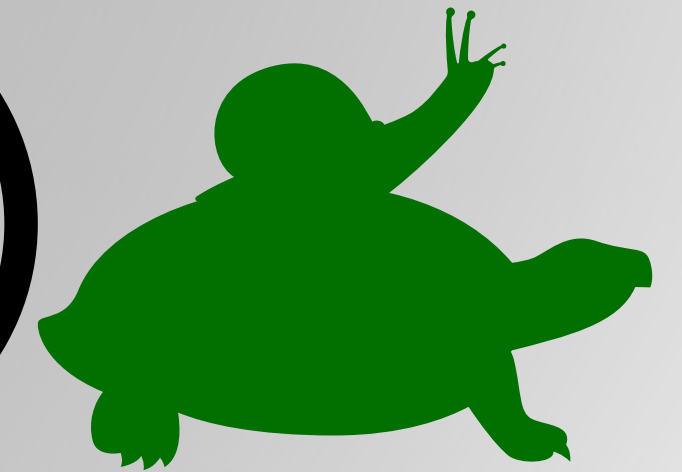
- ⚠ Prélèvements invasifs
- Qualité/quantité de prélèvement
- Laboratoire P3
- Prolongées : 2-8S (jusqu'à 12S)



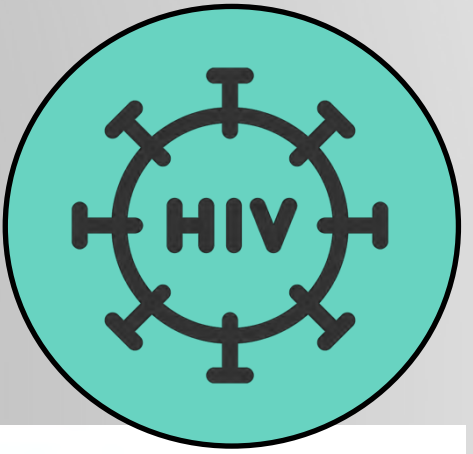
37°C milieux riches



25°C Sabouraud



Traitement de la coinfection Histo-TB



Viewpoints

Histoplasmosis or Tuberculosis in HIV-Infected Patients in the Amazon: What Should Be Treated First?

Mathieu Nacher^{1,2*}, Antoine Adenis^{1,2}, Emilie Sambourg^{2,3}, Florence Huber⁴, Philippe Loïc Epelboin^{2,5}, Emilie Mosnier^{5,6}, Vincent Vantilcke⁷, Julie Dufour^{2,3}, Félix Djossou², Magalie Demar^{2,8}, Pierre Couppié^{2,3}

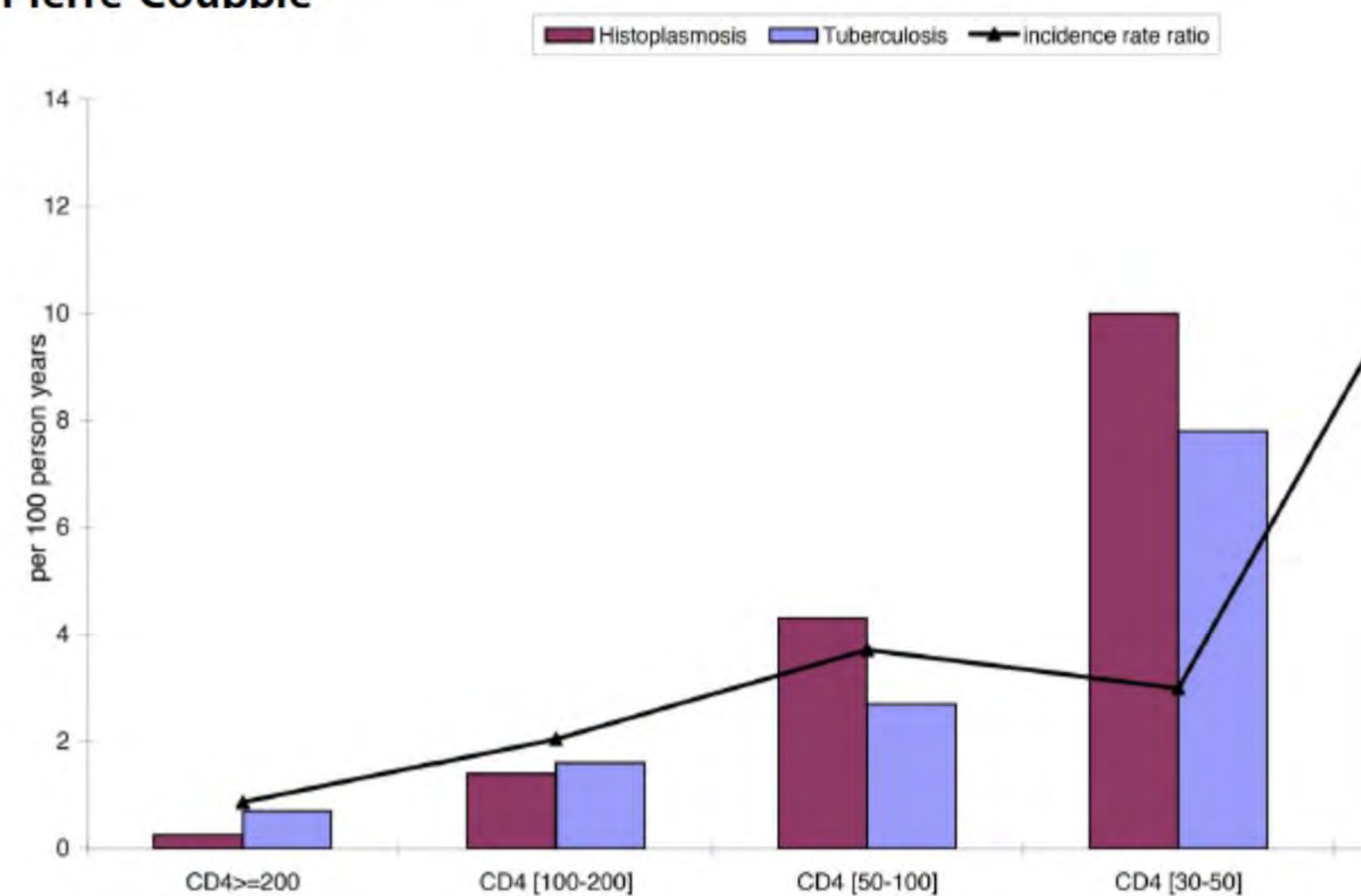


Figure 1. Shows the incidence rate for tuberculosis and histoplasmosis for different CD4 strata. doi:10.1371/journal.pntd.0003290.g001

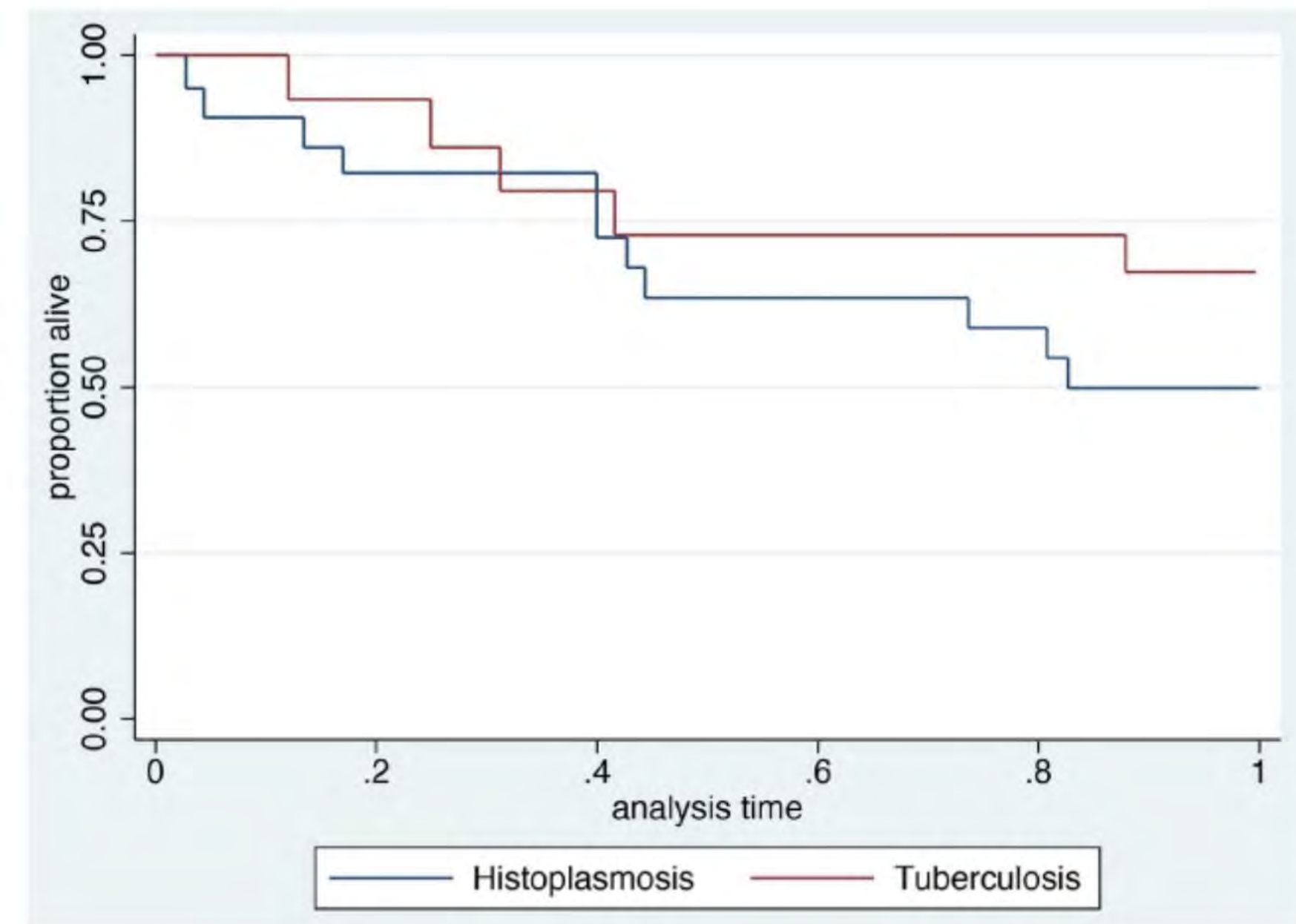


Figure 2. Shows the incidence of death during the first year after histoplasmosis or tuberculosis among patients with CD4 counts less than 200. doi:10.1371/journal.pntd.0003290.g002

L'histoplasmose disséminée

Immune reconstitution inflammatory syndrome

22 cases from 1997-2017

13 infectious IRIS

9 paradoxal IRIS

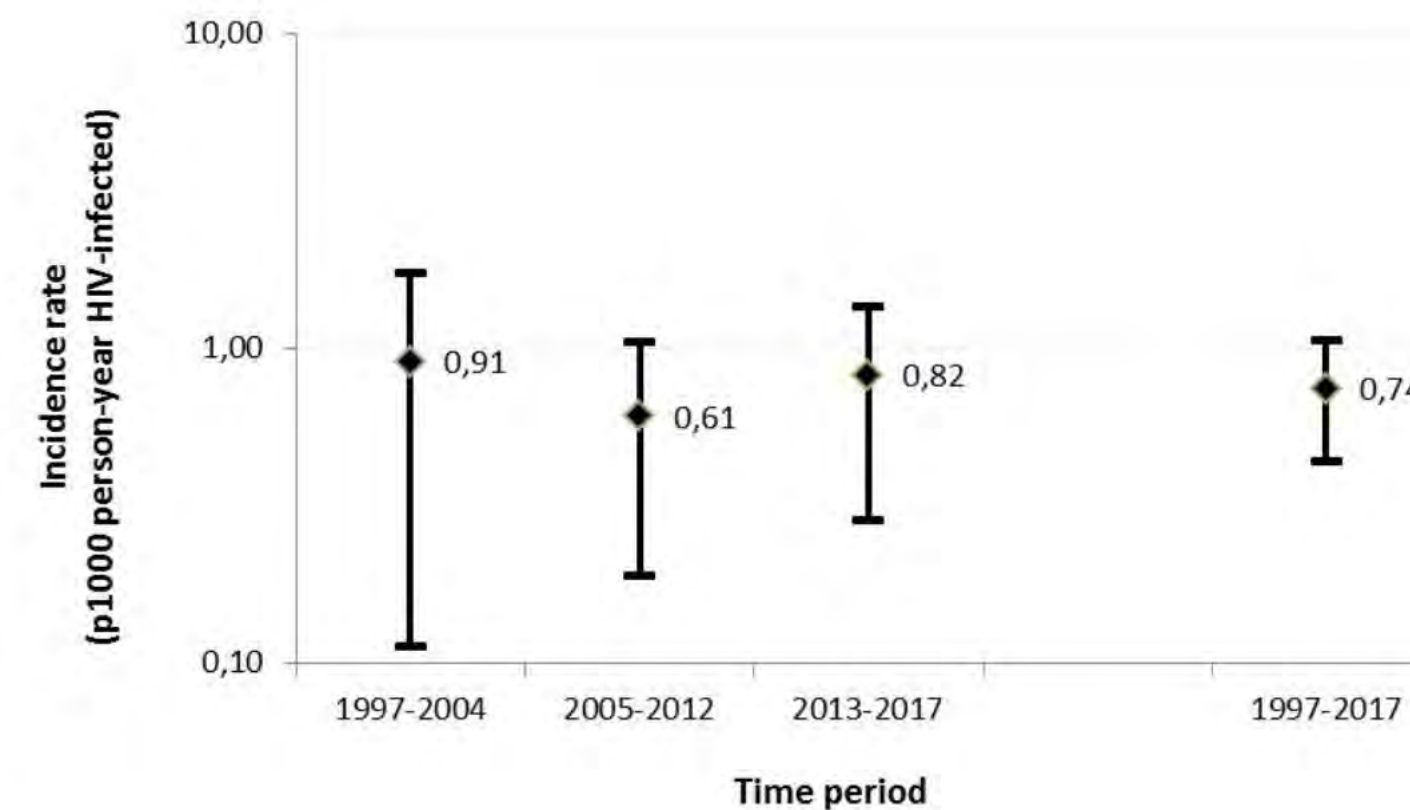
No ART class dependance

High morbidity, No deaths

Similar to the 22 cases published

« Wait and see » attitude

ART and antifungals until clinical resolution



Melzani & al., CID, 2019