IRIS et tuberculose: aspects thérapeutiques

Pr Matthieu Revest,
Maladies Infectieuses et Réanimation Médicale, CHU Rennes
Inserm U 1230, CIC-Inserm 1414 Université de Rennes

Gericco, Pornichet

6 mars 2025

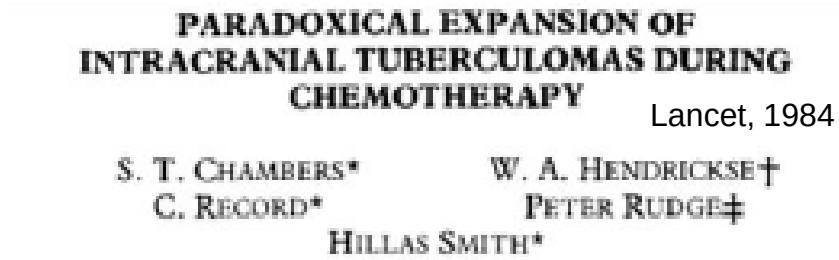
Déclaration d'intérêt

- **Conflits d'intérêt: aucun**

- **Liens d'intérêt:**
  - **Haut Conseil de Santé Publique**
    - **Commission spécialisée Maladies Infectieuses et Emergentes**
  - **Rapport experts HAS**
    - **Groupe infections opportunistes et IRIS**
    - **Groupe traitements antirétroviraux**

Introduction

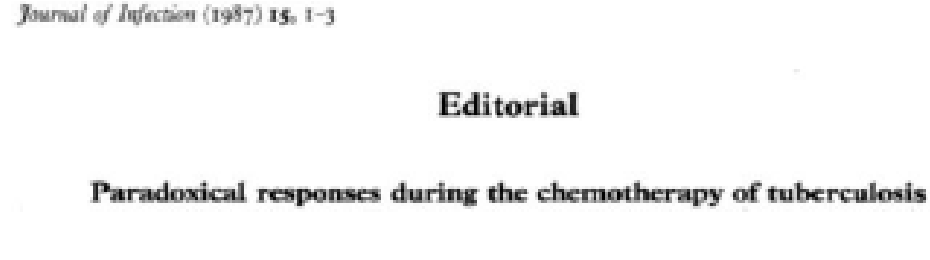
- **Réactions paradoxales connues depuis longtemps**



PARADOXICAL EXPANSION OF INTRACRANIAL TUBERCULOMAS DURING CHEMOTHERAPY

Lancet, 1984

S. T. CHAMBERS* W. A. HENDRICKSE†
C. RECORD* PETER RUDGE‡
HILLAS SMITH*



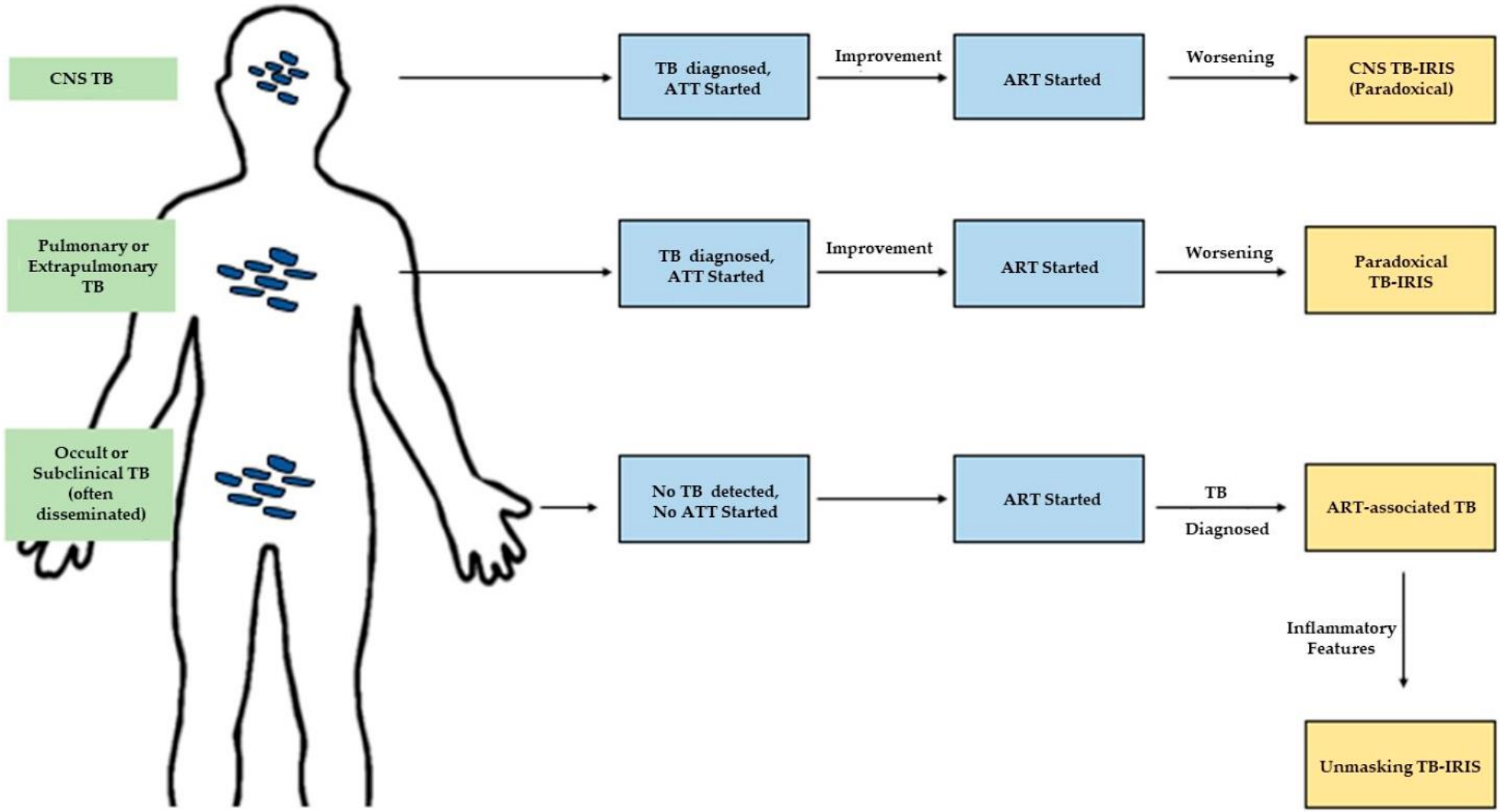
Journal of Infection (1987) 15, 1–3

Editorial

Paradoxical responses during the chemotherapy of tuberculosis

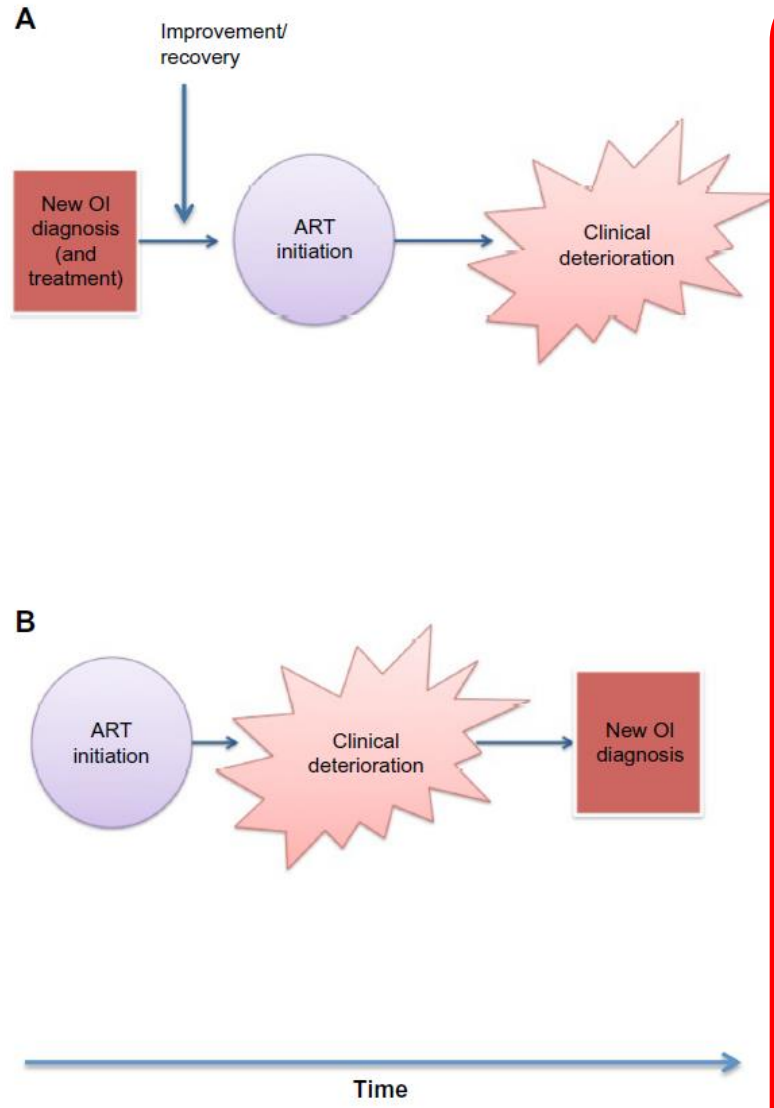
- **Chez les immunodéprimés:**
  - VIH ++++
  - « Unmasking » IRIS
  - Diminution ou arrêt des traitements immunosuppresseurs: CTC, anti-TNF

Introduction



Quinn, Life, 2020

Introduction



Paradoxical IRIS:

Differential diagnosis:

1) ART/OI treatment toxicity

2) OI drug resistance

3) Poor adherence to treatment

4) Other new OI

ART-associated OI (possible scenarios):

1) Unmasking IRIS

or

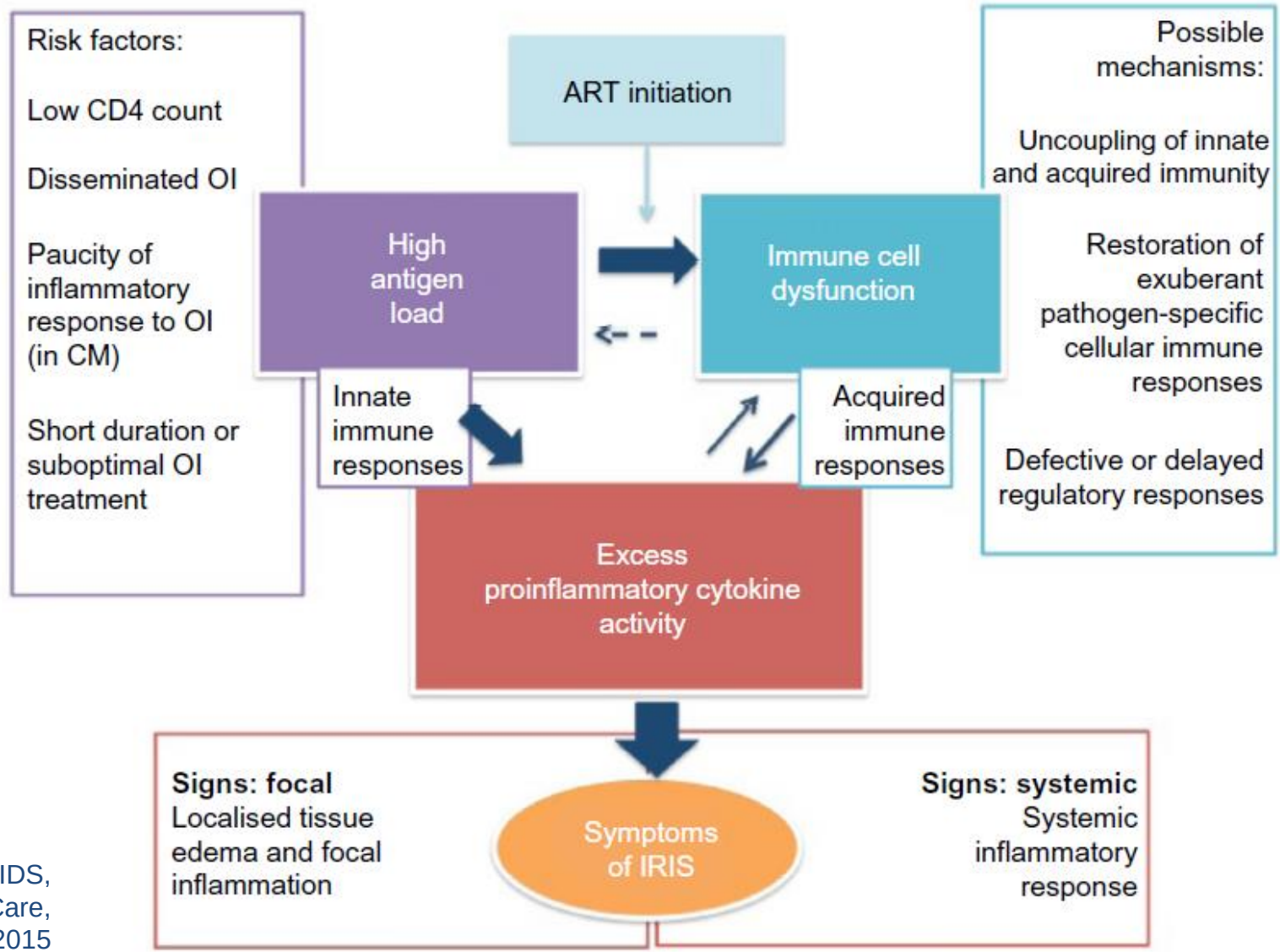
2) Missed OI diagnosis at presentation with clinical progression and presentation that is not unusual

or

3) New OI due to persisting immune deficiency

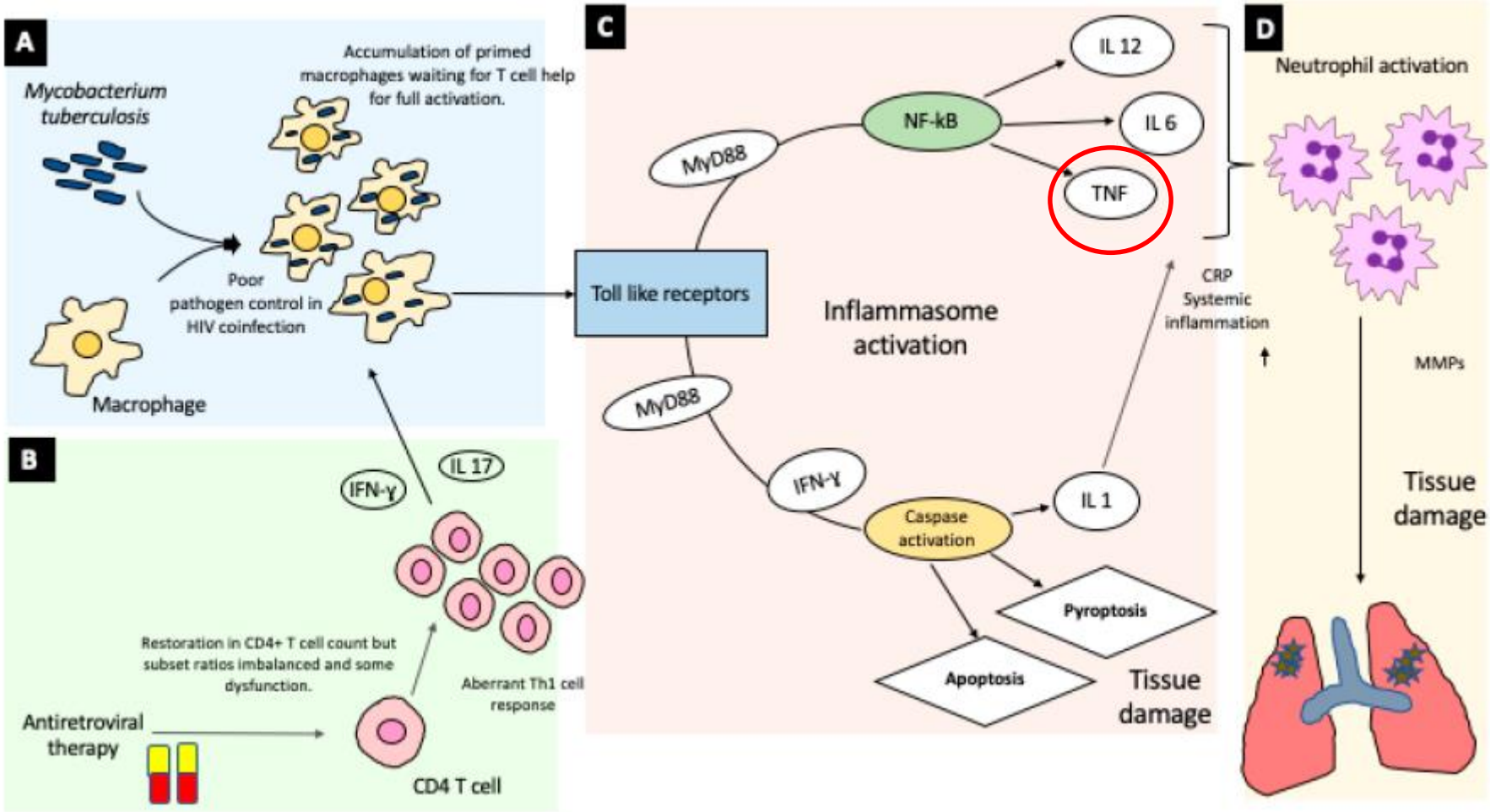
Walker, HIV/AIDS, Research and Pal Care, 2015

Introduction



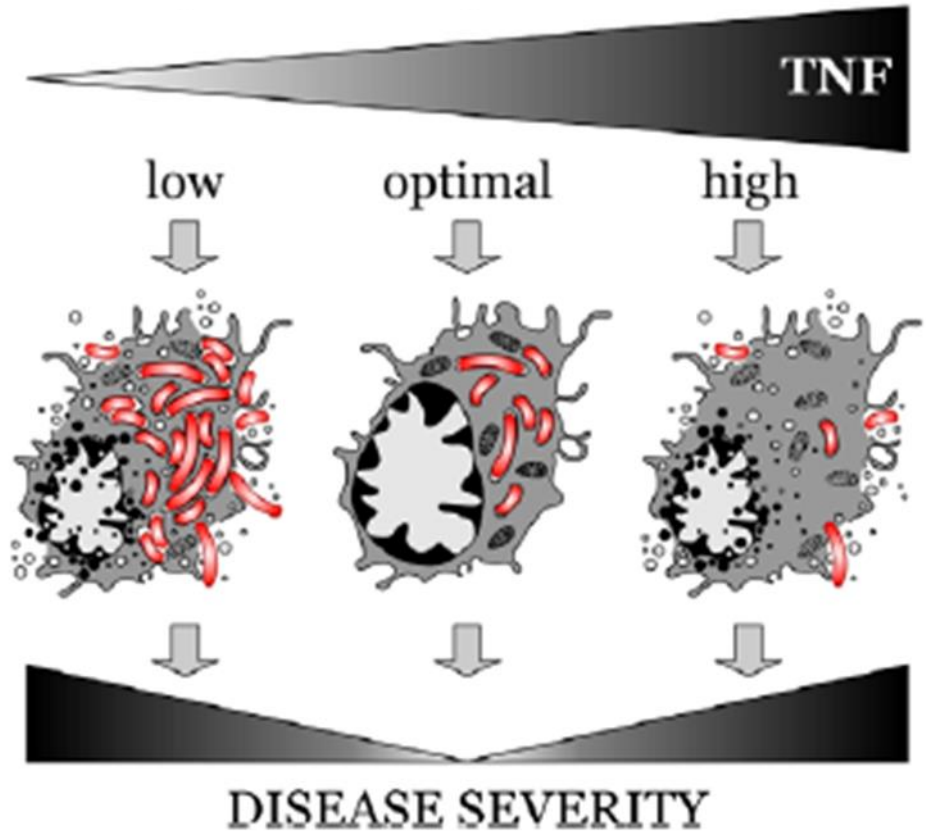
Walker, HIV/AIDS, Research and Pal Care, 2015

Introduction



Quinn, Life, 2020

Introduction



Matty et al, Immunol Rev, 2015

Epidémiologie

Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis

Lancet Infect Dis 2010; 10: 251–61

Monika Müller, Simon Wandel, Robert Colebunders, Suzanna Attia, Hansjakob Furrer, Matthias Egger, for IeDEA Southern and Central Africa

16% des patients avec IRIS

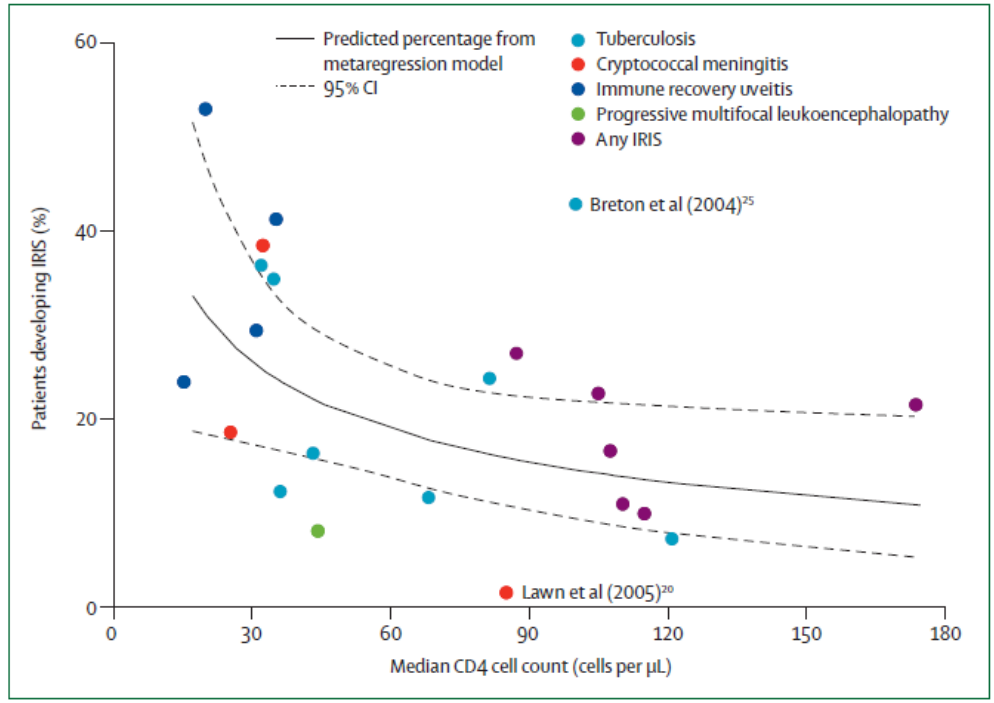


***Figure 3*: Incidence of immune reconstitution inflammatory syndrome (IRIS) according to CD4 cell count at the start of antiretroviral therapy**
Data are provided for 22 studies. Circle size is proportional to weighting in the random-effect model.

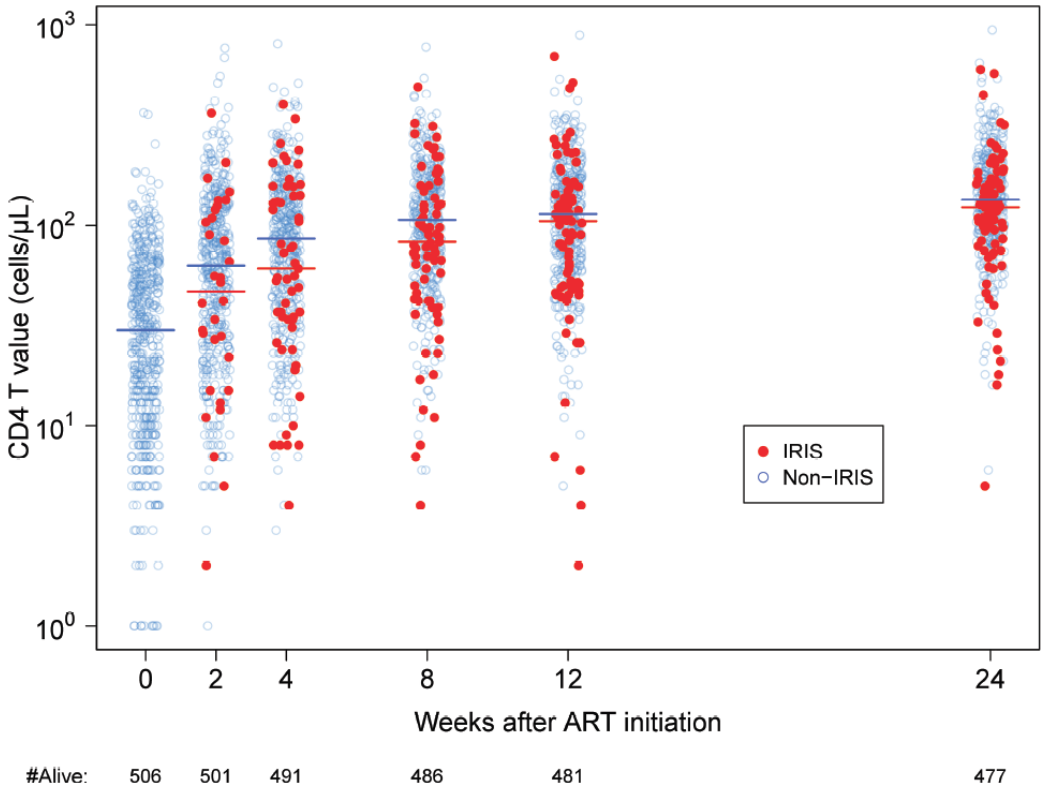
Décès:

- 3,2% des patients avec TB-IRIS
- 20,8% avec crypto

Epidémiologie

Prospective International Study of Incidence and Predictors of Immune Reconstitution Inflammatory Syndrome and Death in People Living With Human Immunodeficiency Virus and Severe Lymphopenia

Kenya, Thaïlande et USA



19,2% d'IRIS
6,5% décès

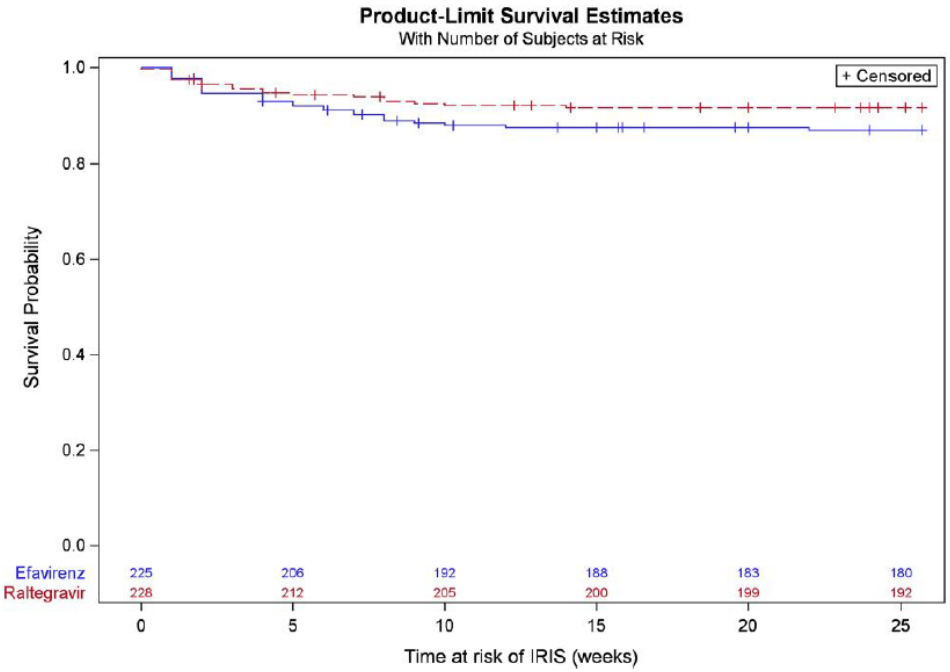
Sereti, CID, 2020

Epidémiologie

Incidence and Predictors of Tuberculosis-associated IRIS in People With HIV Treated for Tuberculosis: Findings From Reflate TB2 Randomized Trial

OFID, 2024

Lara E. Coelho,[1] Corine Chazallon,[2] Didier Laureillard,[3,4] Rodrigo Escada,[1] Jean-Baptiste N'takpe,[2,5] Isabelle Timana,[6] Eugène Messou,[5,7,8] Serge Eholie,[5,8] Celso Khosa,[6] Giang D. Chau,[9] Sandra Wagner Cardoso,[1] Valdiléa G Veloso,[1] Constance Delaugerre,[10,11,12] Jean-Michel Molina,[11,12,13] Beatriz Grinsztejn,[1] Olivier Marcy,[2] and Nathalie De Castro[2,13]



Brésil, Mozambique, Côte d'Ivoire et Vietnam

10,6% d'IRIS

Pas de différence ralte et EFV

Un peu de non-VIH

Incidence, risk factors and treatment of central nervous system immune reconstitution inflammatory syndrome in non-HIV patients with tuberculous meningitis: a multicentre observational study

Internal Medicine Journal **54** (2024) 802–808

Marie Robert,[1] Arthur Mageau,[1] Augustin Gaudemer,[2] Michael Thy,[3] Nathan Peiffer Smadja,[3] Victoire de Lastours,[1] Thomas De Broucker,[4] Thomas Papo,[1,5] Tiphaine Goulenok[1] and Karim Sacré[1,5]

Etude multicentrique française
58 patients avec TB méningée
Traitement standard, 85,7% avec CTC

50% d'IRIS
Pas plus de décès en cas d'IRIS

En multivariée:

- Prise de contraste méningée OR 15,3
- Albumine plasmatique augmentée: OR: 1,2
- Pas la protéinorachie

Introduction ARV

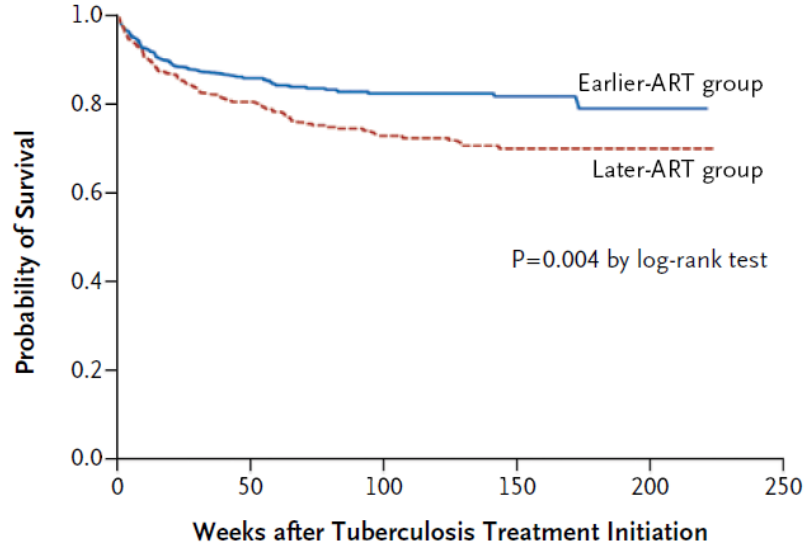
Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

N Engl J Med 2011;365:1471-81.

François-Xavier Blanc, M.D., Ph.D., Thim Sok, M.D., Didier Laureillard, M.D., Laurence Borand, Pharm.D., and Anne E. Goldfeld, M.D., for the CAMELIA (ANRS 1295–CIPRA KH001) Study Team*

Début ARV (d4T, 3TC, EFV)
4 vs 8 semaines

Diminution de 38% de mortalité
Mais que si < 50 CD4



No. at Risk					
Earlier-ART group	332	278	192	101	4
Later-ART group	329	256	168	87	3
No. of Deaths					
Earlier-ART group	0	46	56	57	59
Later-ART group	0	63	85	90	90

Introduction ARV

Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial

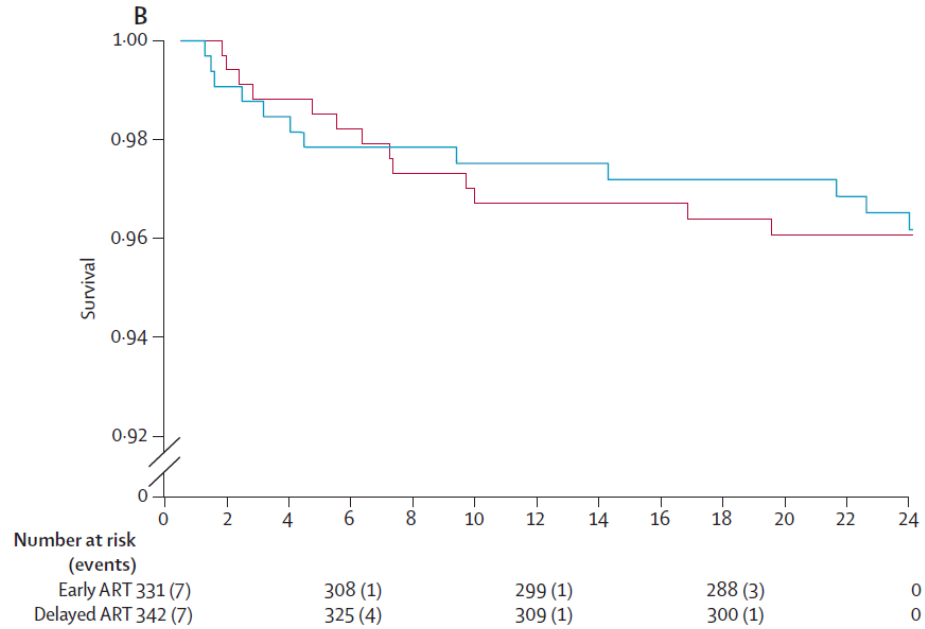
Lancet Infect Dis 2014; 14: 563–71

Sayoki G Mfinanga, Bruce J Kirenga*, Duncan M Chanda*, Beatrice Mutayoba, Thuli Mthiyane, Getnet Yimer, Oliver Ezechi, Cathy Connolly, Vincent Kapotwe, Catherine Muwonge, Julius Massaga, Edford Sinkala, Wanze Kohi, Lucinda Lyantumba, Grace Nyakoojo, Henry Luwaga, Basra Doulla, Judith Mzyece, Nathan Kapata, Mahnaz Vahedi*, Peter Mwaba*, Saidi Egwaga*, Francis Adatu*, Alex Pym*, Moses Joloba, Roxana Rustomjee, Alimuddin Zumla*, Philip Onyebujoh**

Début ARV 2 semaines vs 6 mois

> 200 CD4

Pas d'effet sur mortalité



Recommandations HAS

- **Tuberculose non neuroméningée: début ARV à S2**
- **Tuberculose neuroméningée:**
  - Début à S4
  - Possible S2 si:
    - < 50 CD4
    - Amélioration rapide TB

HAS
HAUTE AUTORITÉ DE SANTÉ

Quel traitement ARV ?

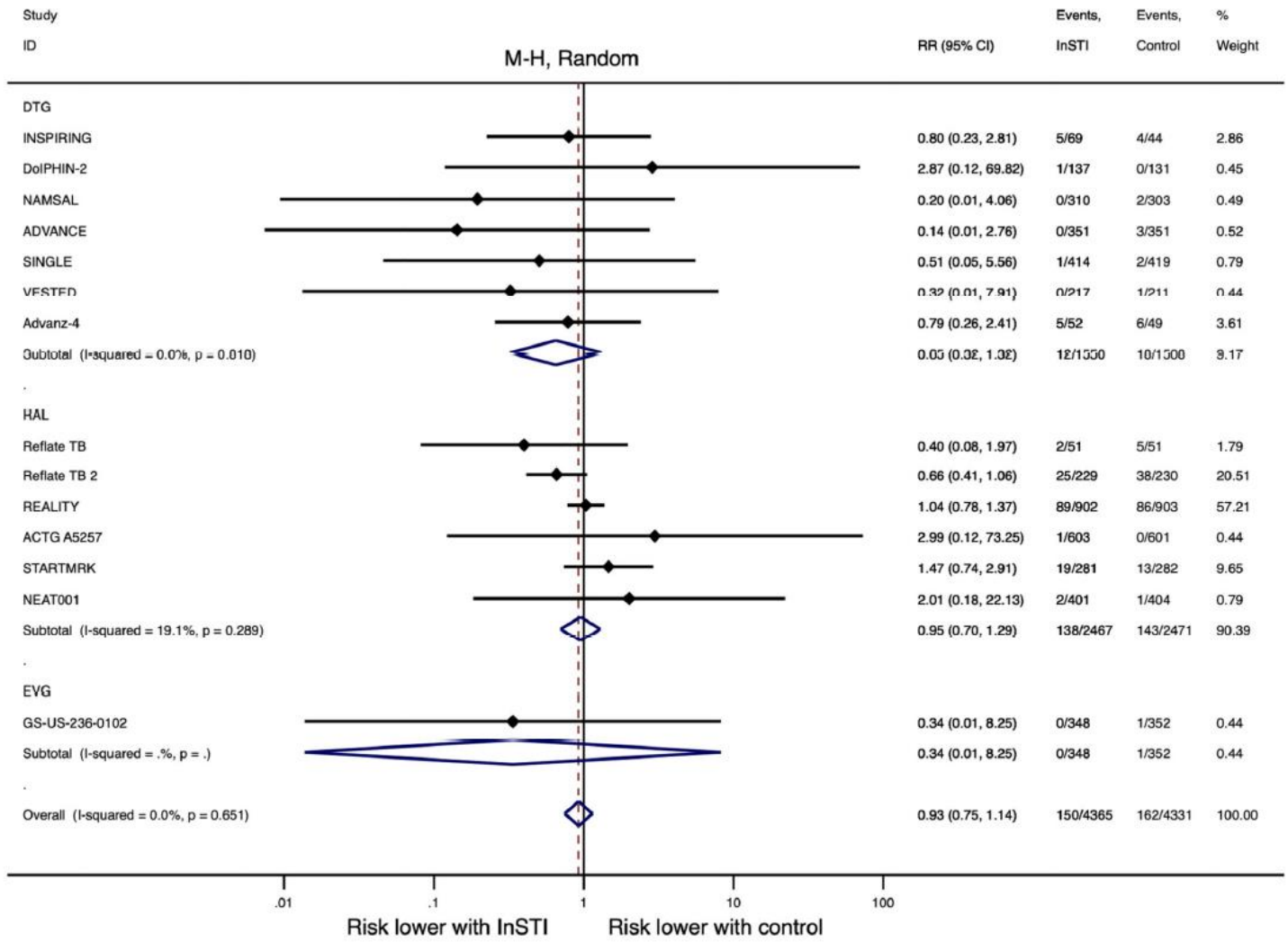


Figure 2. Meta-analysis of IRIS in randomized controlled trials of InSTI

Zhao, JAIDS, 2022

Recommandations HAS

- **Choix des ARV**
- **TDF/FTC ou ABC/3TC avec DTG, RAL ou EFV**

HAS
HAUTE AUTORITÉ DE SANTÉ

Mme D

- Femme, 37 ans
- Cambodgienne
- VIH négative
- Tuberculose pulmonaire et méningée
- Imagerie cérébrale initiale: léger épaississement méningée de la base de crâne
- Traitement anti-T + CTC

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

N Engl J Med 2004;351:1741-51.

Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D.,

Randomisée, double aveugle, vs placebo
Vietnam
545 patients
Dont 16% VIH +
Traitement standard
Anti-T + DXM

DXM:
- 1 semaine IV: 0,3 mg/kg/j
- 1 semaine IV: 0,2 mg/kg/j
- 3 semaines per os:
  - 0,1 mg/kg/j S3
  - Puis 3 mg/j – 1 mg/sem

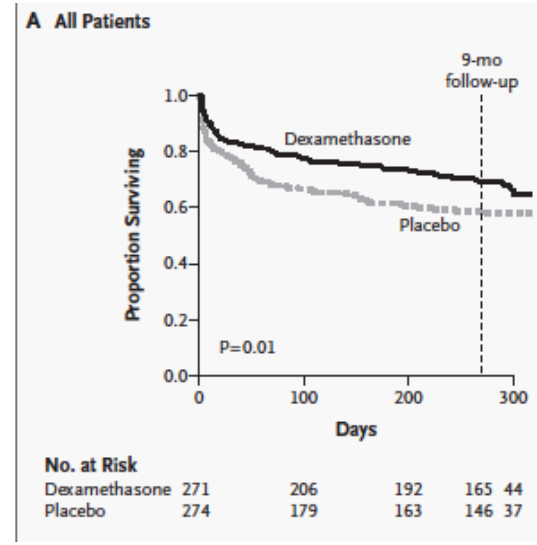


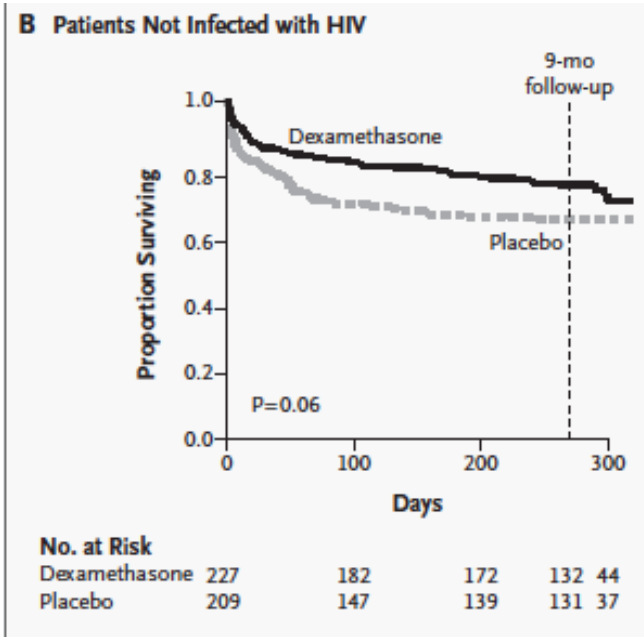
Table 3. Outcomes of 545 Patients Nine Months after Randomization.

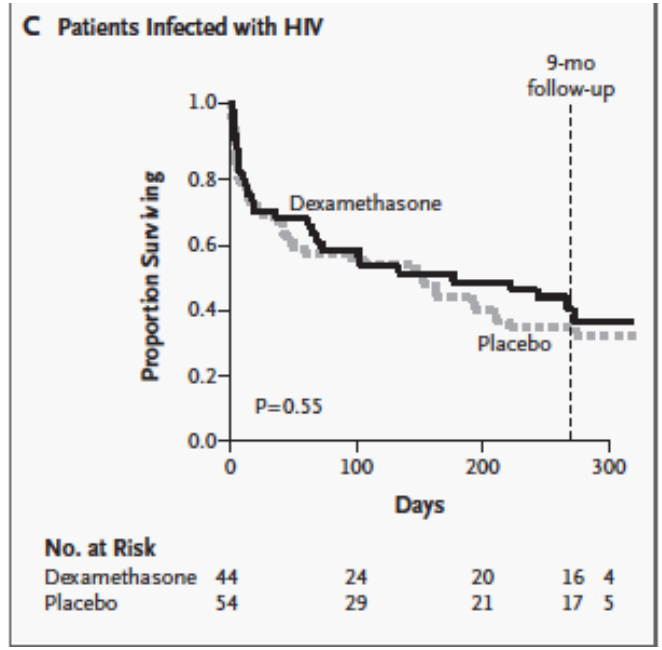
Group	No. of Patients	Outcome			
		Good	Inter-mediate	Severe Disability	Death
		number (percent)			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

N Engl J Med 2004;351:1741-51.

Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D.,





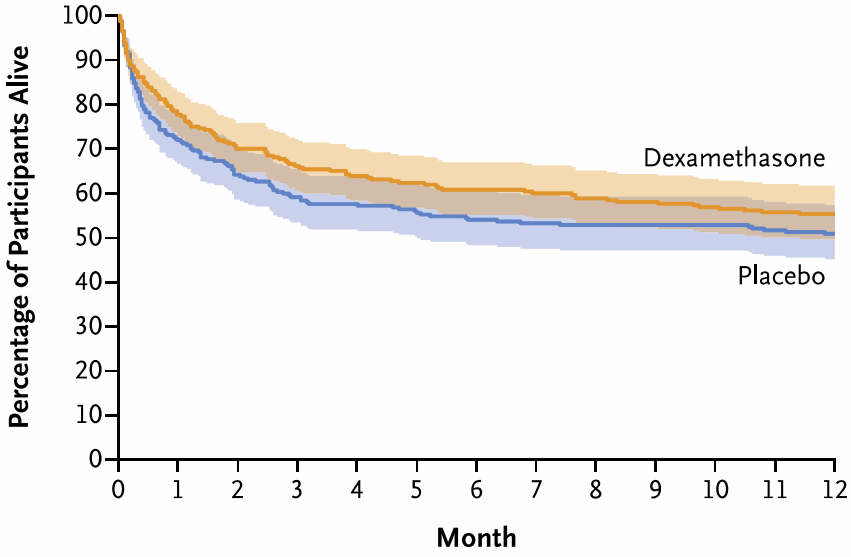
Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

Joseph Donovan, Ph.D., Nguyen D. Bang, Ph.D., Darma Imran, M.D., Ho D.T. Nghia, Ph.D., Erlina Burhan, Ph.D.,

N Engl J Med 2023;389:1357-67.

Vietnam et Indonésie

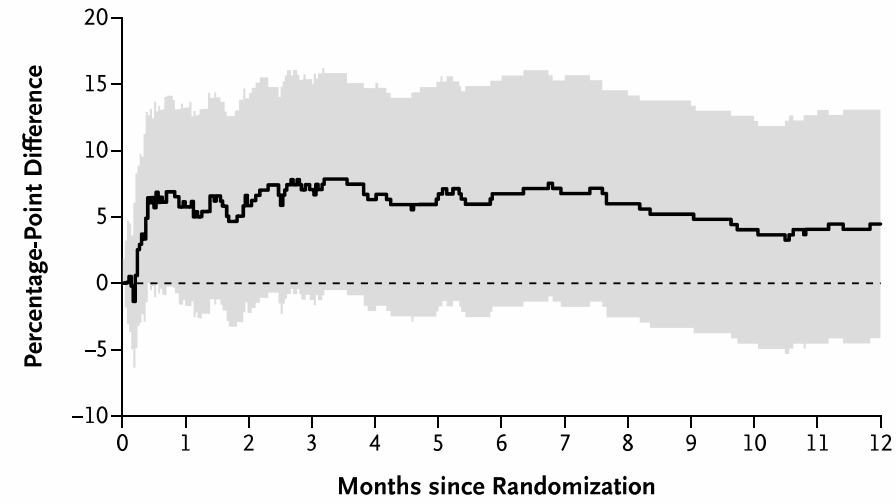
A Death from Any Cause, Intention-to-Treat Population



No. at Risk

Dexamethasone	263	202	182	172	166	161	156	154	151	149	146	143	139
Placebo	257	185	165	152	147	141	137	135	134	134	133	130	127

B Between-Group Differences in Survival, Intention-to-Treat Population



Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

N Engl J Med 2018;379:1915-25.

G. Meintjes, C. Stek, L. Blumenthal, F. Thienemann, C. Schutz, J. Buyze, R. Ravinetto, H. van Loen, A. Nair, A. Jackson, R. Colebunders, G. Maartens, R.J. Wilkinson, and L. Lynen, for the PredART Trial Team

Afrique du Sud
Prednisone: 40 mg/j pdt 14j puis 20 mg/j pdt 14 j

Pas plus d'IO ou de cancer

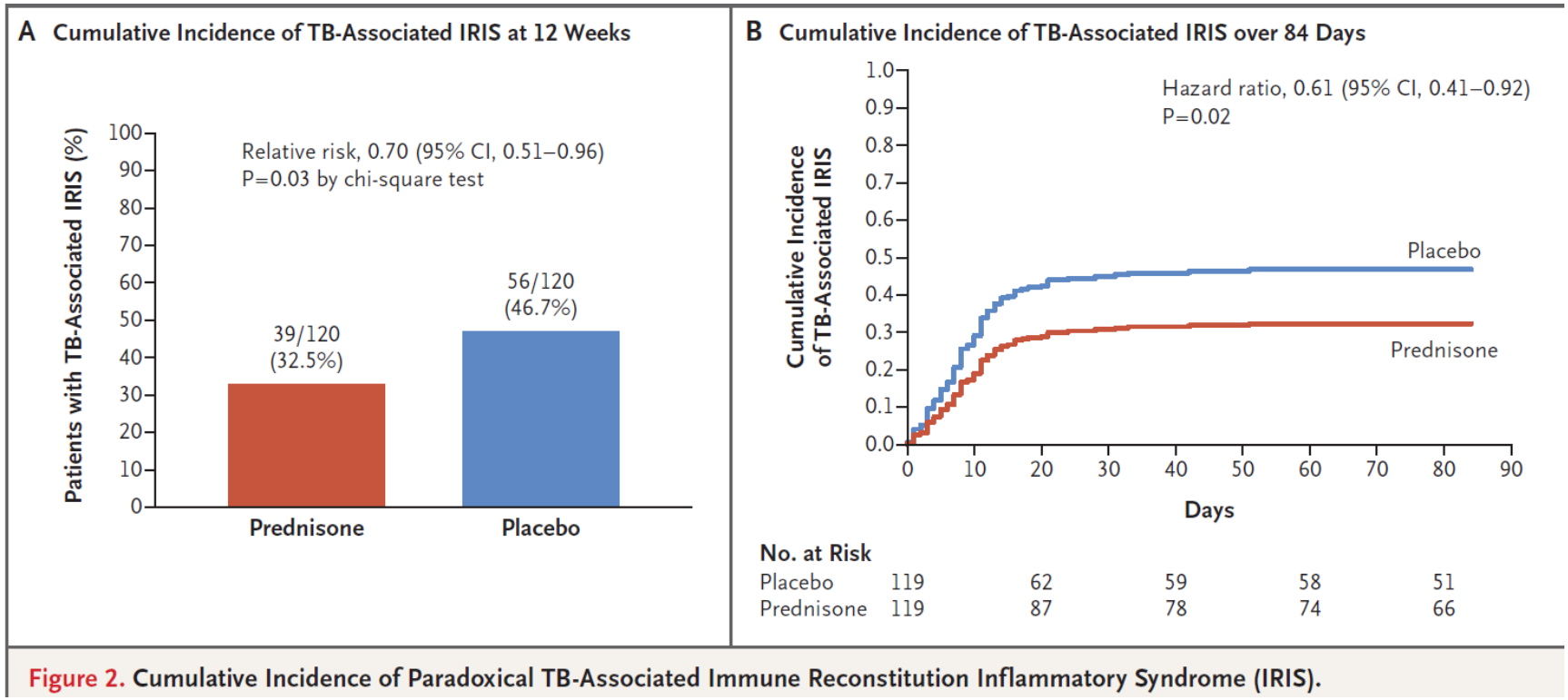


Figure 2. Cumulative Incidence of Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS).

Recommandations HAS

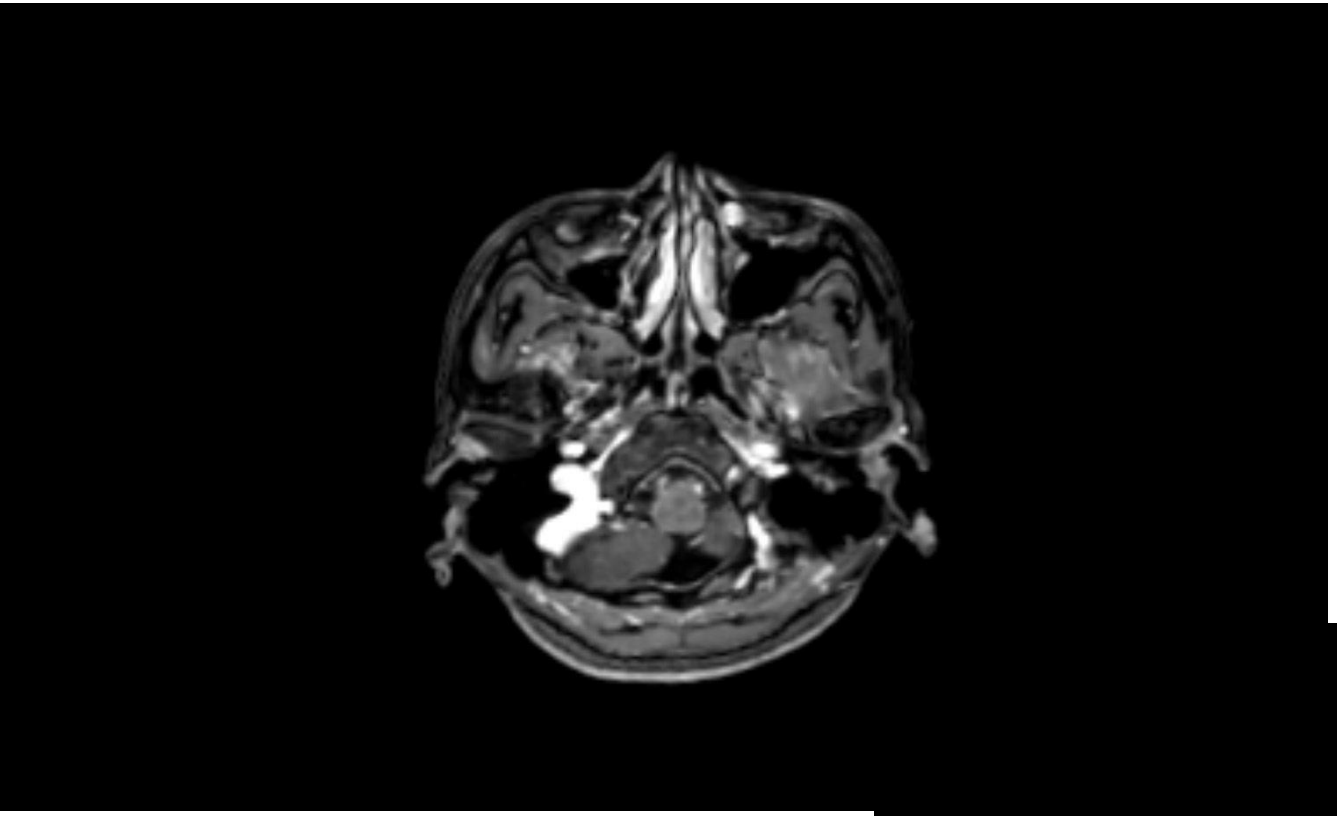
- **Pas de CTC en prophylaxie dans les TB non neuro**
- **Pas de reco émises pour le neuro: à discuter au cas par cas**

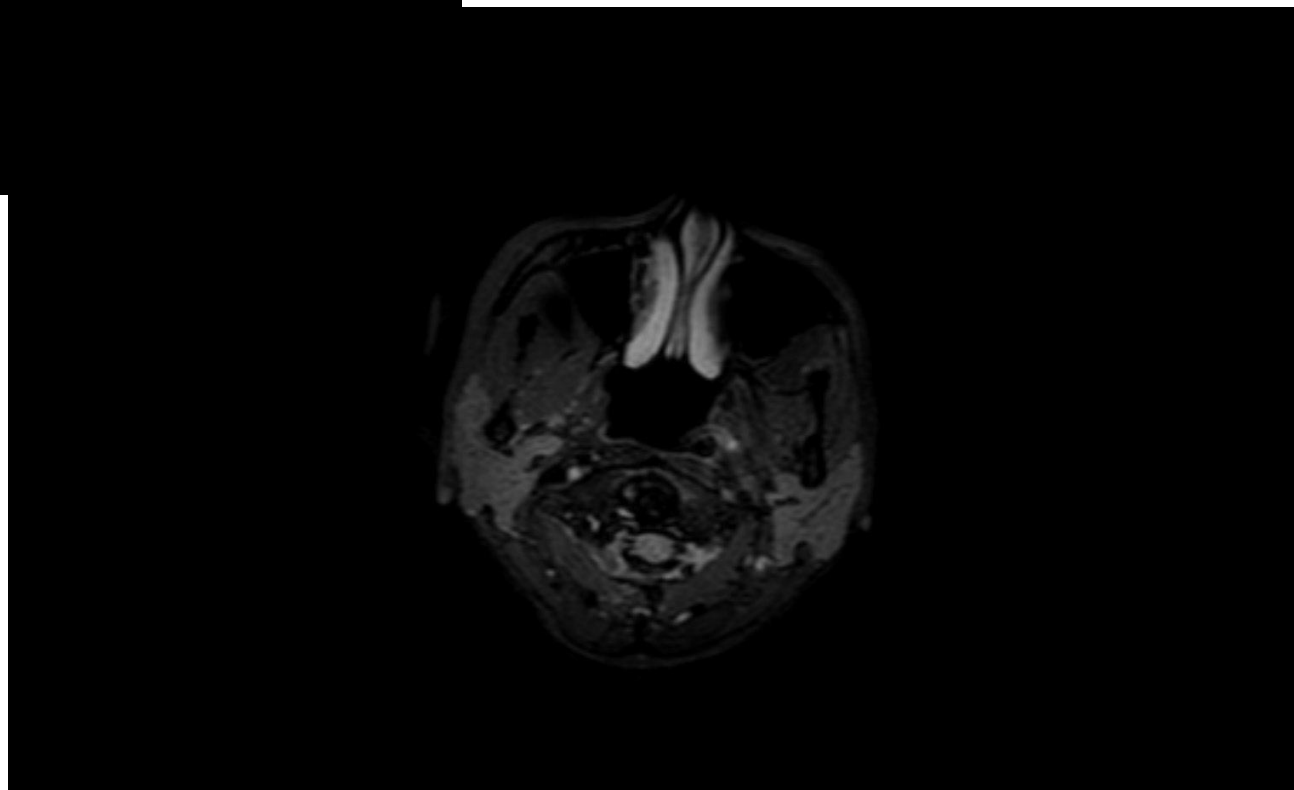
HAS
HAUTE AUTORITÉ DE SANTÉ

Mme D

- **A M3 de traitement**

- **Céphalées, diplopie, hypoacousie**





Mme D

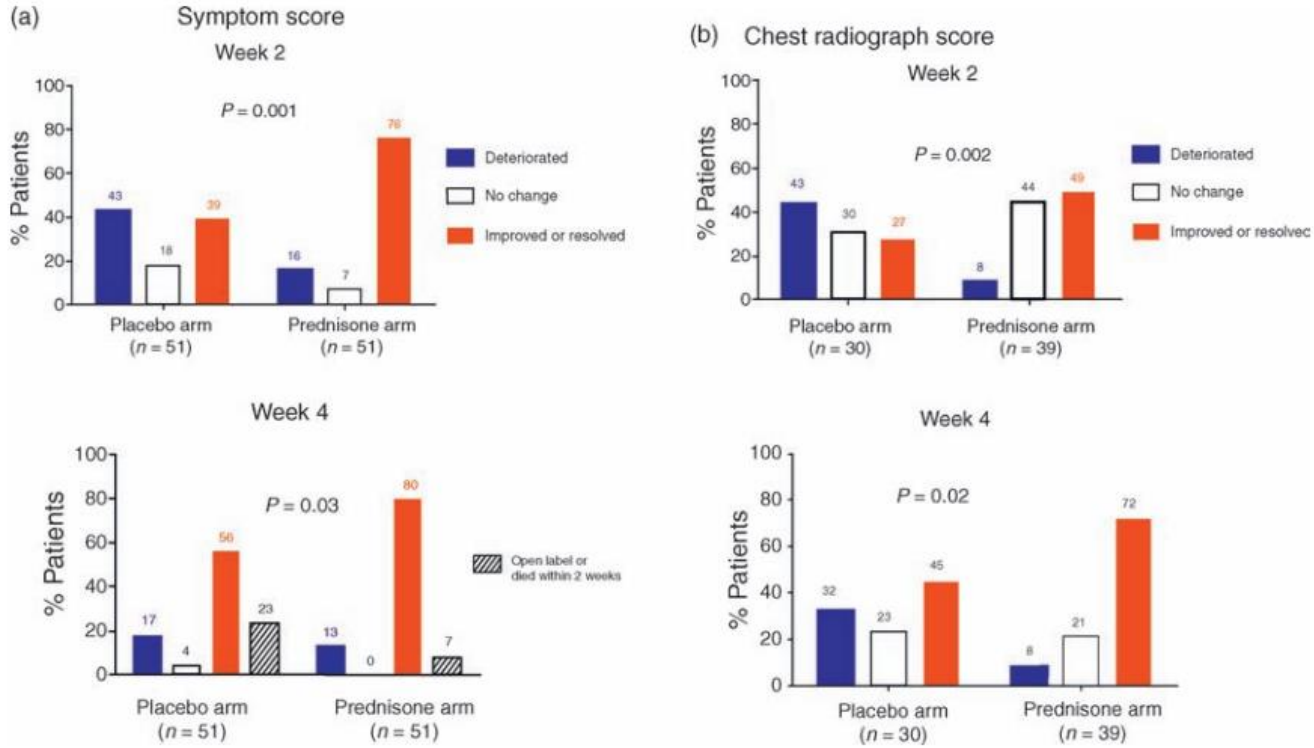
- A M3 de traitement
- Céphalées, diplopie, hypoacousie
- Reprise d'une corticothérapie 1 mg/kg/j
- Amélioration

Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome

AIDS 2010, **24**:2381–2390

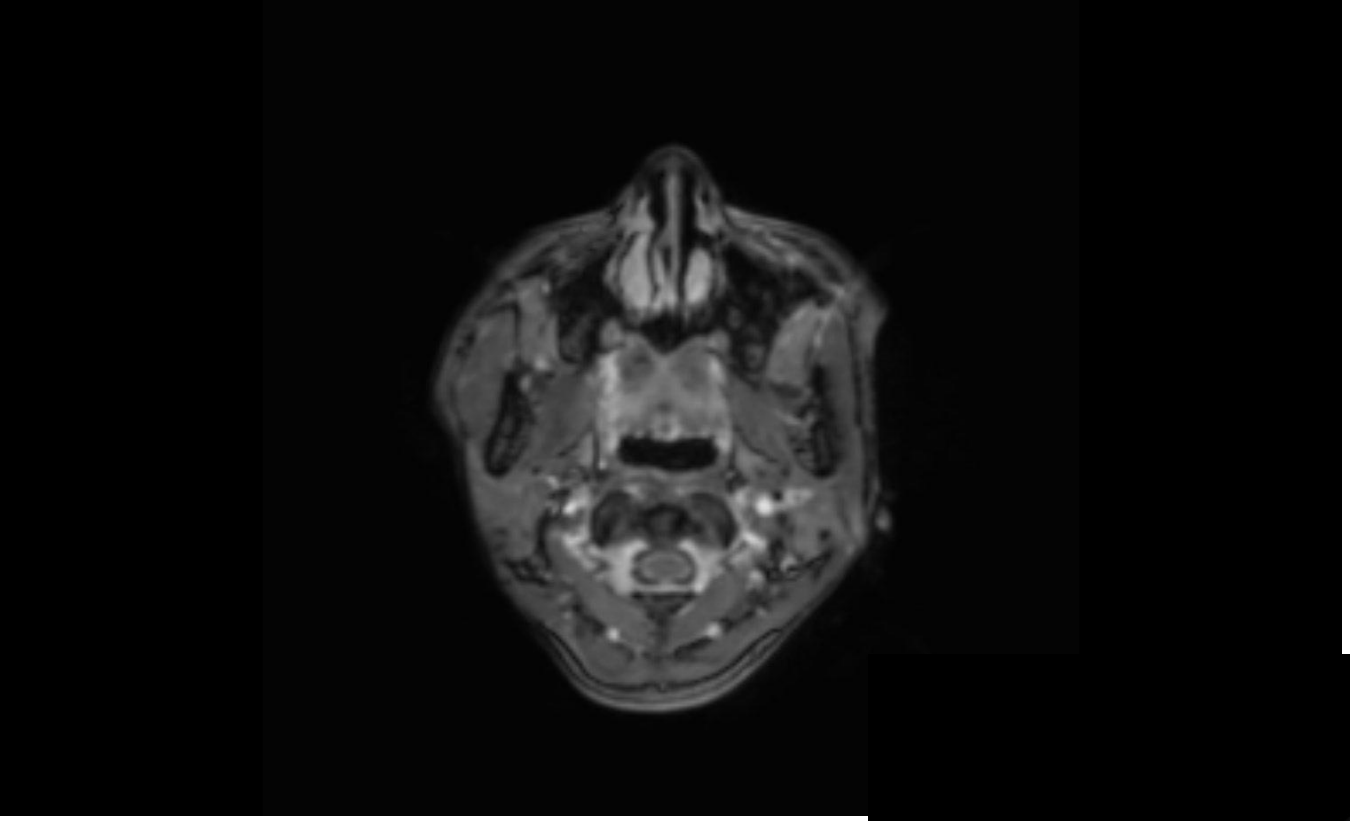
Graeme Meintjes[a,b,c], Robert J. Wilkinson[a,b,c,d,e], Chelsea Morroni[a,f],

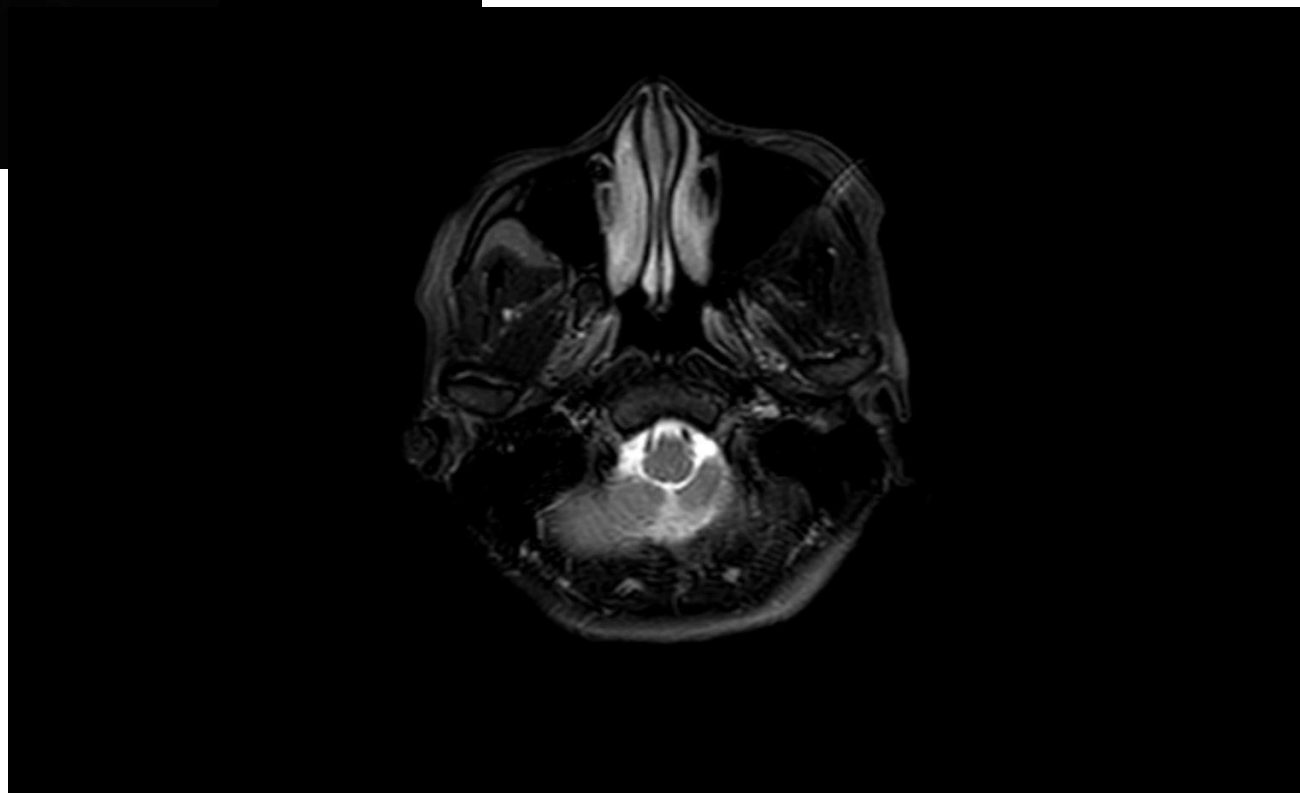
TB avec IRIS
55 patients dans chaque bras
1,5 mg/kg/j pendant 14 j puis 0,75 mg/kg/j 14j



Mme D

- A M3 de traitement
- Céphalées, diplopie, hypoacousie
- Reprise d'une corticothérapie 1 mg/kg/j
- Amélioration
- A 30 mg/j (0,5 mg/kg), soit deux mois plus tard, récidives des symptômes majorés, avec troubles de la vigilance





Mme D

- **Bolus de solumédrol**
- **Introduction de thalidomide**

Adjunctive Thalidomide Therapy for Childhood Tuberculous Meningitis: Results of a Randomized Study

Johan F. Schoeman, MBChB, MD; Priscilla Springer, MBChB, FCP; Anita Janse van Rensburg, Dipl Nurs; Sonja Swanevelder, MSc; Willem A Hanekom, MBChB, FCP; Patrick A. J. Haslett, MB, MRCP; Gilla Kaplan, PhD

Journal of Child Neurology / Volume 19, Number 4, April 2004

Table 3. Motor Outcome of Hemiparesis on Admission at 6-Month Follow-Up

Hemiparesis	*Thalidomide (n = 21)*	*Control (n = 4)*	P
Improved	12 (57%)	3 (75%)	1.00
Unchanged	5 (24%)	1 (25%)	Not done
Deteriorated	4 (19%)	0	Not done

Thalidomide Use for Complicated Central Nervous System Tuberculosis in Children: Insights From an Observational Cohort

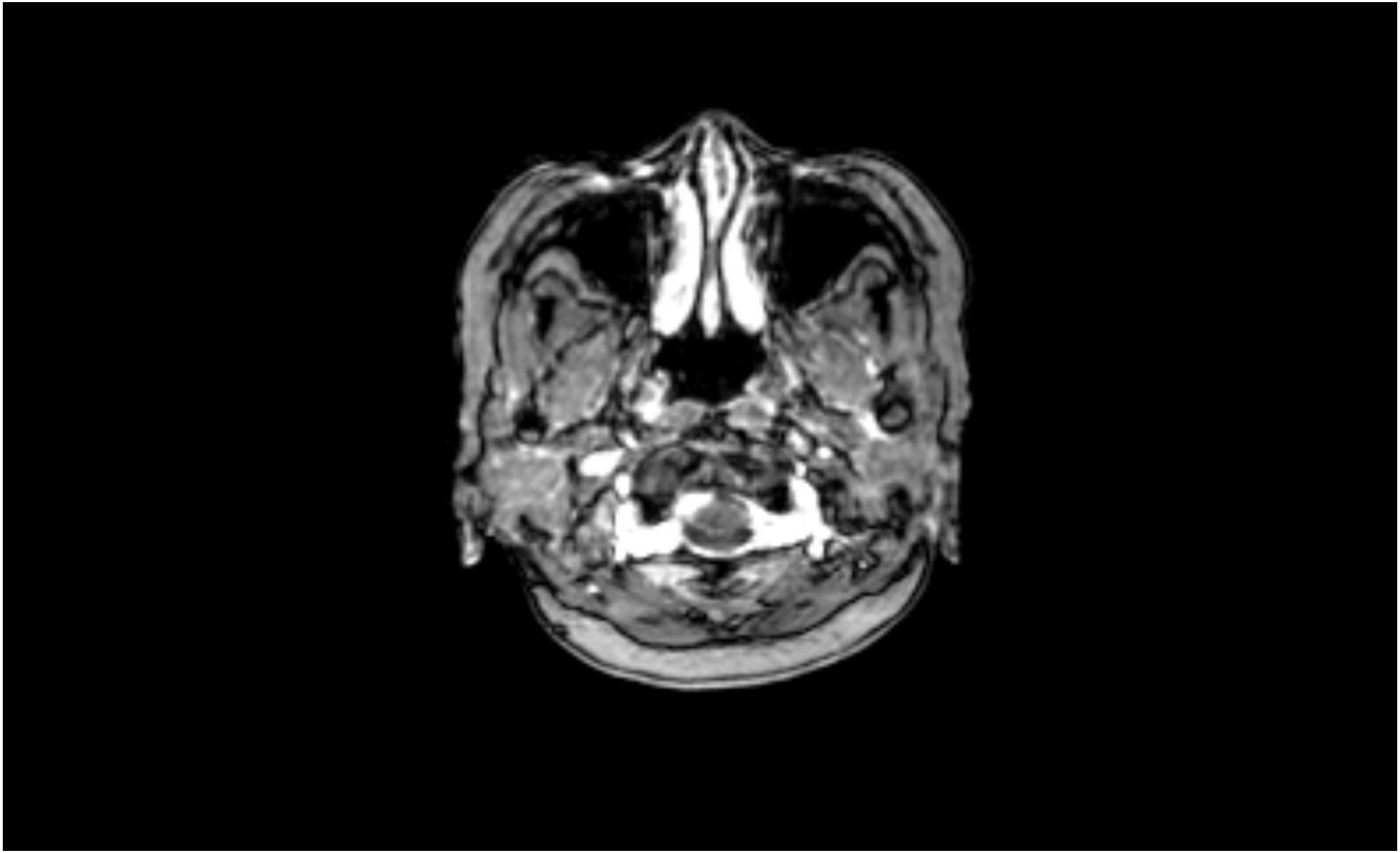
Ronald van Toorn,[1] Regan S. Solomons,[1,©] James A. Seddon,[2,3] and Johan F. Schoeman[1]

Clinical Infectious Diseases® 2021;72(5):e136–45

Rétrospectif, non comparatif, semble bien

Tuberculome(s)

- Bolus de solumédrol
- Introduction de thalidomide
- 1 mois plus tard: troubles de conscience, paraplégie



Tuberculome(s)

- **Infliximab:**
  - **6 cures**
  - **5 mg/kg**
  - **Amélioration clinique majeure**

	Paradoxical reaction (PR) (*n*=12)	Immune reconstitution inflammatory syndrome (IRIS, *n*=12)		Total (*n*=24)
		HIV-infected (*n*=6)	Others (*n*=6)	
Female sex *n/N*	9/12	2/6	3/6	14/24 (58%)
Age, median (IQR)	36 (31–56)	42 (33–49)	29 (27–47)	36 (28–52)
Tuberculosis features				
Neuromeningeal	11/12	2/6	2/6	15/24 (63%)
Pulmonary	4/12	2/6	4/6	10/24 (42%)

Infliximab: 5 mg/kg à S0, S2 et S6

Parfois nécessité de maintenance: 5 mg/kg toutes les 8 semaines

Treatment of PR or IRIS §				
High-dose corticosteroids	12/12	6/6	5/6	23/24 (96%)
Infliximab	8/12	4/6	5/6	17/24 (71%)
Adalimumab	1/12	1/6	1/6	3/24 (13%)
Thalidomide	4/12	2/6	0/6	6/24 (25%)
Outcome				
Initial improvement	12/12	6/6	6/6	24/24
Sequelae	6/11**	0/6	0/6	6/23* (26%)
TNF-α antagonist severe adverse events	2/12	1/6	1/6	4/24 (17%)

Armange, Eur J Clin Microbiol Infect Dis, 2023

Recommandations HAS

- **Corticothérapie si formes sévères**
- **Discuter anti-TNF ou thalidomide si IRIS corticorésistant**

HAS
HAUTE AUTORITÉ DE SANTÉ

Tnf Inhibitors to reduce Mortality in HIV-1 infected PAtients with tuberculosis meNIngitis: a phase II, multicenter, randomized clinical trial

TIMPANI - ANRS 12 404

Tuberculosis and Immune Reconstitution Inflammatory Syndrome in Patients With Inflammatory Bowel Disease and Anti-TNFα Treatment: Insights From a French Multicenter Study and Systematic Literature Review With Emphasis on Paradoxical Anti-TNFα Resumption

Ariane Amoura,[1,2] Thomas Frapard,[3,4] Xavier Treton,[5] Laure Surgers,[6,7] Laurent Beaugerie,[8] Matthieu Lafaurie,[9] Jean Marc Gornet,[10] Raphaël Lepeule,[11] Aurélien Amiot,[12] Etienne Canouï,[13] Vered Abitbol,[14] Antoine Froissart,[15] Mathias Vidon,[16] Yann Nguyen,[1,17] Agnès Lefort,[1,2] and Virginie Zarrouk[1]

Open Forum Infectious Diseases®
2024

- Etude rétrospective
- 36 patients avec MICI (31 Crohn) avec TB durant traitement par anti-TNF
- Temps médian d'anti-TNF de 8 mois
- 86% TB disséminée
- Anti-TNF arrêtés: 100%

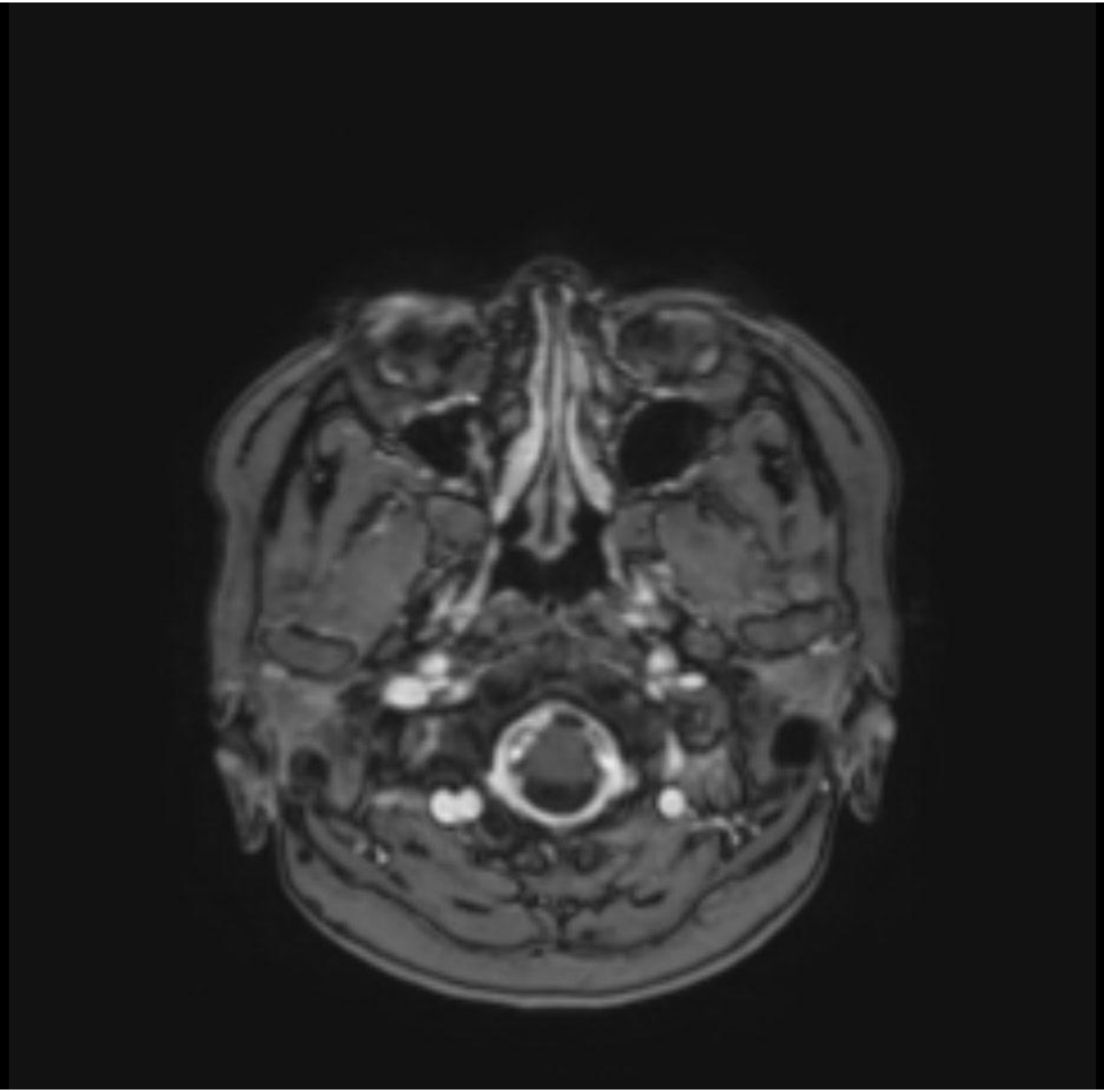
- 47% d'IRIS: CTC 53%, anti-TNF: 33%

- Reprise anti-TNF 66% après 4 mois anti(TB en médiane
- Une seule rechute

Tuberculome(s)

- **Infliximab:**
  - 6 cures
  - 5 mg/kg
  - Amélioration clinique majeure

- **1 an après fin du traitement:**
  - Etat général parfait
  - Pas de déficit moteur
  - Persiste une hypoacousie



Conclusions

- Association IRIS et TB fréquent
- Rarement grave mais peut l'être (méninges)
- Pas de CTC en préventif hors neuro
- Neuro: il reste de la place pour les CTC
- Place croissante des anti-TNF