Cas cliniques neuro-TB

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Mr W, 21 ans

- **Indien**
- **Arrivée en France, 2018 (étudiant)**
- **2019**
  - Céphalées (2 mois)
  - AEG (- 4 kg)
  - Fébricule
  - Diplopie
  - Ralentissement

- **Imagerie cérébrale normale**
- **VIH neg**
- **PL**
  - 354 éléments/mm3, 80% lymphos
  - Prot. 4 g/L
  - Glycorachie 1 mmol/L (HGT 4)
  - Recherche BAAR négative

Que faites vous?

1. Isolement respiratoire ‘air’
2. Imagerie thoracique
3. PCR BK sur le LCS
4. Test IGRA
5. Nouvelle PL avec gros volume LCS (120 gouttes)

Que faites vous?

1. **Isolement respiratoire ‘air’**
2. **Imagerie thoracique**
3. **PCR BK sur le LCS**
4. Test IGRA
5. **Nouvelle PL avec gros volume LCS (120 gouttes)**

British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children

Guy Thwaites [a,*,h], Martin Fisher [b,i], Cheryl Hemingway [c,j], Geoff Scott [d,k], Tom Solomon [e,l], John Innes [f,g,m]

- **Messages**
  - Urgence thérapeutique
  - Corticoides pour tous
  - Rentabilité meilleure si 6 mL LCS

Cerebrospinal fluid	
Clear appearance	80–90%
Opening pressure >25 cm H_20	50%
Leucocyte count ($\times 10^3$/ml)	5–1000
Neutrophils	10–70%
Lymphocytes	30–90%
Protein (g/L)	0.45–3.0[a]
Lactate (mmol/L)	5.0–10.0
CSF glucose:blood glucose < 0.5	95%

Thwaites GE et al. J Infect 1989

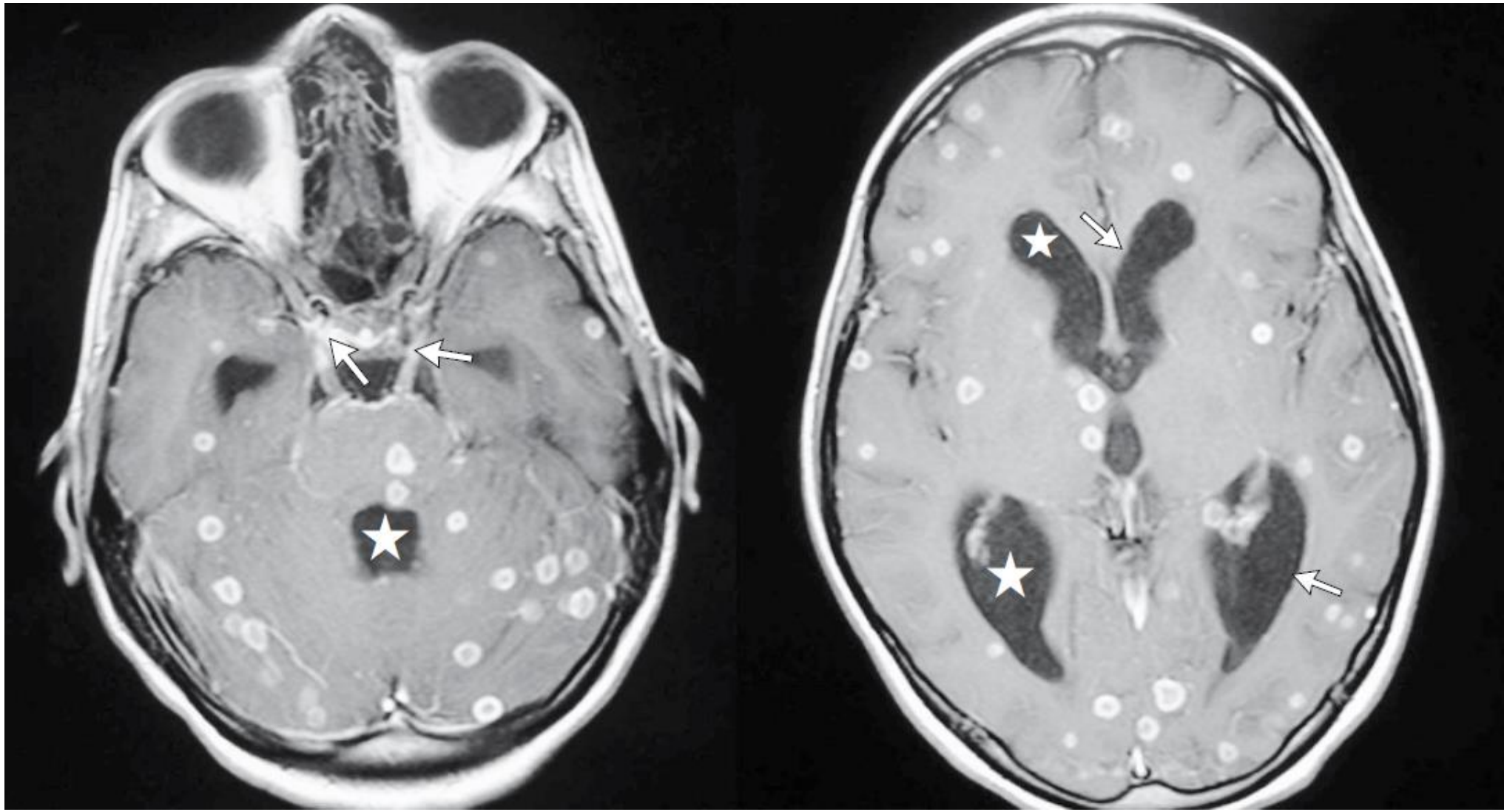
Tout revient négatif. Que proposez vous?

1. Attendre les cultures de LCS
2. Quadrithérapie anti-TB
3. Corticothérapie
4. Test IGRA sur le LCS
5. Nouvelle PL avec gros volume LCS (120 gouttes)

Tout revient négatif. Que proposez vous?

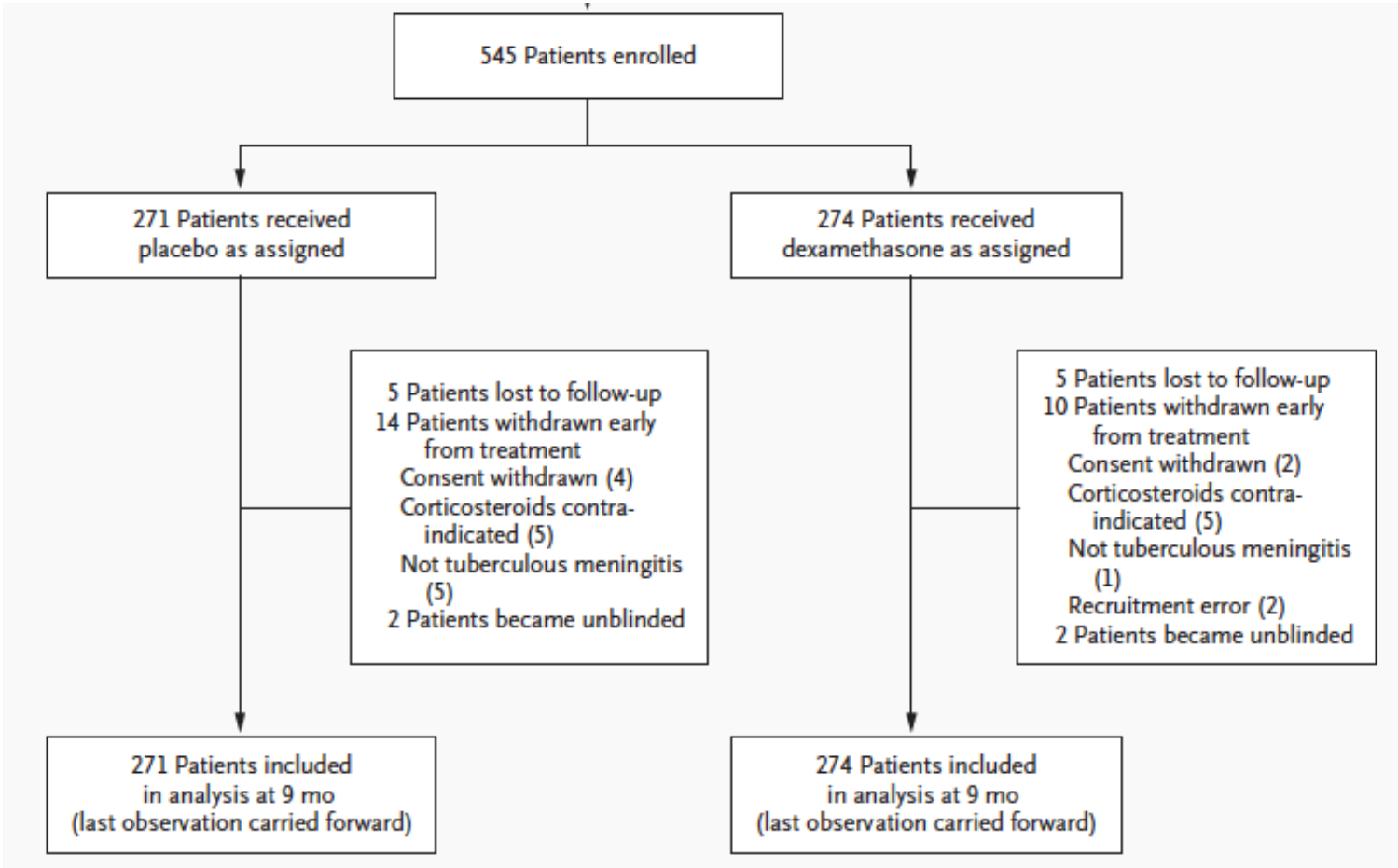
1. Attendre les cultures de LCS
2. **Quadrithérapie anti-TB**
3. **Corticothérapie**
4. Test IGRA sur le LCS
5. Nouvelle PL avec gros volume LCS (120 gouttes)

J45: dégradation rapide fonctions sup



ORIGINAL ARTICLE

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults



Thwaites GE et al. N Engl J Med 2004

Dexamethasone in TB meningitis

Poor GCS patients Intravenous dexamethasone for 4 weeks

Week	Dose Dexamethasone IV
1	0.4mg/Kg/Day
2	0.3
3	0.2
4	0.1
Taper as oral Dexamethasone 4mg/day, 3mg/day, 2mg/day & 1mg/day each for 1 week	

Dexamethasone in TB meningitis

Week	Dose Dexamethasone IV
3	0.2
4	0.1
Taper as oral Dexamethasone 4mg/day, 3mg/day, 2mg/day & 1mg/day each for 1 week	

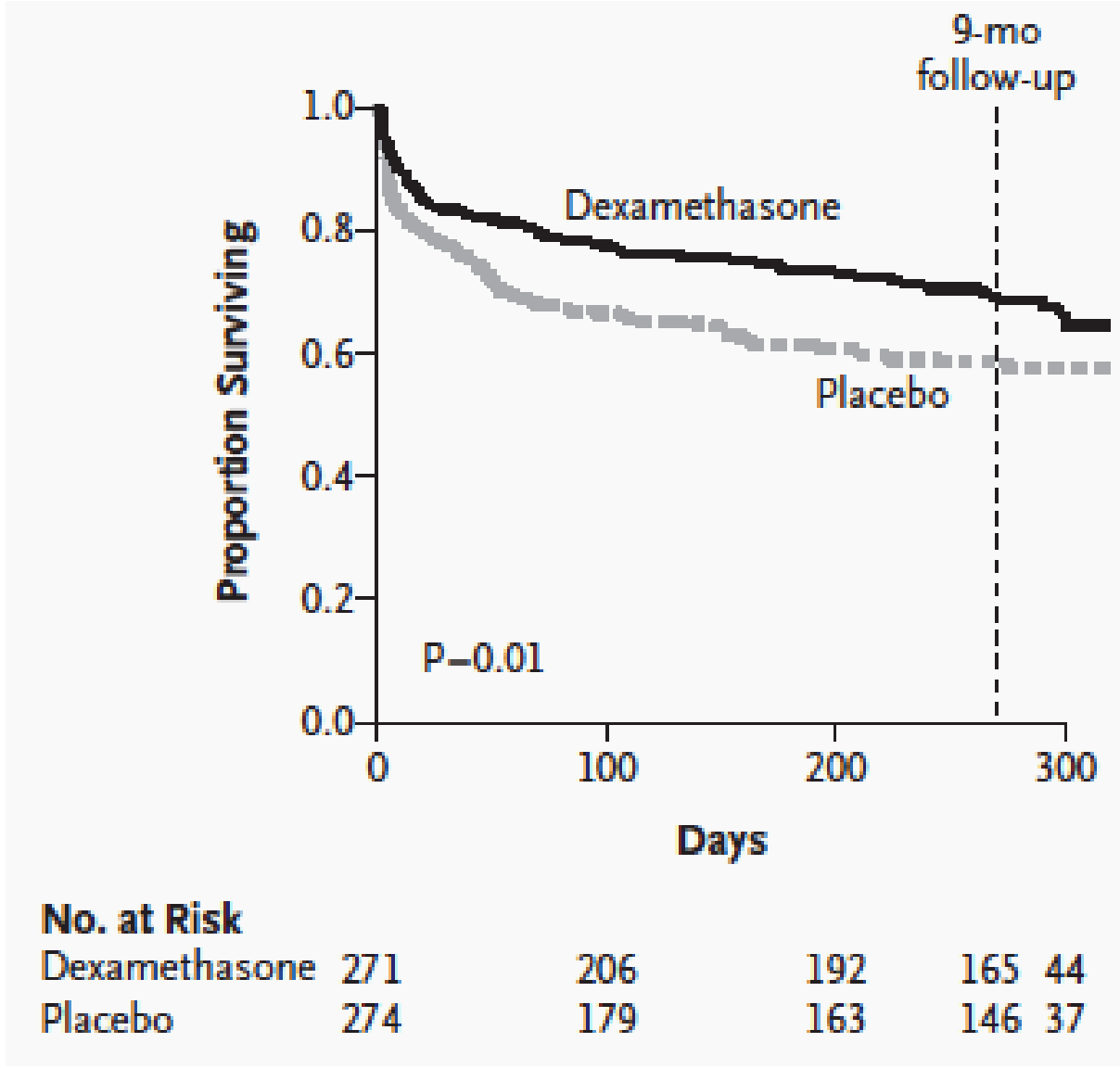
Pronostic en fonction de la gravité initiale

TABLE 1. British Medical Research Council clinical criteria for the severity of TBM[a]

Stage/grade	Classic criterion[b]	Contemporary criterion[c]
I	Fully conscious and no focal deficits	Alert and oriented without focal neurological deficits
II	Conscious but with inattention, confusion, lethargy, and focal neurological signs	Glasgow coma score of 14-11 or 15 with focal neurological deficits
III	Stuporous or comatose, multiple cranial nerve palsies, or complete hemiparesis or paralysis	Glasgow coma score of 10 or less, with or without focal neurological deficits

Outcome and Group	Dexamethasone	Placebo	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Death				
All patients	87/274 (31.8)	112/271 (41.3)	0.69 (0.52–0.92)	0.01
Grade				
I	15/90 (16.7)	26/86 (30.2)	0.47 (0.25–0.90)	0.02
II	38/122 (31.1)	50/125 (40.0)	0.71 (0.46–1.1)	0.11
III	34/62 (54.8)	36/60 (60.0)	0.81 (0.51–1.29)	0.38
Relative risk of death stratified according to grade†			0.68 (0.52–0.91)	0.007
HIV status				
Negative	57/227 (25.1)	67/209 (32.1)	0.72 (0.51–1.02)	0.07
Positive	27/44 (61.4)	37/54 (68.5)	0.86 (0.52–1.41)	0.55

Thwaites et al, NEJM 2004



Thwaites GE et al. N Engl J Med 2004

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., Dau T.T. Huong, M.Sc., Nguyen T.T. Hiep, M.D., Lam H.B. Ngoc, B.Sc., Dang V. Thanh, M.D.,

La dexaméthasone est-elle bénéfique au cours des TB neuro-méningées des PVVIH ?

- **Etude randomisée multicentrique double aveugle**
- **Vietnam, n = 520**
  - *Jamais reçu d'ARV = 50%*
  - *CD4 < 50/mm^3 = 50%*
- **Dexaméthasone, 6-8 semaines**
- **Critère principal: Survie à M12**

Donovan J et al. N Engl J Med 2023

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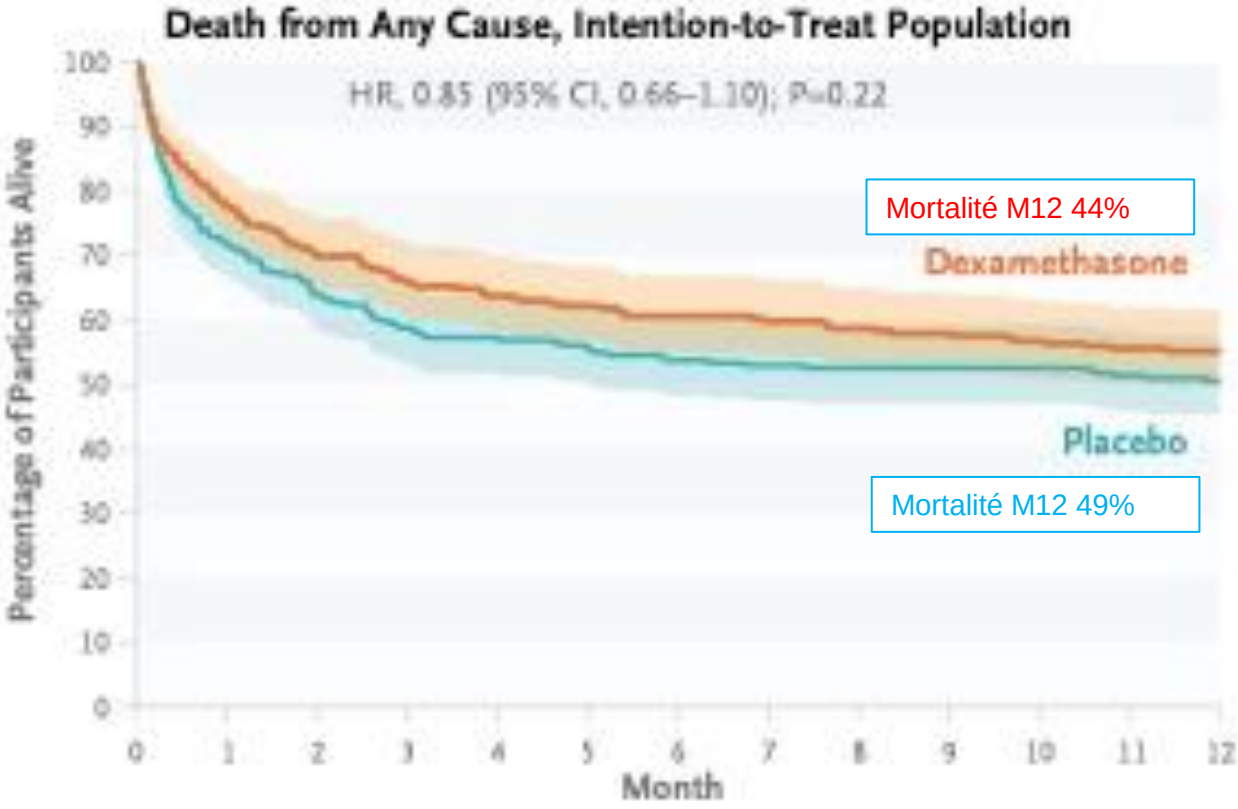
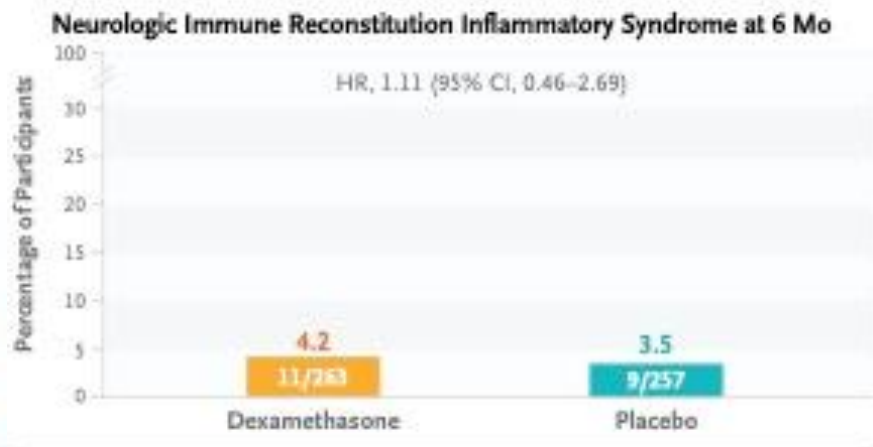


Mortalité M12 44%

Mortalité M12 49%



Dexaméthasone sans intérêt pour les TB neuro-méningées des PVVIH ?

Donovan J et al. N Engl J Med 2023

Quelles autres indications des CTC ?

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Recommendation 7: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis *(conditional recommendation; very low certainty in the evidence)*.

Supplementary Appendix B, Evidence Profile 14). However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction [76].

Nahid P et al. Clin Infect Dis 2016

Prednisolone and *Mycobacterium indicus pranii* in Tuberculous Pericarditis

B.M. Mayosi, M. Ntsekhe, J. Bosch, S. Pandie, H. Jung, F. Gumedze, J. Pogue, L. Thabane, M. Smieja, V. Francis, L. Joldersma, K.M. Thomas, B. Thomas, A.A. Awotedu, N.P. Magula, D.P. Naidoo, A. Damasceno, A.C. Banda,

- **Etude randomisée multicentrique double aveugle**
- **Afrique du Sud, n = 1400**
  - *2/3 PVVIH*
  - *Jamais reçu d'ARV = 85%*
- **Prednisolone:** 120 mg/j (S1), puis 90 (S2), 60 (S3), 30 (S4), 15 (S5), 5 (S6)
- **Critère principal composite:**
  - *Décès*
  - *Tamponnade => drainage*
  - *Péricardite constrictive*

Mayosi BM et al. N Engl J Med 2014

Prednisolone and *Mycobacterium indicus pranii* in Tuberculous Pericarditis

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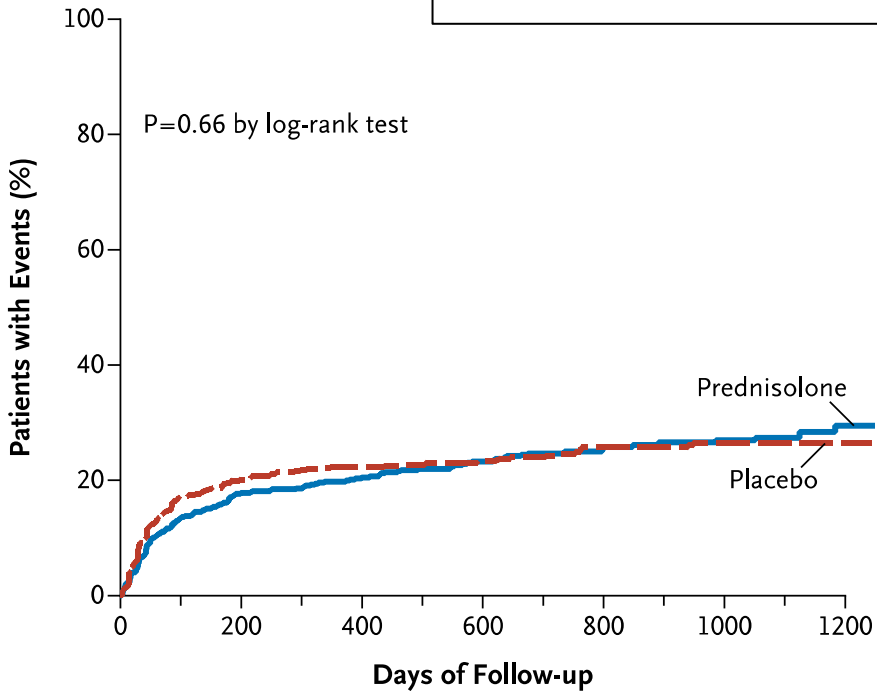
Etude stoppée pour futilité après médiane de 2 ans de suivi

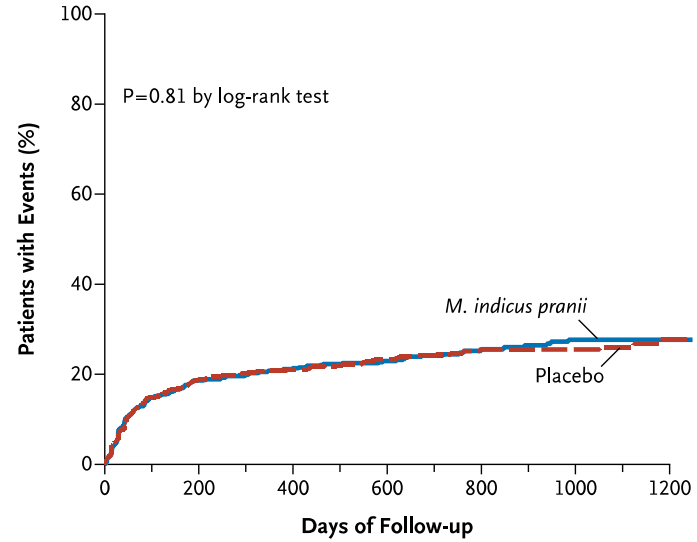
A Prednisolone Comparison



No. at Risk

Prednisolone	706	600	511	502	426	418	335	306	186	182	106	65	60
Placebo	694	572	487	473	404	395	316	289	185	181	111	84	73

B *Mycobacterium indicus pranii* Comparison



No. at Risk

M. indicus pranii	625	527	491	484	410	401	321	289	182	176	106	73	62
Placebo	625	524	488	480	420	420	330	306	189	187	111	76	71

Mayosi BM et al. N Engl J Med 2014

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Outcome	Prednisolone (N = 706)		Placebo (N = 694)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*		
Primary composite outcome: death, cardiac tamponade, or constrictive pericarditis	168 (23.8)	14.3	170 (24.5)	14.8	0.95 (0.77–1.18)	0.66
Secondary outcomes						
Death from any cause	133 (18.8)	10.6	115 (16.6)	9.1	1.15 (0.90–1.48)	0.26
Cardiac tamponade	22 (3.1)	1.8	28 (4.0)	2.3	0.77 (0.44–1.35)	0.37
Constrictive pericarditis	31 (4.4)	2.58	54 (7.8)	4.56	0.56 (0.36–0.87)	0.009
Hospitalization	146 (20.7)	13.27	175 (25.2)	16.7	0.79 (0.63–0.99)	0.04

Mayosi BM et al. N Engl J Med 2014

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Outcome	Prednisolone (N = 706)		Placebo (N = 694)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*		
Opportunistic infection	78 (11.0)	6.89	68 (9.8)	5.91	1.16 (0.84–1.61)	0.36
Candida infection	54 (7.6)	4.68	36 (5.2)	3.01	1.52 (1.00–2.32)	0.05
Cancer	13 (1.8)	1.05	4 (0.6)	0.32	3.27 (1.07–10.03)	0.03
HIV-related cancer	9 (1.3)	0.73	1 (0.1)	0.08	9.04 (1.14–71.33)	0.04
Immune reconstitution disease	2 (0.3)	0.16	1 (0.1)	0.08	2.02 (0.18–22.28)	0.56

Mayosi BM et al. N Engl J Med 2014

Quelles autres indications des CTC ?

- **Formes graves**
- **Formes cachectiques + miliaires**
- **Compressions ?**

  - **=> discussions multidisciplinaires**

Quelles sont les principales pistes pour intensifier le traitement des neuro-TB ?

1. Rifampicine per os fortes doses (35 mg/kg/j)
2. Rifampicine intraveineuse
3. Linézolide
4. Lévofloxacine
5. Bédaquiline

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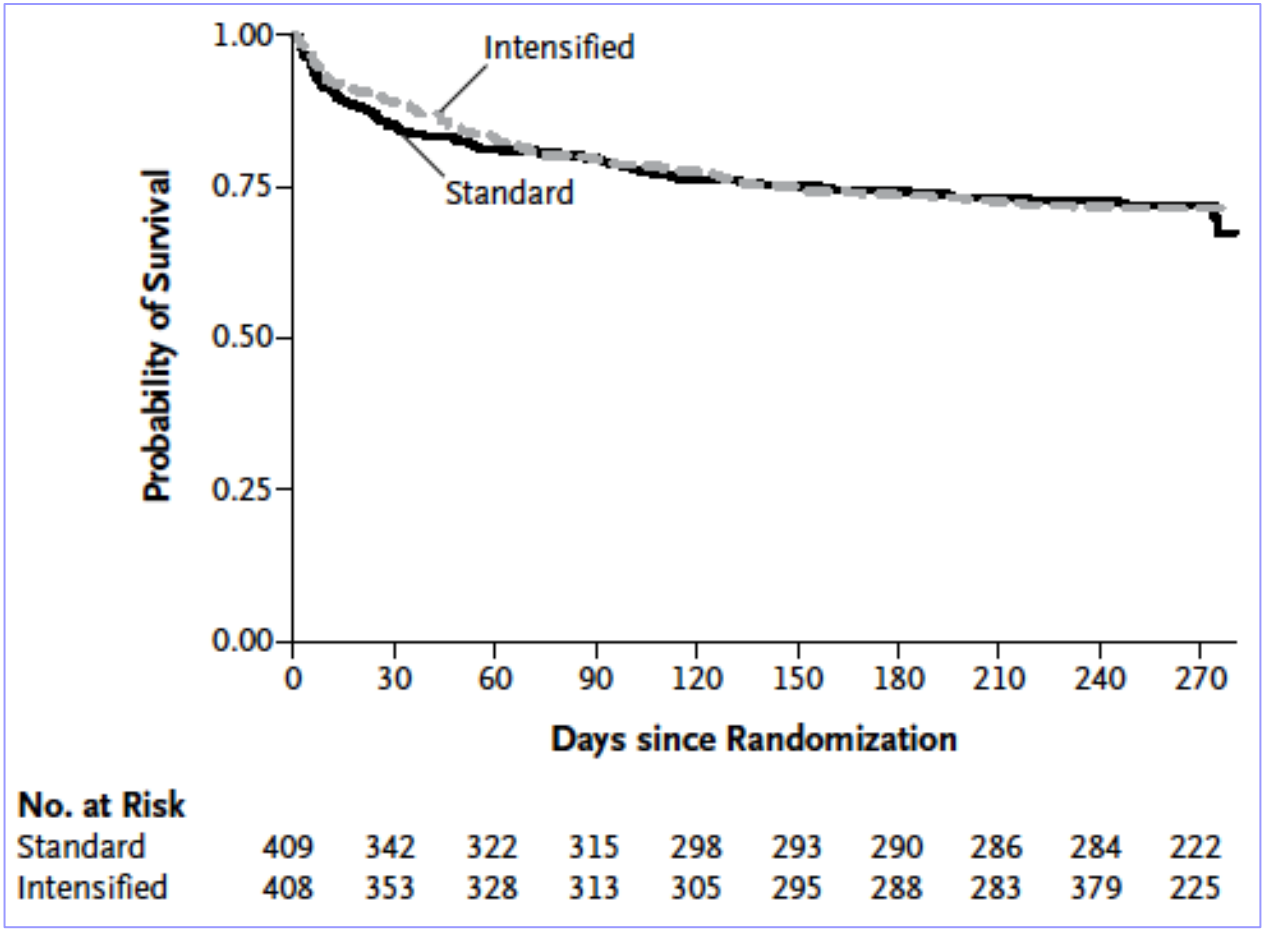
5. Bédaquiline

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

- **Traitement TB neuro-méningée intensifié**
  - Total 9 mois
  - 2RHZE/7RH
  - Dexamethasone => S8
  - Bras ‘intensifié’ => S8
    - **RMP 15 mg/kg/j**
    - **Lévoflo 20 mg/kg/j**



Heemskerk AD et al. N Engl J Med 2016

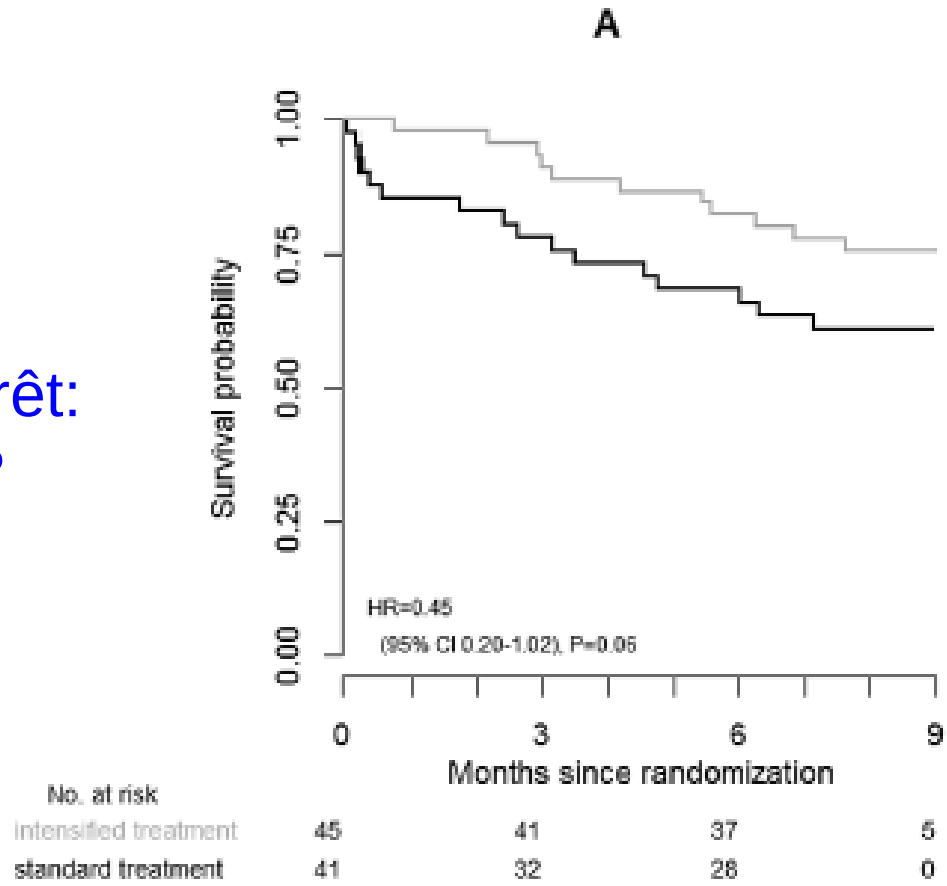
Clinical Infectious Diseases

Clinical Outcomes of Patients With Drug-Resistant Tuberculous Meningitis Treated With an Intensified Antituberculosis Regimen

Clinical Infectious Diseases® 2017;65(1):20–8

A. Dorothee Heemskerk,[1,2] Mai Thi Hoang Nguyen,[1] Ha Thi Minh Dang,[1,3] Chau Van Vinh Nguyen,[1,4] Lan Huu Nguyen,[3] Thu Dang Anh Do,[1] Thuong Thuy Thuong Nguyen,[1] Marcel Wolbers,[1,2] Jeremy Day,[1,2] Thao Thi Phuong Le,[1] Bang Duc Nguyen,[1,3] Maxine Caws,[1,5] and Guy E. Thwaites[1,2]

Un groupe avec intérêt:
TB INH-R / RMP-S ?



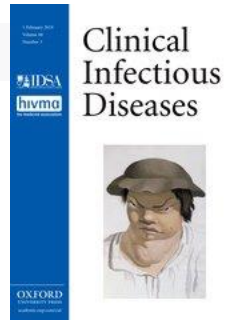
Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

High-Dose Oral and Intravenous Rifampicin for the Treatment of Tuberculous Meningitis in Predominantly Human Immunodeficiency Virus (HIV)-Positive Ugandan Adults: A Phase II Open-Label Randomized Controlled Trial

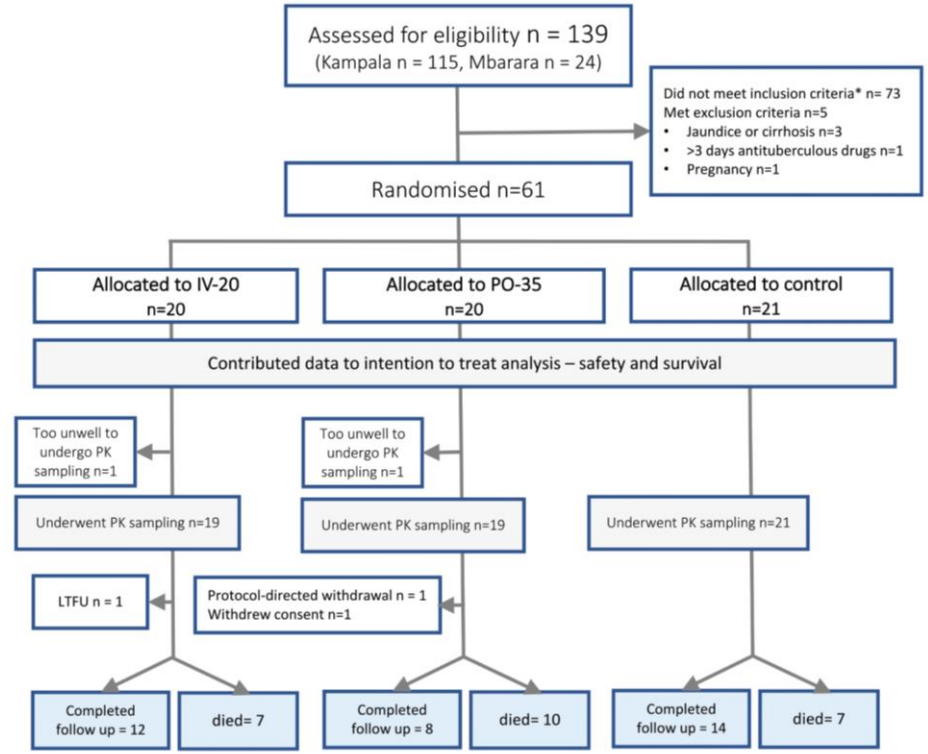
Fiona V. Cresswell,[1,2,3] David B. Meya,[2] Enock Kagimu,[2] Daniel Grint,[4] Lindsey te Brake,[5] John Kasibante,[2] Emily Martyn,[1] Morris Rutakingirwa,[2] Carson M. Quinn,[6] Micheal Okirwoth,[2] Lillian Tugume,[2] Kenneth Ssembambulidde,[2] Abdu K. Musubire,[2] Ananta S. Bangdiwala,[7] Allan Buzibye,[2] Conrad Muzoora,[8] Elin M. Svensson,[5,9] Rob Aarnoutse,[5] David R. Boulware,[10,a] and Alison M. Elliott[1,3,a]



- **Traitement TB neuro-méningée + intensifié**
  - RHZE standard
  - *Avec RMP* ***iv 20 mg/kg***
  - *Avec RMP* ***oral 35 mg/kg***

✓**Etude pilote (n=61)**

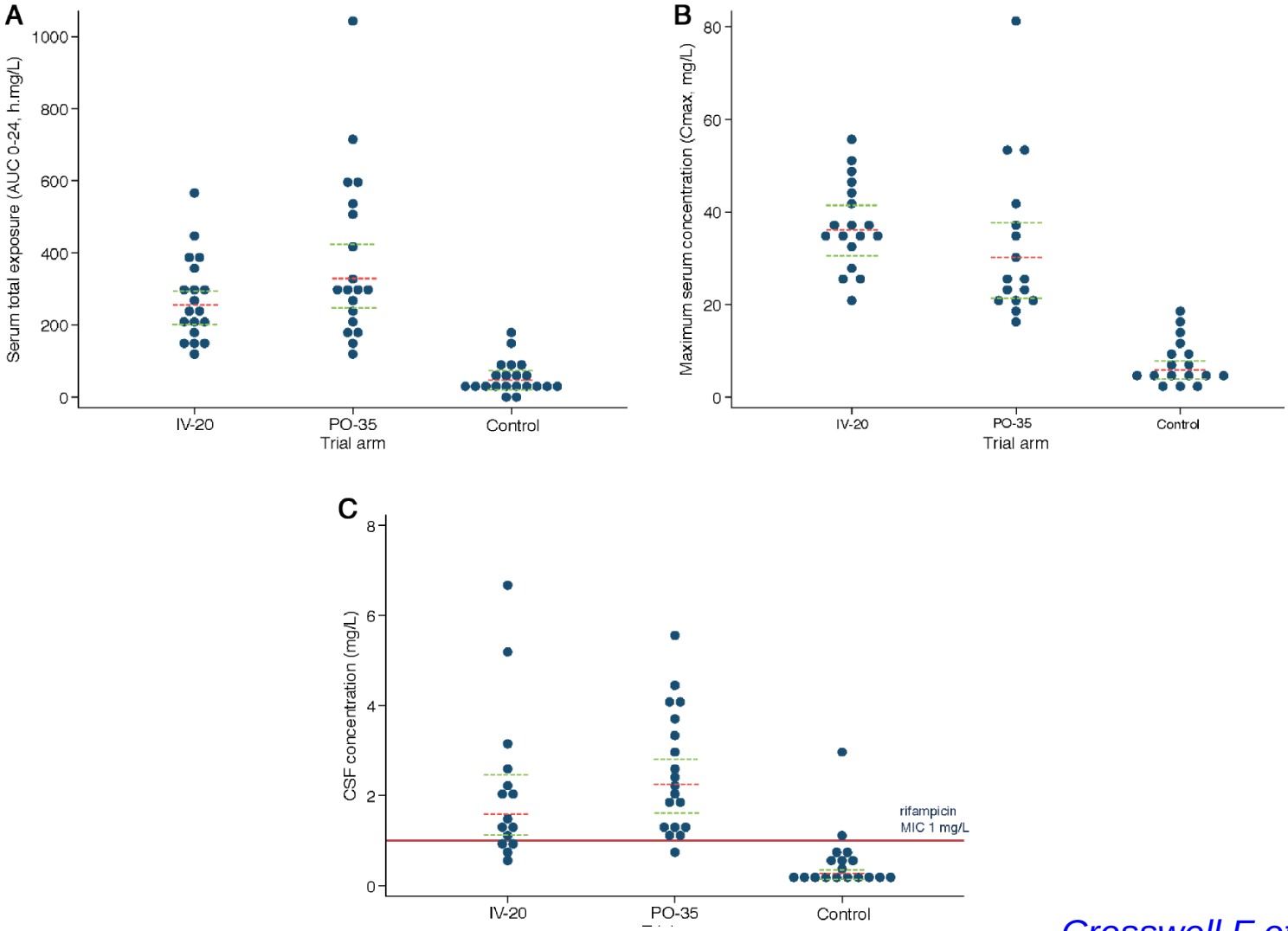
✓**PK + tolérance**



Cresswell F et al. Clin Infect Dis 2021

High-Dose Oral and Intravenous Rifampicin for the Treatment of Tuberculous Meningitis in Predominantly Human Immunodeficiency Virus (HIV)-Positive Ugandan Adults: A Phase II Open-Label Randomized Controlled Trial

Clinical Infectious Diseases



Cresswell F et al. Clin Infect Dis 2021

Clinical Infectious Diseases

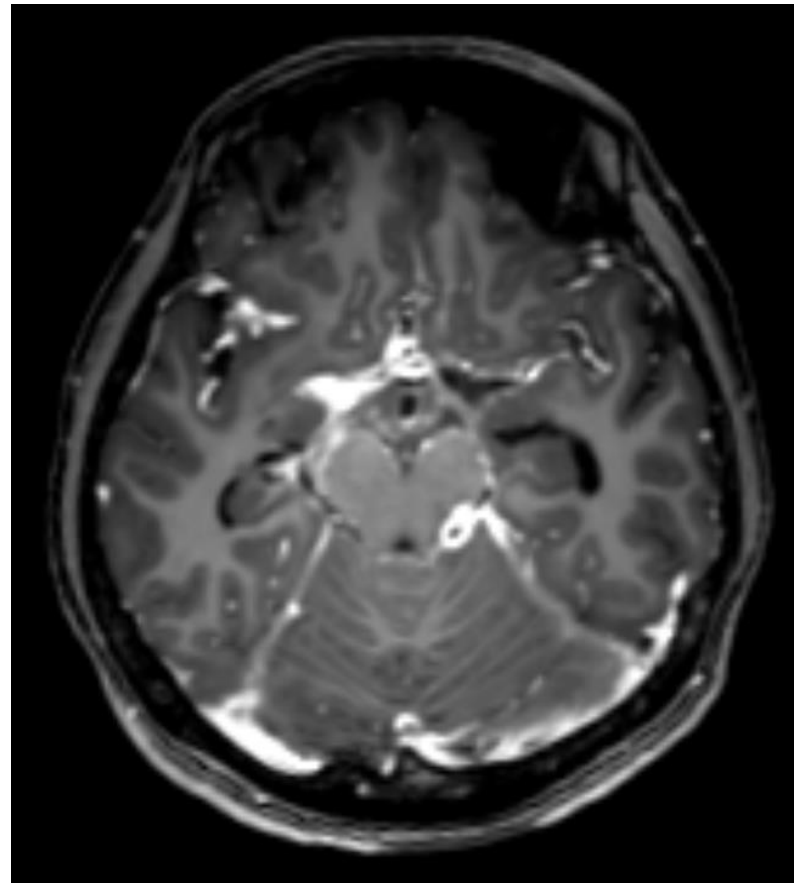
MAJOR ARTICLE

A Phase 2A Trial of the Safety and Tolerability of Increased Dose Rifampicin and Adjunctive Linezolid, With or Without Aspirin, for Human Immunodeficiency Virus–Associated Tuberculous Meningitis: The LASER-TBM Trial

Angharad G. Davis,[1,2,3] Sean Wasserman,[3,4] Cari Stek,[3,5] Mpumi Maxebengula,[3] C. Jason Liang,[6] Stephani Stegmann,[3] Sonya Koekemoer,[3] Amanda Jackson,[3] Yakub Kadernani,[3] Marise Bremer,[3] Remy Daroowala,[3,5] Saalikha Aziz,[3] Rene Goliath,[3] Louise Lai Sai,[3] Thandi Sihoyiya,[3] Paolo Denti,[7] Rachel P. J. Lai,[1,5] Thomas Crede,[8] Jonathan Naude,[8] Patryk Szymanski,[8] Yakoob Vallie,[9] Ismail Abbas Banderker,[8] Muhammed S. Moosa,[9] Peter Raubenheimer,[4] Sally Candy,[10] Curtis Offiah,[11] Gerda Wahl,[12] Isak Vorster,[10] Gary Maartens,[3,7] John Black,[12] Graeme Meintjes,[3,4] and Robert J. Wilkinson[1,2,3,4,5]

Femme, 33 ans, Cambodgienne

- AEG, fièvre (1 mois), dyspnée, confusion (Avr 2015)

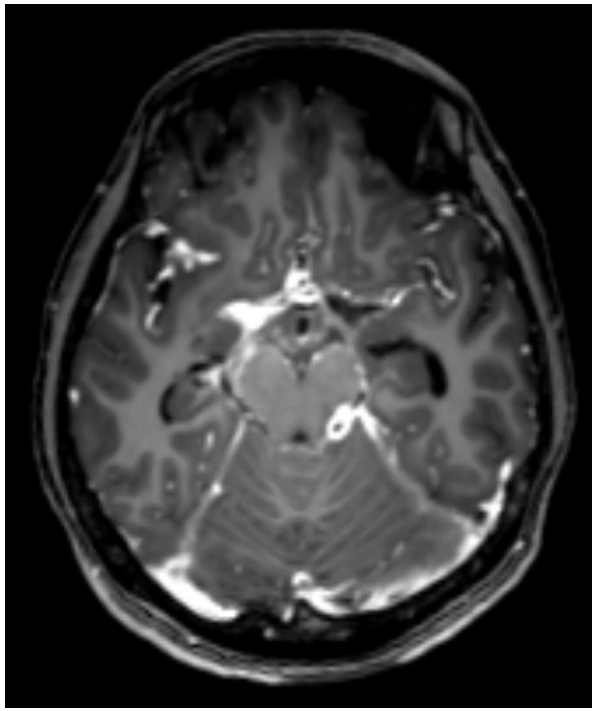


- Méningite
  - 300 élts/mm3 (90% lymphos)
  - Prot. 3 g/L
  - Glycorachie 25% de la glycémie
- **PCR BK+**
- VIH neg
- **Anti-TB + CTC**

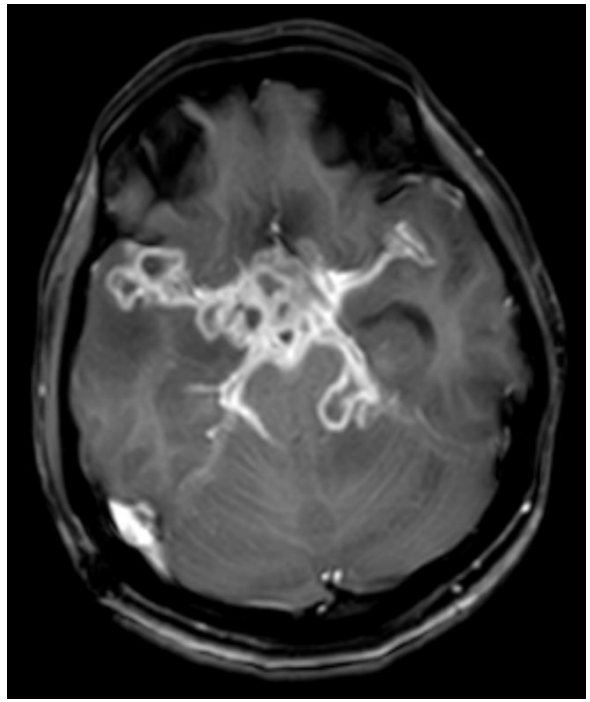
Femme, 33 ans, Cambodgienne

- Initialement mieux, mais à J30 (début baisse CTC), aggravation

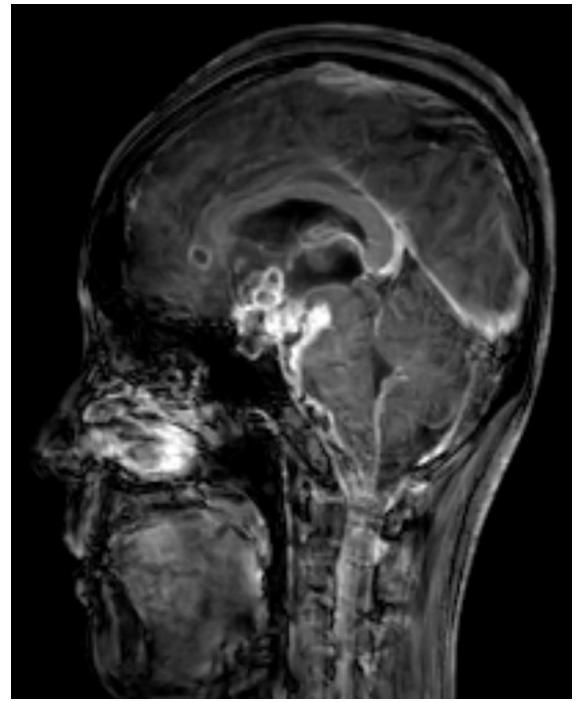
J1



J30



J30



Femme, 33 ans, Cambodgienne

- Initialement mieux, mais à J30 (début baisse CTC), aggravation
- Hydrocéphalie non communicante => avis neurochir

  => dérivation + septotomie
- **Contrôle PL J30:**
  - Méningite lymphocytaire, 300 => 200 élts/mm3
  - Protéinorachie: 3 => 2 g/l
  - Hypoglycorachie: 25% => 35%

Que pensez-vous de cette évolution du LCS?

1. C’est habituel, dans les méningites bactériennes, de garder des anomalies majeures sur plusieurs semaines
2. Cette évolution du LCS confirme l’échec thérapeutique
3. Cette évolution du LCS est classique dans la neuro-TB
4. Refaire la PL était une erreur, ça ne sert à rien
5. Je ne pense rien, je vais regarder dans la littérature

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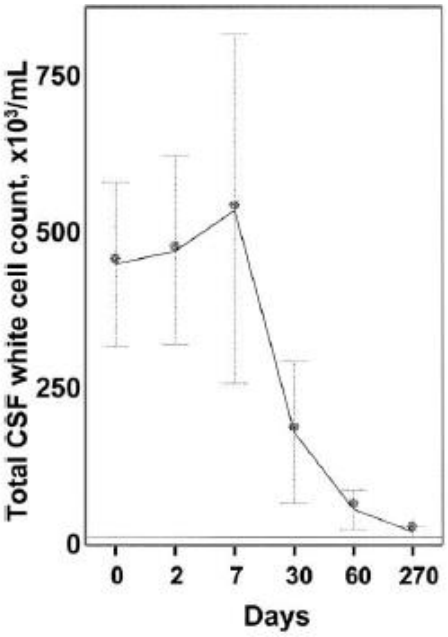
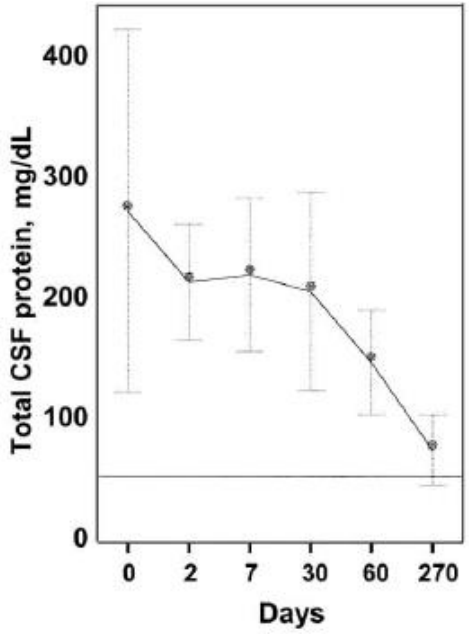
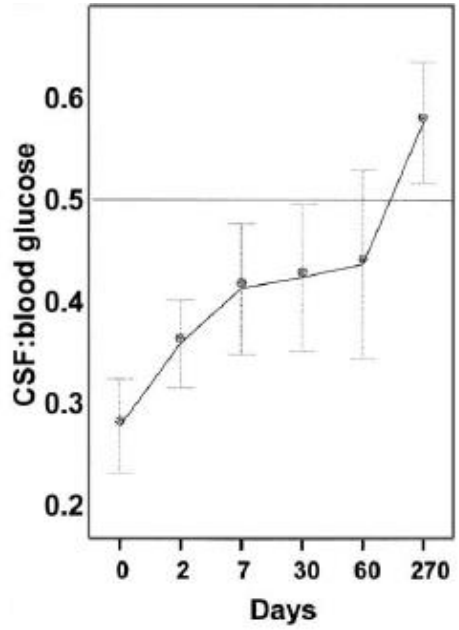
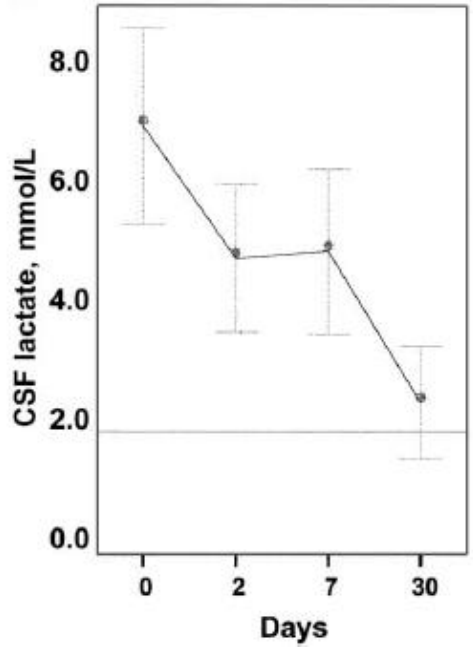
Pathophysiology and Prognosis in Vietnamese Adults with Tuberculous Meningitis







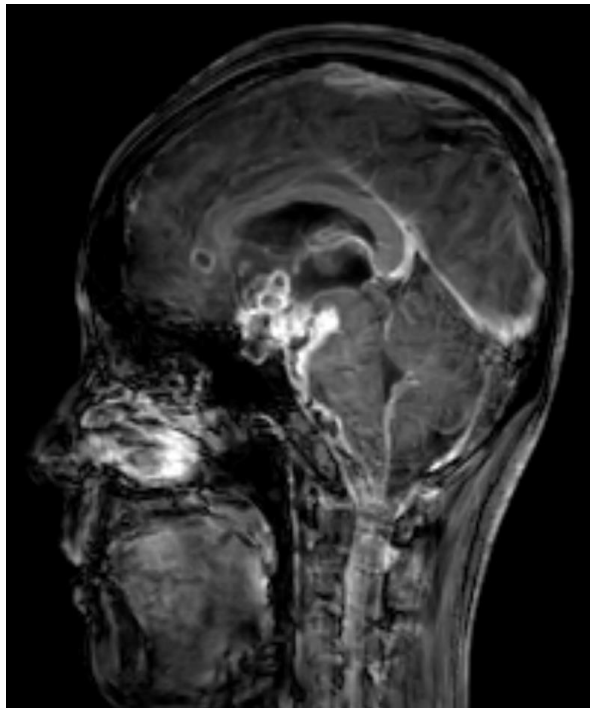


Thwaites GE et al. J Infect Dis 2003

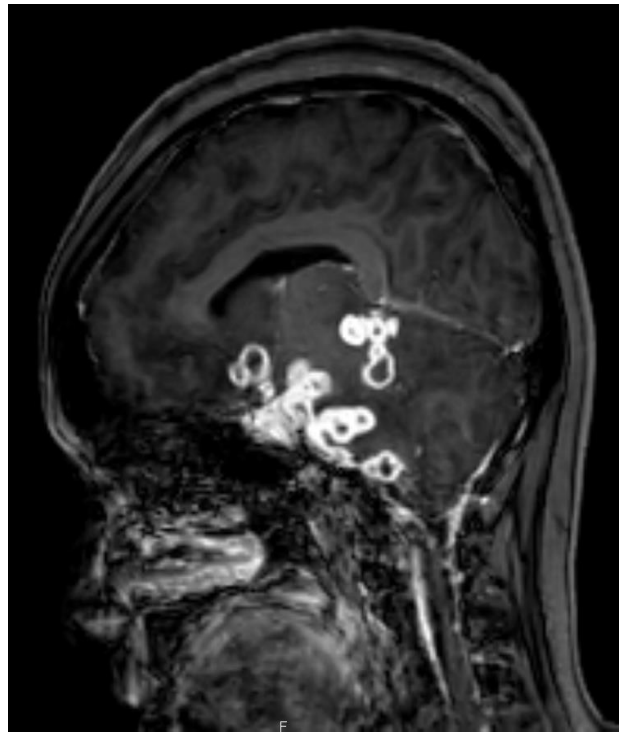
Femme, 33 ans, Cambodgienne

- Reprise CTC 1 mg/kg/j, mieux, mais cortico-dépendance +++

J30



J220



J220

Que proposez-vous ?

1. On poursuit à 1 mg/kg/j de prednisolone pendant 1 an
2. On intensifie le traitement anti-TB (RMP fortes doses)
3. Traitement anti-TNF
4. Discussion chirurgicale pour exérèse lésions principales
5. Je ne sais pas, je demande à ceux qui connaissent…

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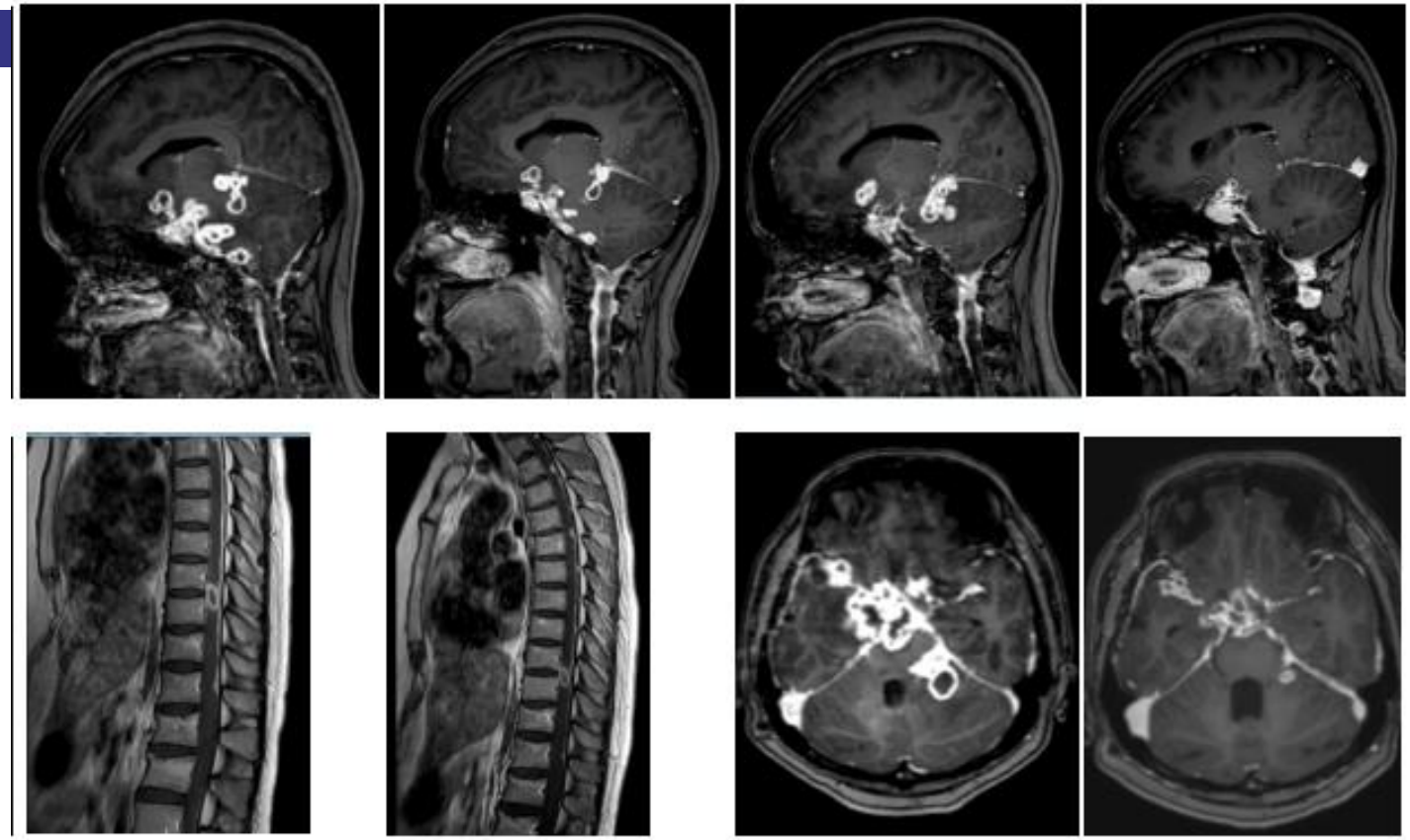

December 2015

March 2016

May 2016

February 2017

3 injections of Infliximab

6 injections of Infliximab

Stop antituberculous therapy

Stop corticotherapy

The use of TNF-α antagonists in tuberculosis to control severe paradoxical reaction or immune reconstitution inflammatory syndrome: a case series and literature review

Lucas Armange[1,2] · Adèle Lacroix[3] · Paul Petitgas[1] · Cédric Arvieux[1] · Caroline Piau-Couapel[4] · Patrice Poubeau[2] Matthieu Revest[1] · Pierre Tattevin[1]

	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%)
Lymph nodes	2/12	2/6	2/6	6/24 (25%)
Miliary	2/12	2/6	2/6	6/24 (25%)
Others[£]	3/12	2/6	1/6	6/24 (25%)

Armange L et al. Eur Clin Microbiol Infect Dis 2023

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	Paradoxical reaction (PR) (*n*=12)	Immune reconstitution inflammatory syndrome (IRIS, *n*=12)		Total (*n*=24)
		HIV-infected (*n*=6)	Others (*n*=6)	
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%)

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Aucune flambée de TB sous infliximab (n=24)

=> Nos 'propositions'

- **Infliximab** pour TB neuro-méningées cortico-résistantes ou cortico-dépendantes

- **5 mg/kg à S0, S2 et S6,** puis
  - surveillance armée
  - ou 'maintenance' (5 mg/kg toutes les 8 semaines) ?

Armange L et al. Eur Clin Microbiol Infect Dis 2023

Neuro-TB: messages

Gold standard 2024

- ✓ **Traitement prolongé (9-12 mois), monitoring PK, CTC systématiques**

Perspectives

- ✓ **Traitements intensifiés (RMP fortes doses, FQ, linézolide, aspirine ?)**

(INTENSE-TBM: Intensified tuberculosis treatment to reduce the high mortality of tuberculous meningitis in HIV- infected and uninfected patients)

- ✓ **Anti-TNF précoces pour TB neuro-méningées (+/- CTC) ?**

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