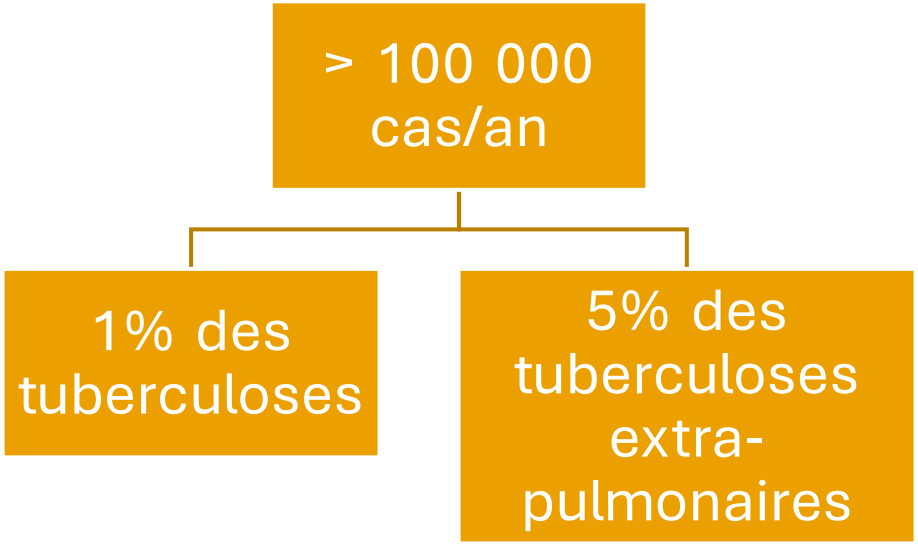
Traitement de la tuberculose neuro-méningée perspectives et défis

Rim Abdelmalek

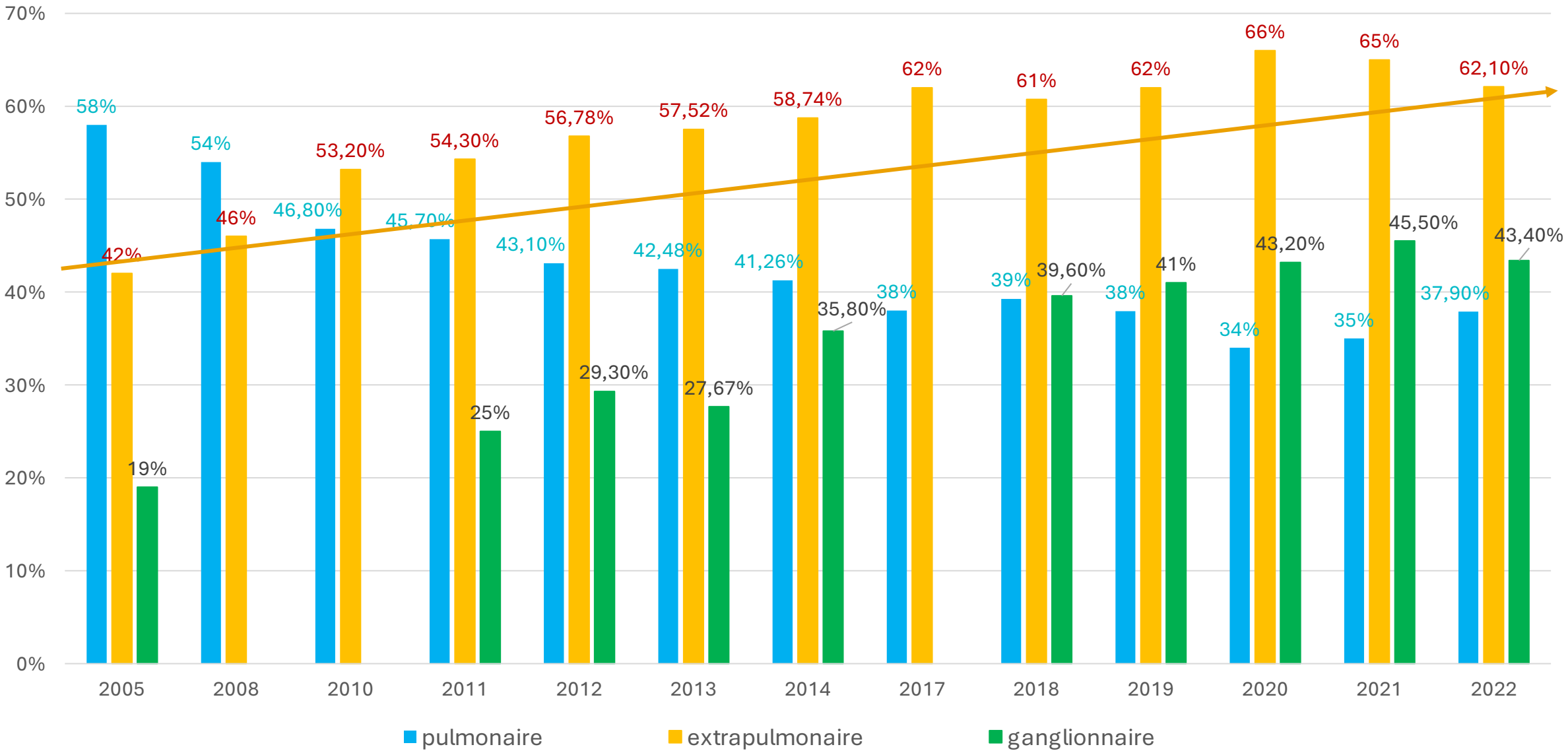
24/5/2025

Maladie grave



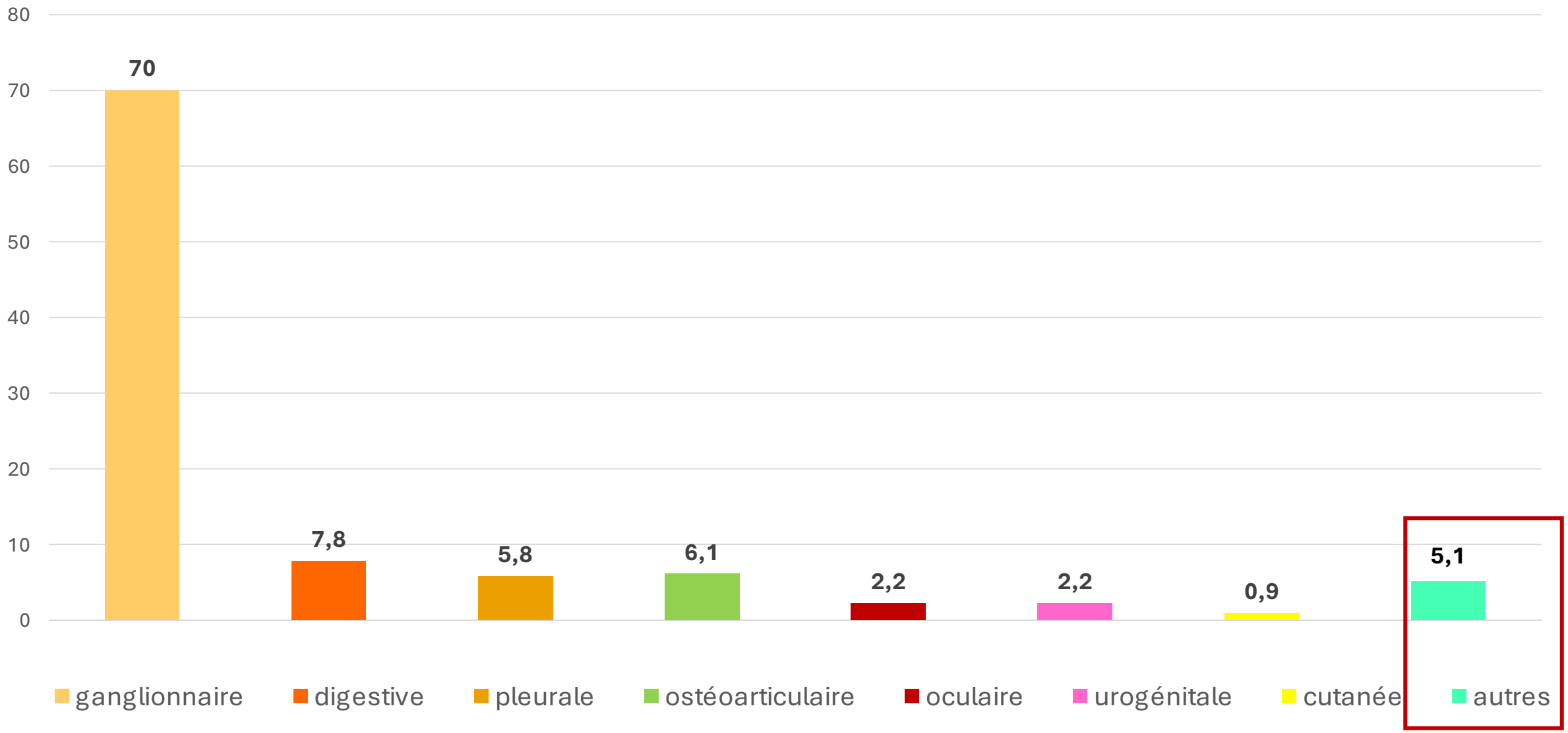
Tuberculose en Tunisie

PNLT



Localisations extra-pulmonaires 2022

PNLT



Données maladies infectieuses Rabta

124 cas

- 9 ans

Morbi-mortalité importante
Diagnostic tardif
Aggravation paradoxale

Evolution

- Réanimation 19
  15,3%
- Neurochirurgie 13
  10,4%
  - 5 hydrocéphalie
  - 8 exérèse masse/abcès
  - 1 biopsie
- Décès 33
  26,6%

91 survivants

- 8 perdus de vue
- 37 séquelles : 29,8%
  (40,6%)
  - 19 déficit neurologique
  - 11 troubles cognitifs
  - 9 céphalées chroniques
  - 7 épilepsie

Maladie grave / réanimation

Majoration pression intra-crânienne

Infarctus cérébral

Tuberculome

Hyponatrémie
SIADH

Réaction paradoxale

Arachnoïdite
Hydrocéphalie

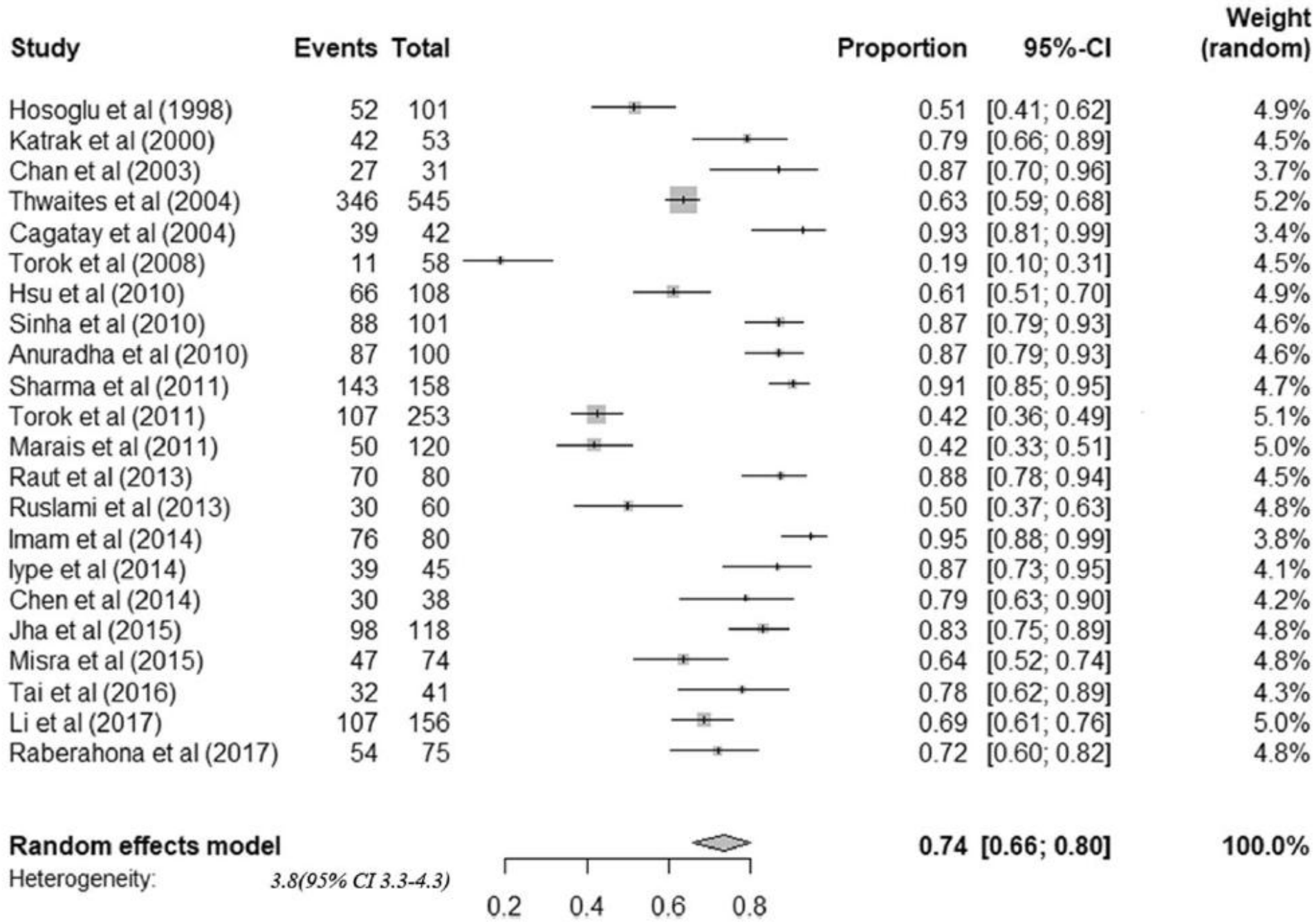
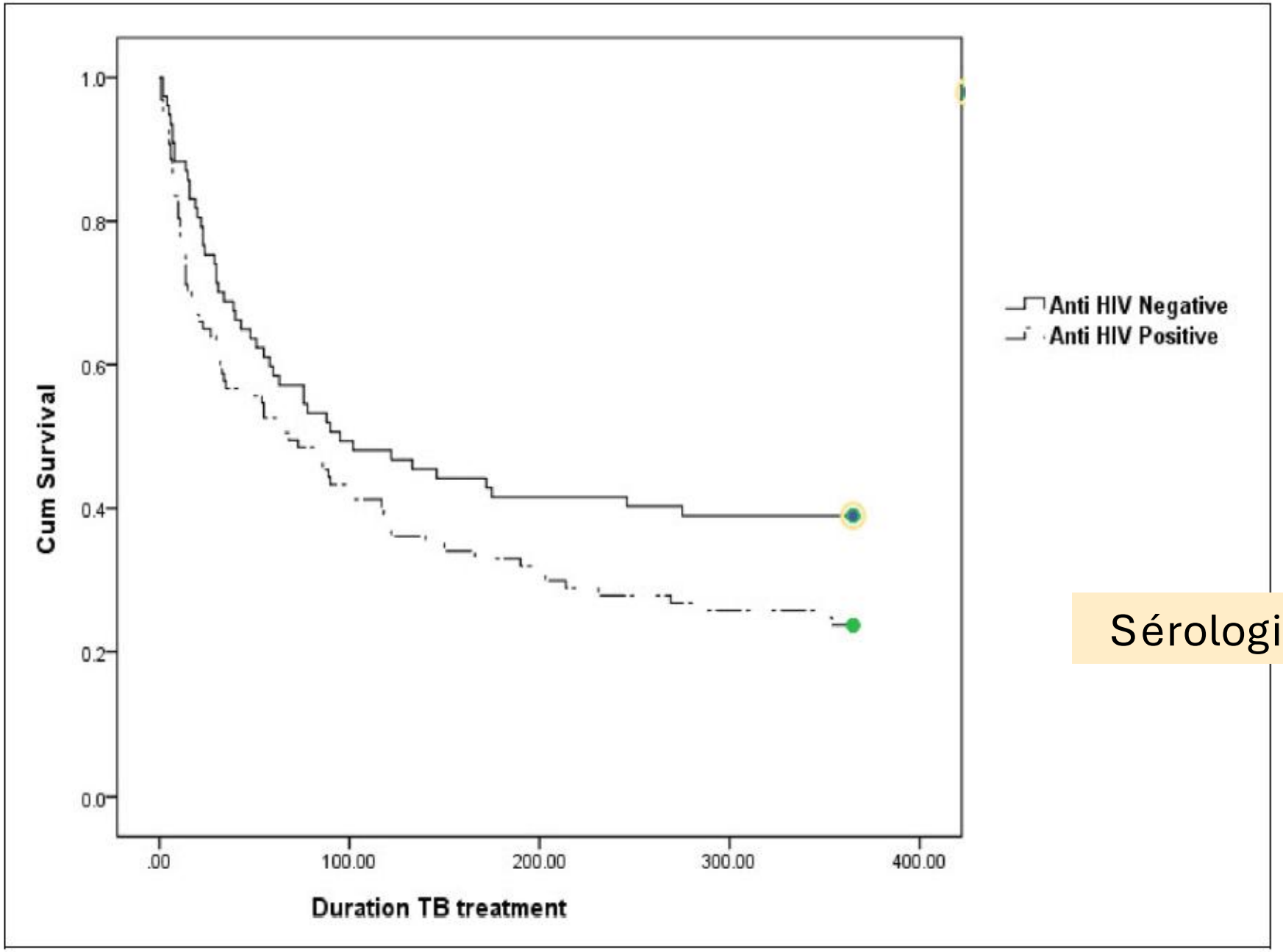


Fig. 4 Frequency of neurological sequelae among survivors



Sérologie VIH +++

Figure 2. Kaplan–Meier curves of time to tuberculous meningitis (TBM) treatment failure stratified by human immunodeficiency virus (HIV) status.

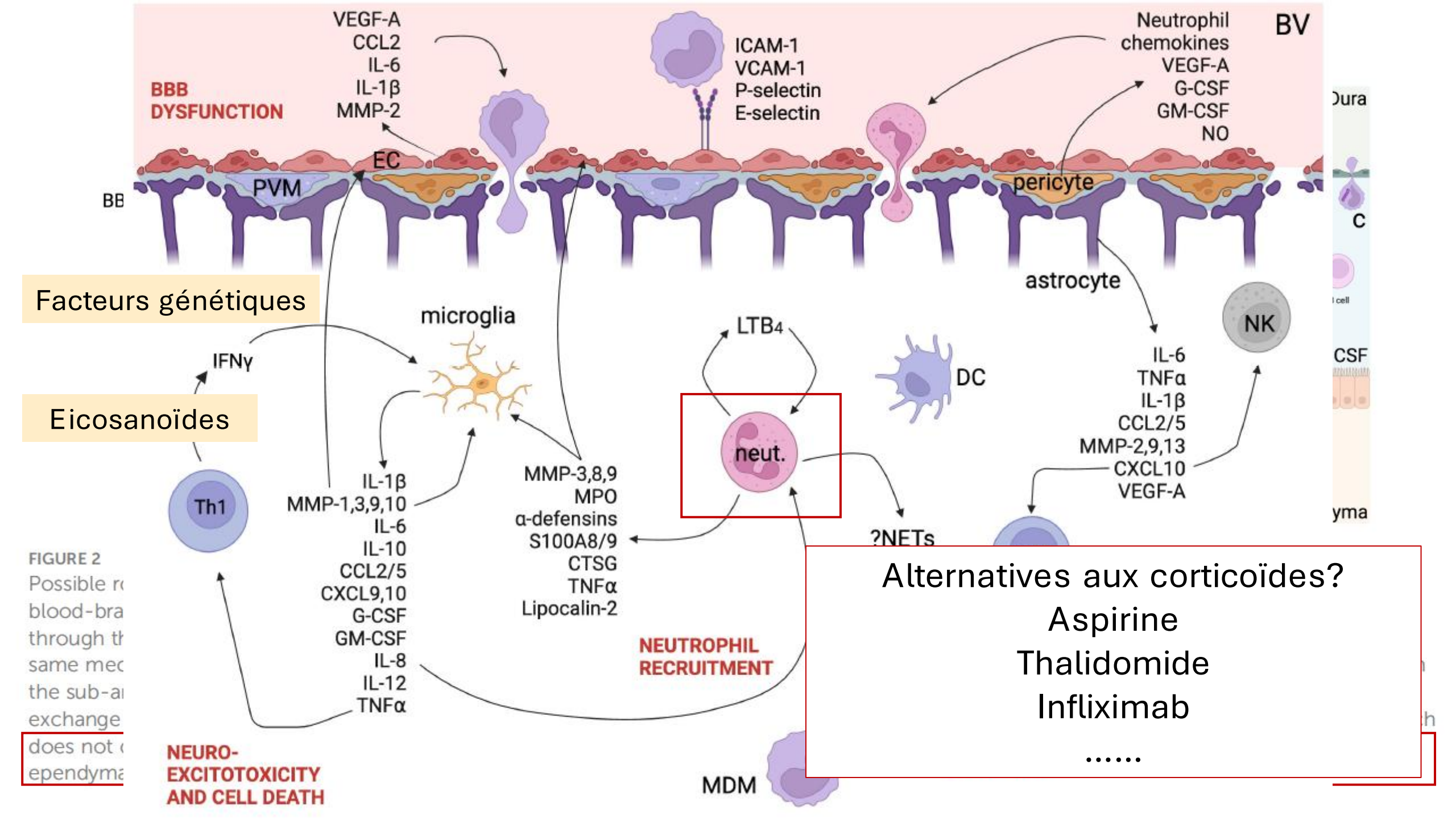


FIGURE 2
Possible r
blood-bra
through th
same mec
the sub-ar
exchange
does not
ependyma

Alternatives aux corticoïdes?
Aspirine
Thalidomide
Infliximab
.....

Attention !!

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DOI: 10.1002/rcr2.910

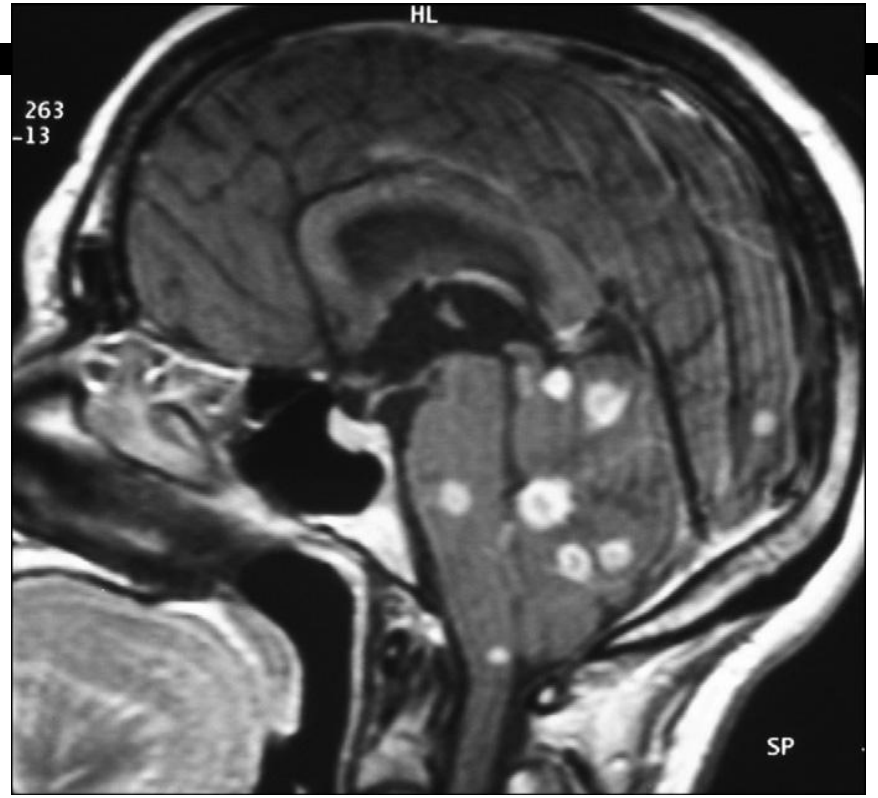
CASE REPORT

Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports OPEN ACCESS APSR

WILEY

The challenge of differentiating tuberculous meningitis from bacterial meningitis

Momoko Kurihara[1,2] | Tomonori Kuroki[1] | Yushi Nomura[1] | Otohiro Katsube[1] | Takafumi Umetsu[1] | Toshio Numao[1] | Taro Shimizu[3] | Kumiya Sugiyama[1,4]



International Journal of Infectious Diseases (2006) 10, 372–377

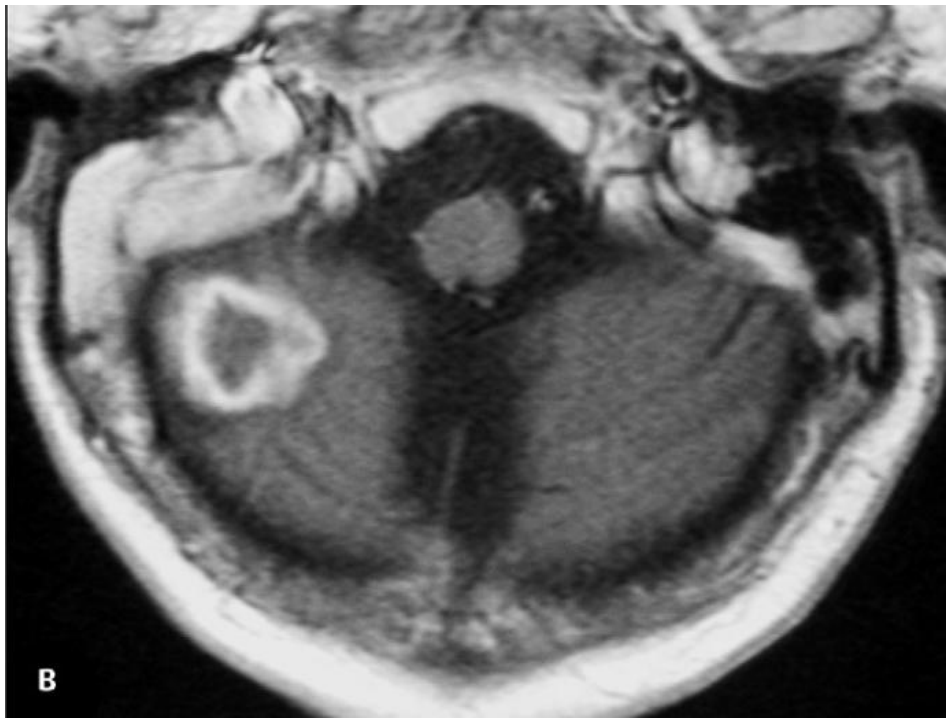
ELSEVIER

INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

http://intl.elsevierhealth.com/journals/ijid

Tuberculous meningitis in adults: MRI contribution to the diagnosis in 29 patients

Rim Abdelmalek, Fakher Kanoun*, Badreddine Kilani, Hanène Tiouiri, Faycal Zouiten, Ahmed Ghoubantini, Taoufik Ben Chaabane



Maladies infectieuses

en ligne sur / *on line on*
www.masson.fr/revues/pm
www.sciencedirect.com

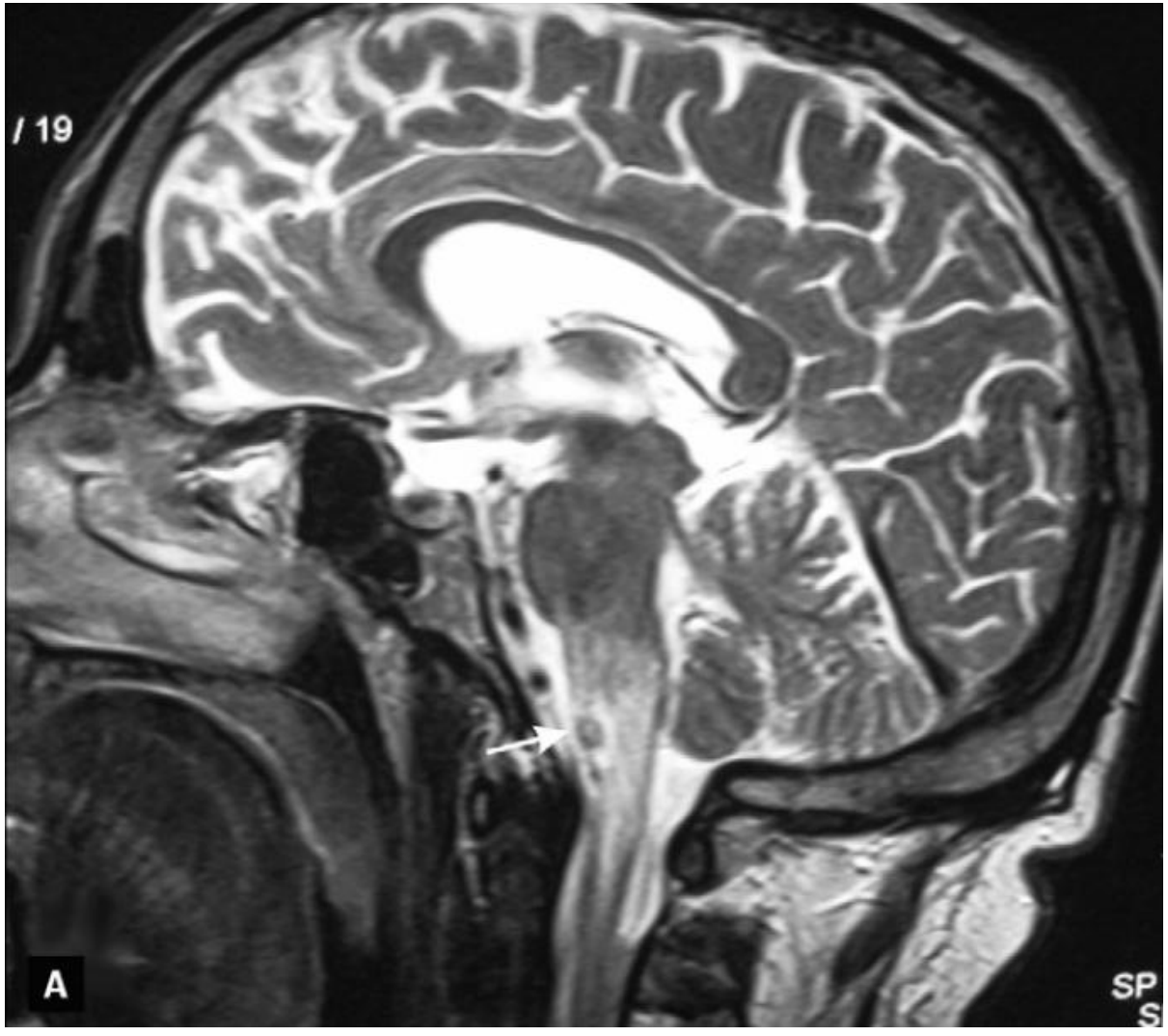
Presse Med. 2008; 37: 634-642

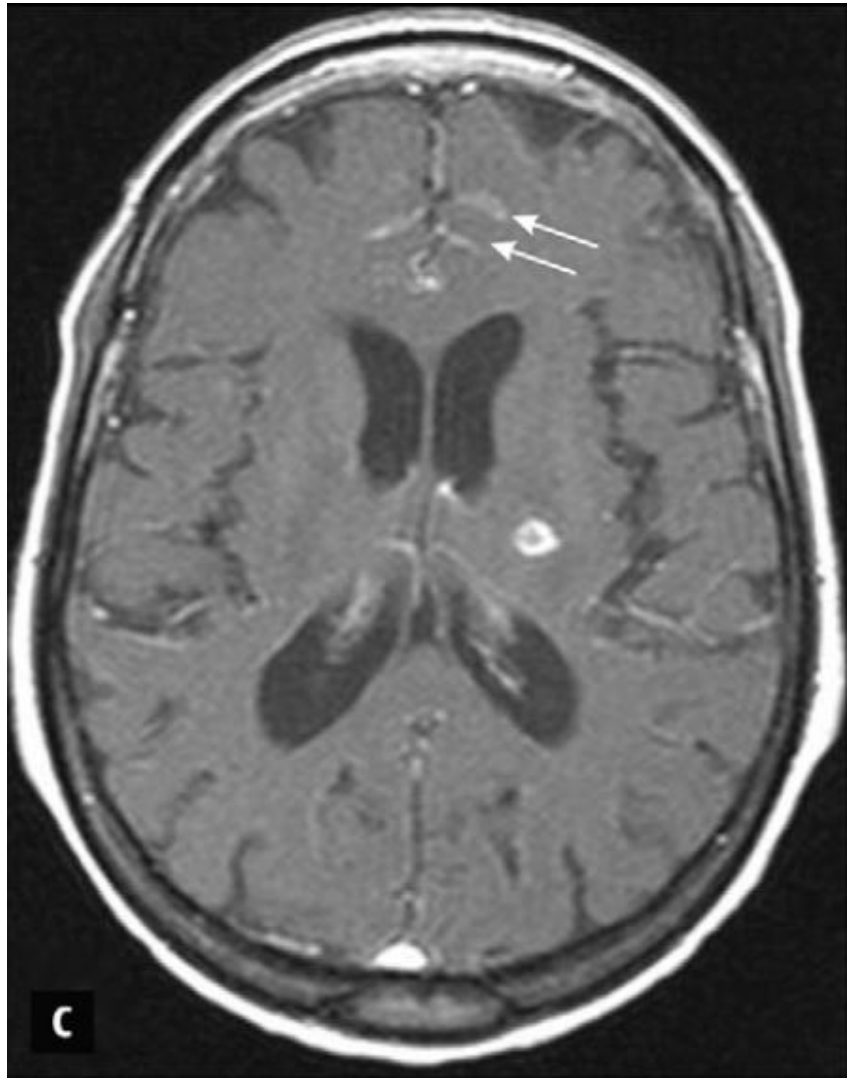
Mise au point

Apport de l'IRM dans le diagnostic de la tuberculose du système nerveux central

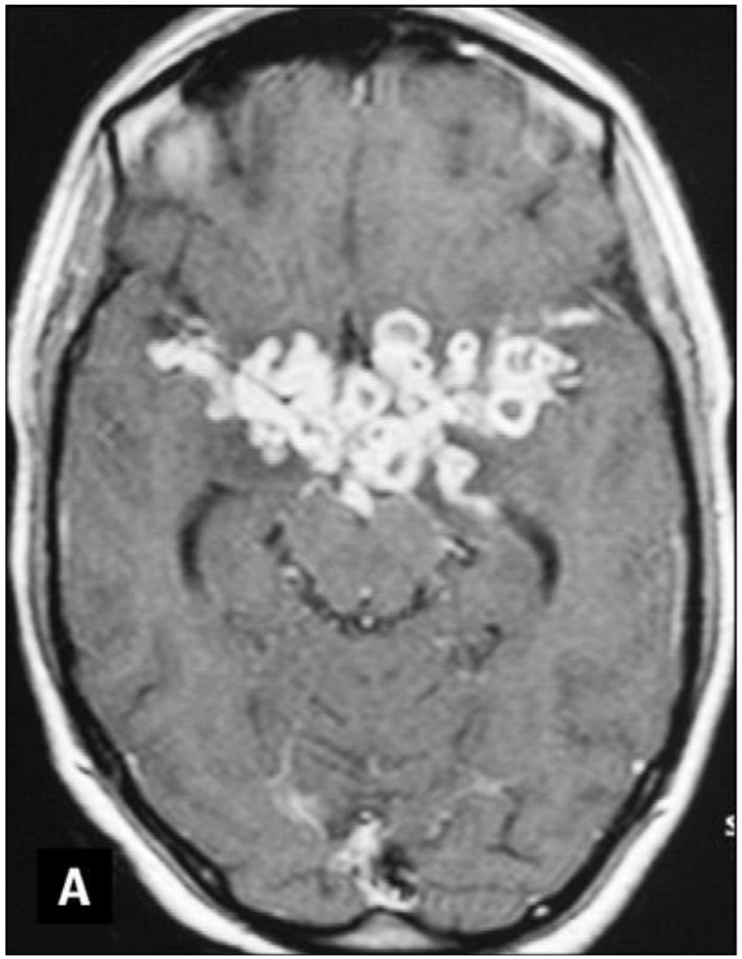
Kais Nouira[1], Radhouane Allani[1], Rym Abdelmalek[2], Olfa Azaiez[1], Lamia Laamari[2], Monia Ben Messaoud[1], Emna Menif[1]

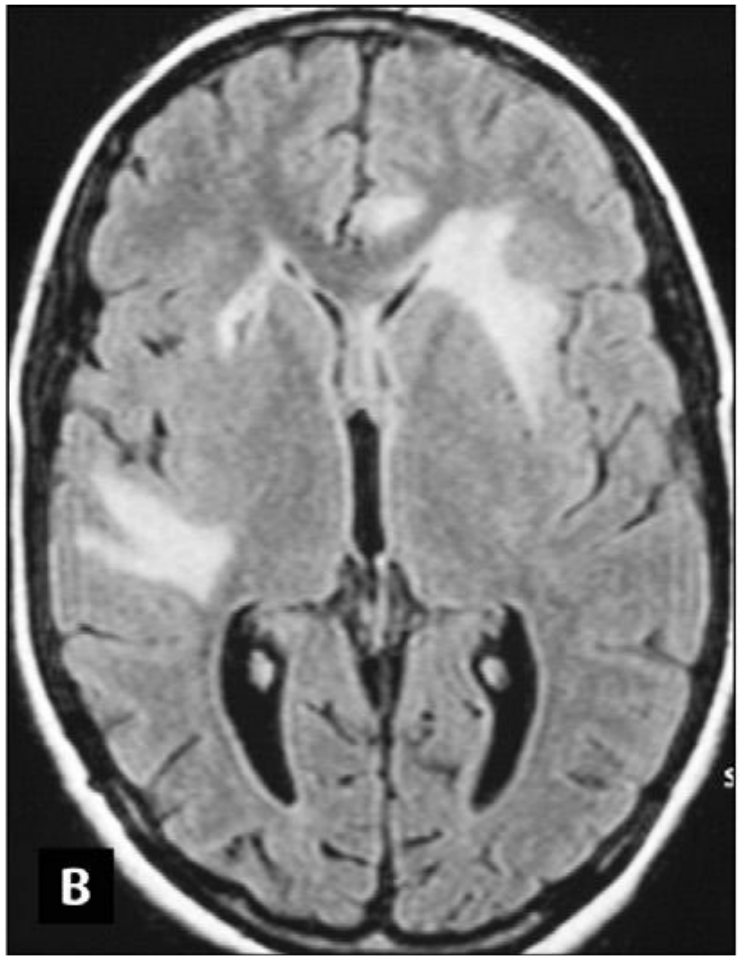
Tuberculome, leptoméningite

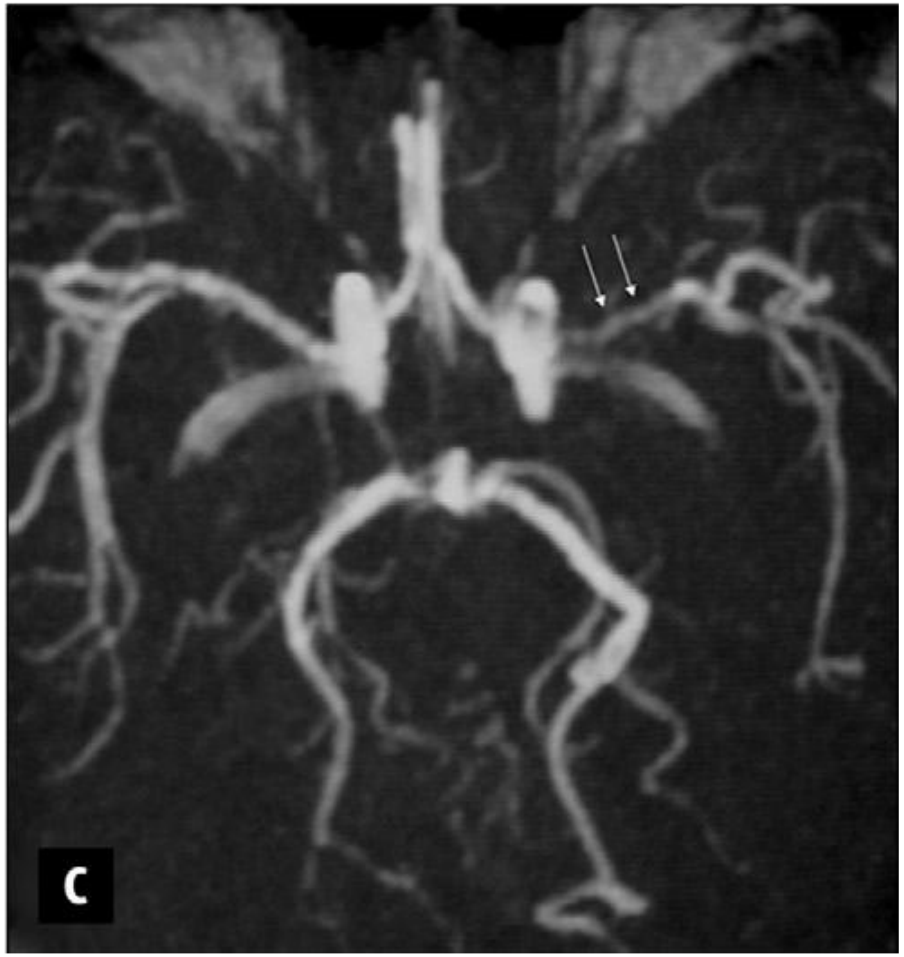




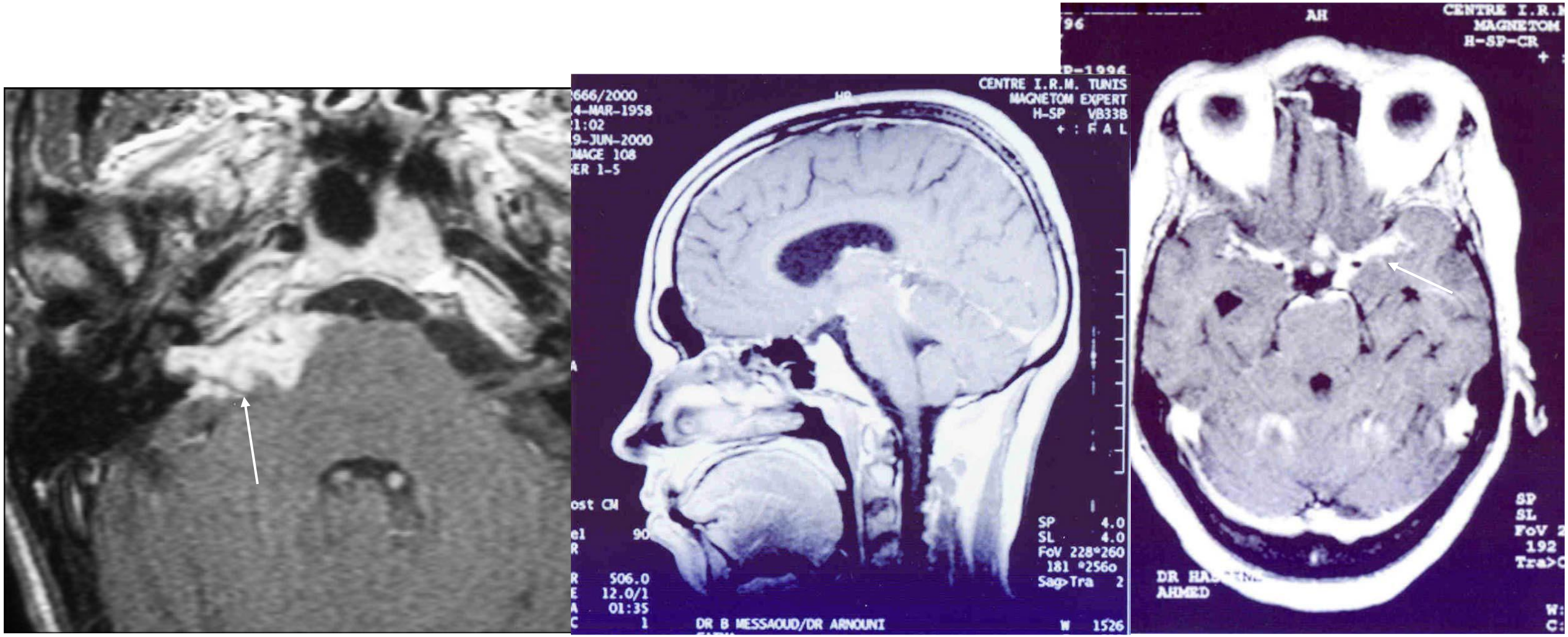
Arachnoïdite, tuberculomes vascularite, ischémie





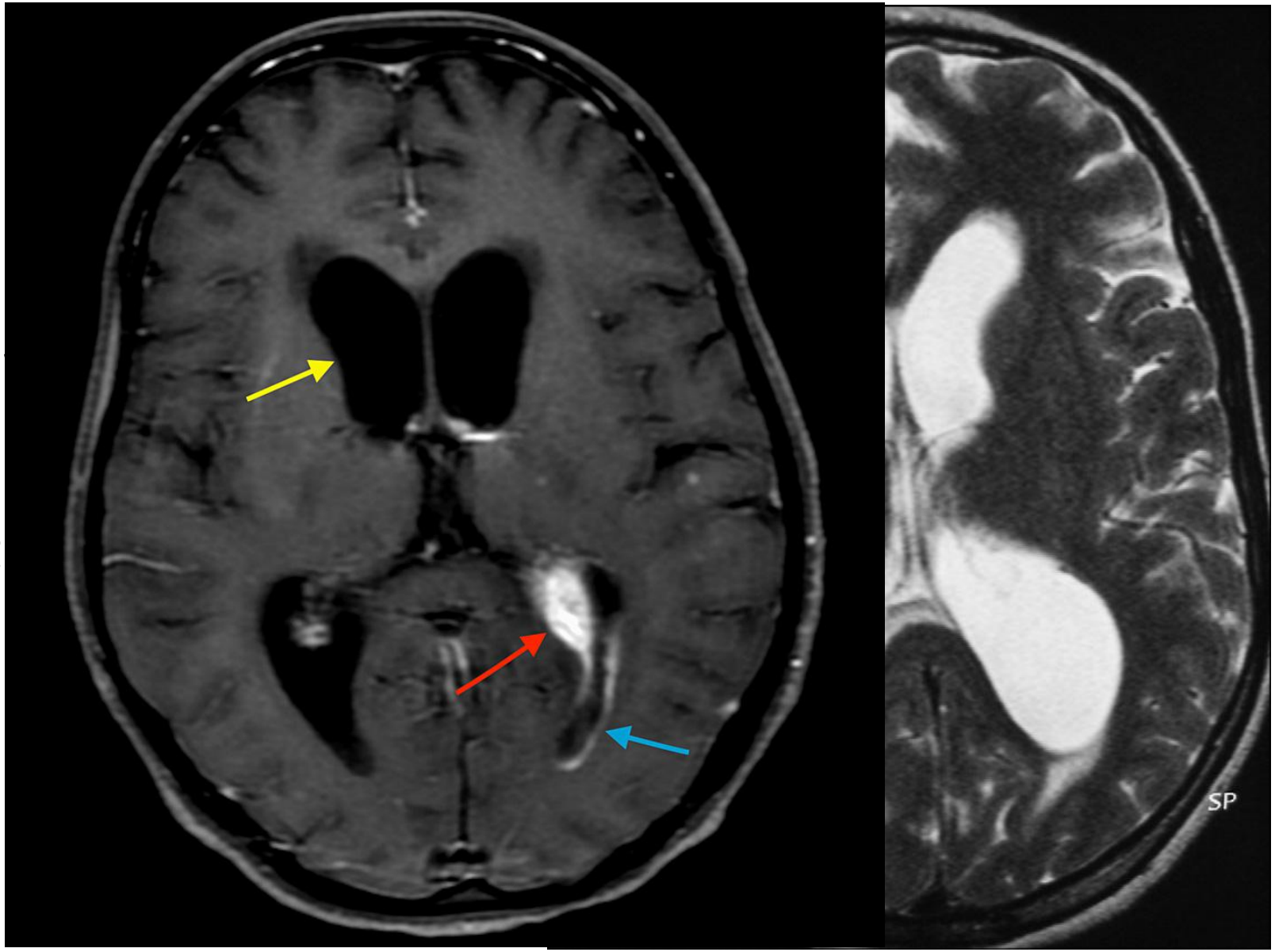


Pachyméningite

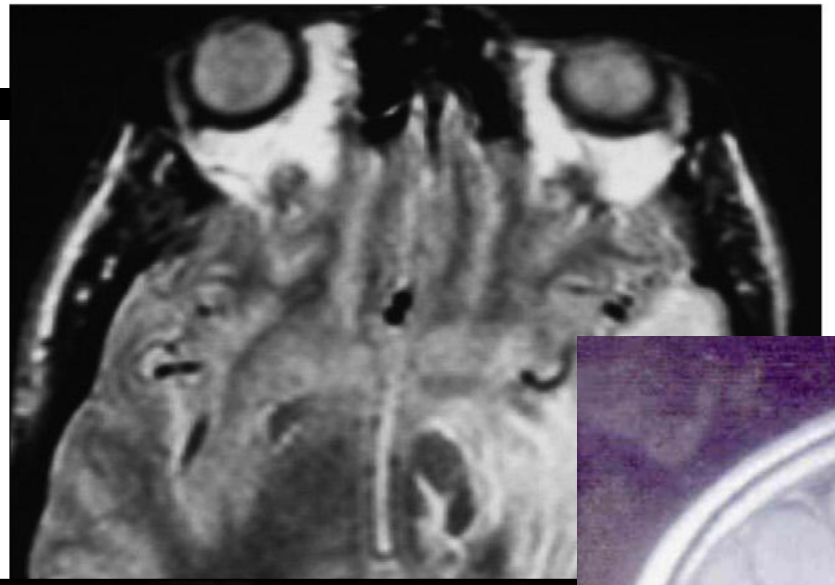


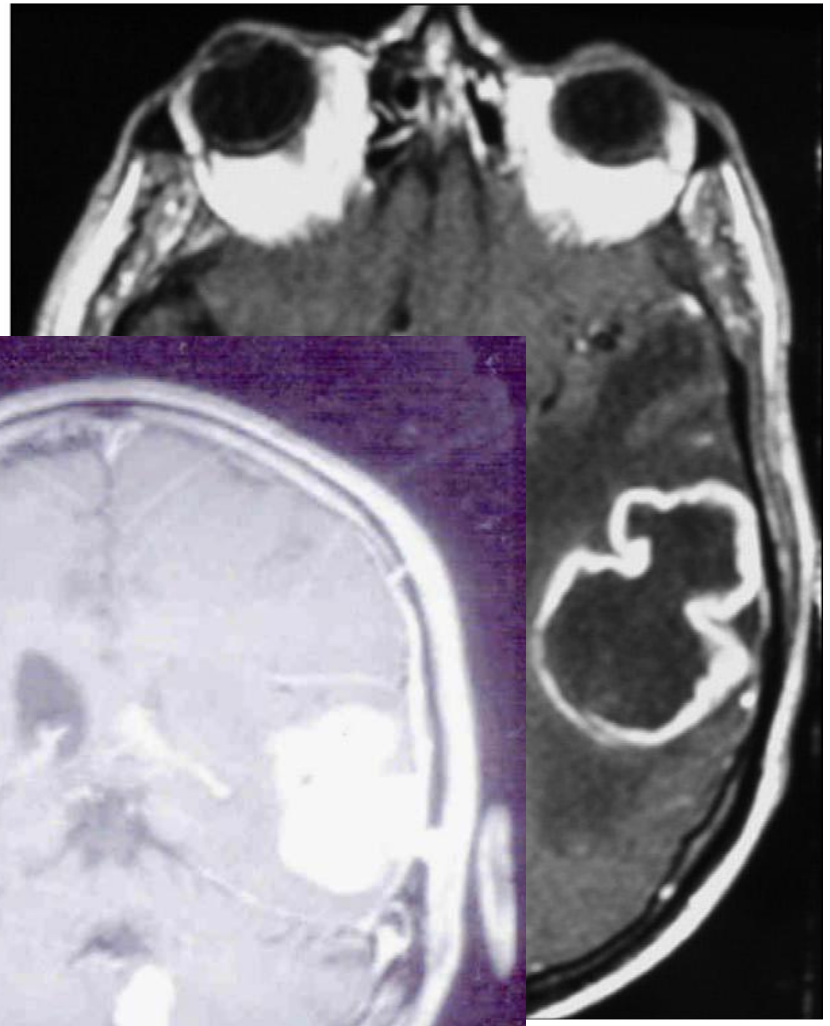
Hydrocéphalie

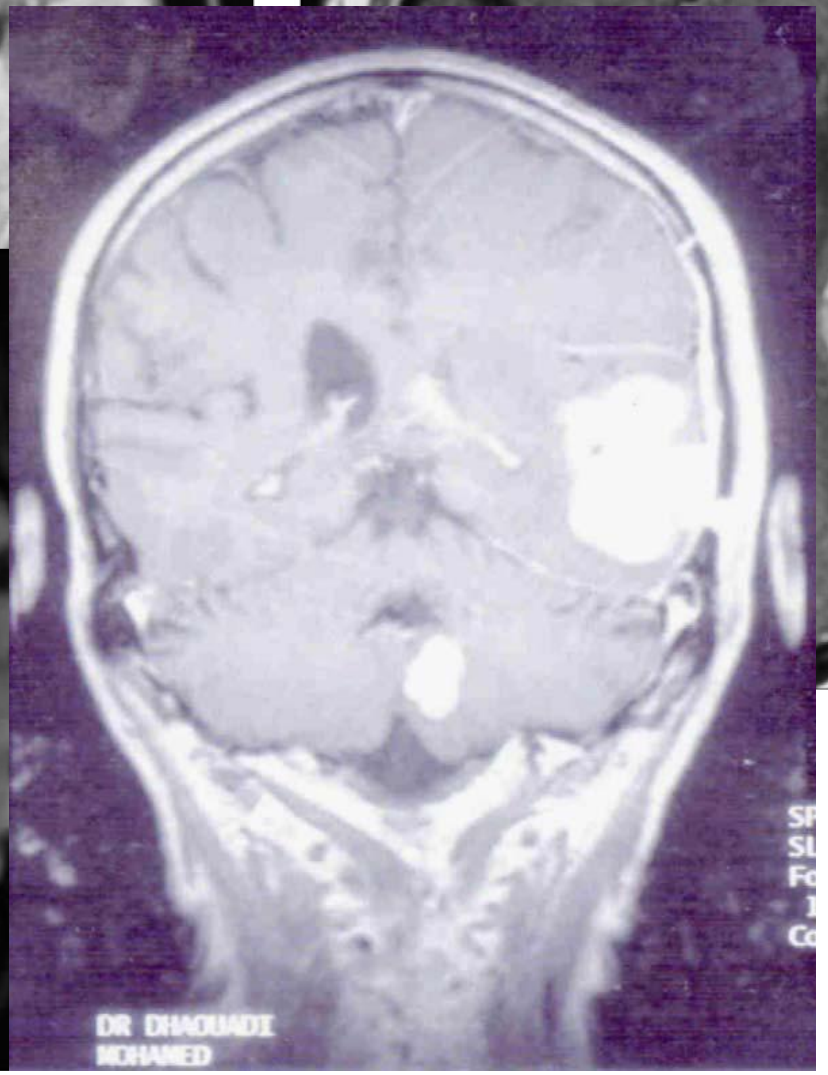
- 1ère découverte tuberculo
  méningée
  - 1836
  - 6 enfants hydrocéphalie aig
- Installation
  - À la découverte
  - Aggravation paradoxale

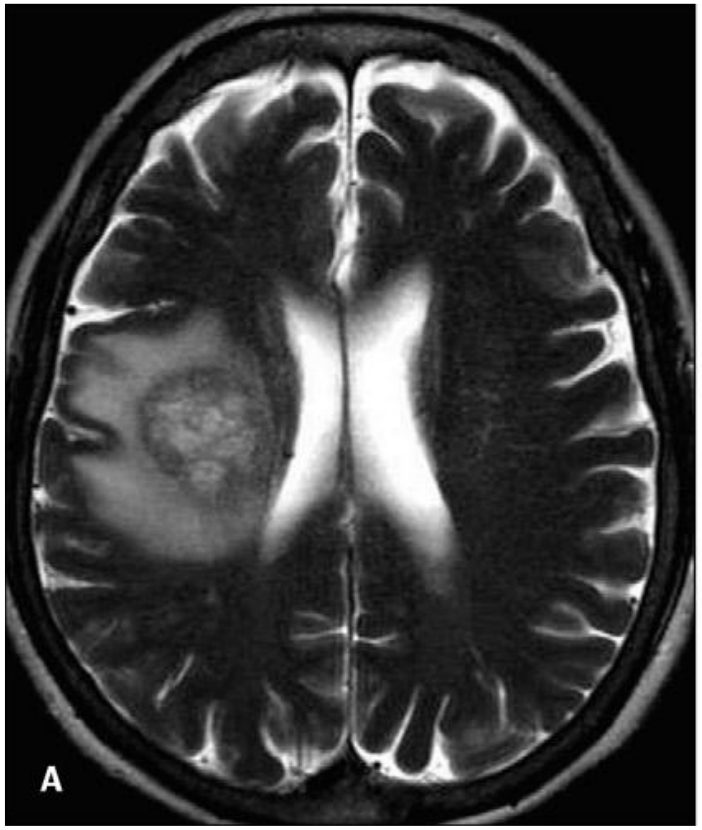


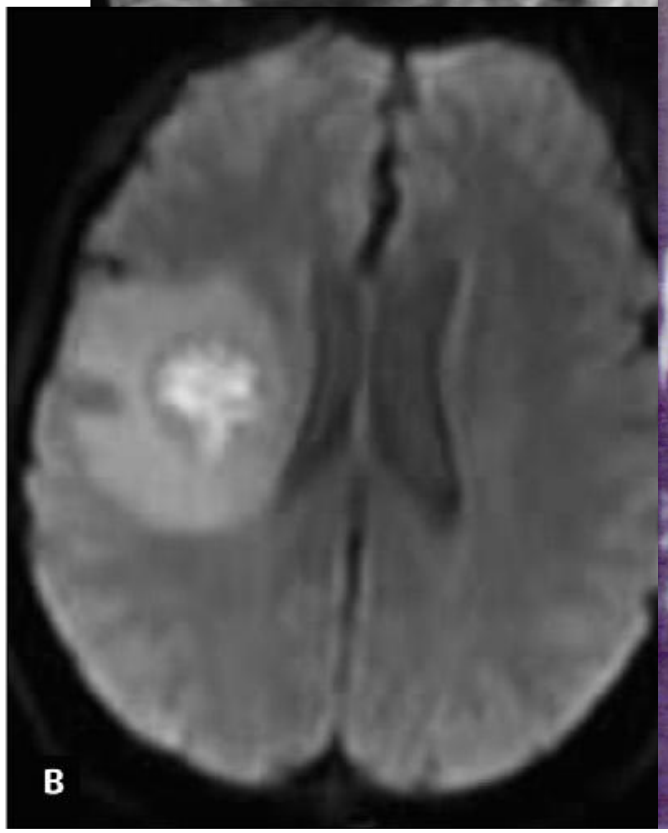
Abcès tuberculeux

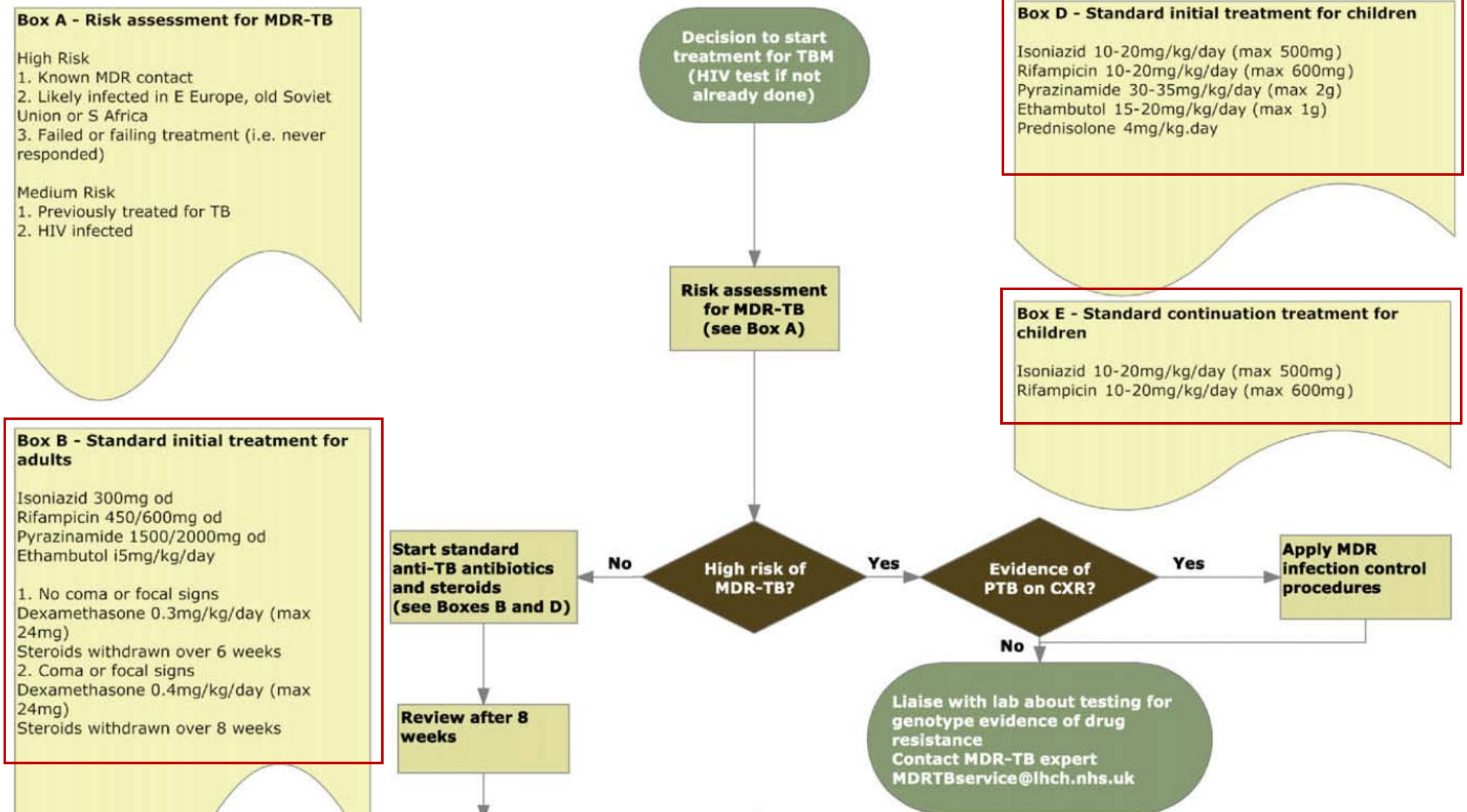











Box A - Risk assessment for MDR-TB
High Risk
1. Known MDR contact
2. Likely infected in E Europe, old Soviet Union or S Africa
3. Failed or failing treatment (i.e. never responded)
Medium Risk
1. Previously treated for TB
2. HIV infected
Decision to start treatment for TBM (HIV test if not already done)
Risk assessment for MDR-TB (see Box A)
Box D - Standard initial treatment for children
Isoniazid 10-20mg/kg/day (max 500mg)
Rifampicin 10-20mg/kg/day (max 600mg)
Pyrazinamide 30-35mg/kg/day (max 2g)
Ethambutol 15-20mg/kg/day (max 1g)
Prednisolone 4mg/kg.day
Box E - Standard continuation treatment for children
Isoniazid 10-20mg/kg/day (max 500mg)
Rifampicin 10-20mg/kg/day (max 600mg)
Box B - Standard initial treatment for adults
Isoniazid 300mg od
Rifampicin 450/600mg od
Pyrazinamide 1500/2000mg od
Ethambutol i5mg/kg/day
1. No coma or focal signs
Dexamethasone 0.3mg/kg/day (max 24mg)
Steroids withdrawn over 6 weeks
2. Coma or focal signs
Dexamethasone 0.4mg/kg/day (max 24mg)
Steroids withdrawn over 8 weeks
Start standard anti-TB antibiotics and steroids (see Boxes B and D)
No
High risk of MDR-TB?
Yes
Evidence of PTB on CXR?
Yes
Apply MDR infection control procedures
No
Review after 8 weeks
Liaise with lab about testing for genotype evidence of drug resistance
Contact MDR-TB expert
MDRTBservice@lhch.nhs.uk

Journal of Infection (2009) **59**, 167—187

Table 5 Recommended treatment regimen for CNS tuberculosis caused by fully susceptible *M. tuberculosis*.

Drug	Daily dose		Route	Duration
	Children	Adults		
Isoniazid	10—20 mg/kg (max 500 mg)	300 mg	Oral	12 Months
Rifampicin	10—20 mg/kg (max 600 mg)	450 mg (<50 kg) 600 mg (≥50 kg)	Oral	12 Months
Pyrazinamide	30—35 mg/kg (max 2 g)	1.5 g (<50 kg) 2.0 g (≥50 kg)	Oral	2 Months
Ethambutol	15—20 mg/kg (max 1 g)	15 mg/kg	Oral	2 Months

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

Journal of Infection (2009) 59, 167–187

Table 6 Corticosteroid regimens used in controlled trials associated with significant improvements in outcome.

Trial	Girgis et al.[193]	Schoeman et al.[194]	Thwaites et al.[111]	
Age of subjects	60% <14 years (median 8 years)	<14 years	>14 years	
MRC Grade	All grades	Grade II and III	Grade I	Grade II and III
Drug	Dexamethasone	Prednisolone	Dexamethasone	Dexamethasone
Time	Dose/route	Dose/route	Dose/route	Dose/route
Week 1	12 mg/day im (8 mg/day if <25 kg)	4 mg/kg/day[b]	0.3 mg/kg/day iv	0.4 mg/kg/day iv
Week 2	12 mg/day im (8 mg/day if <25 kg)	4 mg/kg/day	0.2 mg/kg/day iv	0.3 mg/kg/day iv
Week 3	12 mg/day im(8 mg/day if < 25 kg)	4 mg/kg/day	0.1 mg/kg/day oral	0.2 mg/kg/day iv
Week 4	Reducing over 3 weeks to stop[a]	4 mg/kg/day	3 mg total/day oral	0.1 mg/kg/day iv
Week 5		Reducing dose to stop[c]	Reducing by 1 mg each week over 2 weeks	4 mg total/day oral
Week 6				Reducing by 1 mg each week over 3 weeks

[a] Dexamethasone tapered to stop over 3 weeks: exact regimen not published.
[b] Route of administration not published.
[c] Prednisolone tapered to stop over unspecified time: regimen not published.

Défis ?

Pas de consensus clair

Trop de complications

Trop de décès

Traitement insuffisant ?

Prevailing practices in the treatment of tuberculous meningitis (TBM): a cross-sectional study

Postgrad Med J 2019;**95**:348–349.
doi:10.1136/postgradmedj-2019-136486

1.What is the duration of antitubercular treatment (ATT) you give in patients with tuberculous meningitis (TBM)? (n=273)

Response	N (%)
6 months	0 (0.0%)
9 months	24 (8.9%)
12 months	124 (45.9%)
18 months	122 (45.2%)
Others	3 (1.0)

2. Does your regimen of TBM depend on the stage of TBM? (n=220)

Yes	86 (39.1)
No	83 (37.7)
Maybe	51 (23.2)

3. How long do you give intensive phase? (n=216)

2 months	87 (40.3)
3 months	129 (59.7)

4. Which ATT regimen do you prefer in patients with TBM during the intensive phase? (n=218)

HRZE	93 (42.7)
HRZS	58 (26.6)
HRZES	54 (24.8)
HRZLfx	13 (6.0)
Other (please specify)	0 (0.0%)

5. Which ATT regimen do you prefer in patients with TBM during the continuation phase? (n=218)

HR	93 (42.7)
HRZ	121 (55.5)
HRLfx	4 (1.8)

6. Which antiepileptic drug do you prefer to give in patients with TBM? (n=218)

Leviteracetam	195 (89.4)
Carbamazepine	5 (2.3)
Oxcabazepine	6 (2.8)
Phenytoin	12 (5.5)

Table 2 – CSF penetration of first-line and second-line antituberculous drugs [2].

	Standard daily dose for adults	Estimated ratio of CSF to plasma concentration	Comments
Isoniazid	300 mg	80–90%	Essential drug; good CSF penetration throughout treatment
Rifampicin	450 mg (weight < 50 kg) or 600 mg (weight ≥ 50 kg)	10–20%	Essential drug, despite relatively poor CSF penetration; higher doses might improve effectiveness
Pyrazinamide	1.5 g (weight < 50 kg) or 2.0 g (weight > 50 kg)	90–100%	Excellent CSF penetration throughout treatment
Ethambutol	15 mg/kg	20–30%	Poor CSF penetration once meningeal inflammation resolves
Streptomycin	15 mg/kg (1 g maximum)	10–20%	Poor CSF penetration once meningeal inflammation resolves
Kanamycin	15 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Amikacin	15–20 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Moxifloxacin	400 mg	70–80%	Good CSF penetration
Levofloxacin	1000 mg	70–80%	Good CSF penetration
p-Aminosalicylic acid	10–12 g	No data	Probably very poor CSF penetration unless meninges are inflamed
Ethionamide or Protionamide	15–20 mg/kg (1 g maximum)	80–90%	Good CSF penetration
Cycloserine	10–15 mg/kg	80–90%	Good CSF penetration
Linezolid	1200 mg	40–70%	Variable interindividual CSF pharmacokinetics
Capreomycin	15–20 mg/kg	No data	

Table 4: Suggested intensified TBM regimen and administration for high resource settings

Drug	Individual drugs	Dose	Formulation	Administration	Paediatric dose
First-line					
Rifampicin	Isoniazid*	5 mg / kg p.o. or i.v.	tablet 200 mg or injection fluid 100 mg/ml, 3 ml	orally i.v. bolus: in 3-5 min i.v. infusion: add the dose to 100 ml NaCl 0.9%, administer within 0.5 h	10-20mg/kg
Isoniazid	Rifampicin*	30-35 mg/kg p.o or 15 mg/kg i.v. .	capsule (150 or 300 mg), tablet (600 mg) or powder for infusion fluid 600 mg (Rifadin®, Sanofi-Aventis)	orally i.v. infusion: dissolve 600 mg in 10 ml water for injection, add the correct dose to 250 ml NaCl 0.9%, administer in 1.5 h. Minimal volume is 100 ml, administration in 0.5 h.	<30 kg: 7-15 ng/kg; ≥30 kg: 4 to 6mg/kg
Pyrazinamide	Pyrazinamide*	30 mg / kg p.o.	tablet 500 mg	orally	30–40mg/kg
Ethambutol	Moxifloxacin*	600 mg p.o. or i.v.**	Tablet 400 mg or infusion fluid,1.6 mg/ml, 250 ml (Avelox®, Bayer)	i.v. infusion: infuse in no less than 1h. No dilution needed.	15–25mg/kg
Levofloxacin	**Optional fifth drug**				<5y: 15–20mg/kg; >5y: 10–15mg/kg
Cycloserine	Linezolid*	600mg bd p.o. or i.v.	tablet 600mg, or infusion fluid, 2 mg/mL, 300 mL	orally, twice daily i.v. infusion: administer within 30-120 minutes, no dilution needed.	10–20mg/kg
Linezolid	Amikacin	15 mg / kg i.v.	Injection fluid 250 mg/ml, 2 ml	i.v. infusion: add the dose to 100-200 ml NaCl 0.9%, administer in 0.5-1.0 h	<11y: 10mg/kg three times daily; >11y:

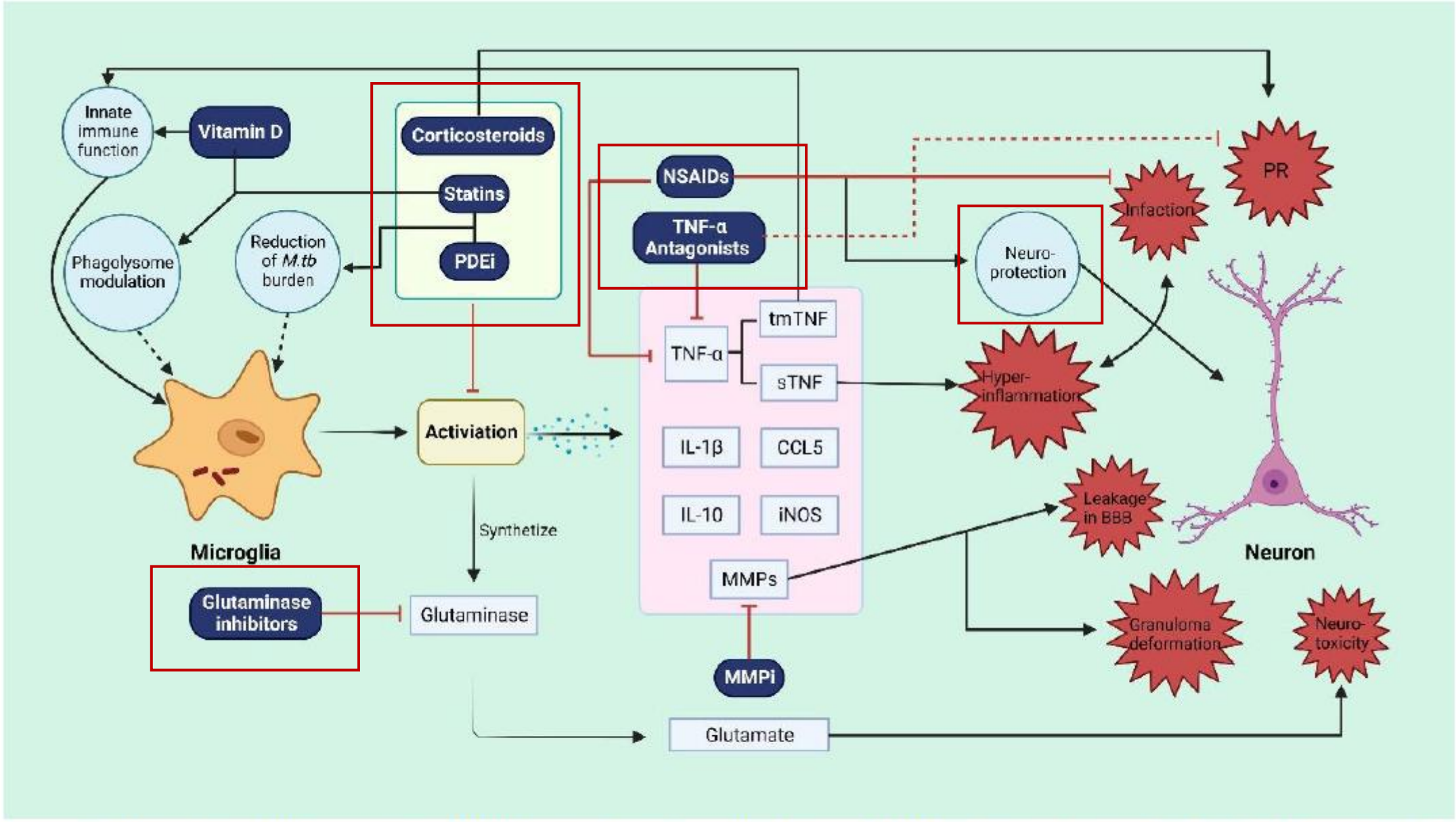
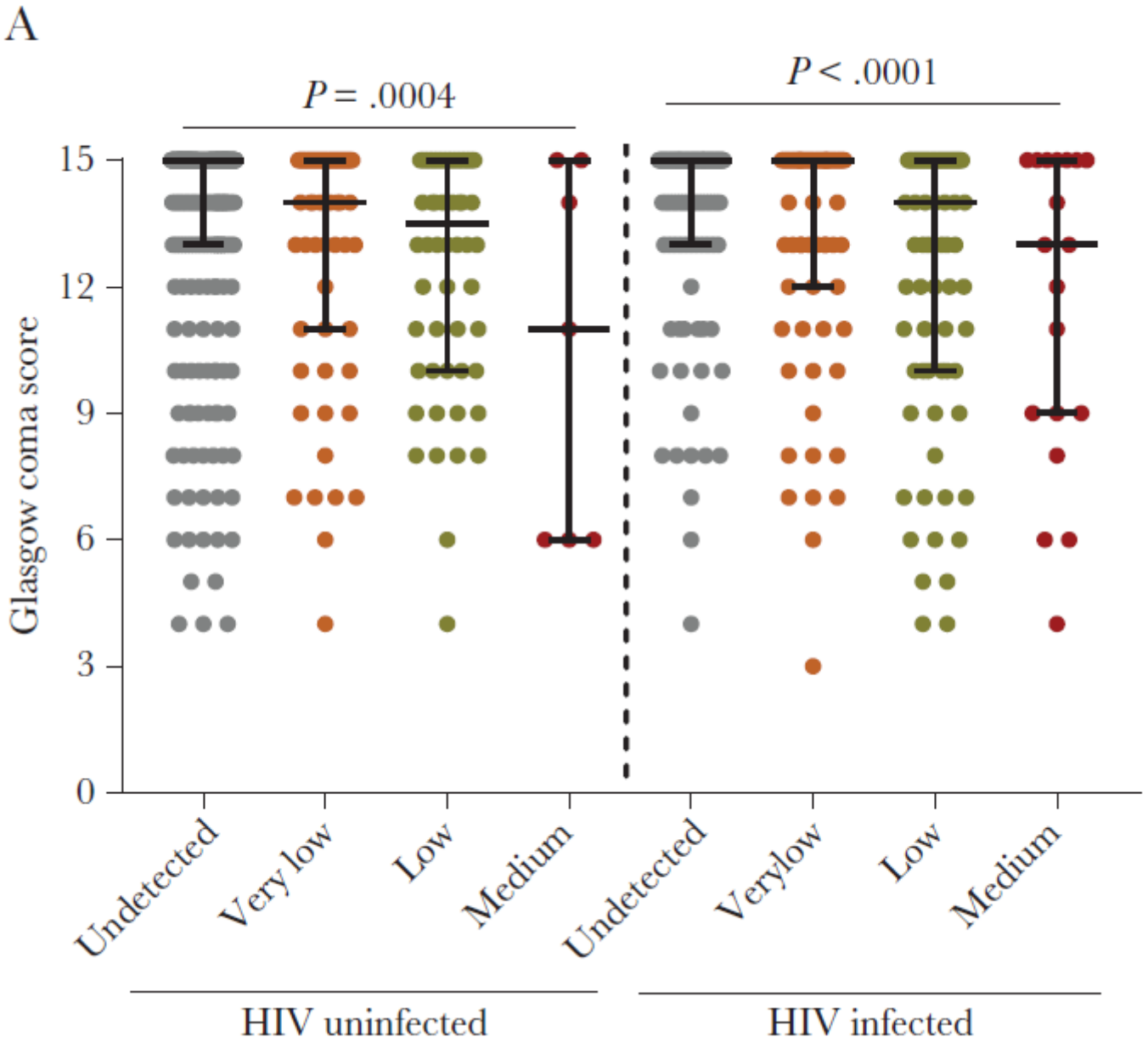
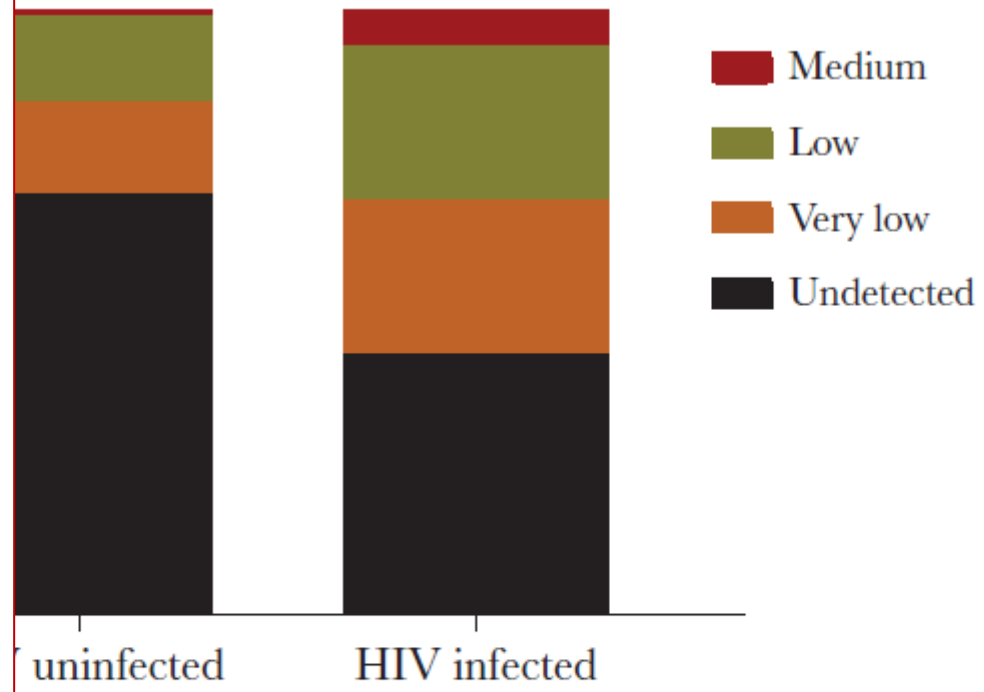


Figure 2. Overview of the emerging HDT targets for microglia during M. tb infection. Once activated by the recognition of M. tb, microglia function as immune surveillance agents to remove bacilli. The drugs listed in this figure target various pathways to interrupt inflammatory reactions. The dashed lines indicate the need for more direct evidence to prove an absolute correlation between symbols. The figure was created with Bio-Render. com.

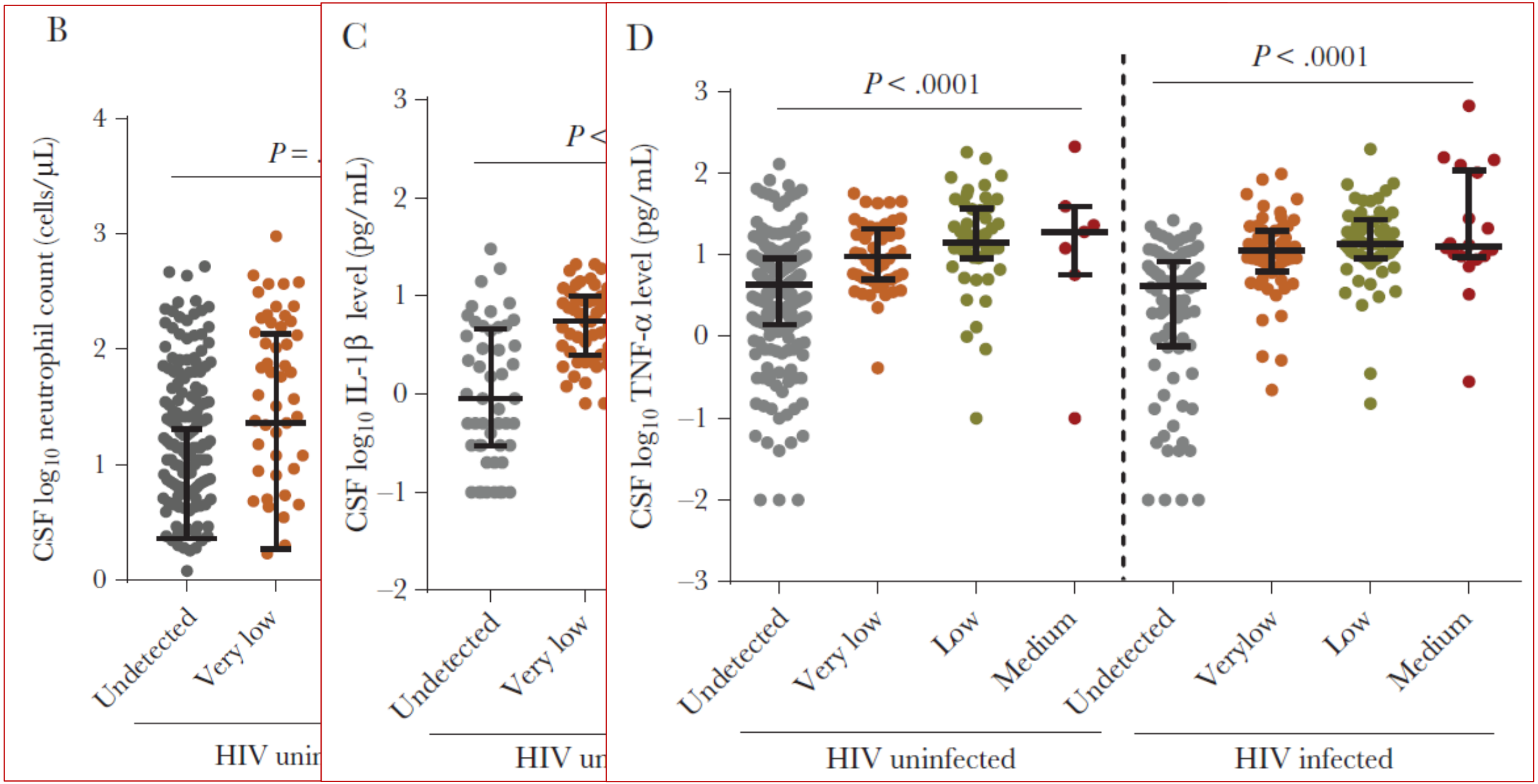
Table 2 Univariable and multivariable analysis of risk factors for CNS-IRIS in patients with TBM

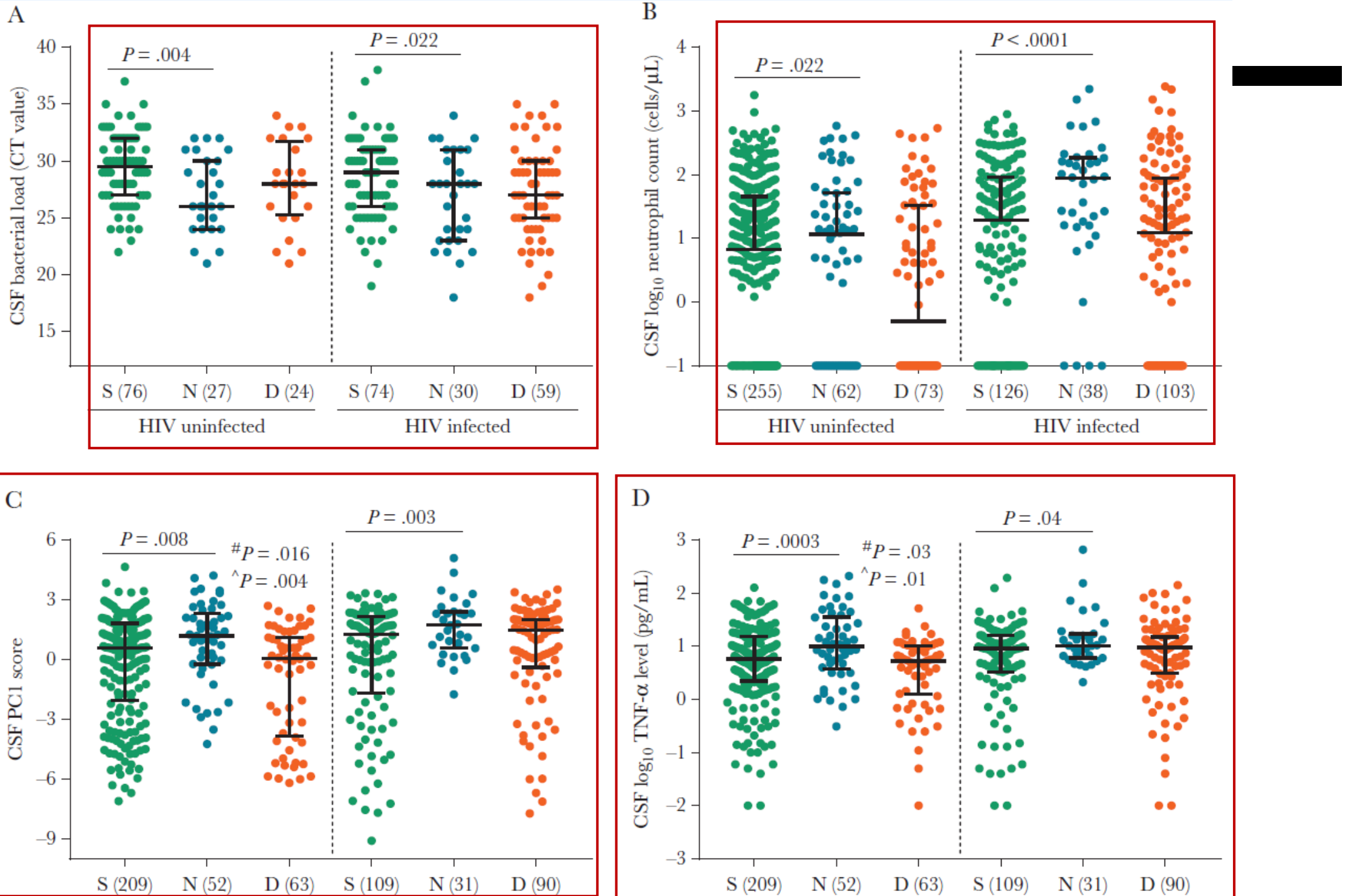
	Univariate analysis	Multivariable analysis
	OR (95% CI)	OR (95% C
Age at diagnosis	0.98 (0.94–1.01)	
Sex (male)	1.67 (0.53–5.46)	
Native of endemic area	13.9 (1.45–1865)†	1.17 (0.05–19
Body mass index	0.86 (0.66–1.07)	
Immunosuppressive treatment	0.31 (0.01–2.59)	
Fever	2.30 (0.40–17.9)	
CNS manifestations		
Headaches	1.98 (0.67–6.09)	
Confusion	0.42 (0.13–1.28)	
Seizures	0.20 (0.03–0.90)	0.03 (0.0–1.3
Focal neurological deficits	0.79 (0.20–3.04)	
Extra-CNS involvement	1.00 (0.11–8.85)	
Lymphopenia	1.00 (0.26–3.89)	
C-reactive protein	1.00 (0.99–1.01)	
Albumin	1.17 (1.03–1.36)	1.21 (1.02–1.
CSF analysis		
White blood cells	1.00 (1.00–1.00)	
Neutrophils	0.99 (0.96–1.01)	
Lymphocytes	1.01 (0.99–1.04)	
Protein	1.33 (0.97–2.53)	
Blood–glucose ratio < 0.6	1.67 (0.49–5.92)	
Brain MRI findings		
Tuberculoma	0.65 (0.12–3.29)	
Infarct	2.32 (0.40–18.1)	
Vasculitis	1.05 (0.18–6.26)	
Meningeal enhancement	6.65 (1.89–26.9)	15.3 (1.19–1193.5)
Hydrocephalus	13.1 (2.09–258)	1.34 (0.03–236.9)
Oedema	1.67 (0.50–5.69)	
Treatment received at TBM diagnosis		
IRPE at start	3.24 (0.39–67.9)	
Steroids	1.0 (0.21–4.68)	
IV pulse	0.56 (0.18–1.71)	
Anti-seizure	0.45 (0.12–1.56)	
Surgery	5.87 (0.86–117)	





ad in 692 participants with tuberculous meningitis who were
n = 404) infected with human immunodeficiency virus (HIV)
uberculosis treatment. Data are percentages of participants
low, low, and medium *Mycobacterium tuberculosis* levels.


B
CSF log10 neutrophil count (cells/μL)
4
3
2
1
0
P =
Undetected
Very low
HIV unin
C
CSF log10 IL-1β level (pg/mL)
3
2
1
0
−1
−2
P <
Undetected
Very low
HIV un
D
CSF log10 TNF-α level (pg/mL)
3
2
1
0
−1
−2
−3
P < .0001
P < .0001
Undetected
Very low
Low
Medium
Undetected
Verylow
Low
Medium
HIV uninfected
HIV infected


A
CSF bacterial load (CT value)
40
35
30
25
20
15
P = .004
P = .022
S (76)
N (27)
D (24)
S (74)
N (30)
D (59)
HIV uninfected
HIV infected
B
CSF log10 neutrophil count (cells/μL)
4
3
2
1
0
−1
P = .022
P < .0001
S (255)
N (62)
D (73)
S (126)
N (38)
D (103)
HIV uninfected
HIV infected
C
CSF PC1 score
6
3
0
−3
−6
−9
P = .008
#P = .016
^P = .004
P = .003
S (209)
N (52)
D (63)
S (109)
N (31)
D (90)
D
CSF log10 TNF-α level (pg/mL)
3
2
1
0
−1
−2
−3
P = .0003
#P = .03
^P = .01
P = .04
S (209)
N (52)
D (63)
S (109)
N (31)
D (90)

Perspectives ?

Agir sur les molécules

Agir sur les doses

Agir sur IRIS

Agir sur perte de sel

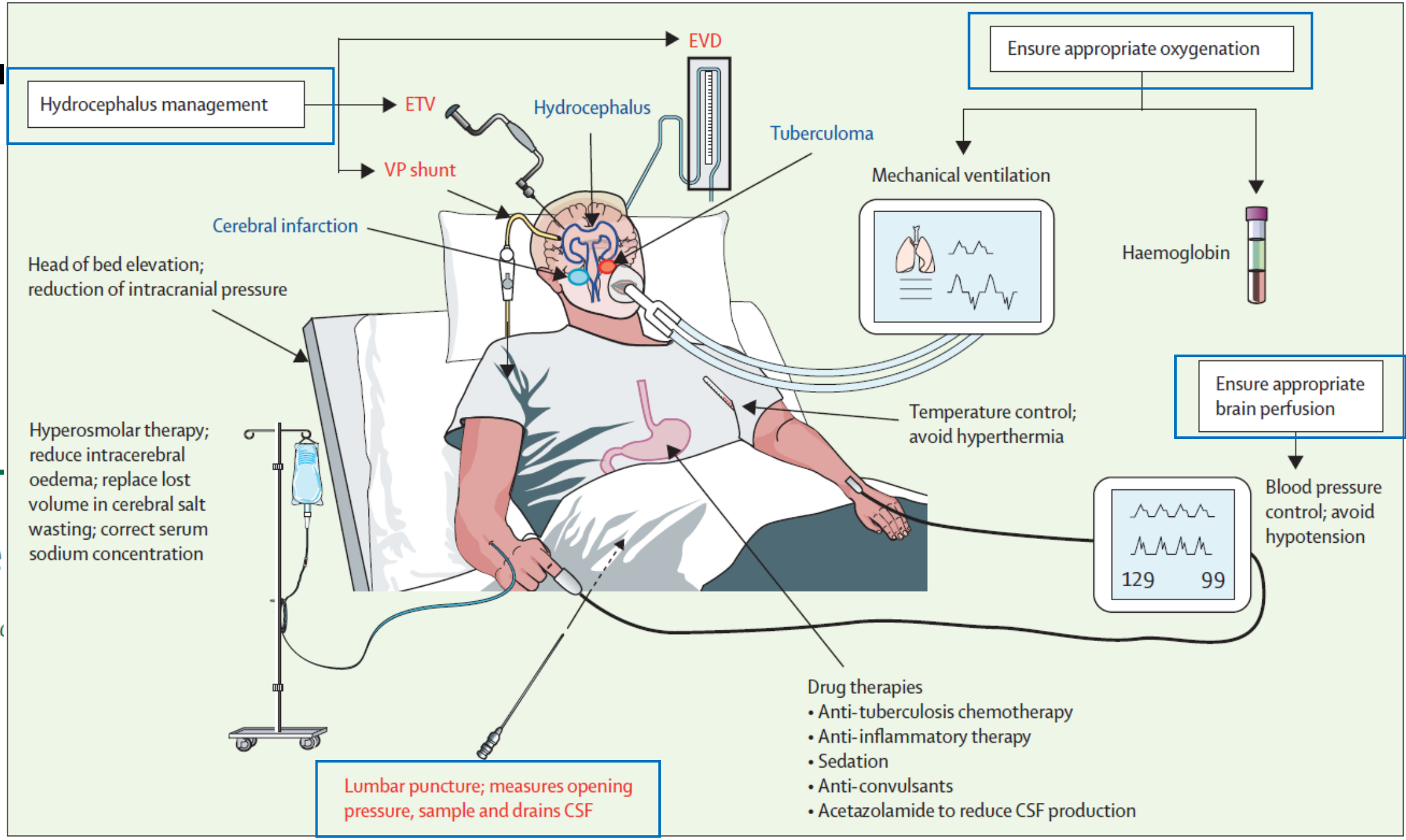


Figure 2: **Potential strategies for management of intracranial pressure and maintenance of brain perfusion in critically ill individuals with tuberculous meningitis** Avoiding and reducing high intracranial pressure, and preserving brain perfusion and oxygenation in critically ill individuals with tuberculous meningitis

Table 1: Modified Vellore grading for patients with tuberculous meningitis and hydrocephalus

Grading	Clinical features
I	GCS 15
	Headache, vomiting, fever ± neck stiffness
	No neurological deficit
II	GCS 15
	Neurological deficit present
III	GCS 9-14
	Neurological deficit may or may not be present
IV	GCS 3-8
	Neurological deficit may or may not be present

uberculous and Nuances

Hydrocéphalie communicante

- Corticoïdes
- Acetazolamide
- Duirétiques

Hydrocéphalie obstructive

- Dérivation vetriculo-péritonéale
- Ventriculostomie endoscopique V3

Table 3 Major ongoing and recently completed TBM clinical trials

Name	Phase/design	*N*	Countries	Antimicrobial interventions	Host-directed interventions*	Start–end
Ongoing						
ALTER	II	60	Uganda	1. R 10 mg/kg	Nil	2021–2023
LAST ACT	III	640	Vietnam	Nil	1. LTA4H TT-genotype:	2018–2022
Completed						
ACT HIV NCT03092817	III Parallel	520	Vietnam Indonesia HIV-positive only	Nil	1.Dexamethasone 2. Placebo	2017–2022
LASER-TBM NCT03927313	IIb parallel	100	South Africa	1. R 10 mg/kg 2. R 35 mg/kg + LZD 1200 mg 4 wks then 600 mg 4 wks	1. Aspirin 1000 mg 6 wks added to half of the intensified arm	2019–2021
RifT ISRCTN42218549	II	60	Uganda	1.R 10 mg/kg 2. R 35 mg/kg 3. R 20 mg/kg intravenous	Nil	2019–2020
ReDEFINe NCT02169882	II	60	Indonesia	1.R 450 mg 2. R 900 mg 3. R 1350 mg	Nil	2014–2017
TBM-KIDS NCT02958709	II	37	India Malawi Children 6 months–12 years	1: R 30 mg/kg + E 2: R 30 mg/kg + Lfx 3: Standard WHO regimen	Nil	2017–2019

TABLE 2 | Baseline characteristics of patients in each enrolled trial.

References	HIV	Median CD4 count (cell/μl)	Corticosteroids	Follow-up period	Standard rifampin dosage (mg/kg/day)	Standard treatment regimen	High rifampin dosage (mg/kg/day)	Intervention time	Intensified regimen	Outcomes
Cresswell et al. (15)	56	50	All	6 m	10	HRZE	Arm 1: IV-20 Arm 2: PO-35	8 weeks	HRZE	①②③
Heemskerk et al. (11)	349	38	All	9 m	10	HRZE	PO-15	8 weeks	HRZELfx	②③
Ruslami et al. (10)	7	NA	All	6 m	10	HRZEMfx	IV-13	14 days	HRZEMfx	①②③
Ding et al. (14)	100	NA	All	9 m	10	HRZE	PO-15	8 weeks	HRZELfx	①
Dian et al. (16)	6	NA	All	6 m	10	HRZE	Arm 1: PO-20 Arm 2: PO-30	30 days	HRZE	①②③
Wasserman et al. (13)	49	113	All	6 m	10	HRZE	Arm 1: IV-20 Arm 2: PO-35	56 days	Arm 1: HRZELzd, Arm 2: HRZELzd, and Asp	①

HIV, human immunodeficiency virus; m, months; H, isoniazide; R, rifampin; E, ethambutol; Z, pyrazinamide; Mfx, moxifloxacin; Lfx, levofloxacin; Lzd, linezolid; Asp, aspirin; IV, intravenous; PO, per os. ① Pharmacokinetic parameters; ② survival; ③ adverse events.

FIGURE 1 | Flow diagram of studies.

*nggui Wang† and Jian-Qing He**

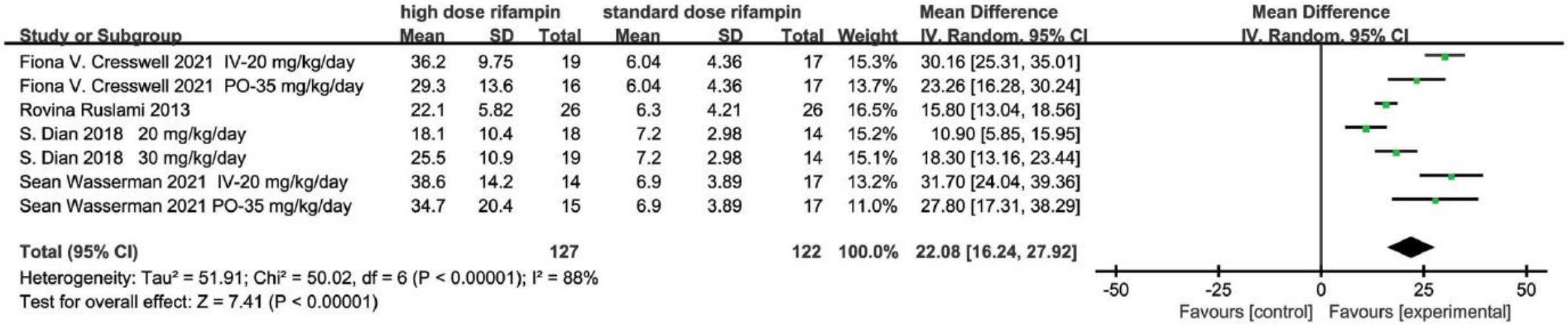


FIGURE 3 | Forest plot result of the maximum concentration of rifampin in plasma.

Meilleure concentration sérique / AUC rifampicine

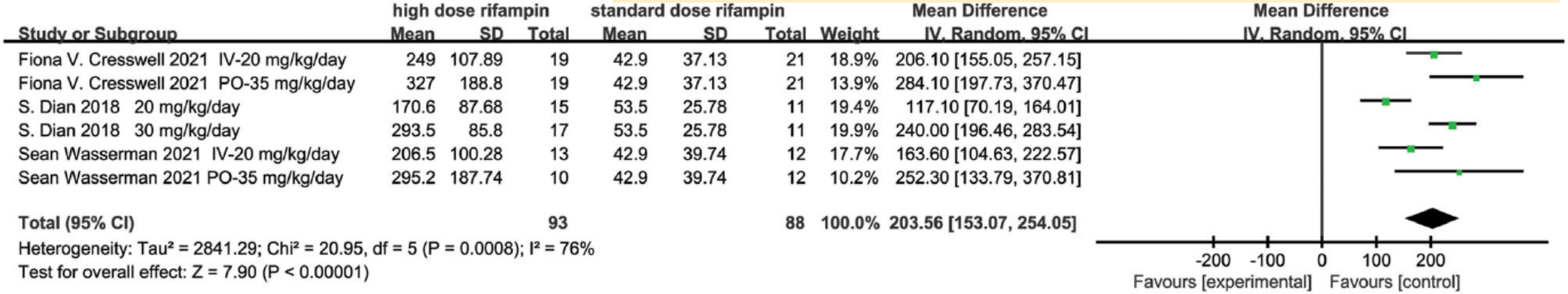
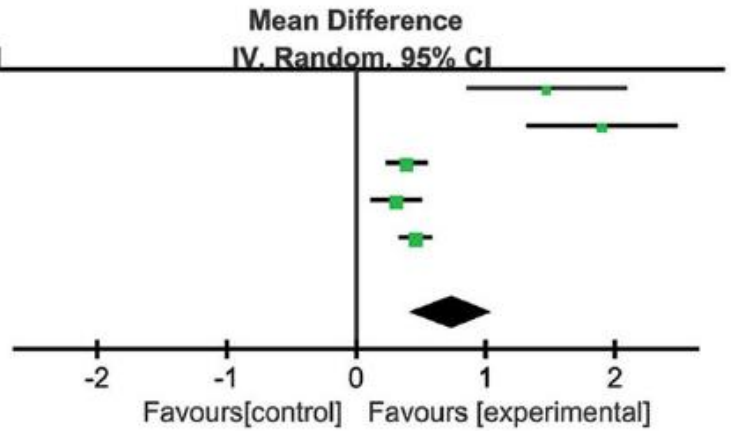


FIGURE 4 | Forest plot result of the AUC0-24 of rifampin.

A

Study or Subgroup	high dose rifampin Mean	SD	Total	standard dose rifampin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fiona V. Cresswell 2021 IV-20 mg/kg/day	1.74	1.2	15	0.27	0.28	18	13.0%	1.47 [0.85, 2.09]
Fiona V. Cresswell 2021 PO-35 mg/kg/day	2.17	1.27	19	0.27	0.28	18	13.7%	1.90 [1.31, 2.49]
Rovina Ruslami 2013	0.6	0.39	25	0.21	0.13	25	24.5%	0.39 [0.23, 0.55]
S. Dian 2018 20 mg/kg/day	0.59	0.39	16	0.28	0.09	12	23.7%	0.31 [0.11, 0.51]
S. Dian 2018 30 mg/kg/day	0.74	0.24	16	0.28	0.09	12	25.1%	0.46 [0.33, 0.59]
Total (95% CI)			**91**			**85**	**100.0%**	**0.74 [0.42, 1.05]**

Heterogeneity: Tau² = 0.10; Chi² = 36.33, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.59 (P < 0.00001)



Meilleure concentration LCS rifampicine

B

Study or Subgroup	high dose rifampin Mean	SD	Total	standard dose rifampin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fiona V. Cresswell 2021 IV-20 mg/kg/day	0.57	0.48	8	0.15	0.08	9	38.5%	0.42 [0.08, 0.76]
Fiona V. Cresswell 2021 PO-35 mg/kg/day	0.45	0.49	9	0.15	0.08	9	41.4%	0.30 [-0.02, 0.62]
Junjie Ding 2019	0.35	2.14	115	0.19	1.4	118	20.1%	0.16 [-0.31, 0.63]
Total (95% CI)			**132**			**136**	**100.0%**	**0.32 [0.11, 0.53]**

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)

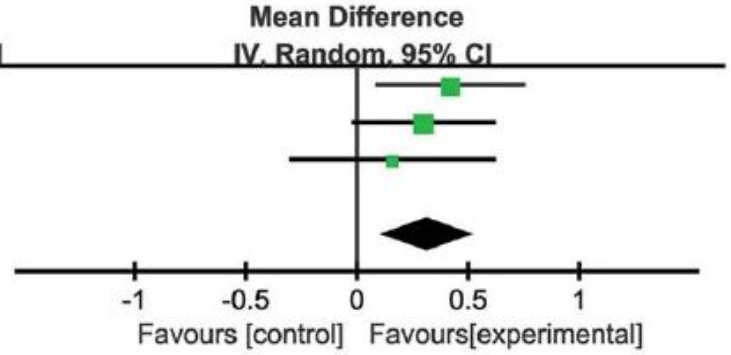


FIGURE 5 | Forest plot results of the concentration of rifampin in CSF. **(A)** The result in the first 3 days; **(B)** the result at day 14.

Study or Subgroup	high dose rifampin Events	Total	standard dose rifampin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
A. Dorothee Heemskerk 2016	113	408	114	409	39.0%	0.99 [0.80, 1.24]
Fiona V. Cresswell 2021 IV-20 mg/kg/day	7	20	7	21	10.7%	1.05 [0.45, 2.46]
Fiona V. Cresswell 2021 PO-35 mg/kg/day	10	20	7	21	13.0%	1.50 [0.71, 3.17]
Rovina Ruslami 2013	10	29	20	31	18.9%	0.53 [0.30, 0.94]
S. Dian 2018 20 mg/kg/day	9	20	7	20	12.4%	1.29 [0.60, 2.77]
S. Dian 2018 30 mg/kg/day	3	20	7	20	6.0%	0.43 [0.13, 1.43]
Total (95% CI)		**517**		**522**	**100.0%**	**0.92 [0.67, 1.26]**
Total events	152		162			

Heterogeneity: Tau² = 0.05; Chi² = 7.90, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 0.51 (P = 0.61)

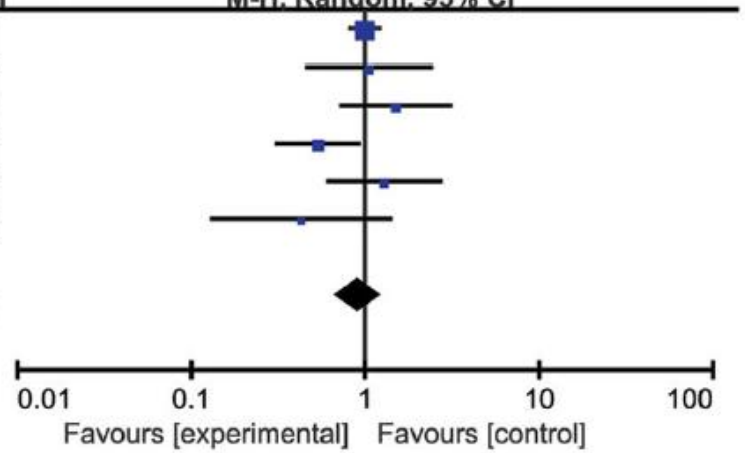


FIGURE 6 | Forest plot result of mortality.

Pas de différence sur mortalité

- Effets indésirables similaires

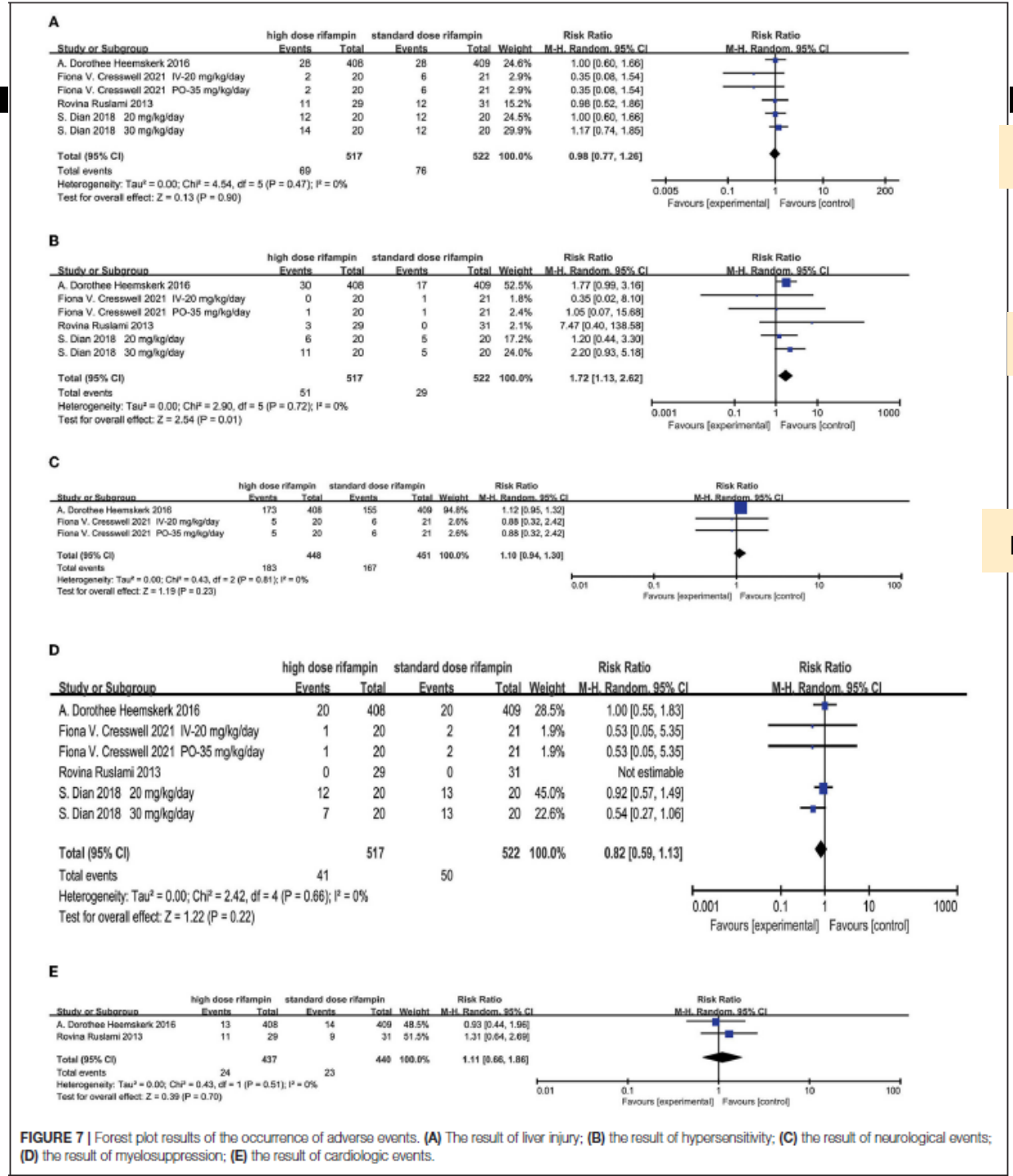


FIGURE 7 | Forest plot results of the occurrence of adverse events. **(A)** The result of liver injury; **(B)** the result of hypersensitivity; **(C)** the result of neurological events; **(D)** the result of myelosuppression; **(E)** the result of cardiologic events.

Foie

Allergie

neurologiques

MO

Cœur

Table 2. Rifampicin Pharmacokinetic Data by Treatment Arm

	IV-20	PO-35	Control	*P* value[a]
AUC_{0-8} (h × mg/l)[b]				
n observations[c]	19	19	20	
Geometric mean (95% CI)	163 (142–186)	162 (129–203)	30.5 (21.7–42.8)	<.001
Ratio to control	5.33	5.31	…	
P value[d]	<.001	<.001	…	
AUC_{0_24} (h × mg/l)[e]				
n observations	19	19	21	
Geometric mean (95% CI)	249 (202–306)	327 (248–430)	42.9 (29.2–63.0)	<.001
Ratio to control	5.80	7.62	…	
P value[d]	<.001	<.001	…	
C_{max} (mg/L)[b]				
n observations[g]	19	16	17	
Geometric mean (95% CI)	36.2 (31.8–41.2)	29.3 (23.0–37.5)	6.04 (4.20–8.68)	<.001
Ratio to control	5.99	4.86	…	
P value[d]	<.001	<.001	…	
n (%) achieving TDM target of >8 mg/L	20 (100)	20 (100)	10 (47.62)	<.0001[f]
T_{max} (hours)				
Median (range)	2.35 (1.83–3.85)	4.05 (2.17–7.33)	2.83 (2.08– 8.25)	.002[g]
C_{CSF} (mg/L)				
n observations	15	19	18	
Geometric mean (95% CI)	1.74 (1.20–2.53)	2.17 (1.64–2.86)	.27 [h] (.17– .45)	.058
Ratio to control	6.44	8.00	…	
P value[d]	<.001	<.001		
n (%) with detectable CSF level	15 (100)	19 (100)	8 (44)	<.001 [f]
n (%) with concentration above rifampicin MIC (1 mg/L)	14 (93.3%)	18 (94.7%)	2 (11.1%)	<.001 [f]
Median (IQR) hours post-dose	4.70 (3.28–5.92)	4.55 (3.08–6.20)	4.83 (3.78–5.5)	

t al

frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 20 January 2025
DOI 10.3389/fimmu.2024.1535447

Indicator	Category	Standard-Dose Group (N=32)	High-Dose Group (N=87)	Statistic (χ^2)	*P*
Cranial Imaging Improvement	No	5 (62.5)	14 (37.8)	0.785	0.376
	Yes	3 (37.5)	23 (62.2)		
Chest Imaging Improvement	No	5 (31.2)	19 (39.6)	0.356	0.551
	Yes	11 (68.8)	29 (60.4)		
Disability or Mortality (3 Months)	No	22 (68.8)	77 (88.5)	6.530	0.011
	Yes	10 (31.3)	10 (11.5)		
Disability or Mortality (12 Months)	No	19 (59.4)	75 (86.2)	10.150	0.001
	Yes	13 (40.6)	12 (13.8)		

Jiangmen Central Hospital, China
Binggang Liu,
The Central Hospital of Yongzhou, China

119 patients
Recherche polymorphisme gène NAT2 (Acétyleur lent/intermédiaire/rapide)
300 mg vs 600 mg/jour

Table 1
Pharmacokinetic (PK) parameters of pyrazinamide after a daily dose of 1500 mg in tuberculous meningitis

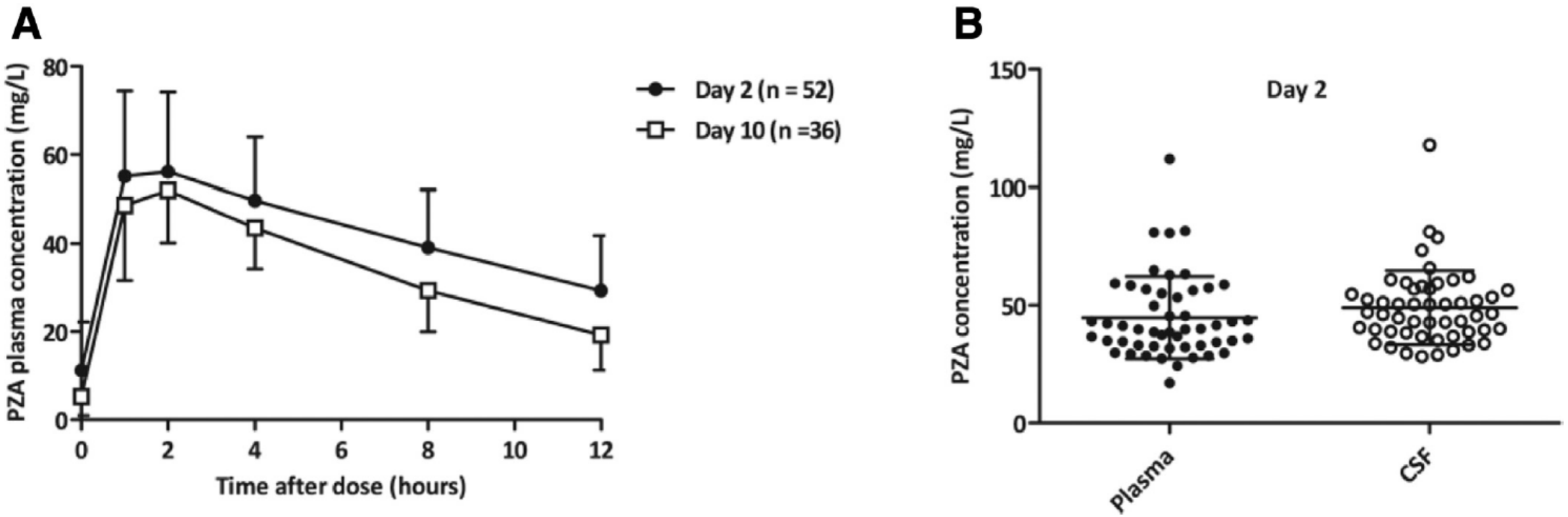
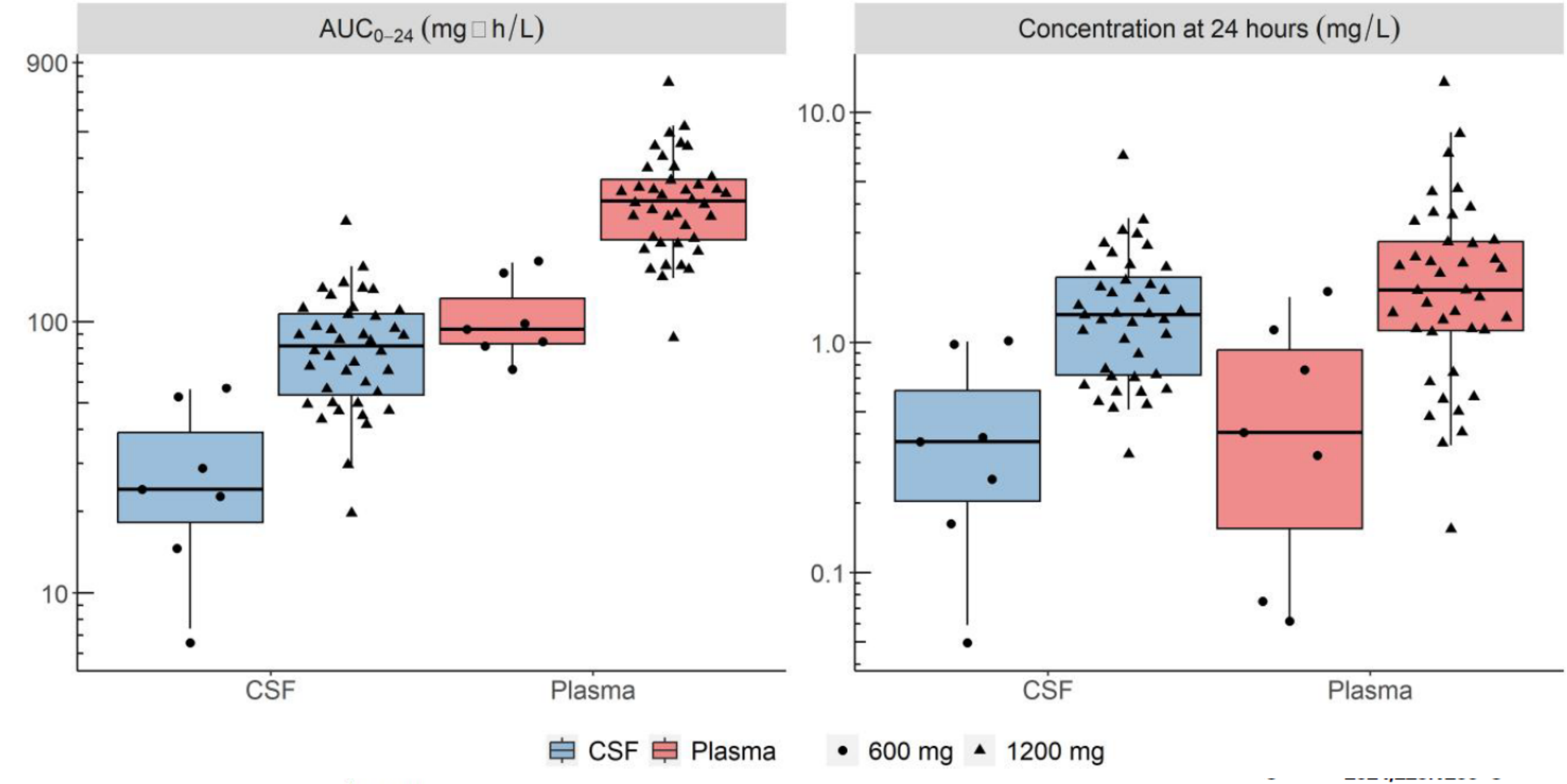


Fig. 1. Pharmacokinetic profiles of pyrazinamide (PZA) after a daily dose of 1500 mg in tuberculous meningitis patients: (A) plasma concentration versus time curves of PZA on Day 2 and Day 10 of treatment (mean ± standard deviation); and (B) individual plasma concentrations calculated at the time of cerebrospinal fluid (CSF) sampling and measured CSF concentrations ($n = 51$) of PZA on Day 2 of treatment. Bars represent the mean ± standard deviation.

[b] Paired samples *t*-test on log-transformed data of 36 patients for whom PK data were available both on Day 2 and Day 10.

[c] Wilcoxon signed-rank test between Day 2 and Day 10.

Dose recommandée 33,3 mg/kg/jour


AUC0–24 (mg □ h/L)
900
100
10
CSF
Plasma
Concentration at 24 hours (mg/L)
10.0
1.0
0.1
CSF
Plasma
CSF
Plasma
600 mg
1200 mg

Perspectives

2019-2025 / 400 enfants

Antituberculeux

- RFD 35 mg/kg/jour
- INH 20 mg/kg/jour
- Levofloxacine 20 mg/kg/jour
- Pyrazinamide 40 mg/kg/jour

Open access Protocol

BMJ Open

Effectiveness and safety of shortened intensive treatment for children with tuberculous meningitis (SURE): a protocol for a phase 3 randomised controlled trial evaluating 6 months of antituberculosis therapy and 8 weeks of aspirin in Asian and African children with tuberculous meningitis

Aspirine 20 mg/kg/jour

- Inhibe cyclo-oxygénase
- Réduit thromboxane
- Déclenche médiateurs pro-résolution

Huynh J, *et al. BMJ Open* 2025;**15**:e088543. doi:10.1136/bmjopen-2024-088543

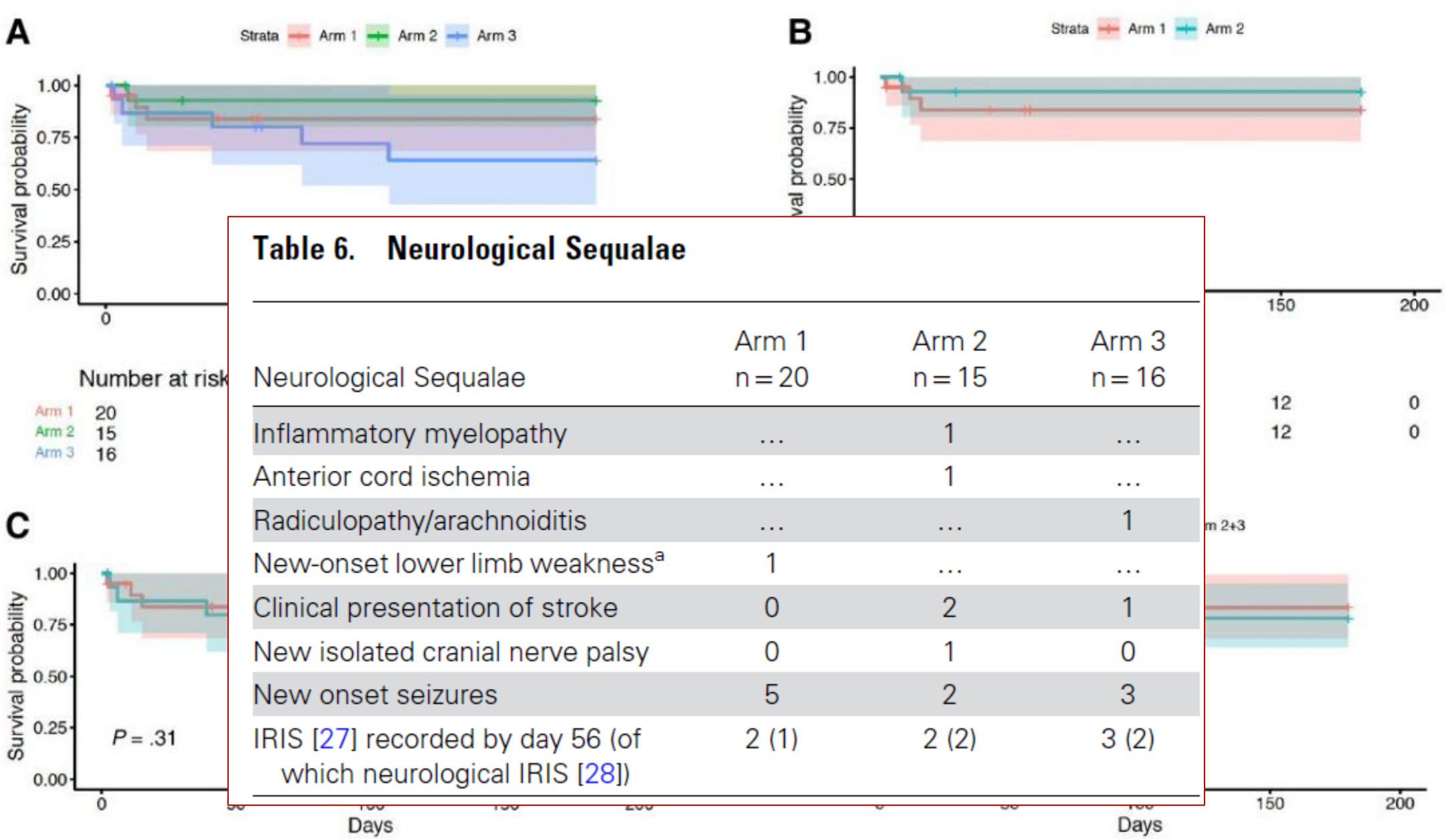
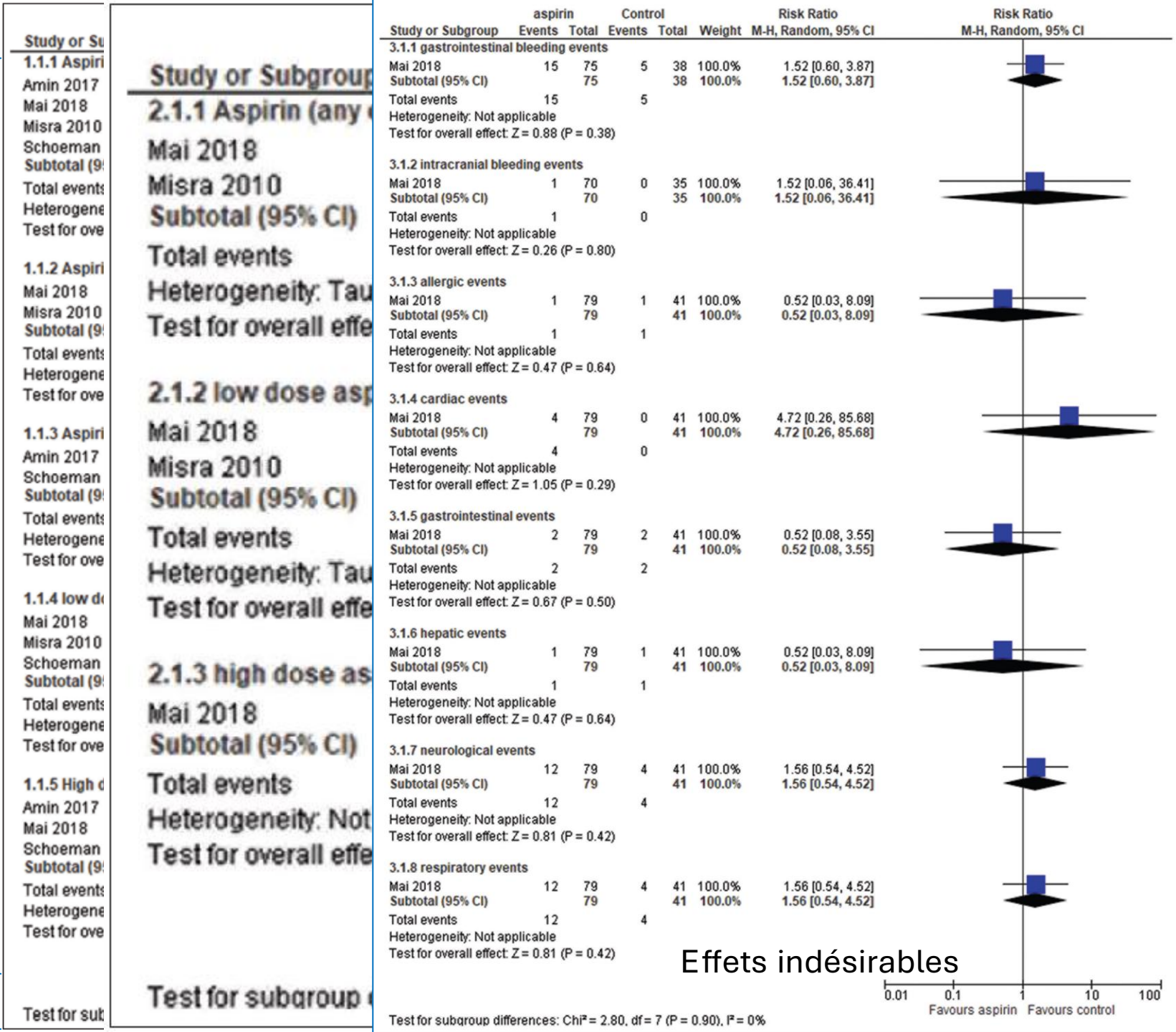


Table 6. Neurological Sequalae

Neurological Sequalae	Arm 1 n = 20	Arm 2 n = 15	Arm 3 n = 16
Inflammatory myelopathy	…	1	…
Anterior cord ischemia	…	1	…
Radiculopathy/arachnoiditis	…	…	1
New-onset lower limb weakness[a]	1	…	…
Clinical presentation of stroke	0	2	1
New isolated cranial nerve palsy	0	1	0
New onset seizures	5	2	3
IRIS [27] recorded by day 56 (of which neurological IRIS [28])	2 (1)	2 (2)	3 (2)



Effets indésirables

Clinical Case Report

Medicine®

OPEN

Thalidomide in the treatment of human immunodeficiency virus-negative tuberculous meningitis

A case report

Ping Liu, MM, Ning Pei, MM, Xuhui Liu, MM, Wei Huang, MM, Shuihua Lu*

Medicine 2020;99:40(e22639).

- Thalidomide 200 mg/jour x 2 mois
- Inhibe sécrétion TNF alpha
- IRIS réfractaire aux corticoïdes

- Dose min 6 mg/kg/jour x 2 mois
- Dose max 12-24 mg/kg/jour
- Durée max 8 mois

Table 2. **Biologics and other immunomodulatory therapies in TBM; summary of published case reports.**

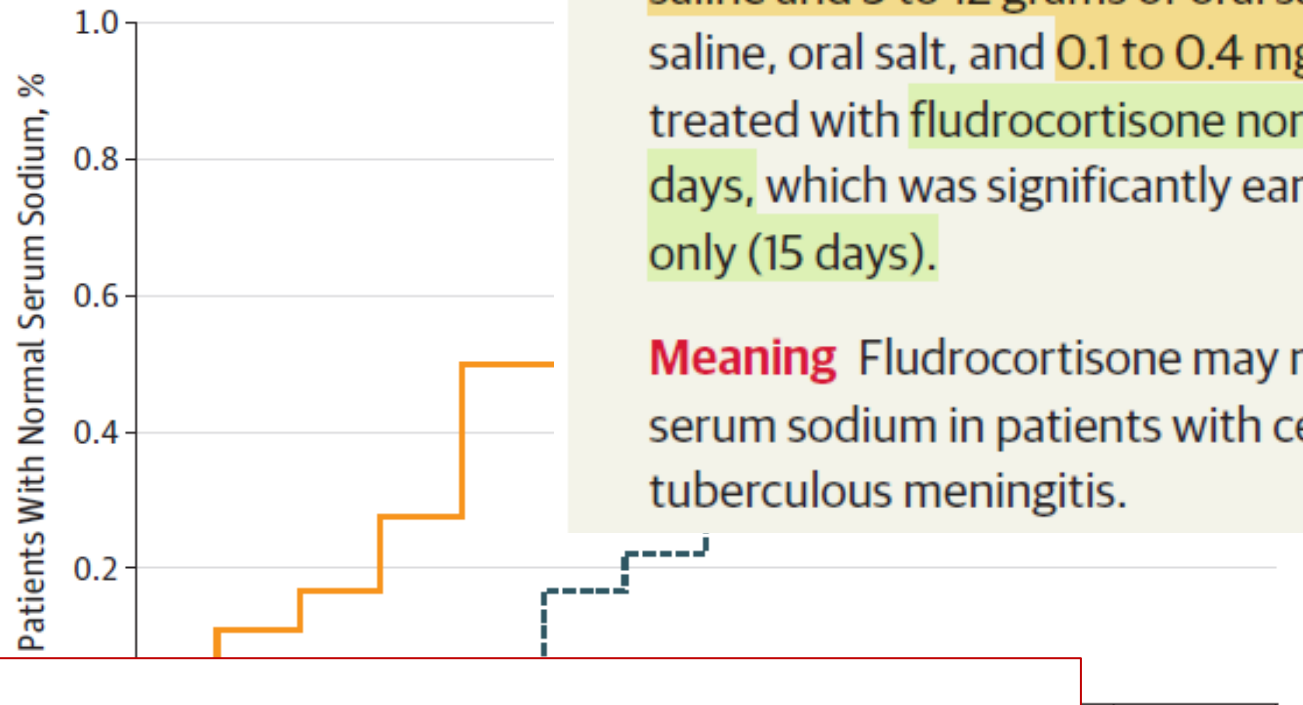
Reference	Drug	Dose	Mechanism	Clinical outcome
Blackmore[51]	Infliximab	10mg/kg, three doses at monthly intervals	Anti-TNF	Given after 4 months due to ongoing clinical deterioration, despite treatment with dexamethasone and cyclophosphamide; resulted in clinical improvement.
Jorge[52]	Infliximab	10mg/kg, three doses at monthly intervals	Anti-TNF	Young adult with juvenile idiopathic arthritis, treated with infliximab developed disseminated TB. With stopping of infliximab, neurological deterioration occurred with isolation of *M.tb* in CSF, with no improvement with corticosteroids. Infliximab re-initiation led to neurological improvement.
Molten[53]	Infliximab	Case 1: 10mg/kg, three doses at monthly intervals Case 2: 5mg/kg, three doses at 6 week intervals	Anti-TNF	Two cases describing paradoxical worsening after initiation of TBM treatment, unresponsive to dexamethasone. In both cases, clinical improvement occurred following administration of infliximab.
Abo[54]	Infliximab	5mg/kg, three doses at weeks 1, 3 and 7	Anti-TNF	Paradoxical worsening (optochiasmatic arachnoiditis, leading to loss of vision) on starting TB treatment in a 7 year old with TBM, despite dexamethasone. Clinical improvement occurred following infliximab administration.
Keeley[56]	Anakinra	100 mg subcutaneously daily	Interleukin-1 receptor antagonist	Two cases of steroid dependant neurotuberculosis (paradoxical worsening when steroids stopping). In both cases, patients responded to anakinra therapy.
A. Gonzalez-Duarte[58]	Cyclophosphamide	750mg/m^3 every 3 weeks	Alkylating agent of nitrogen mustard type.2	Clinical improvement
Celloti[57]	Cyclophosphamide	750mg/m^3 every 3 weeks	Alkylating agent of nitrogen mustard type.2	Clinical improvement
Lee[72]	Adalimumab	40mg SC, total 3 doses every 2 weeks	Anti-TNF	Clinical improvement
Lwin[73]	Adalimumab	40mg SC, every 2 weeks for 3 months	Anti-TNF	Clinical improvement of TBM IRIS refractory to steroid treatment

TNF = tumor necrosis factor

Findings In this randomized clinical trial, 36 patients with tuberculous meningitis with cerebral salt wasting were randomized to receive either an 0.9% solution of intravenous saline and 5 to 12 grams of oral salt supplementation per day or saline, oral salt, and 0.1 to 0.4 mg fludrocortisone per day. Patients treated with fludrocortisone normalized serum sodium levels in 4 days, which was significantly earlier than those receiving saline only (15 days).

Meaning Fludrocortisone may result in earlier normalization of serum sodium in patients with cerebral salt wasting as a part of tuberculous meningitis.

Figure 2. Kaplan-Meier Graph of the Time to Serum Sodiu
With Cerebral Salt Wasting



Probabilities of serum sodium correction differed significantly among the 2 groups (log-rank $\chi^2_1 = 8.29$; $P = .004$).

Conclusions

Fludrocortisone results in earlier normalization of serum sodium levels in patients with TBM who are experiencing CSW. However, in this study, administration of the drug did not affect polyuria or the overall outcome of TBM.

Host directed therapies for TBM

	Activity in TBM	Clinical use	CNS exposure	Safety
Corticosteroids	Large RCTs: Adults: 25% lower mortality [3], smaller effect for MRC grade 2/3 and with longer follow up [71]; no effect on disability; uncertain effect in HIV [26]. Scarce data among African adults and Asian paediatric TBM	Guideline- recommended for all patients with TBM, including IRIS and paradoxical reactions	Good	Excellent in TBM RCT [76]
Aspirin	Small RCT: Possibly fewer new-onset strokes at high doses among adults with TBM [65]	Not in routine clinical use, evaluated in adults and children with new TBM diagnosis	Good	No signal of severe bleeding events [77]
Thalidomide	Individual case reports of resolution from mass lesions and blindness related to optochiasmatic arachnoiditis (children)	Steroid-refractory TBM or paradoxical reactions	Good	Dose related toxicity, paediatric RCT stopped prematurely for safety [60]
TNF blockers (infliximab)	Case series [57,59,78] and matched retrospective cohort [58] showing clinical benefit in TBM	Steroid-refractory TBM or paradoxical reactions	Good	No serious safety signals, Risk of secondary infection
Anti-IL1 (anakinra)	Case reports in TBM [70,79]	Steroid-refractory TBM or paradoxical reactions	Good	Good safety profile, associated with mild neutropenia
mTOR inhibitors	RCT: Less post-TB lung disease	No experience in TBM	Unknown	Well tolerated in an RCT for PTB
JAKi	Cases reports for HLH / HLH-TB [80]	No experience in TBM		Good safety profile, associated with VZV/HSV

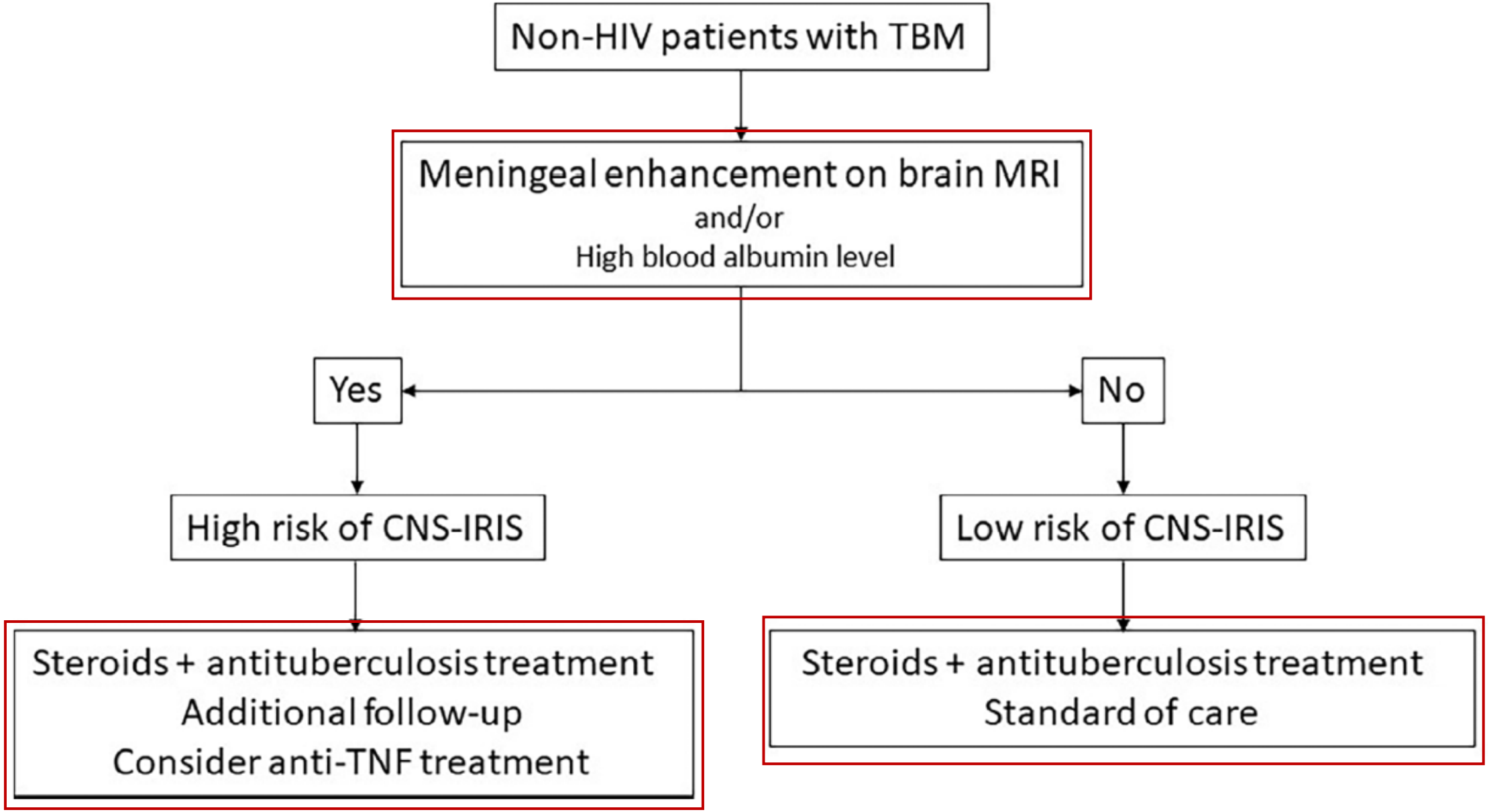


Figure 2 Management of patients with TBM according to risk factors for CNS-IRIS identified at diagnosis. CNS, central nervous system; IRIS, immune reconstitution inflammatory syndrome; TBM, tuberculous meningitis.

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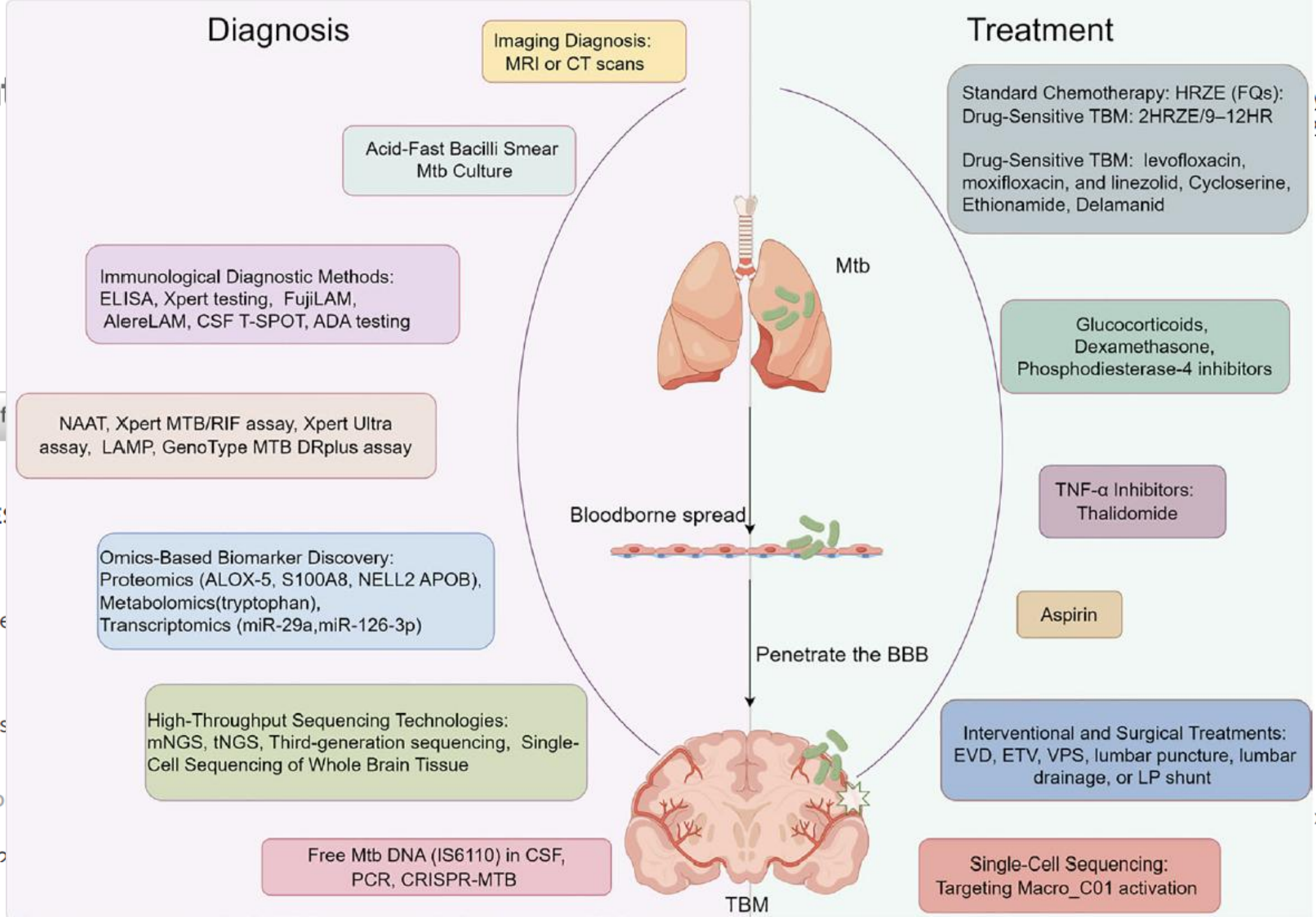

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ol of Medicine,

Conclusion

Prise en charge en pleine révolution

IRIS: Anti-TNF ?

Prolonger quadrithérapie ?

Prolonger PZD ?

Eviter ETB ?

Associer de principe

- Quinolones ?
- Linezolide ?

Aspirine

- De principe ?
- Posologie ?
- Si PNN élevés ?