

Atteintes neurologiques centrales au cours de l'infection par le VIH

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Université
de Paris



- Définitions et épidémiologie des complications neurologiques du VIH en réanimation
- Questions-clés pour le diagnostic et la prise en charge
- Traitement antirétroviral / IRIS
- Quel pronostic ?

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Primo-infection VIH

- **Symptomatique: 40-90 %**
- Syndrome viral aigu persistant > 7 jours, 10-15 jours après la contamination
- Amendement des symptômes en 2-4 semaines

- **Manifestations neurologiques 15%**

Encéphalite

Myélopathie

Méningite aiguë lymphocytaire

Neuropathies périphériques

PFP, polyneuropathie aiguë

Sd de Guillain-Barré

Complications neurologiques du VIH

Primary processes

HIV dementia

Vacuolar myelopathy

Cerebrovascular disease

Inflammatory demyelinating polyneuropathy

Aseptic meningitis

Distal symmetrical polyneuropathy

Mononeuritis multiplex

Myopathy

Secondary processes

Toxoplasmosis

Progressive multifocal leukoencephalopathy

Primary CNS lymphoma

Cryptococcus neoformans infection

Cytomegalovirus encephalitis

Cytomegalovirus polyradiculopathy

Tuberculous meningitis

Neurosypilis

Nocardia infection

Aspergillus infection

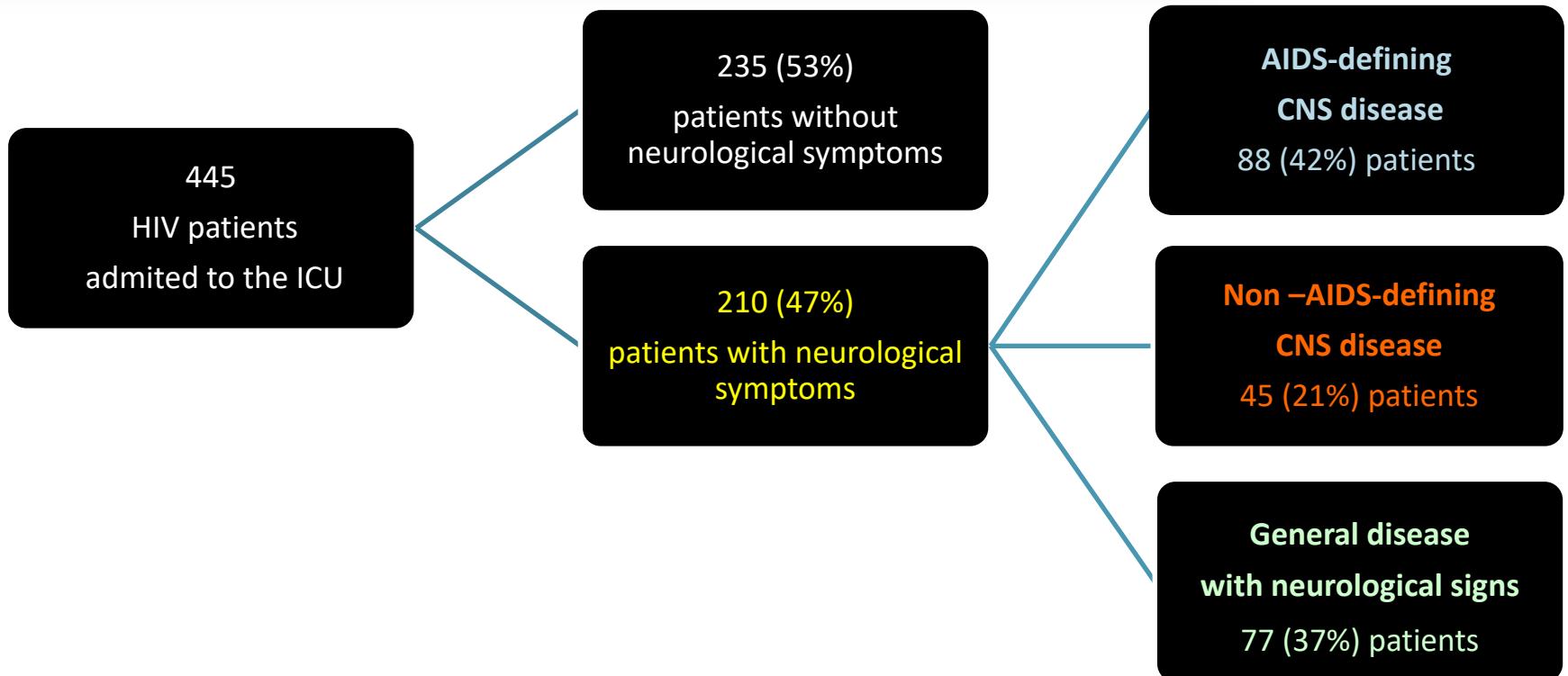
Multicenter AIDS Cohort Study, 1996–2011



Mean incidence rate of HIV-1-associated neurologic diseases during
4 time periods in the Multicenter AIDS Cohort Study, all ages
(expanded from reference⁵)

Diagnosis	1990-1992, predominantly monotherapy ⁵	1993-1995, predominantly dual therapy ⁵	1996-1998, predominantly early HAART ⁵	1999-2011, HAART (current study)
HIV dementia	21.1	17.8	10.5	1 (0.6-1.7)
Cryptococcal meningitis	5.0	2.5	1.5	0.4 (0.2-0.9)
Toxoplasmosis	5.4	3.8	2.2	0
Progressive multifocal leukoencephalopathy	2.0	1.8	1.5	0.07 (0-0.05)
CNS lymphoma	2.8	4.3	0.4	0.1 (0-0.5)

Neurological complications of HIV infection in critically ill patients: Clinical features and outcomes



Neurological complications of HIV infection in critically ill patients: Clinical features and outcomes

Bichat Medical ICU, 2001-2007

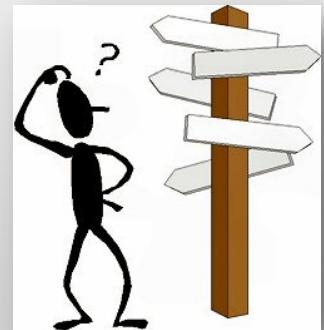
	N=210
AIDS-defining CNS disease	88 (42)
Cerebral toxoplasmosis	47 (22)
Tuberculous meningitis	14 (7)
HIV-associated encephalitis	11 (5)
Cryptococcosis	8 (4)
Progressive multifocal leukoencephalitis	4 (2)
Cerebral lymphoma	4 (2)
Non-AIDS-defining CNS disease	45 (21)
Epilepsy	15 (7)
<i>Streptococcus pneumoniae</i> meningitis	9 (4)
Systemic disease with neurological signs	77 (37)
Sepsis	36 (17)
Metabolic or toxic disorders	25 (12)

Data are numbers (%)

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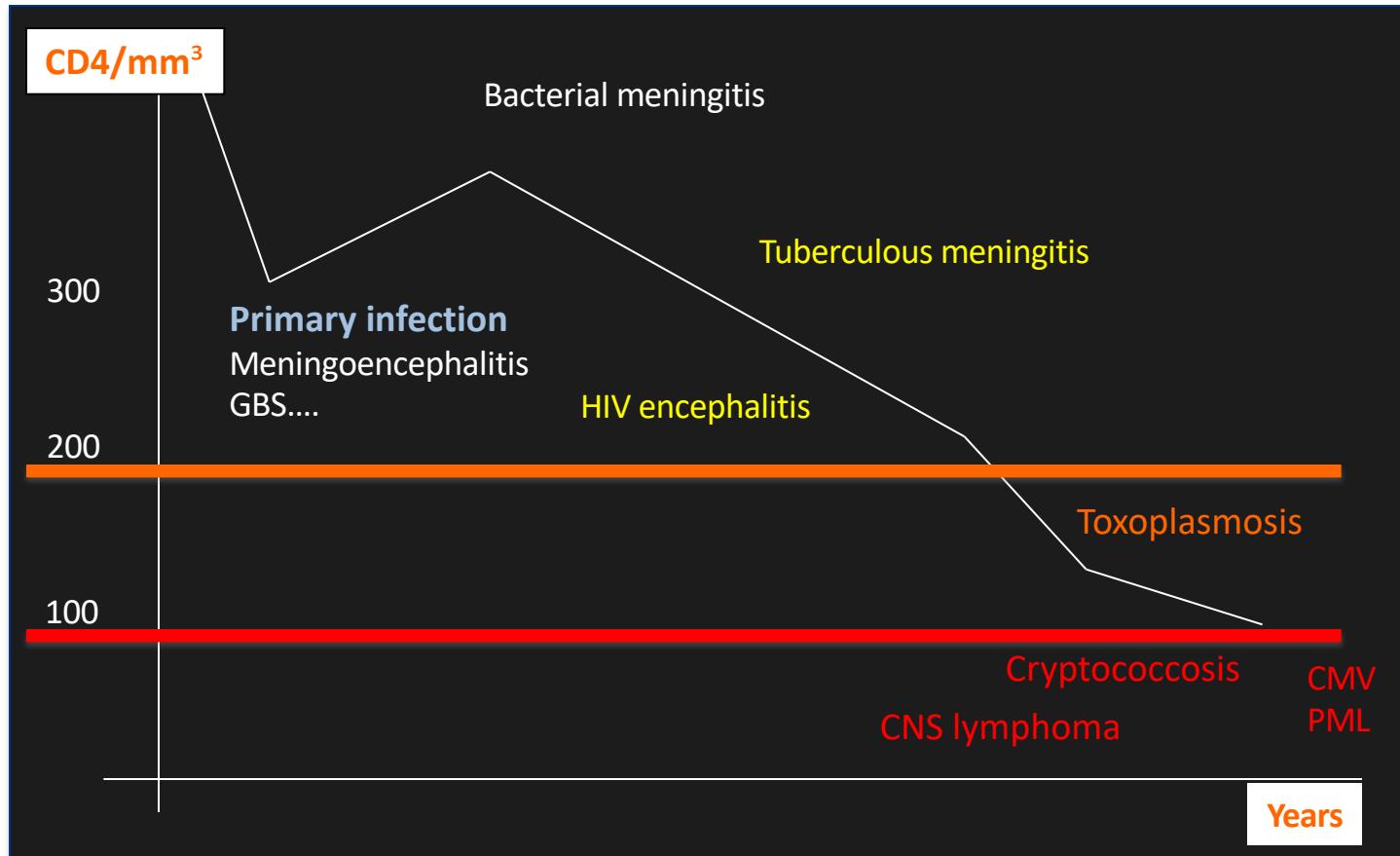
6 points-clés

1. **Histoire de l'infection VIH, ATCDs neurologiques ?**
2. **Immunodépression (λ , CD4....)**
3. **Traitements: Prophylaxie IO ? ARV ? Observance ?**
4. **Mode d'installation des troubles**
5. **Imagerie cérébrale injectée (IRM > TDM)**
6. **LCR : cultures, PCR, NGS ...**

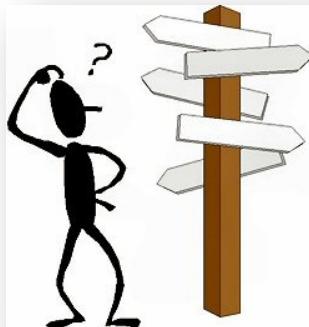


Approche syndromique

Natural history



Diagnostic workup



Imaging

- Neuroimaging with contrast-enhanced MRI or CT
- Chest radiography or CT for tuberculosis

CSF

- Bacterial, fungal, and mycobacterial culture
- White-blood-cell count and differential protein and glucose concentrations
- Cytology and flow cytometry
- PCR for JC virus, Epstein-Barr virus, cytomegalovirus, *Toxoplasma gondii*, herpes simplex virus types 1 and 2, and varicella zoster virus
- Cryptococcal antigen
- Microscopy for India ink stain (*Cryptococcus*) and acid-fast bacilli (*Mycobacterium tuberculosis*)

Other laboratory tests

- CD4-positive T-cell count
- IgG antibodies to *Toxoplasma gondii* in CSF, blood, and urine

Focal neurological syndromes

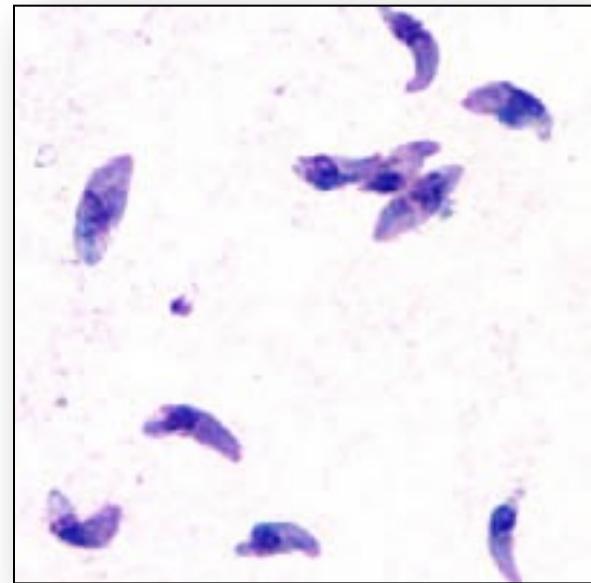
Cerebral toxoplasmosis

CNS lymphoma

PML

Toxoplasmose du SNC

- Parasitose due à **protozoaire** : *Toxoplasma gondii*
- Réactivation kystes +++, rarement primo-infection
- Processus « encéphalitique »
- **Séroprévalence :**
 - 50-75% en Europe
 - < 30% en Scandinavie
 - 15% aux USA
- Stade SIDA : **CD4 < 200 / mm³**
- **2ème IO après pneumocystose**
- **Révélatrice du VIH** 15-20% des cas



Neurologic outcomes and adjunctive steroids in HIV patients with severe cerebral toxoplasmosis

100 ICU patients with cerebral toxoplasmosis

Age, yrs : 40 (34-46)

HIV load, log : 5,3 (5,0-5,8)

CD4, n/mm³ : 25 (8-62)

T° : 37.7° (37.0-38.5)

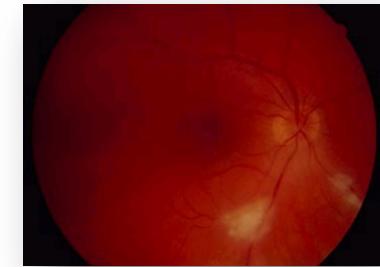
GCS score : 11 (6-14)

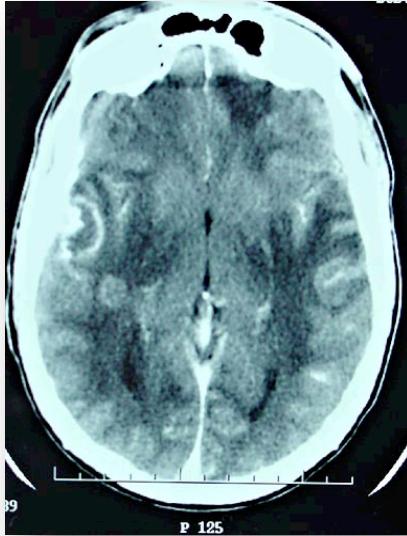
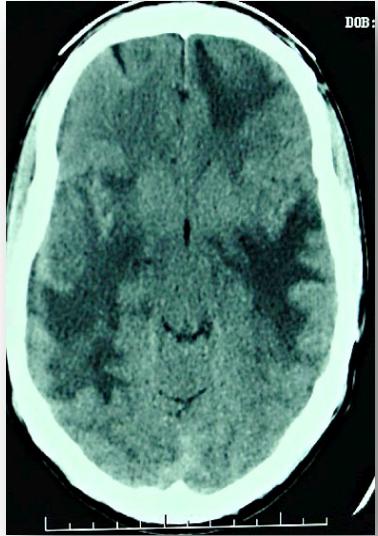
Focal deficit : 59%

Seizures : 36%

Other signs:

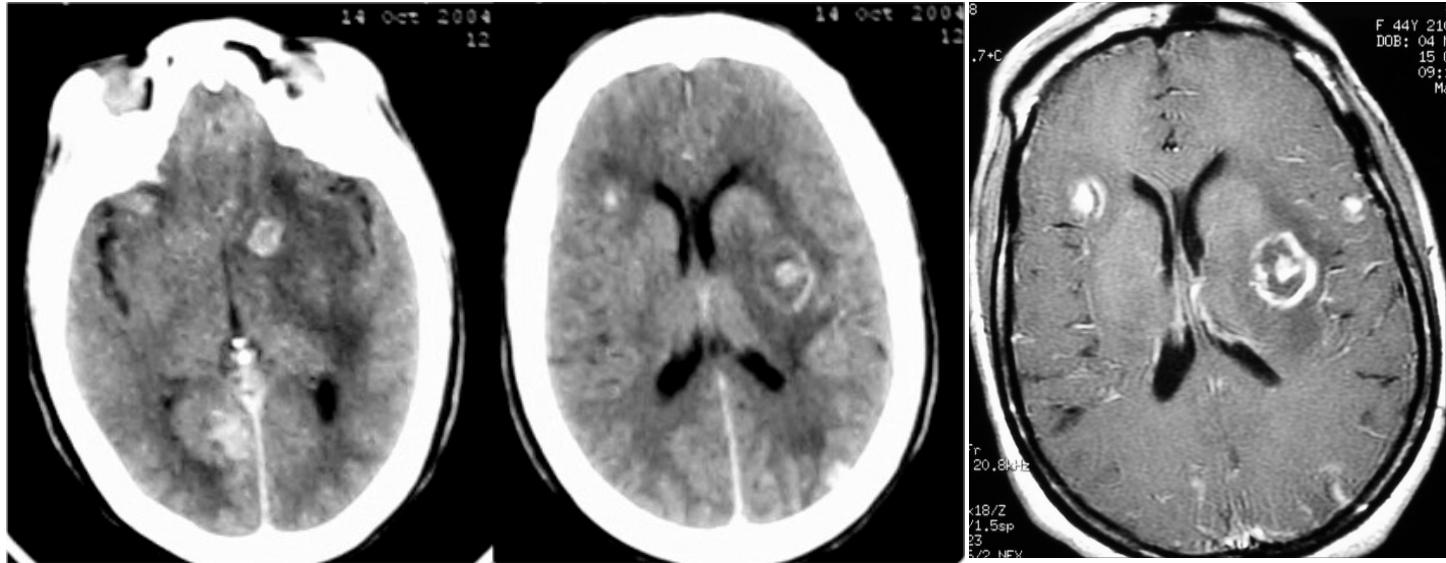
- Chorioretinitis
- Respiratory signs (2-5%)....
- Cytopenia
- Septic shock





Lésions multiples
Abcès
Topographie: sous-corticale, noyaux gris
Oedématueuses

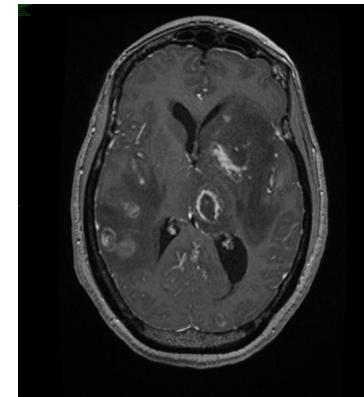
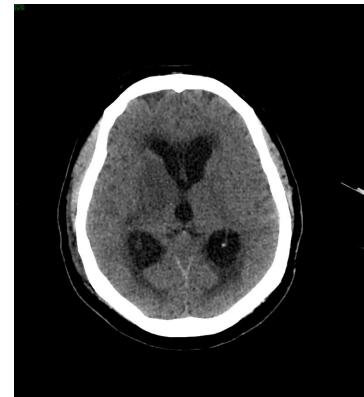
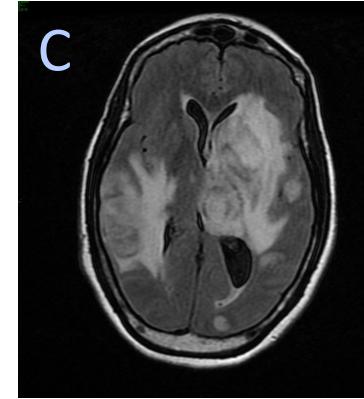
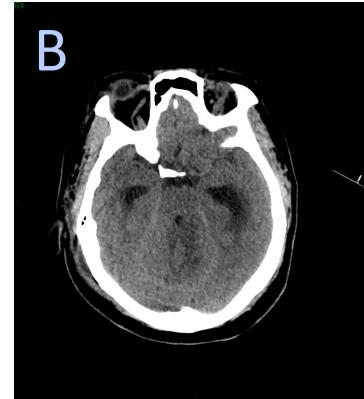
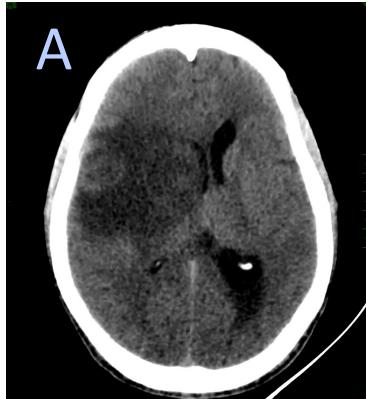
Toxoplasmose du SNC



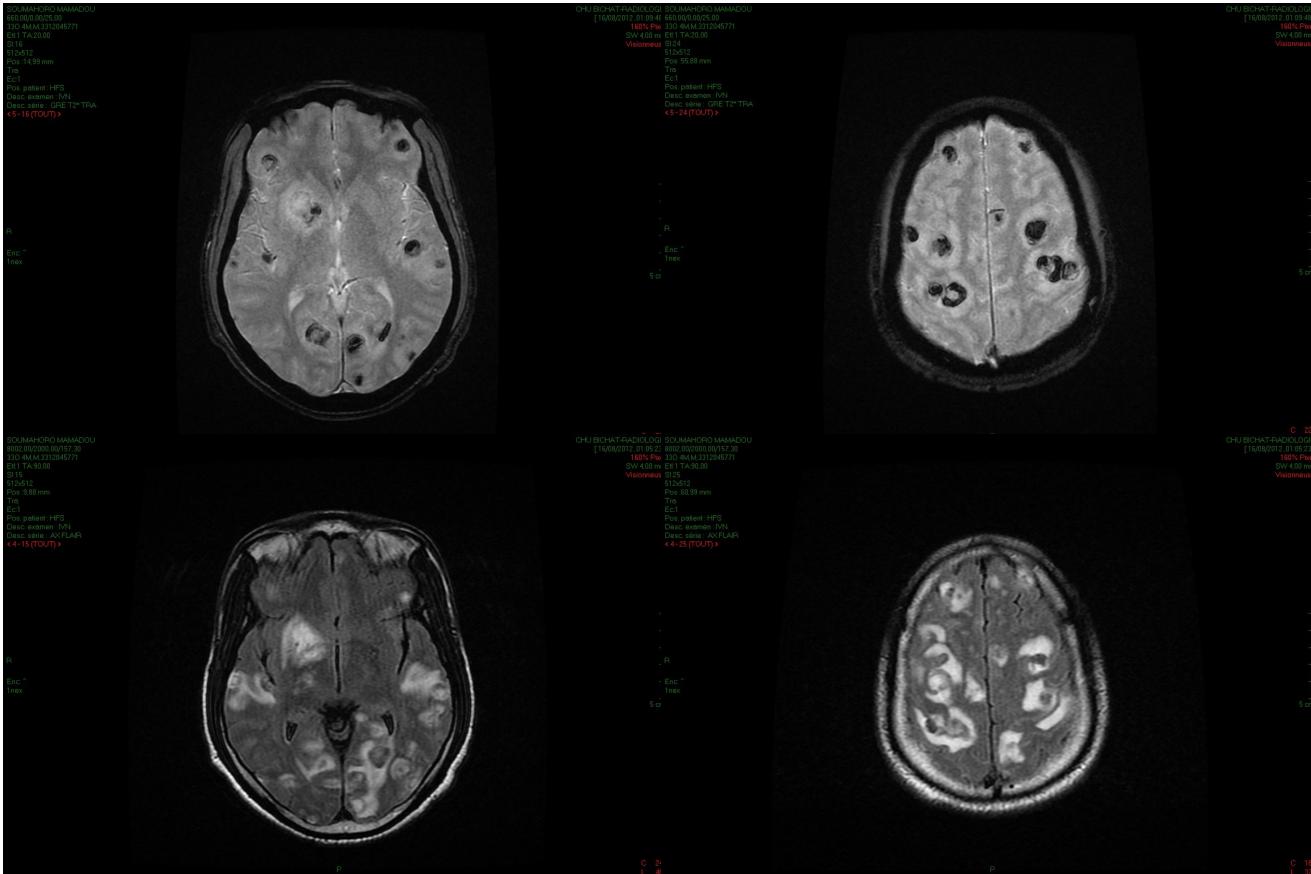
SCANNER INJECTÉ

IRM T1 INJECTEE

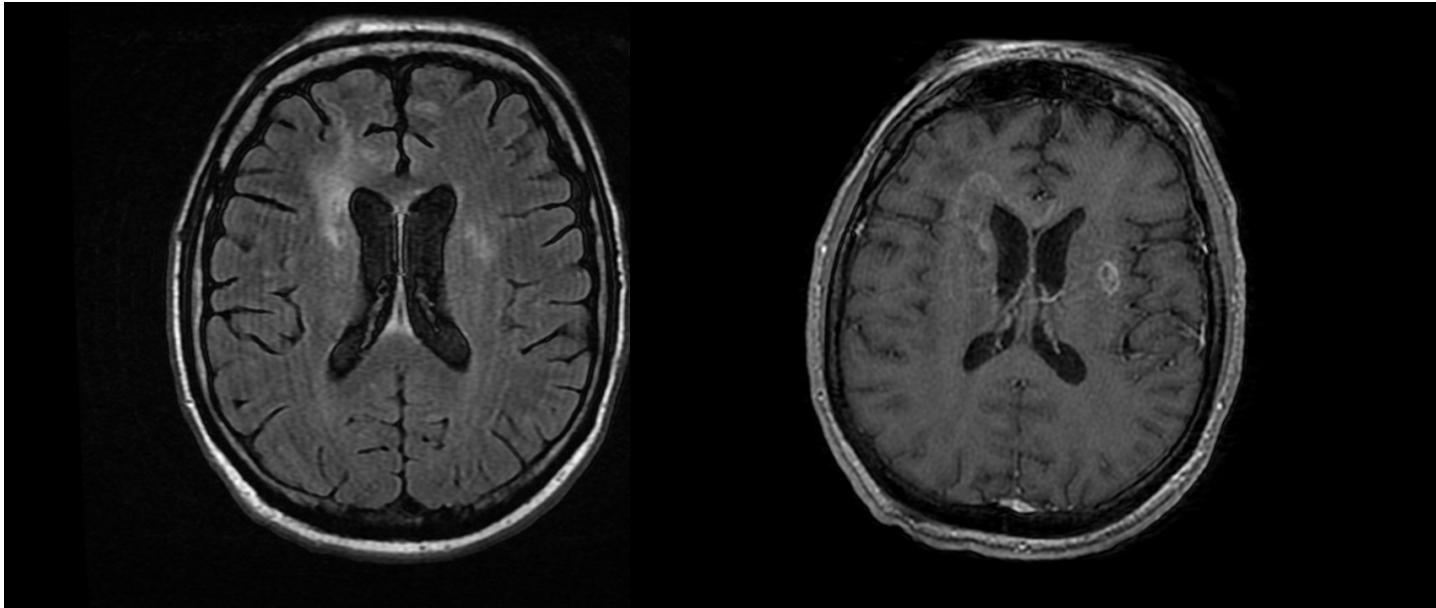
Toxoplasmose du SNC



Toxoplasmose du SNC



Toxoplasmose du SNC



IRM vs TDM

PCR *Toxoplasma gondii*

Toxoplasmose SNC – critères diagnostiques

- Tableau clinique & radiologique compatible
- CD4 < 200 / mm³
- Sérologie TOXO + en IgG
- PCR Toxoplasma LCR :
(Spe 95%, Sen 50%... Négativation sous ttt)
- **Réponse au traitement d'épreuve (14 j)**
Pyriméthamine: 100 mg/j en dose charge, puis 50mg/j
Sulfadiazine: 4g/j
Acide folinique: 25 à 50 mg/j

Toxoplasmose SNC – traitement

- Pyriméthamine – sulfadiazine – acide folinique (AI)
ou
- Pyriméthamine – clindamycine – acide folinique (AI)
- Autres (CIII) :
 - TMP-SMX IV
 - Association TMP-SMX + clindamycine IV
- Corticoïdes : dexaméthasone, si lésion avec effet de masse ?
 - > courte durée
 - > surveillance apparition autres IO (BK, CMV....)
- Anticonvulsivants seulement si convulsions +

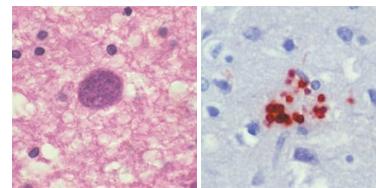
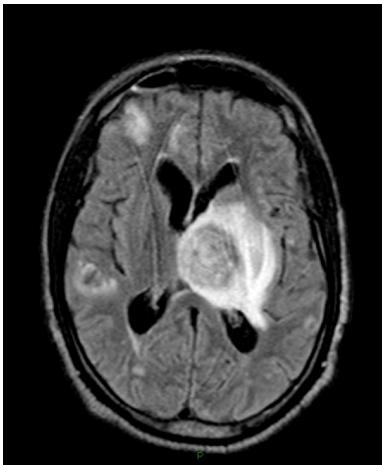
6 semaines
puis ttt entretien

Biopsie cérébrale ?

Diagnostic de certitude

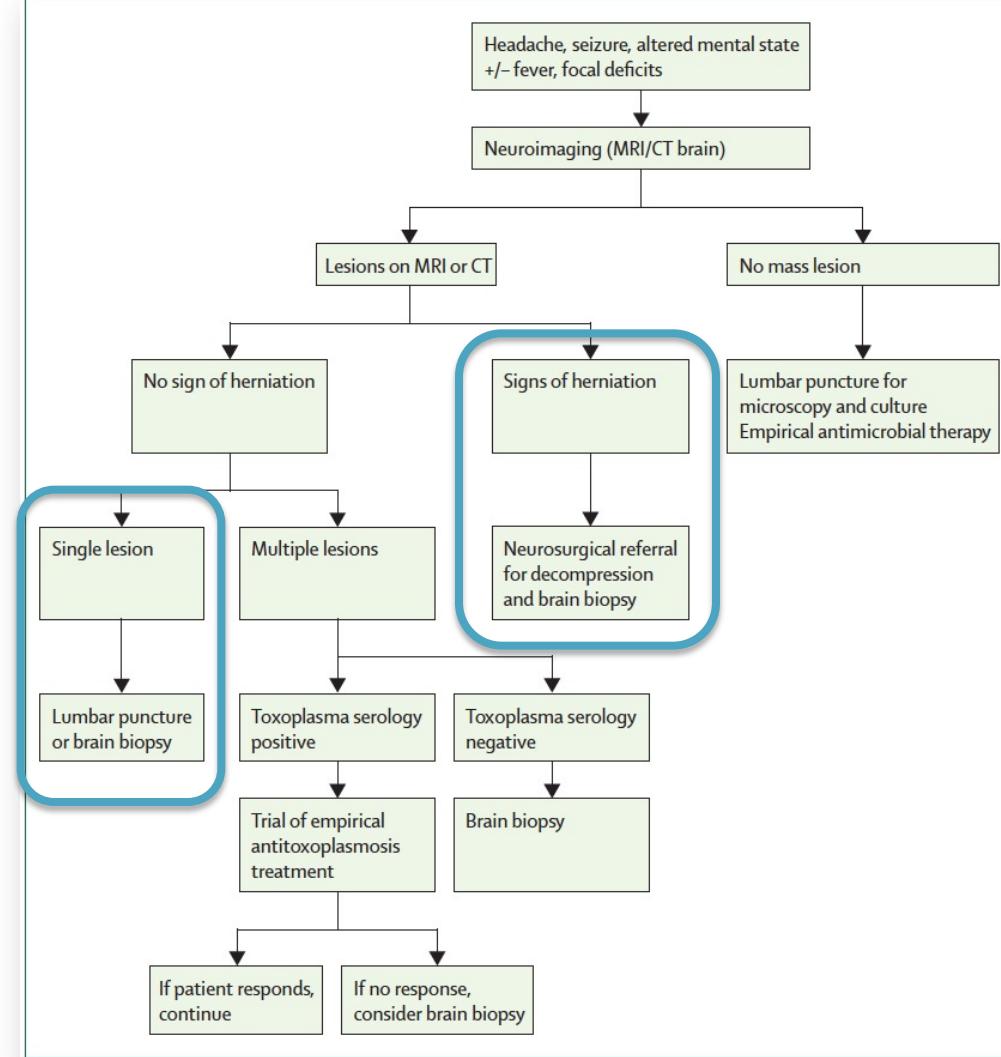
Lésion atypique

Non réponse au ttt d'épreuve à J14

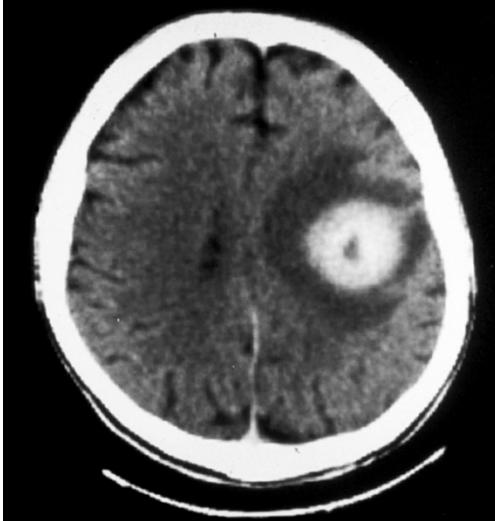


H&E

IHC



Lymphoma of the CNS



CD4<50/microL, Intracranial hypertension symptoms, focal signs

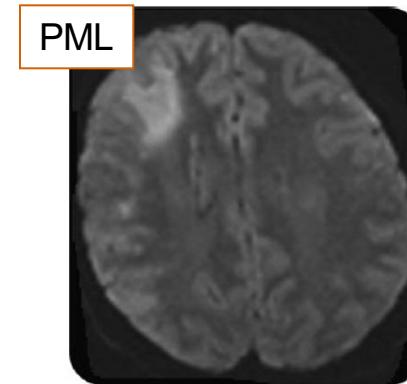
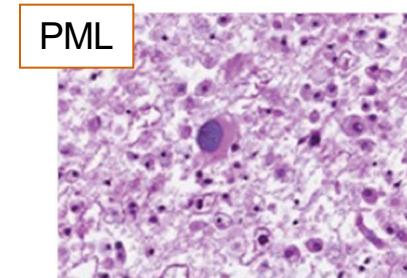
Unique deep lesion, cerebral edema

NO RESPONSE TO ANTI-TOXO THERAPY

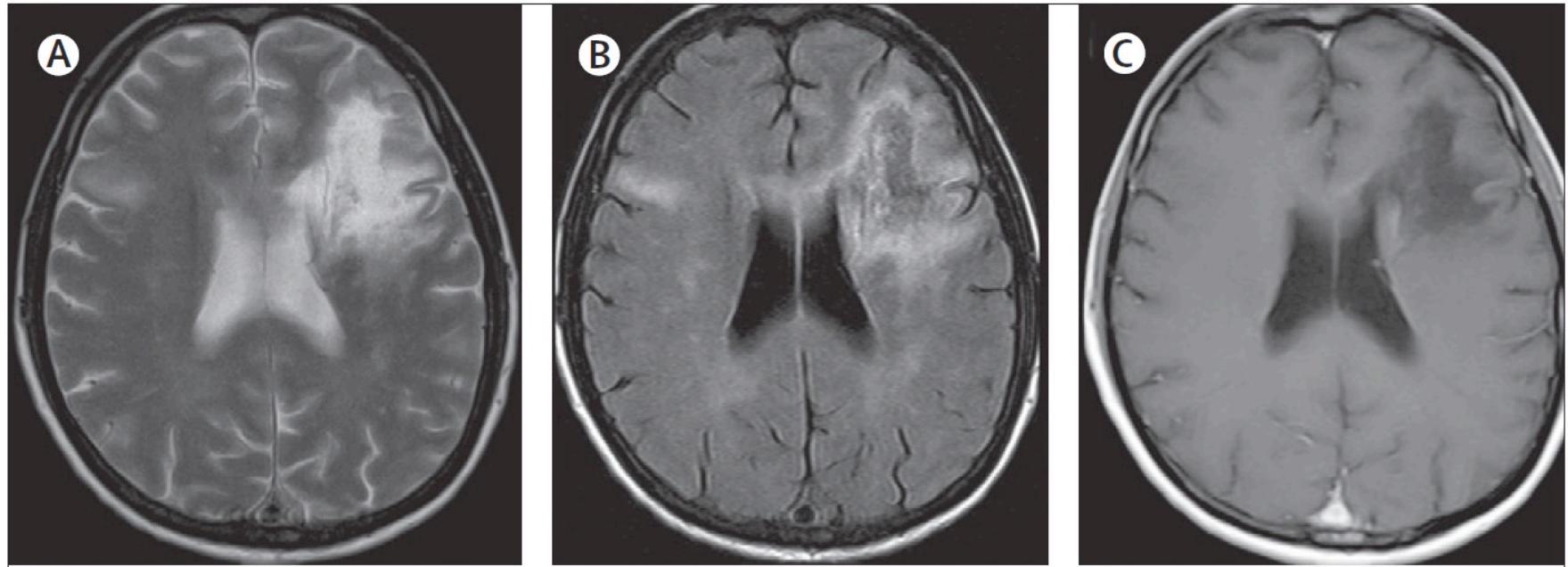
⇒**BRAIN BIOPSY**

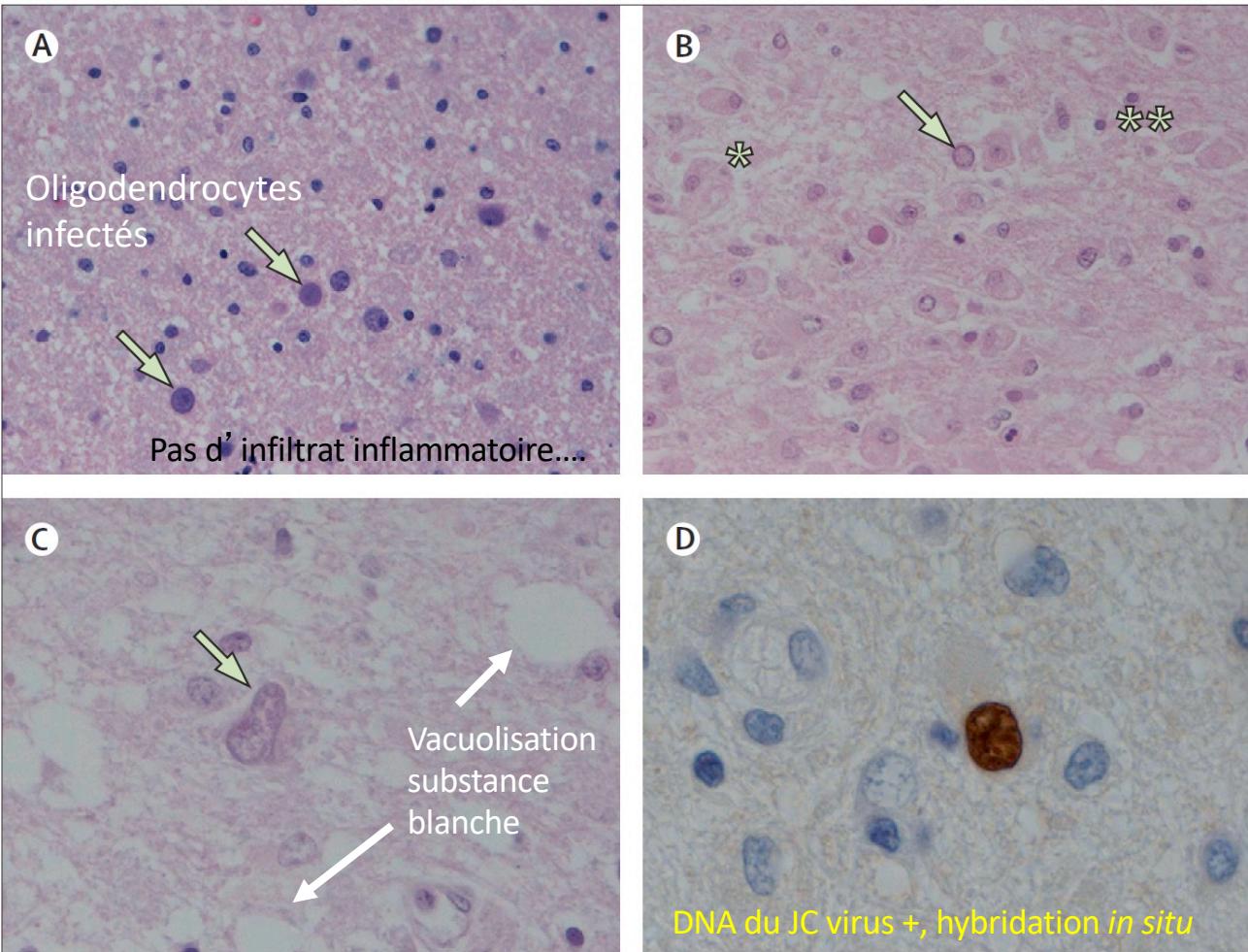
Leucoencéphalopathie multifocale progressive

- Affection **demyélinisante** du SNC, multifocale
- 50 cas/an en F
- Infection **oligodendrocytes** par Polyomavirus JC
- Tableau clinique **progressif** (semaines), **signes focaux**
- **Convulsions** (20%)
- **Pas d' HTIC, pas de fièvre**
- **IRM +++**
- **PCR JC dans le LCR + <75% des cas**
⇒ Répéter PCR si début maladie, patient sous ARV



Leucoencéphalopathie multifocale progressive



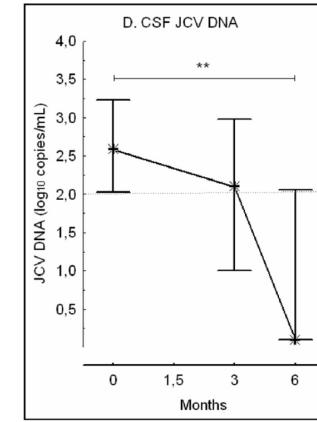
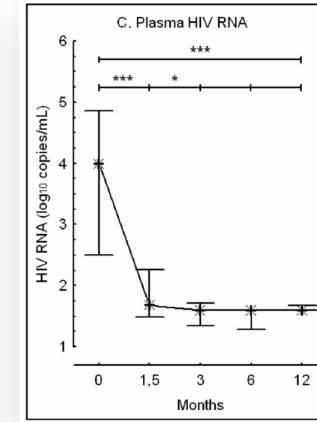
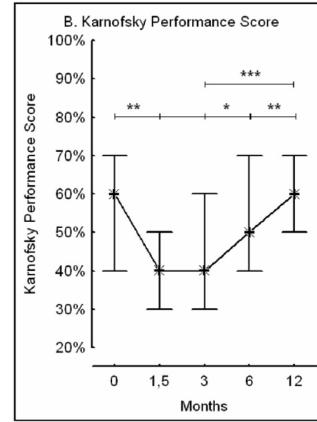
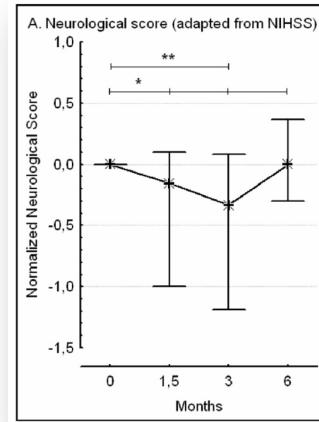


Improved Survival of HIV-1-Infected Patients with Progressive Multifocal Leukoencephalopathy Receiving Early 5-Drug Combination Antiretroviral Therapy

Jacques Gasnault^{1,2,*†}, Dominique Costagliola^{3,4,5,9}, Houria Hendel-Chavez^{2,6}, Anne Dulouost¹, Sophie Pakianather⁴, Anne-Aurélie Mazet⁷, Marie-Ghislaine de Goer de Herve², Rémi Lancar⁴, Anne-Sophie Lascaux⁸, Lydie Porte⁹, Jean-François Delfraissy^{1,2,10}, Yassine Taoufik^{2,6,10} for the ANRS 125 Trial Team

28 patients

cART including enfuvirtide for a duration of 12 months



Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy

Irene Cortese, M.D., Pawel Muranski, M.D., Yoshimi Enose-Akahata, Ph.D.,
Seung-Kwon Ha, D.V.M., Ph.D., Bryan Smith, M.D., MariaChiara Monaco, Ph.D.,
Caroline Ryschkewitsch, B.S., Eugene O. Major, Ph.D., Joan Ohayon, M.S.N.,
Matthew K. Schindler, M.D., Ph.D., Erin Beck, M.D., Ph.D., Lauren B. Reoma, M.D.,
Steve Jacobson, Ph.D., Daniel S. Reich, M.D., Ph.D., and Avindra Nath, M.D.

PD-1 blockade in PML ?

Pembrolizumab at a dose of 2 mg per kilogram of body weight every 4 to 6 weeks to eight adults with PML, each with a different underlying predisposing condition.

Each patient received at least one dose but no more than three doses.

Pembrolizumab reduces JC viral load and increases CD4+ and CD8+ activity against the JC virus.

Clinical improvement or stabilization occurred in 5/8 patients who received pembrolizumab.

Focal neurological syndromes

SIGNS	CEREBRAL TOXOPLASMOSIS	CNS LYMPHOMA	PML
Focal signs	+	+	+
Intracranial hypertension	++	+	-
Seizures	+	+/-	+/-
Fever	+	-	-

MRI Patterns

SIGNS	CEREBRAL TOXOPLASMOSIS	CNS LYMPHOMA	PML
Number of lesions	Multiple	Unique	Multiple
Location	White matter Cortex / basal ganglia	Deep	Subcortical
T1-weighted MRI	Hypointense	Hypo/iso	Hypo
Gado enhancement	+ (Ring)	+ (Nodular)	-
Cerebral edema	++++	+	-
Response to Anti-toxo therapy	regression	extension	extension

Meningoencephalitis ?

Cryptococcal meningitis

Tuberculous meningitis

HIV encephalitis

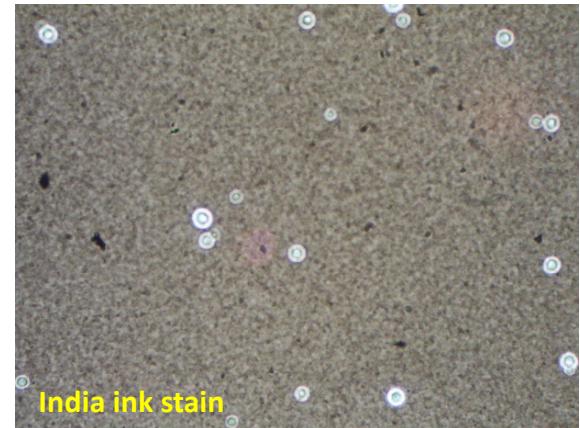
VZV, CMV

Neurosyphilis

...

Cryptococcal meningitis

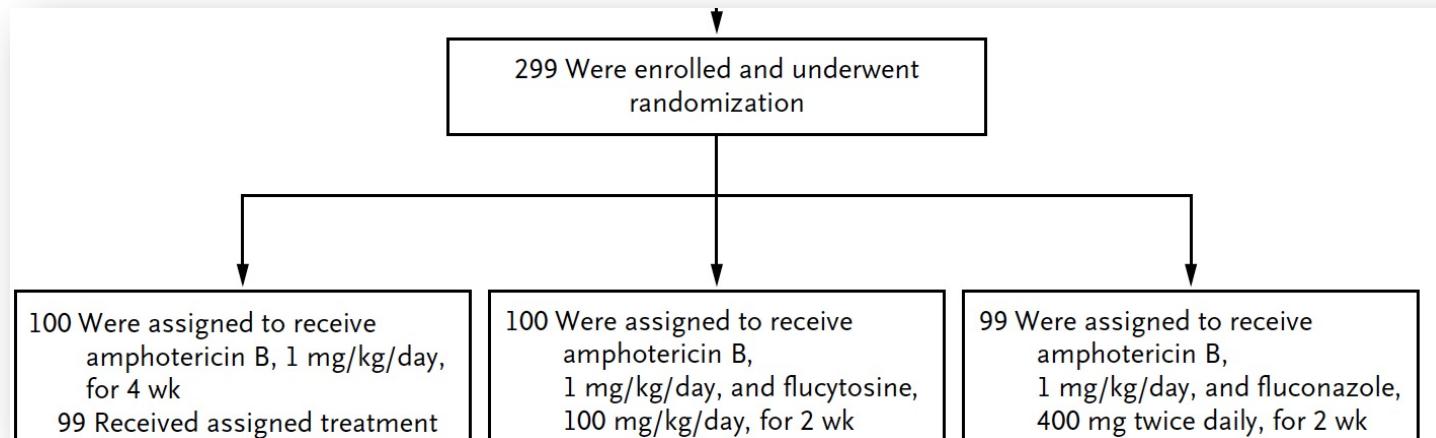
- CD4 < 50 /mm³
- **Subacute meningoencephalitis**
- **CSF:**
 - Elevated opening pressure (> 20mmHg)
 - Pleocytosis, elevated protein levels
 - positive India ink stain (80%) and cryptococcal antigen (95%)
 - Cultures : 3-7 days
- **Disseminated disease (heart, lung, spleen) is common**
=> serum cryptococcal antigen (90%)



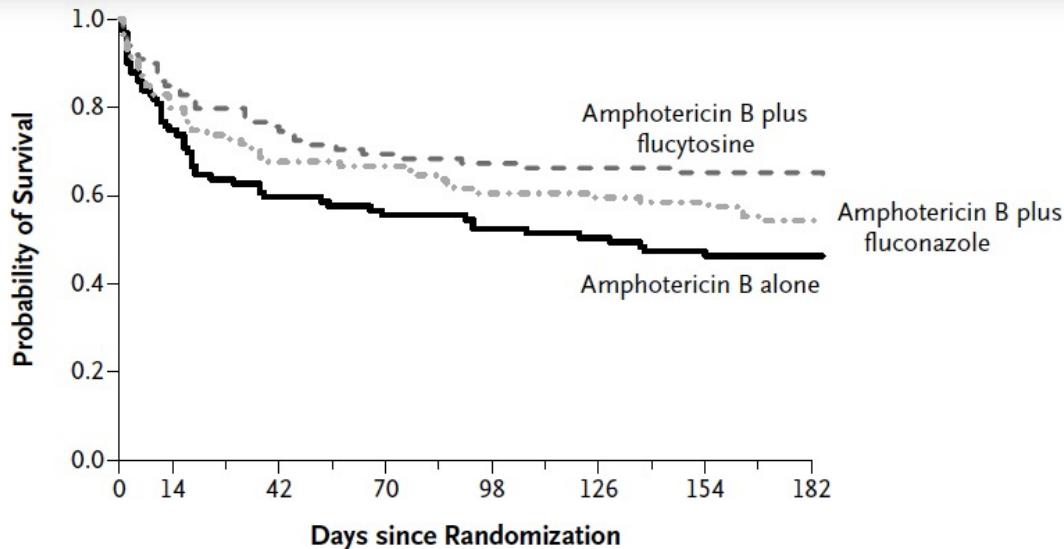
**** CSF Interpretation

Investigation	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	<5	High/very high 100-50000	Slightly increased 5-1000	Slightly increased <500	Normal-high 0-1000
Differential	Lymphocytes	Neutrophilis	Lymphocytes	Lymphocytes	Lymphocytes
CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
Protein (g/l)	<0.45	High >1	Normal-high 0.5-1	High-very high 1.0-5.0	Normal-high 0.2-5.0

Combination Antifungal Therapy for Cryptococcal Meningitis



Combination Antifungal Therapy for Cryptococcal Meningitis

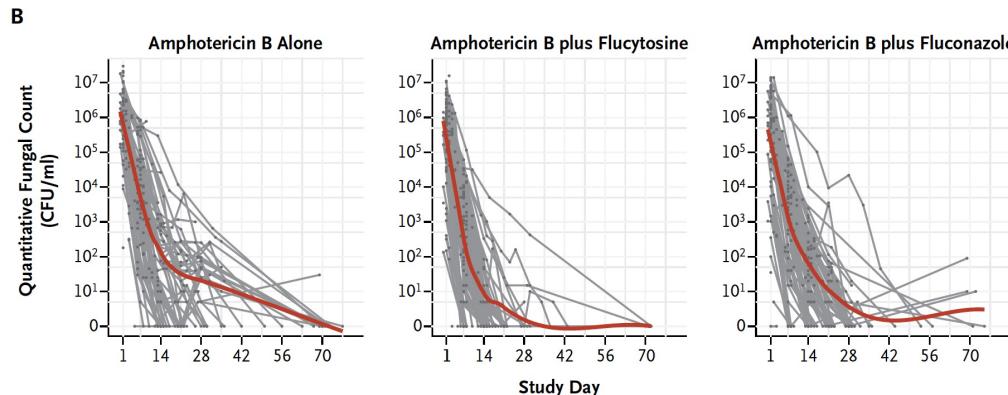


No. at Risk

Amphotericin B alone	99	74	59	54	51	49	46	30
Amphotericin B plus flucytosine	100	84	73	67	64	63	62	46
Amphotericin B plus fluconazole	99	79	67	65	59	58	57	39

Combination Antifungal Therapy for Cryptococcal Meningitis

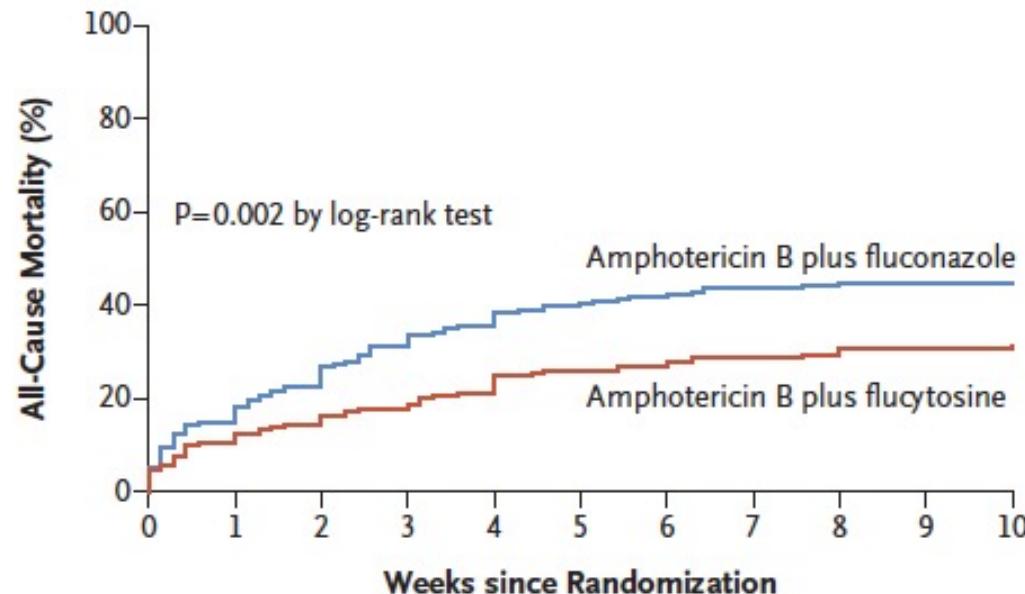
Outcome	Group 1, Amphotericin B (N=99)	Group 2, Amphotericin B and Flucytosine (N=100)	Group 3, Amphotericin B and Fluconazole (N=99)
Probability of survival (95% CI)	0.46 (0.37 to 0.57)	0.65 (0.56 to 0.75)	0.54 (0.45 to 0.65)
Estimated change in CSF fungal count in first 14 days (95% CI) — \log_{10} CFU/ml/day	-0.31 (-0.34 to -0.29)	-0.42 (-0.44 to -0.40)	-0.32 (-0.34 to -0.29)



ORIGINAL ARTICLE

Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

S.F. Molloy, C. Kanyama, R.S. Heyderman, A. Loyse, C. Kouanfack, D. Chanda, S. Mfinanga, E. Temfack, S. Lakhi, S. Lesikari, A.K. Chan, N. Stone, N. Kalata, N. Karunaharan, K. Gaskell, M. Peirse, J. Ellis, C. Chawinga, S. Lontsi, J.-G. Ndong, P. Bright, D. Lupiya, T. Chen, J. Bradley, J. Adams, C. van der Horst, J.J. van Oosterhout, V. Sini, Y.N. Mapoure, P. Mwaba, T. Bicanic, D.G. Lalloo, D. Wang, M.C. Hosseinpour, O. Lortholary, S. Jaffar, and T.S. Harrison, for the ACTA Trial Study Team*



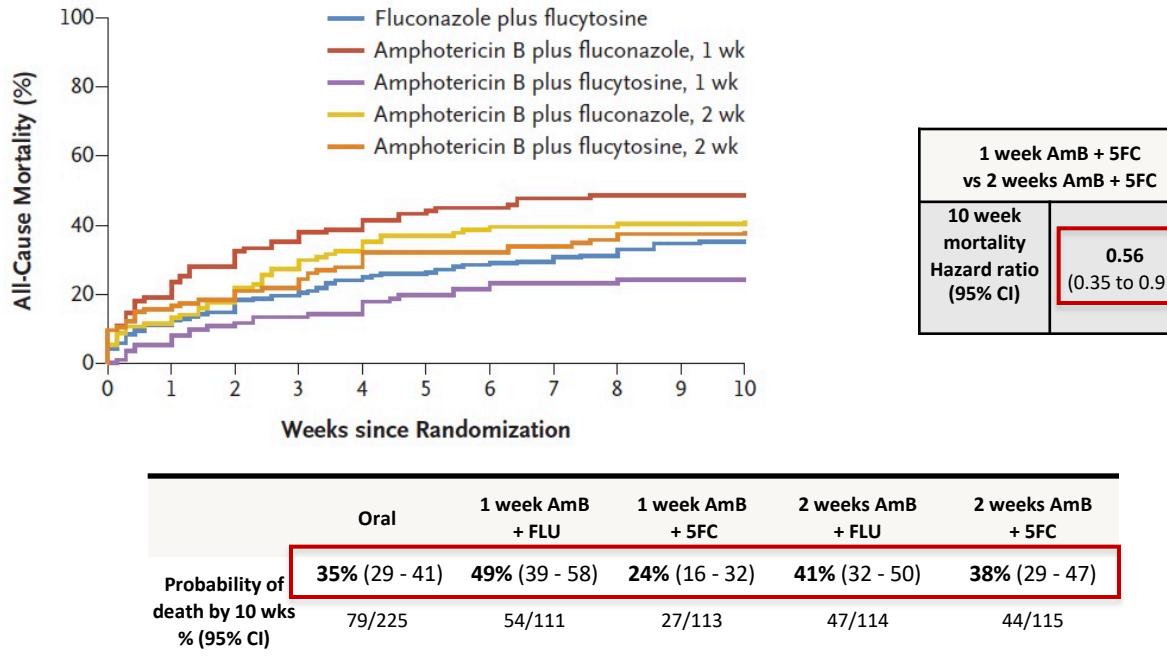
10-week mortality: FLU: **45%** (101/225)

5FC: **31%** (71/228)

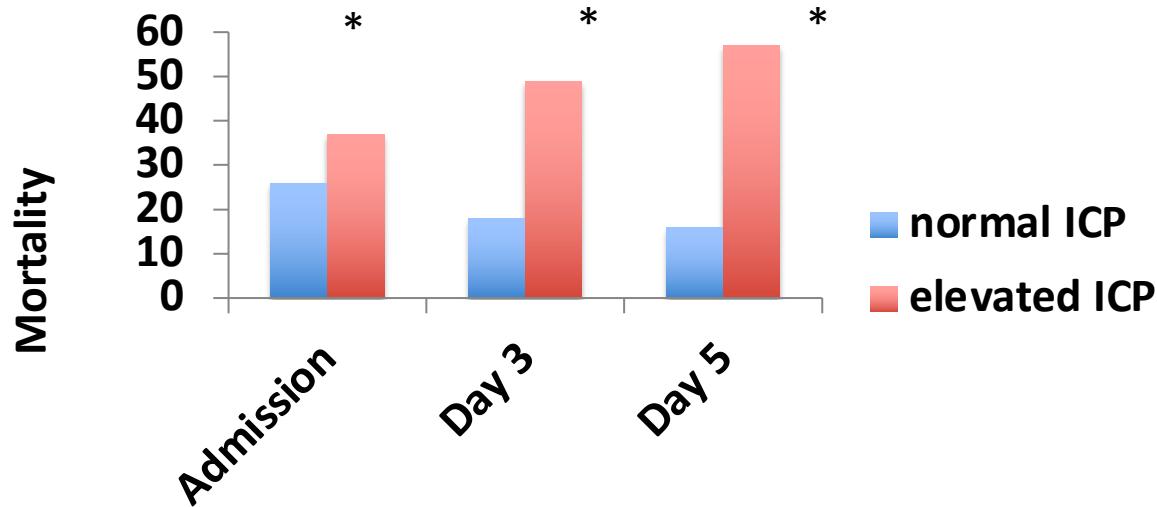
Molloy et al N Engl J Med 2018

Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

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ICP management in Cryptococcosis



Cryptococcal meningitis

Management of INTRACRANIAL PRESSURE +++

Before treatment

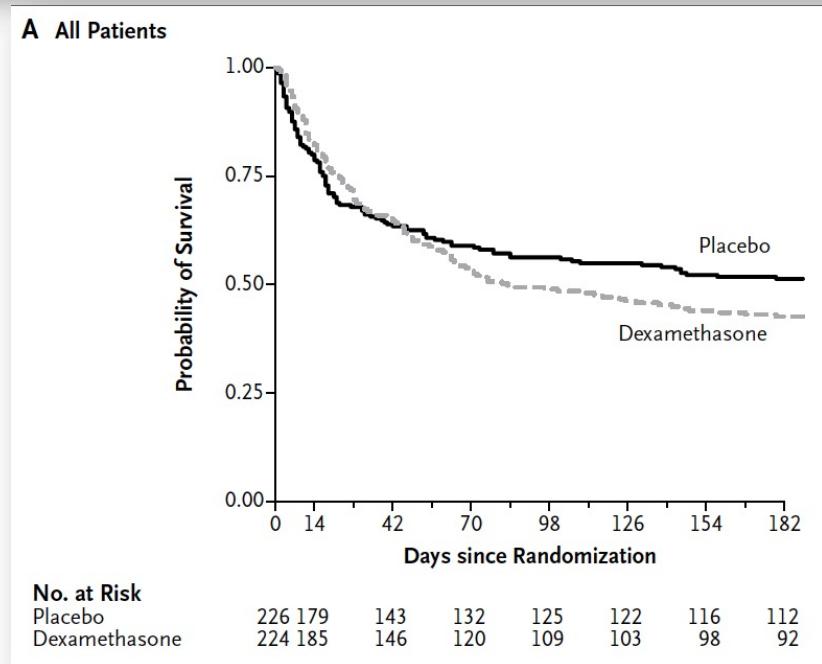
Focal neurological signs, obtunded Radiographic imaging before lumbar puncture to identify mass lesions that may contraindicate lumbar puncture BII

Normal opening pressure Initiate medical therapy, with follow-up lumbar puncture at 2 w AI
Opening pressure >250 mm H₂O Lumbar drainage sufficient to achieve closing pressure ≤200 mm H₂O or 50% of initial opening pressure AII

Follow-up for elevated pressure Repeated drainage daily until opening pressure is stable AII
If elevated pressure persists: Lumbar drain BII

Ventriculoperitoneal shunt BII
Corticosteroids: not recommended for HIV-infected patients, and evidence of benefit for HIV-negative patients is not established CIII

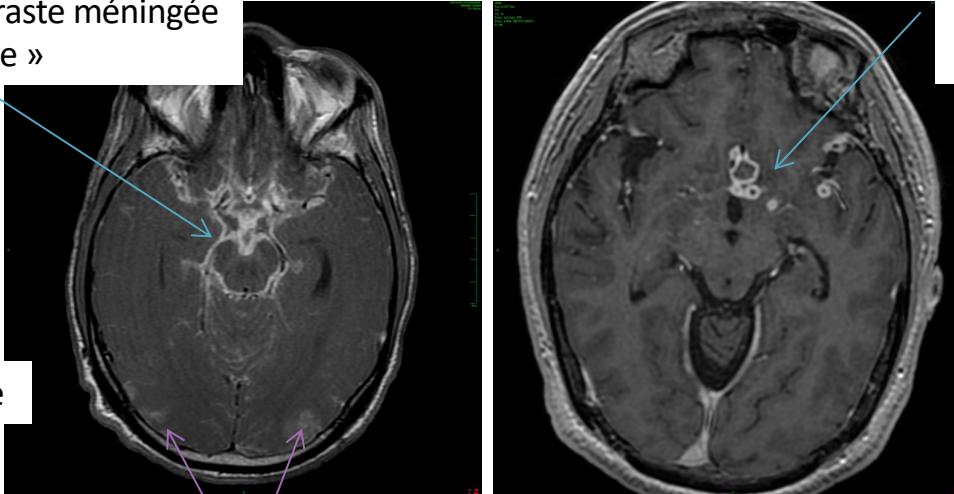
Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis



**** CSF Interpretation

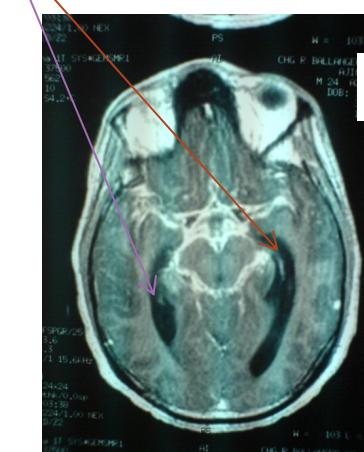
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Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	<5	High/very high 100-50000	Slightly increased 5-1000	Slightly increased <500	Normal-high 0-1000
Differential	Lymphocytes	Neutrophilis	Lymphocytes	Lymphocytes	Lymphocytes
CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
Protein (g/l)	<0.45	High >1	Normal-high 0.5-1	High-very high 1.0-5.0	Normal-high 0.2-5.0

Prise de contraste méningée
« Arachnoïdite »

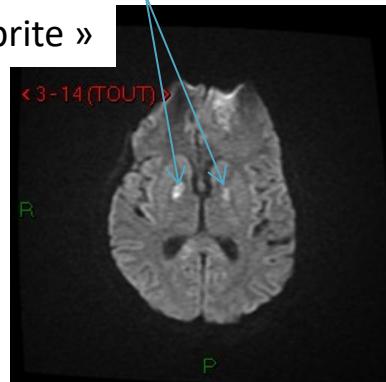


Tuberculomes
Abcès
tuberculeux

Hydrocéphalie



« Cérébrite »



Vascularite



Tuberculous meningitis: more questions, still too few answers



Guy E Thwaites, Ronald van Toorn, Johan Schoeman

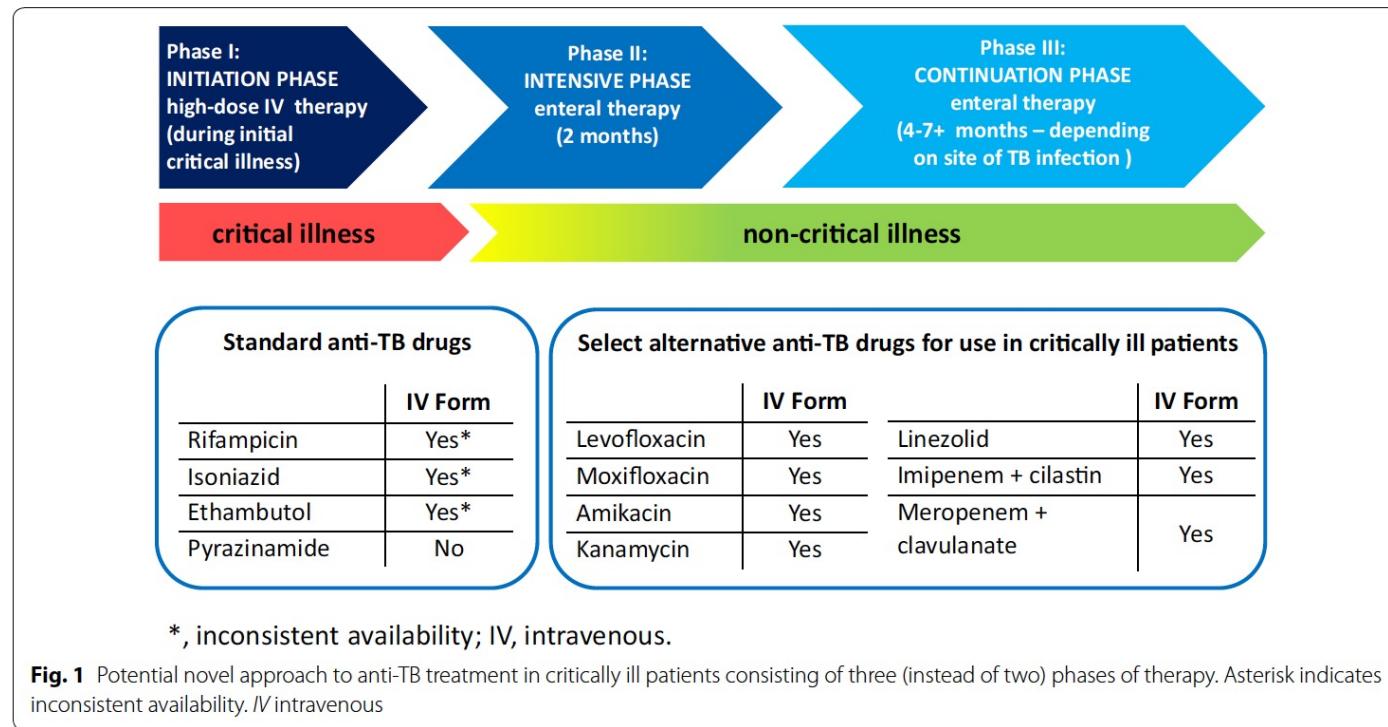
Lancet Neurology 2013

First-line treatment regimens for tuberculous meningitis in children and adults

WHO ^{79,80} and UK ⁵² recommendations				
	Daily dose in children	Daily dose in adults	Route of administration	Duration
Antituberculosis drugs				
Isoniazid	10–20 mg/kg (maximum 500 mg)	300 mg	Oral	12 months
Rifampicin	10–20 mg/kg (maximum 600 mg)	450 mg (weight <50 kg) or 600 mg (weight ≥50 kg)	Oral	12 months
Pyrazinamide	15–30 mg/kg (maximum 2 g)	1·5 g (weight <50 kg) or 2·0 g (weight ≥50 kg)	Oral	2 months
Ethambutol	15–20 mg/kg (maximum 1 g)	15 mg/kg	Oral	2 months
Ethionamide	Not recommended	..		
Adjunctive corticosteroids				
Prednisolone	4 mg/kg*	2·5 mg/kg*	Intravenous initially, then switch to oral when safe to do so	4 weeks then reduce to stop over 4 weeks
Dexamethasone	0·6 mg/kg*	0·4 mg/kg*	Intravenous initially, then switch to oral when safe to do so	Reducing each week to stop over 6–8 weeks

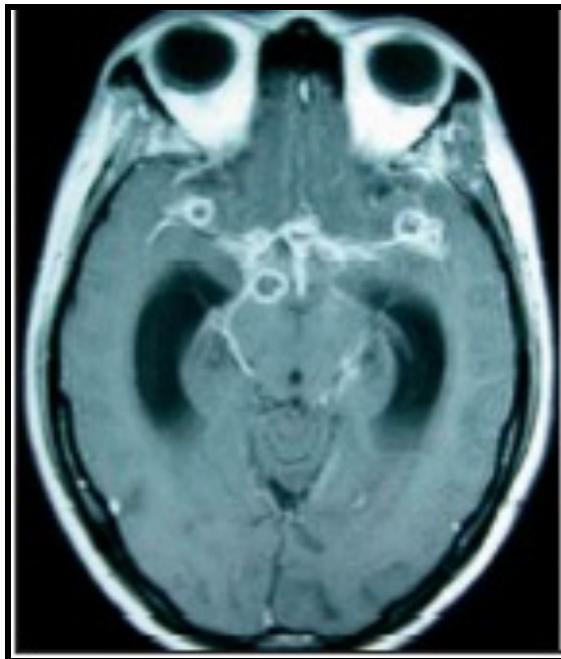
Limiting consumption in tuberculosis: current concepts in anti-tuberculosis treatment in the critically ill patient

Mervyn Mer¹, Alimuddin Zumla² and Martin W. Dünser^{3*}



Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

Guy E. Thwaites et al., N Engl J Med 2004 ; 351 : 1741-51



The NEW ENGLAND
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Corticothérapie

Critères modifiés du BMRC	Clinique	Protocole thérapeutique
I	GCS 15 signes focaux : 0	TTT IV 2 SEMAINES DXM 0.3 mg/kg semaine 1 0.2mg/kg semaine 2 Puis TTT PO 4 semaines
II	GCS 11-14 ou GCS 15 + signes focaux	TTT IV 4 SEMAINES DXM 0.4mg/kg/j semaine 1 0.3mg/kg/j semaine 2 0.2mg/kg/j semaine 3 0.1mg/kg/j semaine 4
III	GCS < 11	Puis TTT PO 4 SEMAINES DXM 4 mg / j Décroissance 1mg/j par semaine

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults



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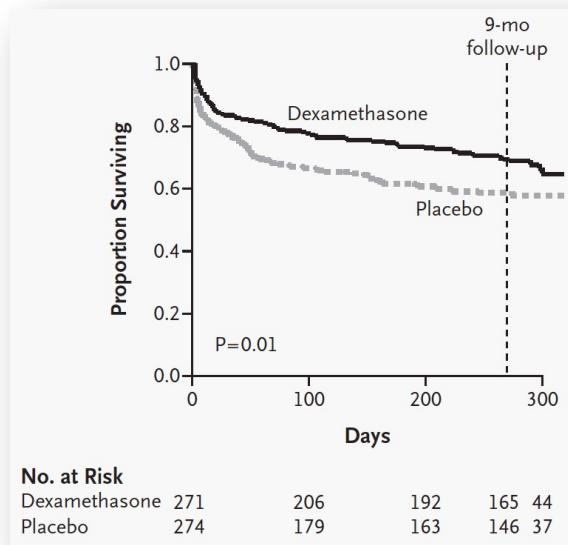
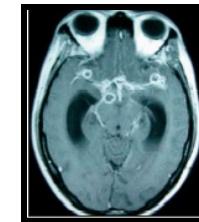


Table 3. Outcomes of 545 Patients Nine Months after Randomization.

Group	No. of Patients	Outcome			
		Good	Intermediate number (percent)	Severe Disability	Death
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

Outcome and Group	Dexamethasone no./total no. (%)	Placebo no./total no. (%)	Relative Risk (95% CI)	P Value
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
Undetermined	3/3 (100)	8/8 (100)	1.16 (0.71–1.91)	0.71
Relative risk of death stratified according to HIV status‡				0.78 (0.59–1.04) 0.08



Adjuvant therapies in critical care: steroids to treat infectious diseases

José Manuel Pereira^{1,2,3*}, Thiago Lisboa^{4,5} and José-Artur Paiva^{1,2,3}

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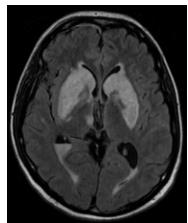
In tuberculosis

A review of 1337 patients with mild to severe tuberculous meningitis showed a quarter mortality reduction with steroids [RR 0.75 (CI 0.65 to 0.87)] [21], at least in the short term. The survival benefit was mostly seen in patients with mild disease and CS have little or no effect if advanced neurologic symptoms are present. In addition, no increased risk of adverse effects was observed. Therefore, adjunctive CS, such as dexamethasone tapering over 4 weeks from 0.3 to 0.4 mg/kg, is recommended for tuberculous meningitis.

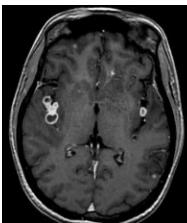
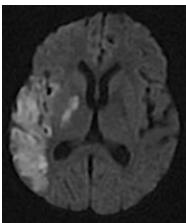


Functional outcomes in adults with tuberculous meningitis admitted to the ICU: a multicenter cohort study

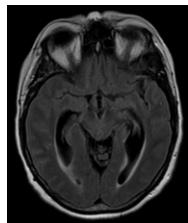
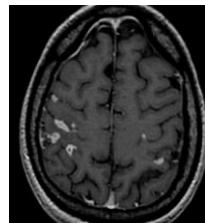
Marie Cantier^{1,16*}, Adeline Morisot², Emmanuel Guérot³, Bruno Megarbane⁴, Keyvan Razazi⁵, Damien Contou⁵, Eric Mariotte⁶, Emmanuel Canet⁶, Etienne De Montmollin⁷, Vincent Dubée⁸, Eric Boulet⁹, Stéphane Gaudry¹⁰, Guillaume Voiriot¹¹, Julien Mayaux¹², Frédéric Pène¹³, Mathilde Neuville¹, Bruno Mourvillier^{1,14}, Stéphane Ruckly¹⁴, Lila Bouadma^{1,14}, Michel Wolff¹, Jean-François Timsit^{1,14}, Romain Sonneville^{1,15*} and ENCEPHALITICA study group



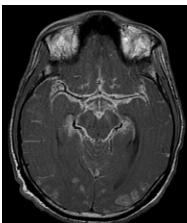
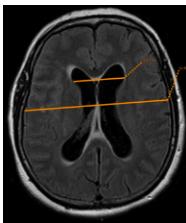
Infarction



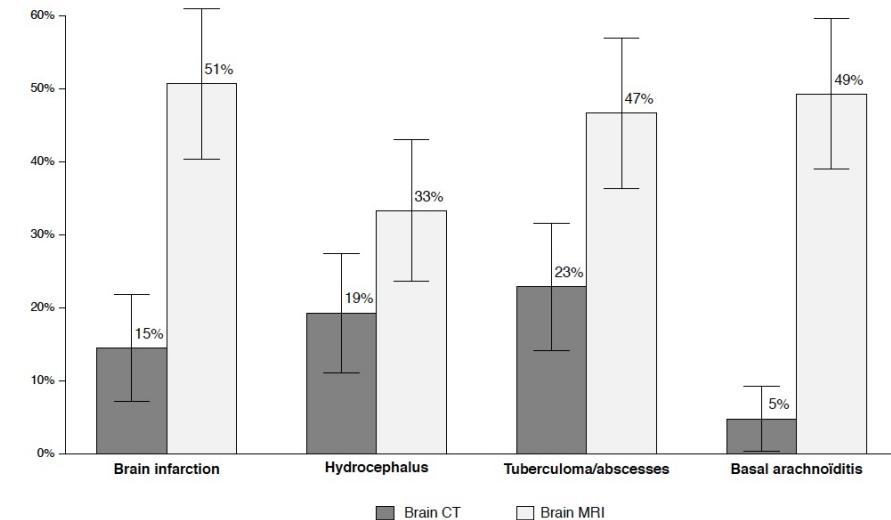
Tuberculomas



Hydrocephalus



Arachnoiditis





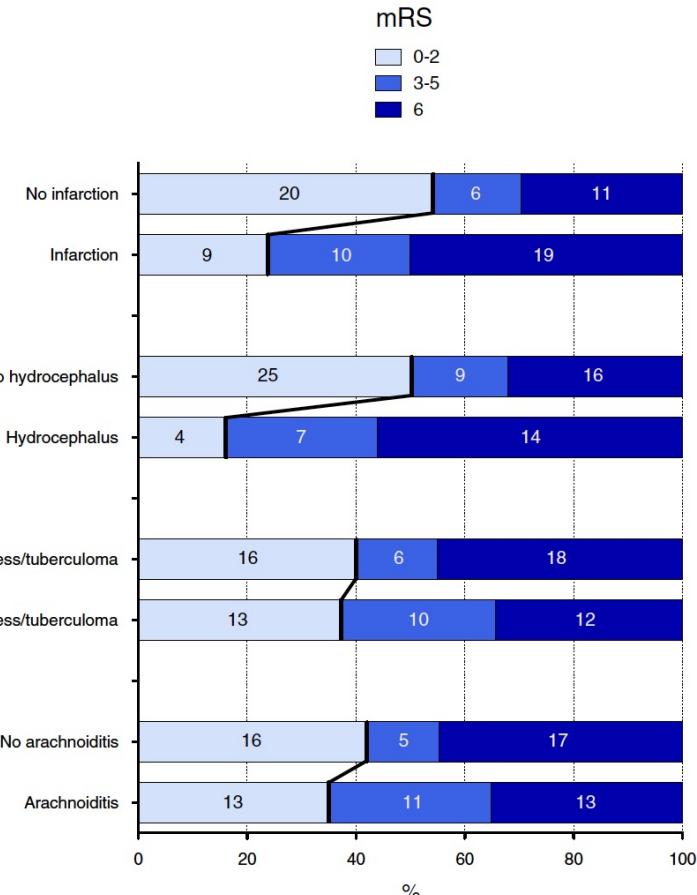
Functional outcomes in adults with tuberculous meningitis admitted to the ICU: a multicenter cohort study

Marie Cantier^{1,16*}, Adeline Morisot², Emmanuel Guéröt³, Bruno Megarbane⁴, Keyvan Razazi⁵, Damien Contou⁵, Eric Mariotte⁶, Emmanuel Canet⁶, Etienne De Montmollin⁷, Vincent Dubée⁸, Eric Boulet⁹, Stéphane Gaudry¹⁰, Guillaume Voiriot¹¹, Julien Mayaux¹², Frédéric Pène¹³, Mathilde Neuville¹, Bruno Mourvillier^{1,14}, Stéphane Ruckly¹⁴, Lila Bouadma^{1,14}, Michel Wolff¹, Jean-François Timsit^{1,14}, Romain Sonneville^{1,15} and ENCEPHALITICA study group

Table 2 Indicators of poor functional outcome by multivariate logistic regression

Variable	Odds ratio	95% CI	p value
Age	1.03	1–1.07	0.04
CSF protein level ≥ 2 g/L	5.31	1.67–16.85	<0.01
Hydrocephalus on brain MRI			
No MRI	Reference	–	–
No hydrocephalus	1.91	0.45–8.13	0.38
Hydrocephalus	17.2	2.57–115.14	<0.01
Adjunctive steroids	0.13	0.03–0.56	<0.01

CI confidence interval, CSF cerebrospinal fluid, MRI magnetic resonance imaging



Encéphalite liée au VIH

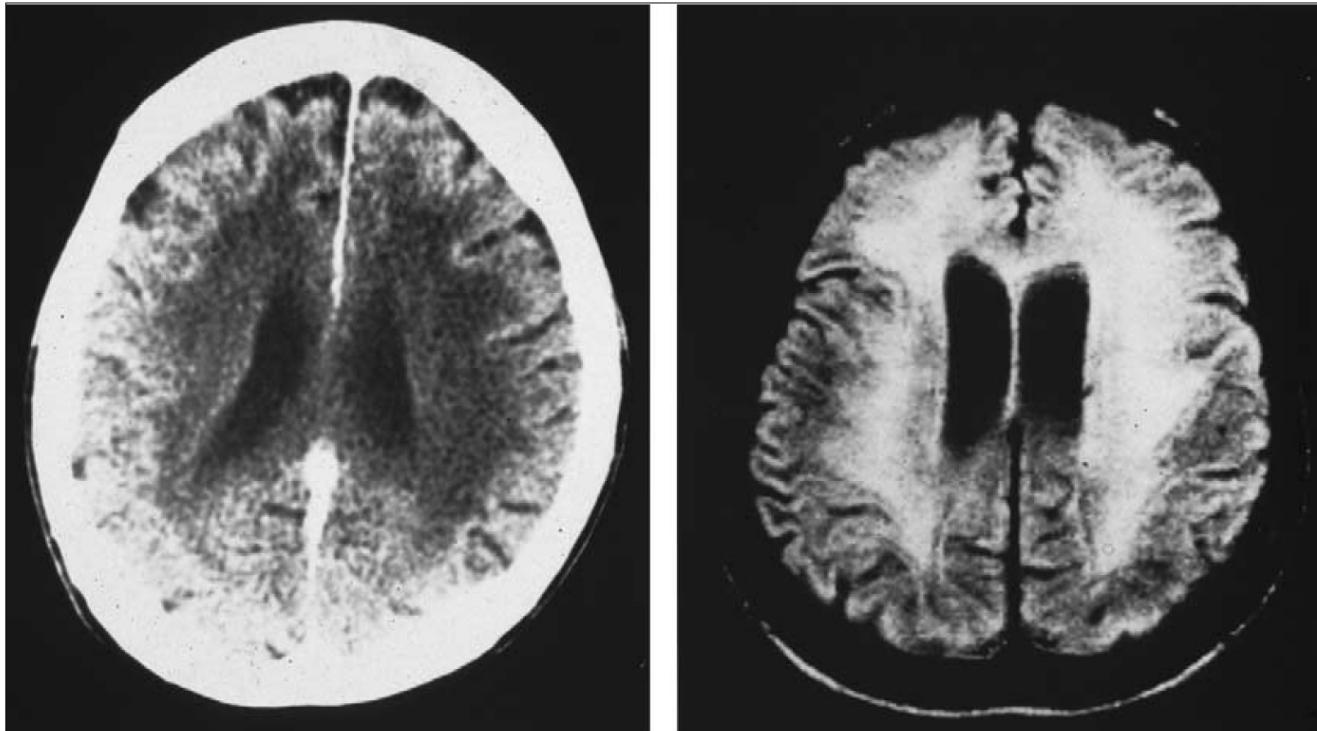
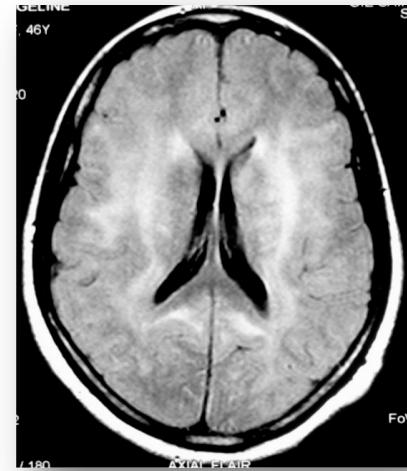


Figure 1: White-matter abnormalities on CT and MRI

Left: CT scan showing ventricular enlargement and white-matter hypodensity. Right: FLAIR MRI showing both cortical and central atrophy, and characteristic confluent signal abnormalities deep within the white matter.

Encéphalite liée au VIH

- Tableau clinique compatible
- IRM Cérébrale, gado +
- LCR :
 - cellularité, protéinorachie
(réaction lymphocytaire possible)
 - Eliminer IO (crypto, JC, CMV, BK.....) +++
 - CV HIV LCR (& génotype de résistance si CV+)
 - Concentration ARV
- CV plasmatique
- Sérologie syphilis (sang/LCR)



Discordance Between Cerebral Spinal Fluid and Plasma HIV Replication in Patients with Neurological Symptoms Who Are Receiving Suppressive Antiretroviral Therapy

Clinical Infectious Diseases 2010;50:000–000

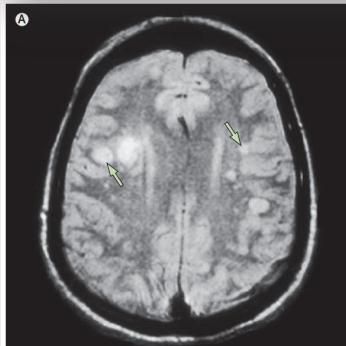
Ana Canestri,^{1,3,6,7} François-Xavier Lescure,³ Stéphane Jaureguiberry,¹ Antoine Moullignier,³ Corinne Amiel,^{3,4,7} Anne Geneviève Marcelin^{2,6,7} Gilles Peytavin,⁵ Roland Tubiana,^{1,3,6,7} Gilles Pialoux,^{3,6} and Christine Katlama^{1,6,7}

- **Tableau neurologique aigu : encéphalopathie, coma....**
(Patients sous cART)
- **CV HIV « discordante »**
 - Élevée dans le LCR
 - < 50 copies / mL dans le sang
- **Amélioration clinique et virologique après modification cART**
(Optimisation avec ARV avec CPE élevée)

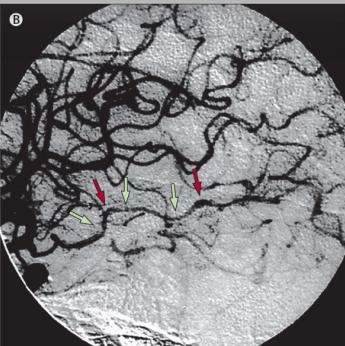
Pénétration-efficacité des ARV dans le SNC

Classe	4	3	2	1
INTI	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Ténofovir
INNTI	Névirapine	Efavirenz	Étravirine	
IP	Indinavir/r	Darunavir/r Fosamprénavir/r Lopinavir/r	Atazanavir (/r)	Nelfinavir Saquinavir/r Tipranavir/r
IE		Maraviroc		Enfuvirtide
II		Raltégravir		

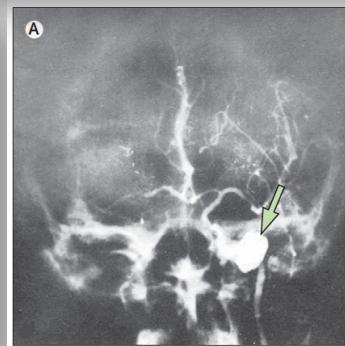
Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment



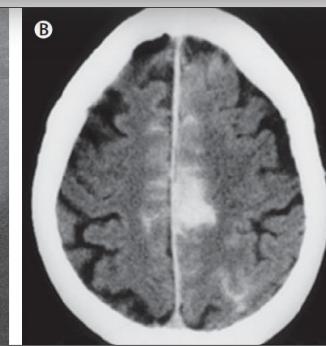
SMALL VESSEL
MULTIFOCAL
VASCULOPATHY



LARGE VESSEL
GRANULOMATOUS
ARTERITIS



MCA ANEURYSM AND SAH



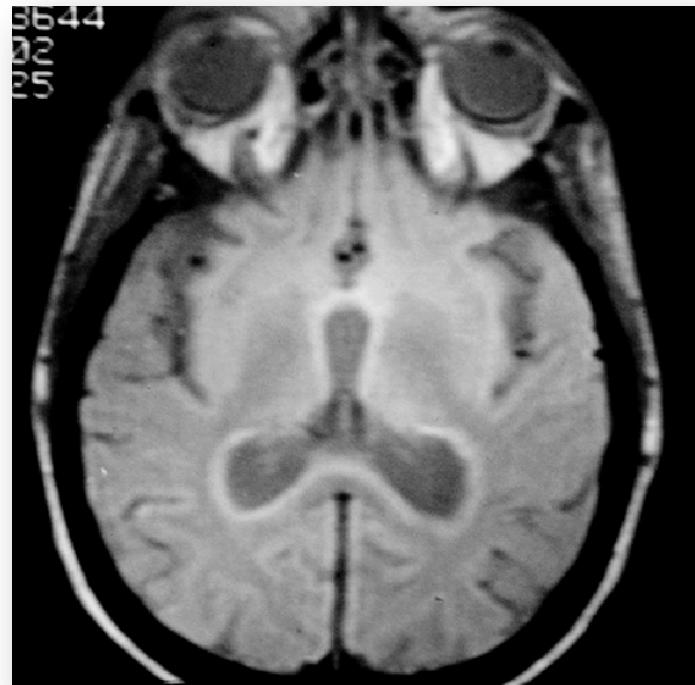
- CSF pleocytosis can include increased red blood cells
- CSF pleocytosis absent in a third of cases
- Detection of VZV antibody superior to that of VZV DNA for diagnosis

ACICLOVIR 15 mg/kg/8h IVL

Encéphalite due au CMV

- CD4<50/mm³
- démence sous-cortico-frontale
- Tableau “encéphalitique” possible
- atteinte myéloradiculaire associée

- IRM / aspect T2 et FLAIR d'épendymite
- PL méningite à prédominance de PNN
- PCR CMV + dans le LCR
- Traitement : ganciclovir + foscarnet



Encéphalopathie « subaiguë »

	Encéphalite VIH	Encéphalite CMV	LEMP
Clinique	Troubles mémoire Troubles langage Ralentissement psy Sd frontal	Confusion Crises convulsives	Signes focaux Crises convulsives
Signes focaux	-	+/-	+
Progression	Mois	Jours, semaines	Semaines, mois
IRM	Leucopathie diffuse Périventriculaire Symétrique Atrophie diffuse	Rien ventriculite	Multifocale Sous corticale Asymétrique
LCR	Eliminer IO	PCR CMV	PCR JC virus 60%

- Définitions et épidémiologie des complications neurologiques du VIH en réanimation
- Questions-clés pour le diagnostic et la prise en charge
- **Traitements antirétroviraux / IRIS**
- Quel pronostic ?

ARV à discuter “en urgence”

- **3 situations**
 - Primo-infection symptomatique
 - LEMP
 - Encéphalite liée au VIH
 - Pour toutes les autres IO, discuter au cas par cas
-

Sd de Restauration Immunitaire (IRIS)

- INTRODUCTION ARV => restauration immunitaire (partielle)
- **Restauration « excessive » => Symptômes (IRIS)**
- **Migration LT vers sites de l' infection**

- 2 formes
 - **Paradoxale** : aggravation d'une IO sous traitement ARV
 - **Démasquée** : IO quiescente démasquée sous traitement ARV

Sd de Restauration Immunitaire (IRIS)

Fréquence d'IRIS	Agents infectieux	Incidence d'IRIS rapporté	Méta-analyse 13103 patients
Fréquent	Mycobacterium tuberculosis Mycobacterium avium complex Cryptococcus neoformans Cytomégavirus	8-45 % 35 % 8-31 % 18-62 %	16,7 % 19,5 % 37,7 %
Peu fréquent	Pneumocystis jirovecii JC virus VZV Kaposi	5-19 % 16 %	16,7 % 12,2 % 6,4 %

IRIS: facteurs de risque

- Immunodépression profonde < 100 CD4 /mm³
- Infection opportuniste disséminée
- Début « précoce » des ARV après début du ttt d'une IO
- Etiologie
 - **Méningite BK** : culture +, cellularité importante
 - **Méningite cryptocoque** : absence de réaction méningée
- +/- augmentation CD4 , baisse rapide CV VIH

Sd de Restauration Immunitaire (IRIS)

Critères Diagnostiques

Critères diagnostiques d'IRIS :

1. apparition de manifestations cliniques après l'introduction d'un traitement antirétroviral efficace (diminution de l'ARN-VIH > 1 log copies/mL). augmentation habituelle des CD4, mais non constante;
2. manifestations cliniques inflammatoires et atypiques;
3. manifestations non expliquées par :
 - a. infection nouvellement acquise,
 - b. échec du traitement d'une infection préalablement identifiée (résistance, non-observance, interaction médicamenteuse, malabsorption),
 - c. effet indésirable des traitements,
 - d. autre cause (infections, tumeurs...).

Immune reconstitution inflammatory syndrome in the CNS of HIV-infected patients

A. Venkataramana, MBBS; C.A. Pardo, MD; J.C. McArthur, MBBS, MPH; D.A. Kerr, MD, PhD; D.N. Irani, MD, PhD; J.W. Griffin, MD; P. Burger, MD; D.S. Reich, MD, PhD; P.A. Calabresi, MD; and A. Nath, MD

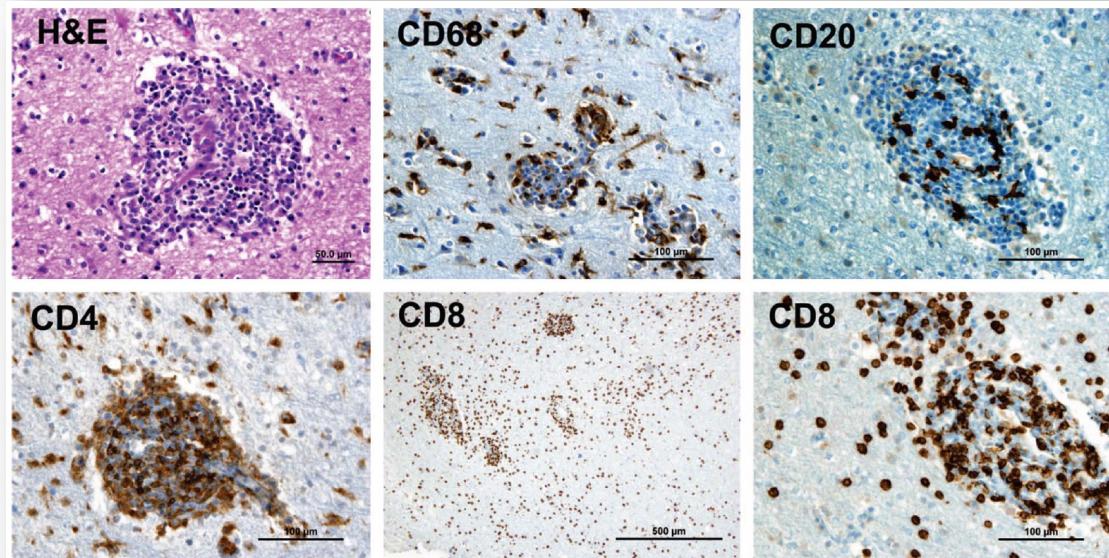
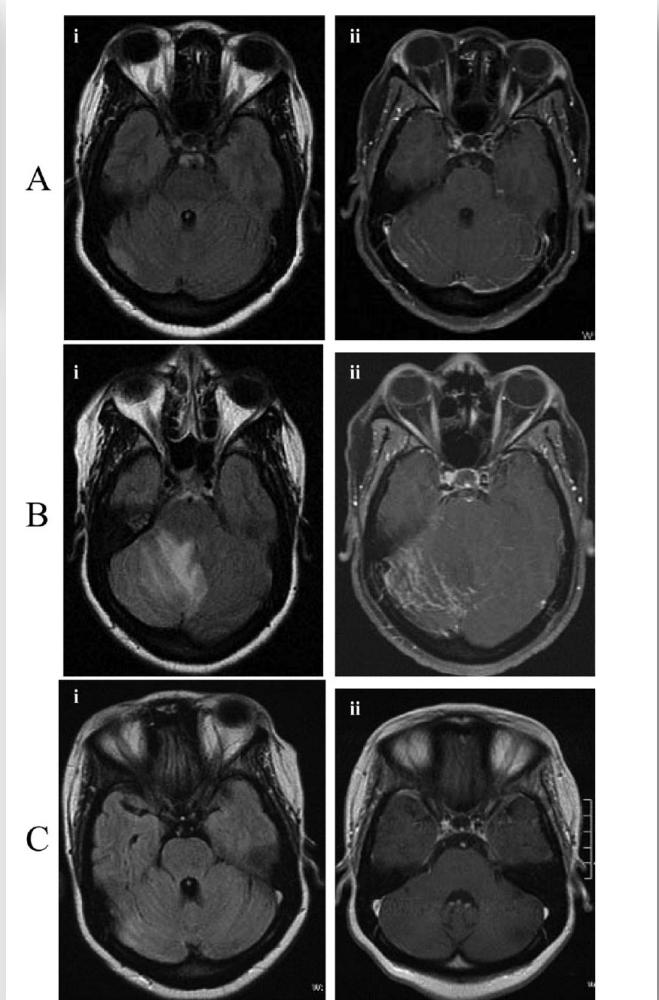


Figure 4. Characterization of inflammatory infiltrate in a patient with HIV dementia and immune reconstitution inflammatory syndrome. Case 3 brain biopsy: Histologic and immunocytochemical studies demonstrated the presence of marked perivascular and parenchymal infiltration by T cells and microglia. Perivascular cuffing in the cerebral cortex (H-E) were comprised of monocytes (CD68), B lymphocytes (CD20), CD4, and CD8 T lymphocytes. In addition to the perivascular infiltration, there was a marked infiltration by CD8 into the cerebral cortex and brain parenchyma.



Sd de Restauration Immunitaire (IRIS)

Principes de ttt

- Prévention : recherche systématique d' une IO avant début ARV +++
- Poursuite des ARV sauf si IRIS menace pronostic vital
- Poursuite/initiation du ttt de l'agent infectieux à l'origine de l' IRIS
- **CORTICOTHERAPIE 1 mg/kg/j de prednisone pour IRIS graves (mycoses, BK) avec atteinte SNC / respiratoires**
 - 2-4 semaines
 - Décroissance rapide
 - Attention risque IO (CMV)
- (Attention anguillulose ...)

Plan

- Quel pronostic ?

Survival after neuroAIDS

Association with antiretroviral CNS Penetration-Effectiveness score

Table 4 Kaplan-Meier estimates of 1-year survival after diagnosis of neurologic AIDS-defining events

	Period	No.	Deaths	12-month survival, % (95% CI)
HIV-related encephalopathy	1992-1995	1,789	1,278	23 (21-25)
	1996-1998	746	316	55 (51-59)
	1999-2004	592	195	65 (61-69)
Progressive multifocal leukoencephalopathy	1992-1995	712	511	20 (17-23)
	1996-1998	345	138	56 (50-62)
	1999-2004	370	158	52 (47-58)
Cerebral toxoplasmosis	1992-1995	2,421	1,275	42 (40-44)
	1996-1998	875	219	73 (70-76)
	1999-2004	1,062	187	82 (79-84)
Cryptococcal meningitis	1992-1995	545	251	50 (46-55)
	1996-1998	237	53	76 (71-82)
	1999-2004	238	38	83 (78-88)

Neurological complications of HIV infection in critically ill patients: Clinical features and outcomes

Table 4 Multivariate analysis of factors associated with mortality.

Characteristic	Odds ratio (95% CI)	p Value
All patients		
Intracranial hypertension	5.09 (2.17–11.91)	<0.001
Vasopressor use	3.92 (1.78–8.60)	<0.001
SAPS II ^a	1.59 (1.31–1.93)	<0.001
Patients with AIDS-defining CNS diseases		
Intracranial hypertension	6.84 (2.03–23.04)	0.002
SAPS II ^a	1.91 (1.35–2.72)	<0.001

SAPS = simplified acute physiology score; AIDS = acquired immune-deficiency syndrome; CNS = central nervous system; CI = confidence interval.

For the 210 patients studied, variables included in the multivariate model were: age, Knaus score (A or B versus C or D), HIV load, SAPS II, Glasgow coma scale score, intracranial hypertension, delirium, acute respiratory failure, invasive mechanical ventilation, vasopressor administration and renal replacement therapy.

For patients with AIDS-associated CNS diseases ($n = 88$), variables included in the multivariate model were $CD4 < 50/\text{mm}^3$, SAPS II, Glasgow coma scale score, intracranial hypertension, acute respiratory failure, invasive mechanical ventilation, vasopressor administration and renal replacement therapy.

^a For each SAPS II increment of 10 points.

Table 2 Univariate and multivariate logistic regression of factors associated with poor outcome (mRS score >2)

	Poor outcome (n = 49) ^a	Functional independence (n = 51) ^a	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Age, y ^b	40 (35-46)	40 (33-46)	1.2 (0.8-1.8)	0.47		
Female sex	22 (45)	25 (49)	0.8 (0.4-1.9)	0.68		
Poor functional status (Knaus C or D)	14 (29)	7 (14)	2.5 (0.9-6.9)	0.07	2.4 (0.8-7.6)	0.09
Positive HIV status known at admission	30 (61)	24 (47)	1.8 (0.8-3.9)	0.16		
CD4 <25 cells/ μ L ^c	30/48 (63)	19/50 (38)	2.7 (1.2-6.2)	0.02	2.7 (1.1-6.7)	0.03
HIV viral load, log ₁₀ /mL	5.3 (4.9-6.0)	5.3 (5.0-5.7)	1.4 (0.8-2.5)	0.28		
GCS						
Score	9 (5-13)	13 (7-14)				
Score ≤8	25 (51)	16 (31)	2.3 (1.1-5.2)	0.05	3.1 (1.2-7.7)	0.02
Seizures or status epilepticus	18 (37)	18 (35)	1.1 (0.5-2.4)	0.89		
Aspiration pneumonia	9 (18)	4 (8)	2.6 (0.8-9.2)	0.13		
Time between hospital admission and ICU admission, d	2 (0-5)	1 (0-3)	1.0 (0.9-1.0)	0.27		
Time between hospital admission and start of specific anti- <i>Toxoplasma gondii</i> therapy, d	1 (0-4)	0 (0-2)	1.0 (0.9-1.1)	0.20		
Any other specific therapy than pyrimethamine-sulfadiazine ^d	17 (35)	10 (20)	2.2 (0.9-5.4)	0.09	1.6 (0.6-4.6)	0.30
Adjunctive steroids	27 (55)	25 (49)	1.3 (0.6-2.8)	0.54		

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale; ICU = intensive care unit; mRS = modified Rankin Scale; OR = odds ratio.

^a Data are presented as median (interquartile range) or number (percentage).

^b Odds ratios were computed per 10-point increment.

^c Obtained in 98 patients.

^d Other specific therapy included pyrimethamine-clindamycin (n = 27) and trimethoprim-sulfametoxazole (n = 1).

Conclusion

- **Complications neurologiques du VIH sont fréquentes chez le malade de réanimation**
- La toxoplasmose reste le **1^{er} diagnostic neurologique en 2021**
- **Pathologie non liée au VIH : 50% des cas**
- On peut être amené à instaurer **ARV en urgence dans certaines situations**
- **Pronostic lié à la présentation clinique +++**
 - GCS, HTIC
 - MRI : Hydrocéphalie
 - CD4