Hospices Civils de Lyon

Neurologie et VIH/SIDA

Dr Thomas Perpoint

SMIT, Croix-Rousse

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Original Articles

ORIGINAL ARTICLE ARCHIVE

Isolation of HTLV-III from Cerebrospinal Fluid and Neural Tissues of Patients with Neurologic Syndromes Related to the Acquired Immunodeficiency Syndrome

David D. Ho, M.D., Teresa R. Rota, M.A., Robert T. Schooley, M.D., Joan C. Kaplan, Ph.D., J. Davis Allan, M.D., Jerome E. Groopman, M.D., Lionel Resnick, M.D., Donna Felsenstein, M.D., Charla A. Andrews, M.S., and Martin S. Hirsch, M.D.

N Engl J Med 1985; 313:1493-1497 | December 12, 1985 | DOI: 10.1056/NEJM198512123132401

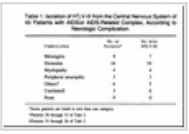
Share:

Abstract

We conducted virus-isolation studies on 56 specimens from the nervous system of 45 patients in order to determine whether human T-cell lymphotropic virus Type III (HTLV-III) is directly involved in the pathogenesis of the neurologic disorders frequently encountered in the acquired immunodeficiency syndrome (AIDS) and the AIDS-related complex. We recovered HTLV-III from at least one specimen from 24 of 33 patients with AIDS-related neurologic syndromes. In one patient, HTLV-III was isolated from the cerebrospinal fluid during acute aseptic meningitis associated with HTLV-III seroconversion. HTLV-III was also isolated from cerebrospinal fluid from six of seven patients with AIDS or its related complex and unexplained chronic meningitis. In addition, of 16 patients with AIDS-related dementia, 10 had positive cultures for HTLV-III in cerebrospinal fluid, brain tissue, or both. Furthermore, we cultured HTLV-III from the spinal cord of a patient with myelopathy and from the sural nerve of a patient with peripheral neuropathy. These findings suggest that HTLV-III is neurotropic, is capable of causing acute meningitis, is responsible for AIDS-related chronic meningitis and dementia, and may be the cause of the spinal-cord degeneration and peripheral neuropathy in AIDS and AIDS-related complex. (N Engl J Med 1985; 313:1493–7.)

MEDIA IN THIS ARTICLE

TABLE 1

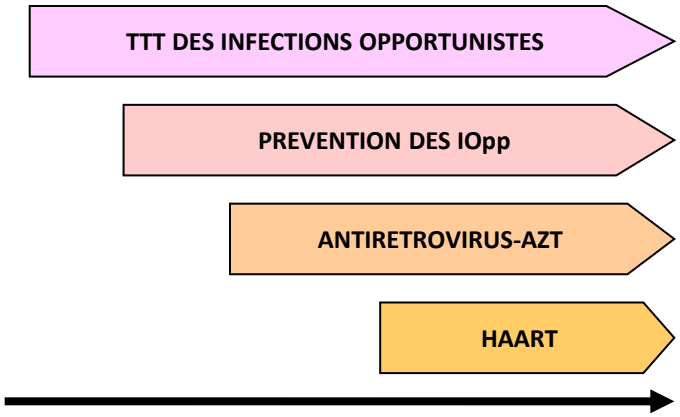


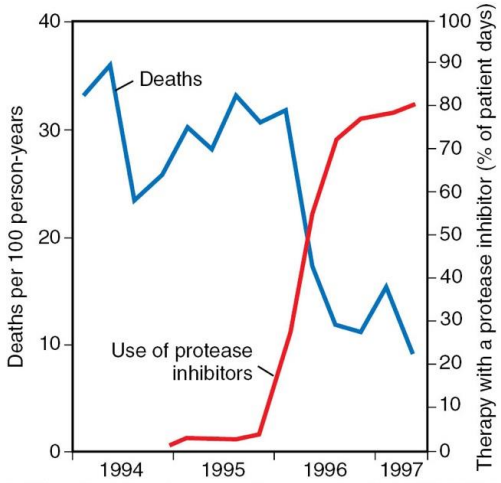
Isolation of HTLV-III from the Central Nervous System of 45 Patients with AIDS or AIDS-Related Complex, According to Neurologic Complication.

TABLE 2

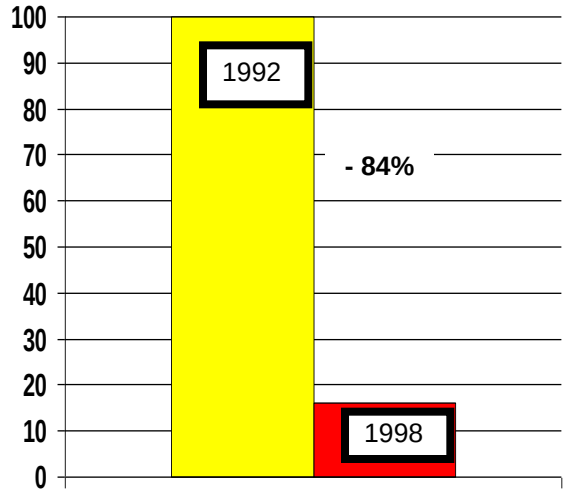
Systemic Diagnoses, Neurologic

Mortalité due au VIH/sida



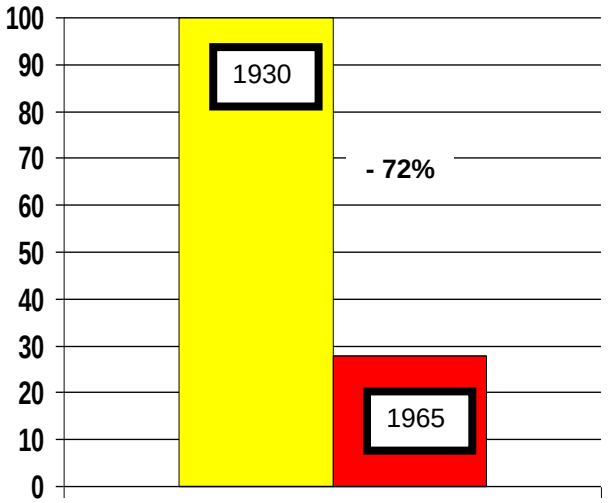


Mortalité relative VIH après HAART



Référence: Swiss HIV Cohort, JAMA 1999; 282:2220

Mortalité relative Pneumocoque après Pénicilline



Reference: Ann. Intern. Med. 1964

Les PVVIH ne meurent plus, donc ils **vieillissent**…

Mortality in HIV+ Pts Similar to General Population When CD4 > 500 for 5-7 Yrs

- Overall mortality in HIV-infected patients 7-fold higher than general population
- **After 6th year of follow-up, mortality among patients with CD4+ cell counts ≥ 500 cells/mm^3 comparable to that of the general population**

Truncation for Duration of Follow-up, Yrs	Median Time Spent With CD4+ Cell Count ≥ 500 cells/mm^3 After Truncated Duration of Follow-up, Yrs (IQR)	Deaths, n	SMR (95% CI)
0 (n = 1208)	4.5 (2.1-7.0)	37	2.5 (1.8-3.5)
1 (n = 1156)	4.2 (2.1-6.4)	29	2.1 (1.4-3.1)
2 (n = 1083)	4.0 (2.1-5.6)	26	2.2 (1.4-3.2)
3 (n = 1031)	3.5 (1.8-4.8)	22	2.1 (1.3-3.2)
4 (n = 967)	3.0 (1.5-3.8)	18	2.1 (1.3-3.4)
5 (n = 864)	2.4 (1.4-3.0)	12	1.9 (1.0-3.2)
6 (n = 763)	1.6 (1.0-2.2)	2	0.5 (0.1-1.6)
7 (n = 610)	0.9 (0.5-1.3)	1	0.5 (0.0-2.6)

Lewden C, et al. J Acquir Immune Defic Syndr. 2007;46:72-77.

90-90-90

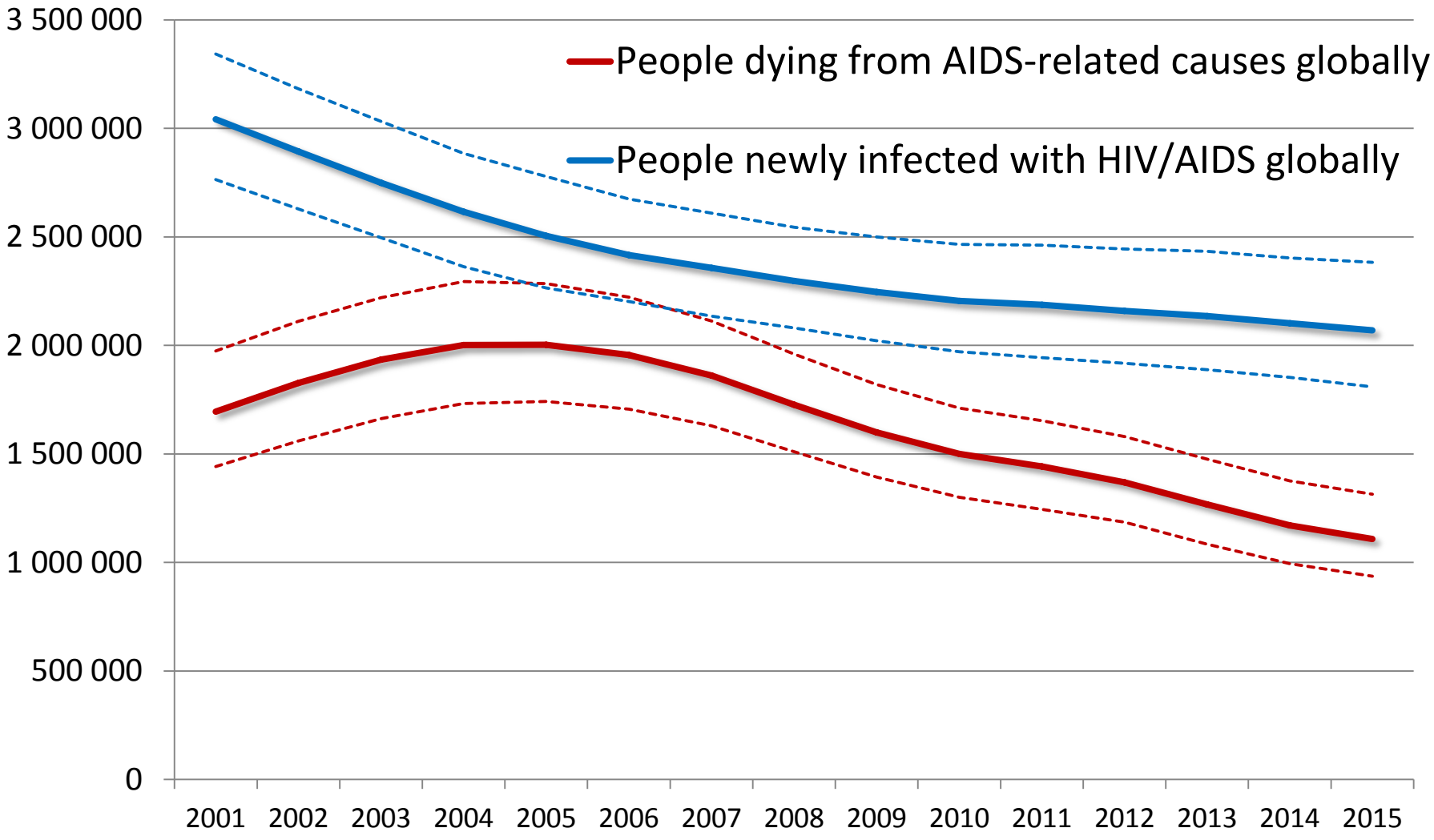
Une cible ambitieuse de traitement pour aider à mettre fin à l'épidémie du sida

Global summary of the AIDS epidemic

Number of people living with HIV in 2015	**Total**	36.7 million [34.0 million – 39.8 million]
	Adults	31.8 million [30.1 million – 33.7 million]
	Women	16.0 million [15.2 million – 16.9 million]
	Children (<15 years)	3.2 million [2.9 million – 3.5 million]
People newly infected with HIV in 2015	**Total**	2.1 million [1.9 million – 2.4 million]
	Adults	1.9 million [1.7 million – 2.1 million]
	Children (<15 years)	240 000 [210 000 – 280 000]
AIDS deaths in 2015	**Total**	1.1 million [940 000 – 1.3 million]
	Adults	1.0 million [1.2 million – 1.5 million]
	Children (<15 years)	190 000 [170 000 – 220 000]

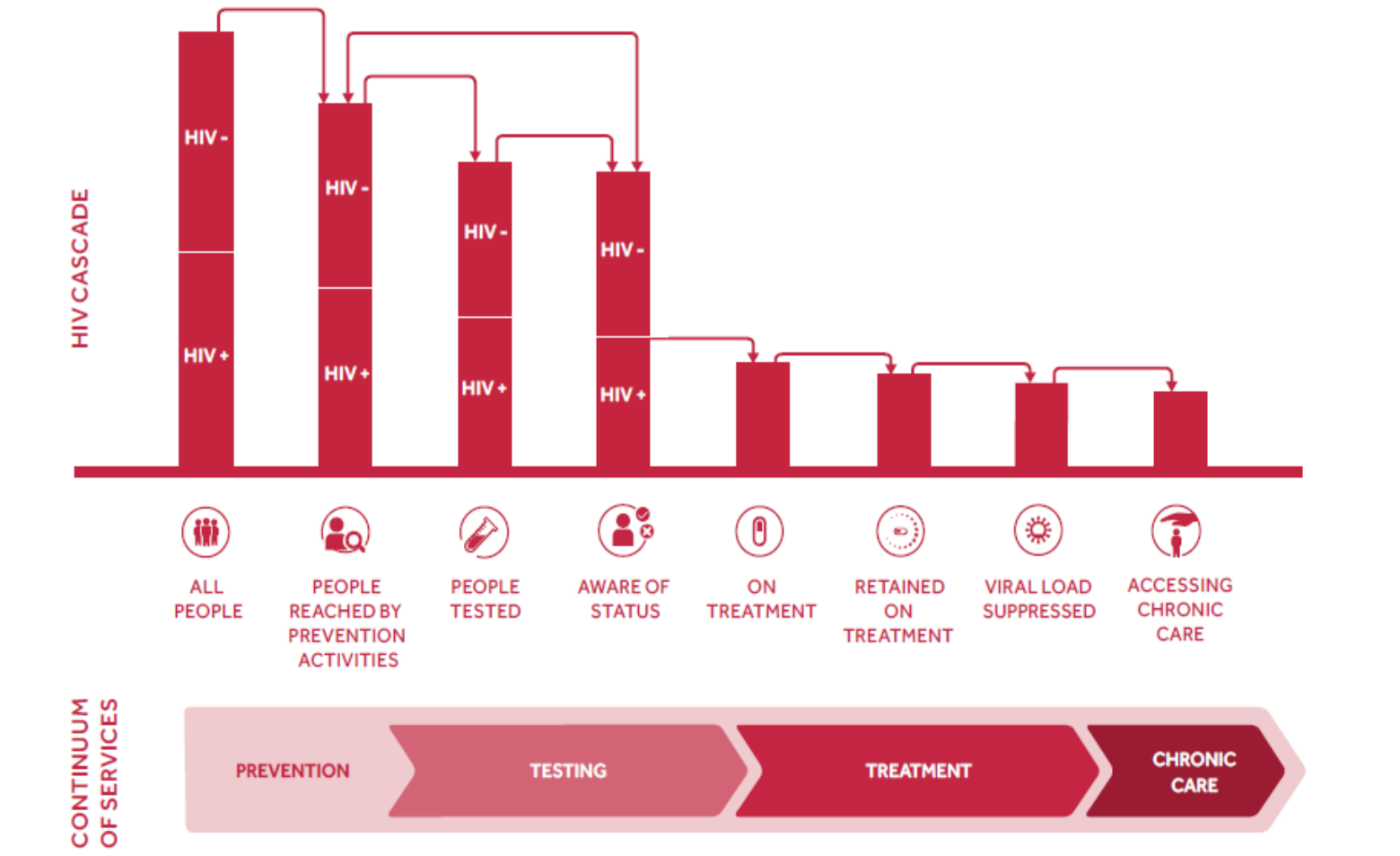
Source: UNAIDS/WHO estimates.

Decline in HIV incidence and mortality over time



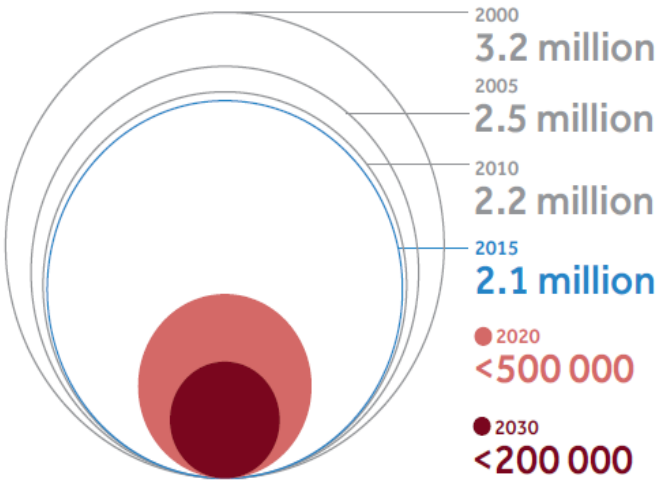
Source: UNAIDS/WHO estimates.

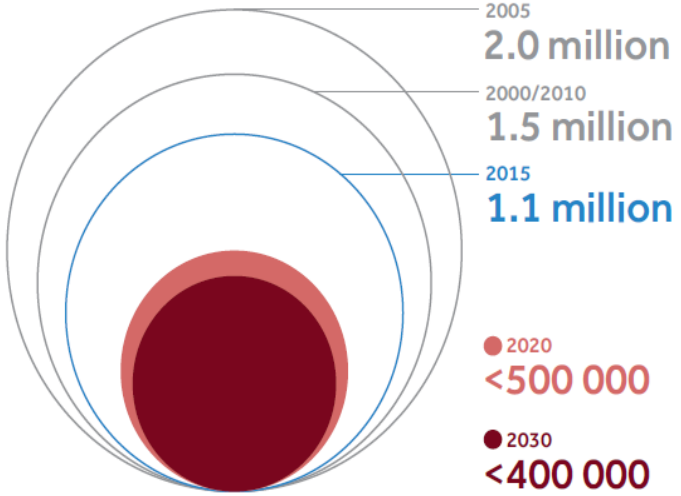
Universal health coverage to end AIDS



Source: Global Health Sector Strategy on HIV, 2016-2021.

Number of people newly infected with HIV

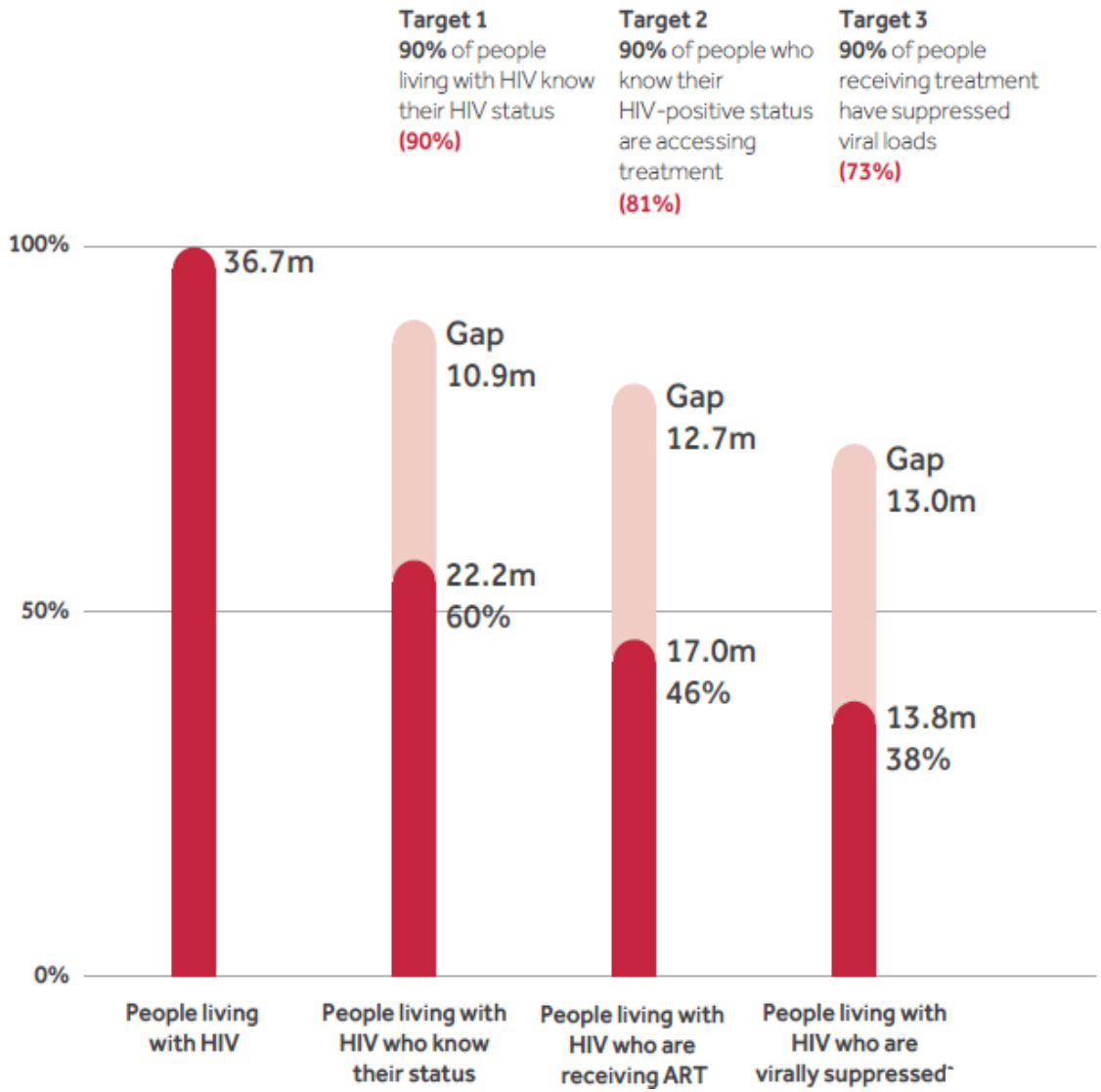




Number of people dying from HIV

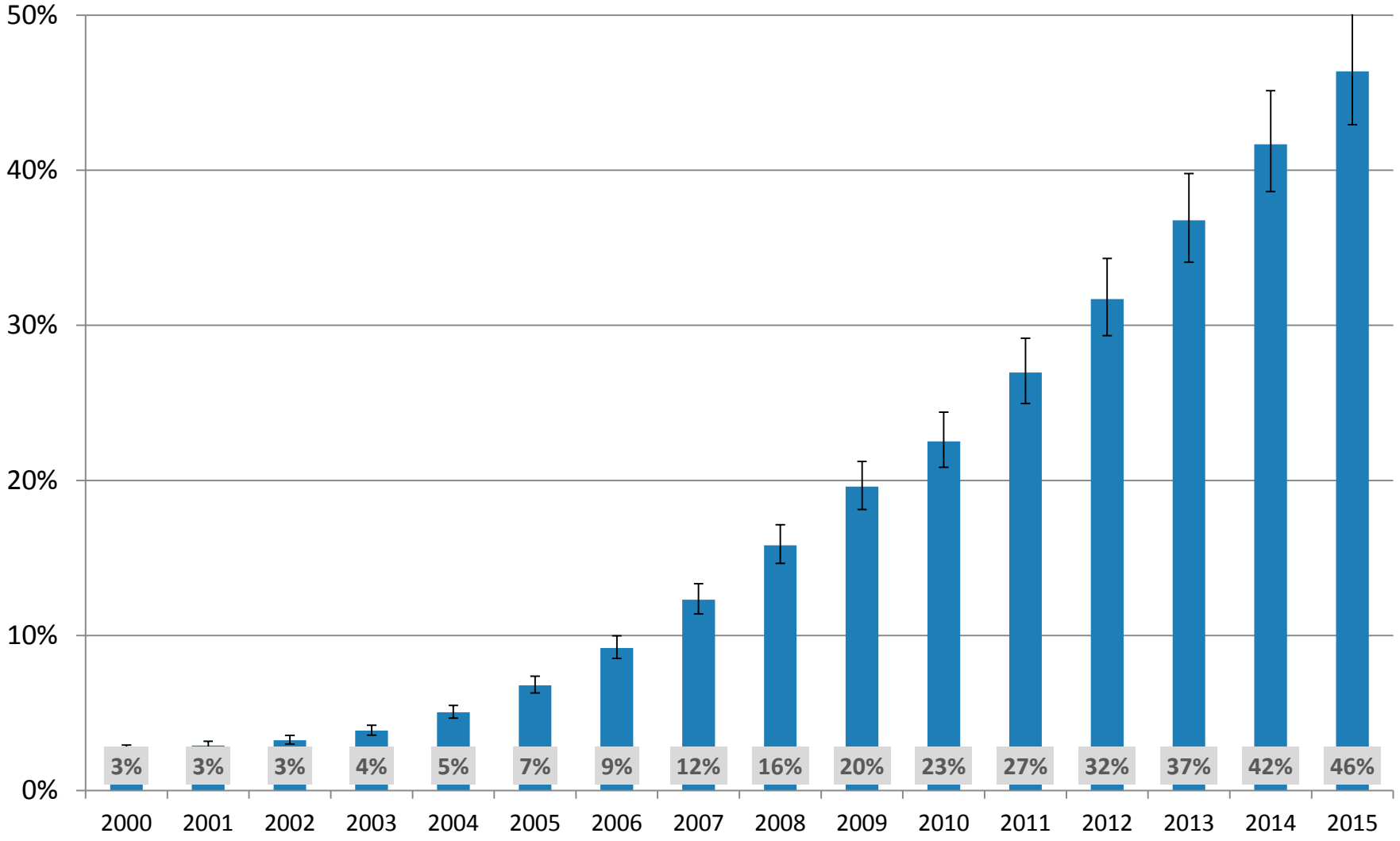
Source: UNAIDS/WHO estimates.
The red shading shows future targets.

Improvements are needed at each stage of the cascade of HIV testing and treatment services, 2015



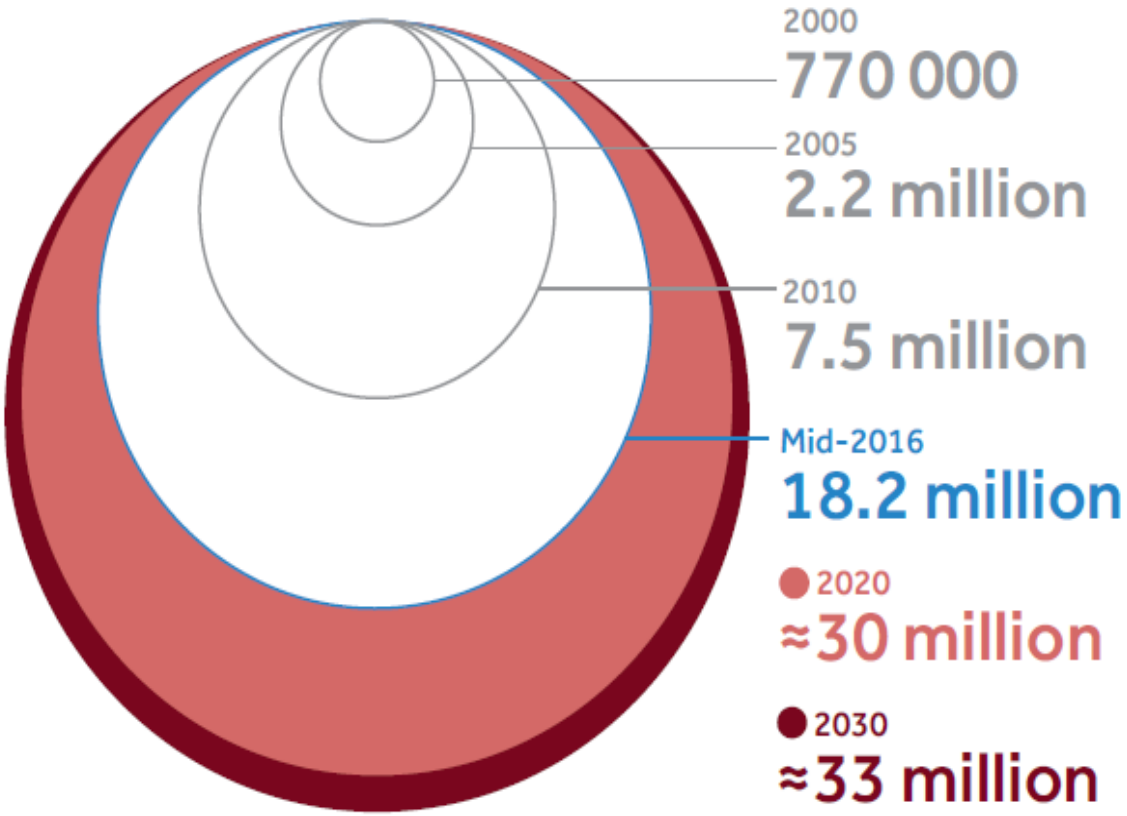
Source: UNAIDS/WHO estimates.

ART coverage over time



Source: UNAIDS/WHO estimates.

Number of people receiving antiretroviral treatment



Source: UNAIDS/WHO estimates.
The red shading shows future targets.

Figure 1 – Nombre estimé de découvertes de séropositivité VIH par année de diagnostic
(Données au 31/12/2014 corrigées pour les délais de déclaration et la sous-déclaration)

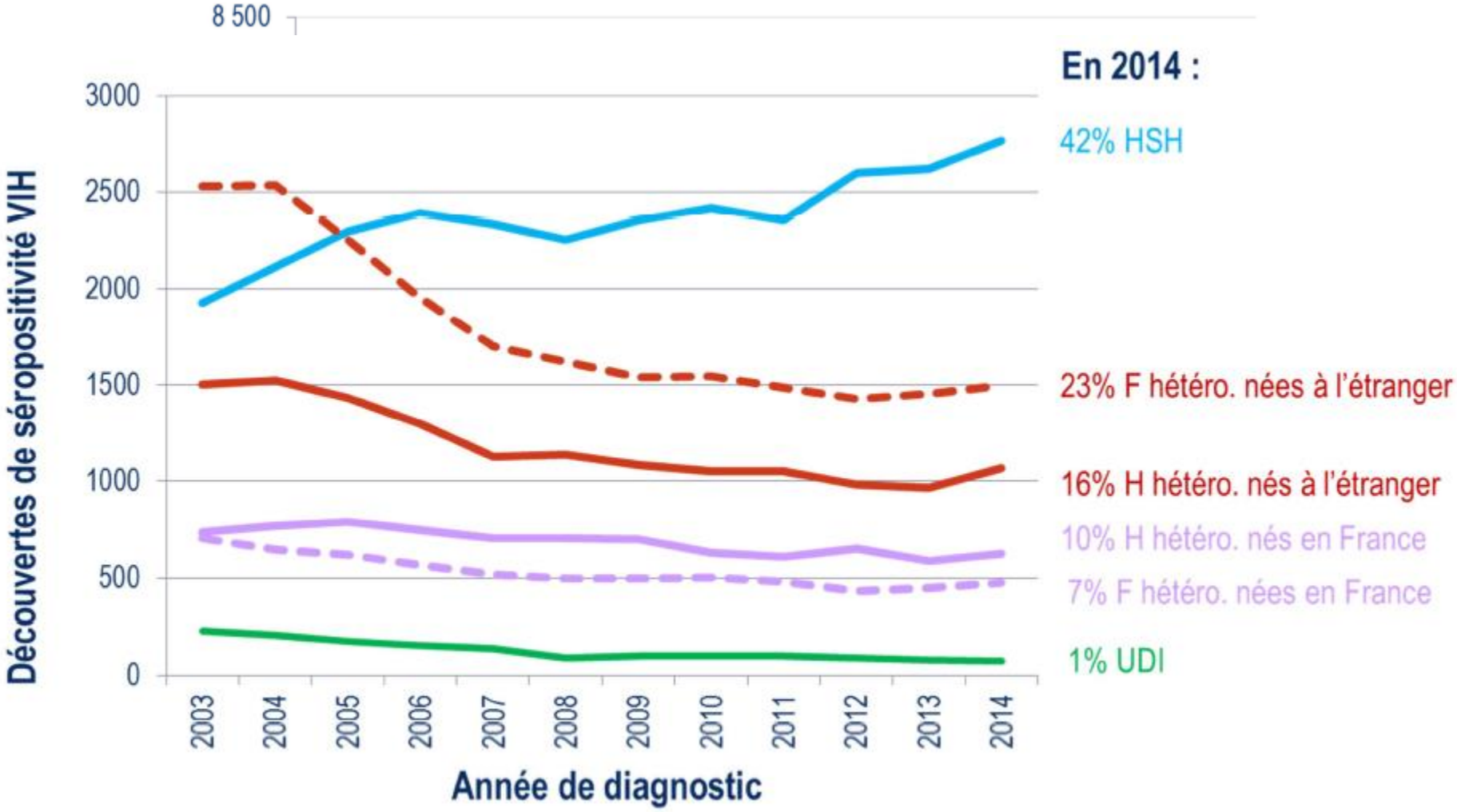
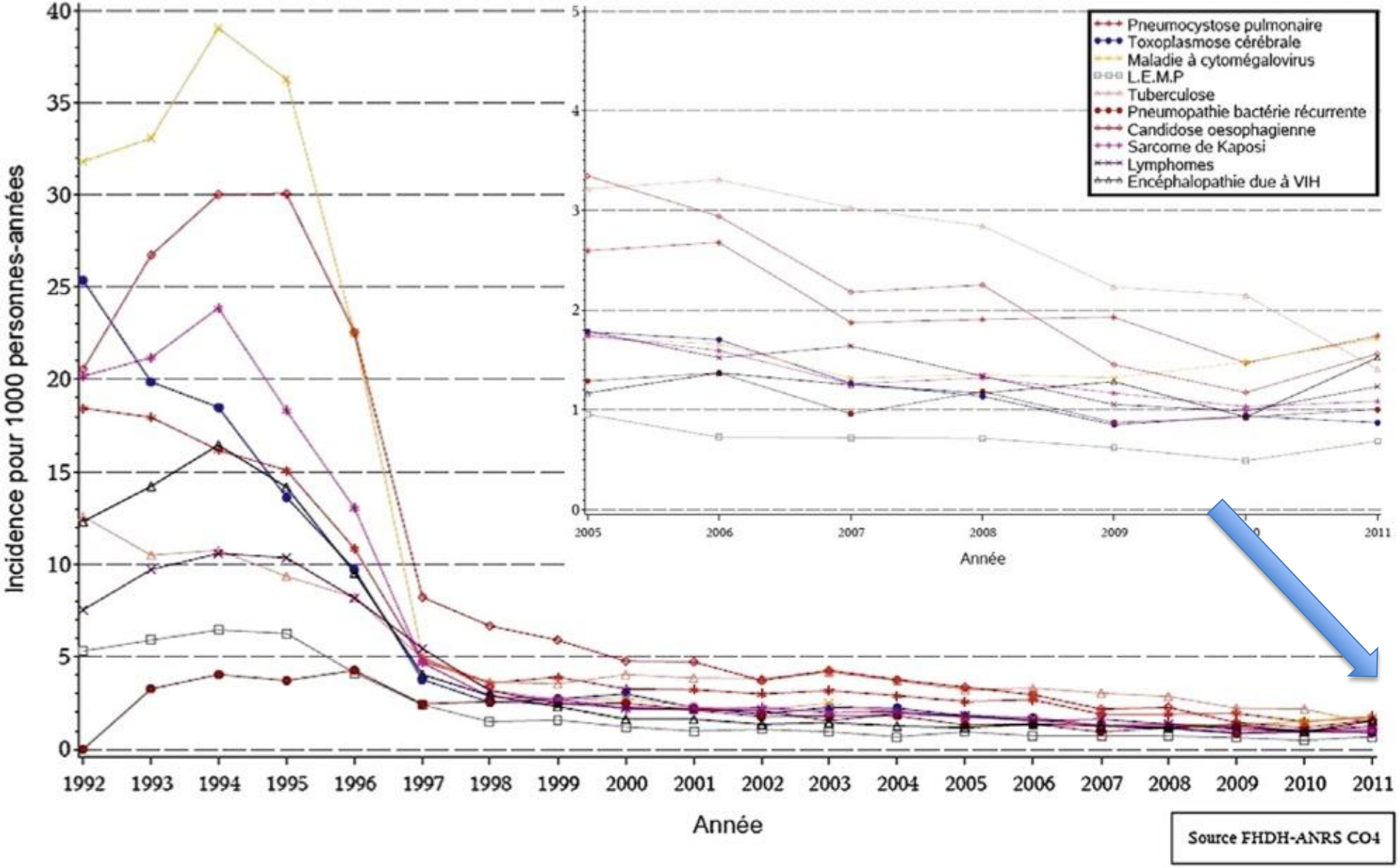


Figure 1 – Nombre estimé de découvertes de séropositivité VIH par année de diagnostic
(Données au 31/12/2014 corrigées pour les délais de déclaration et la sous-déclaration)

En 2014, on estime à environ 1 200 [IC95 % : 1 097-1 345] le nombre de nouveaux diagnostics de sida. Ce nombre diminue lentement depuis le début des années 2000.

Depuis 2010, environ 55% (54% en 2014) des nouveaux cas de sida sont diagnostiqués chez des personnes qui ignoraient leur infection VIH avant le diagnostic de sida, et environ 80% (83% en 2014) chez des personnes qui n'avaient pas reçu de traitement antirétroviral avant le diagnostic de sida. La pneumocystose reste, à l'échelle nationale, la principale pathologie opportuniste inaugurale de sida (28%), les autres pathologies les plus fréquentes étant la tuberculose (15%), la toxoplasmose cérébrale (12%) la candidose œsophagienne (10%) et le Kaposi (8%).

La médiane du nombre de lymphocytes CD4/mm^3 au moment du diagnostic de sida était de 50 en 2014. Les CD4 étaient inférieurs à 200/mm^3 chez 82% des personnes ayant développé un sida en 2014. Lorsque la charge virale était renseignée (90% des diagnostics de sida en 2014), elle était supérieure ou égale à 100 000 copies/ml dans 63% des cas. La charge virale médiane au diagnostic de sida était de 153 915 en 2014. Elle était beaucoup plus faible chez les personnes qui avaient bénéficié de traitement antirétroviral avant le sida (5 925) que chez celles qui n'en avaient pas reçu (197 255).


Incidence pour 1000 personnes-années
Année
Pneumocystose pulmonaire
Toxoplasmose cérébrale
Maladie à cytomégalovirus
L.E.M.P
Tuberculose
Pneumopathie bactérie récurrente
Candidose oesophagienne
Sarcome de Kaposi
Lymphomes
Encéphalopathie due à VIH
Source FHDH-ANRS CO4

J Neurol (2015) 262:1317–1327
DOI 10.1007/s00415-015-7713-8

ORIGINAL COMMUNICATION

Neurological complications of HIV infection in pre-HAART and HAART era: a retrospective study

Angela Matinella[1] · M. Lanzafame[2] · M. A. Bonometti[1] · A. Gajofatto[1] · E. Concia[2] · S. Vento[3] · S. Monaco[1] · S. Ferrari[1]

Received: 26 July 2014 / Revised: 15 March 2015 / Accepted: 16 March 2015 / Published online: 1 April 2015

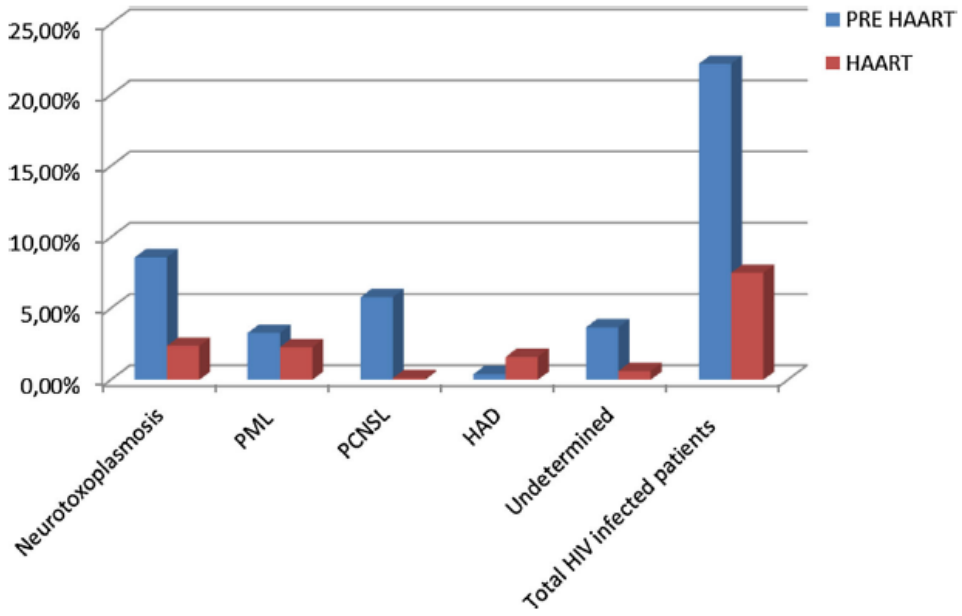


Fig. 1 Percentage of neurological diagnoses over total HIV cases admitted to the Infectious Diseases Unit in the two periods. *PML* progressive multifocal leukoencephalopathy, *PCNSL* primary central nervous system lymphoma, *HAD* HIV-associated dementia

Research Article

HIV-Associated Central Nervous System Disease in Patients Admitted at the Douala General Hospital between 2004 and 2009: A Retrospective Study

Henry Namme Luma,[1,2] Benjamin Clet Nguenkam Tchaleu,[1,3] Elvis Temfack,[1] Marie Solange Doualla,[1,2] Daniela Pamela Ntchankam Ndenga,[3] Yacouba Njankouo Mapoure,[1,4] Alfred Kinyuy Njamnshi,[2,5] and Vincent-de-Paul Djientcheu[2,5]

[1] *Department of Internal Medicine, Douala General Hospital, P.O. Box 4856, Douala, Cameroon*
[2] *Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon*
[3] *Université des Montagnes, Bangangte, Cameroon*
[4] *Faculty of Medicines and Pharmaceutical Sciences, University of Douala, Douala, Cameroon*
[5] *Yaoundé Central Hospital, Yaoundé, Cameroon*

Correspondence should be addressed to Henry Namme Luma; hnluma@yahoo.com

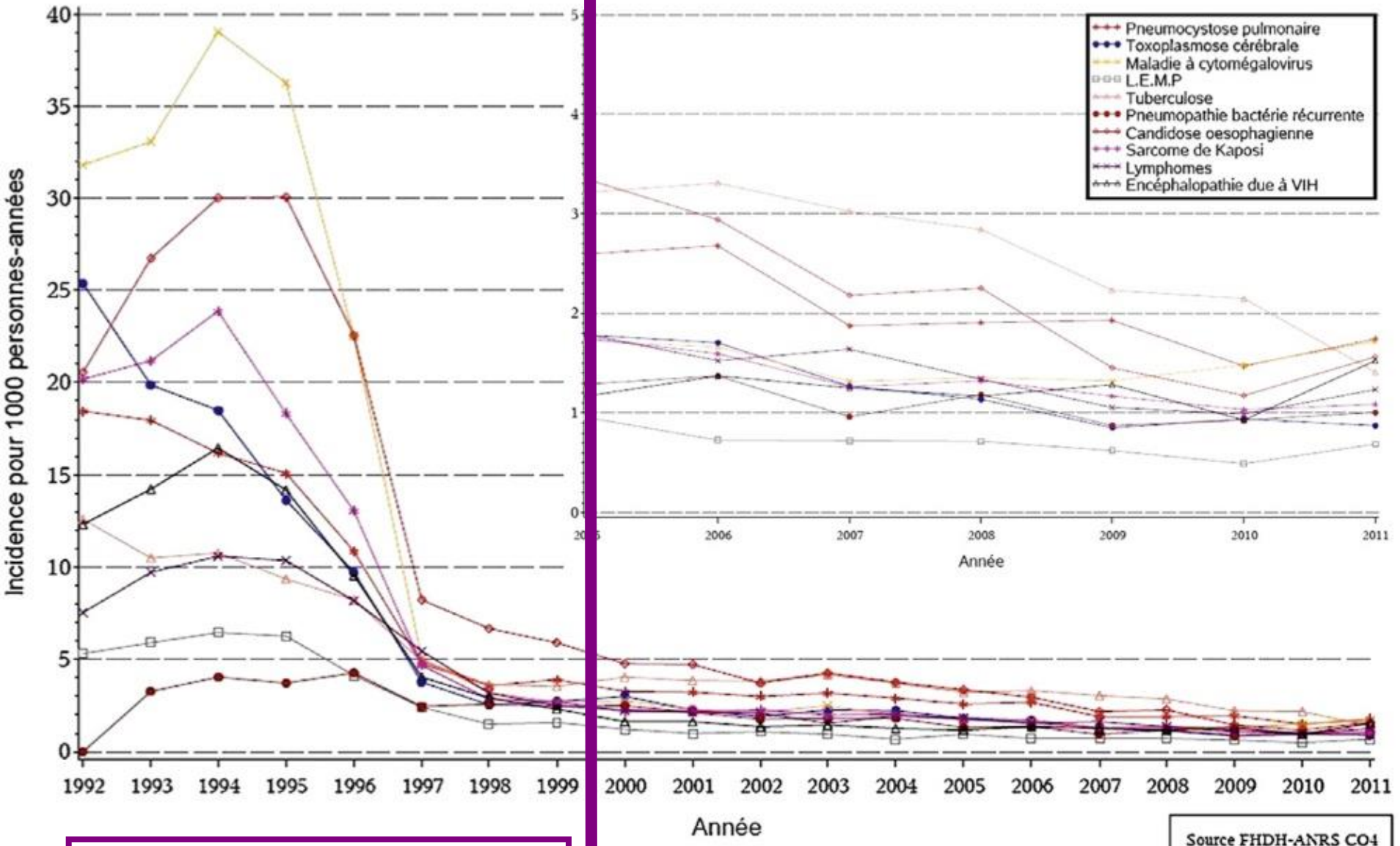
Received 9 November 2012; Revised 22 January 2013; Accepted 22 January 2013

Academic Editor: D. A. Katzenstein

Background. Studies on HIV-associated central nervous system (CNS) diseases in Cameroon are rare. The aim of this study was to describe the clinical presentation, identify aetiological factors, and determine predictors of mortality in HIV patients with CNS disease. *Methods*. From January 1, 2004 and December 31, 2009, we did at the Douala General Hospital a clinical case note review of 672 admitted adult (age ≥ 18 years) HIV-1 patients, and 44.6% (300/672) of whom were diagnosed and treated for HIV-associated CNS disease. *Results*. The mean age of the study population was 38.1 ± 13.5 years, and median CD4 count was 49 cells/mm^3 (interquartile range (QR): 17–90). The most common clinical presentations were headache (83%), focal signs (40.6%), and fever (37.7%). Toxoplasma encephalitis and cryptococcal meningitis were the leading aetiologies of HIV-associated CNS disease in 32.3% and 25% of patients, respectively. Overall mortality was 49%. Primary central nervous system lymphoma (PCNSL) and bacterial meningitis had the highest case fatality rates of 100% followed by tuberculous meningitis (79.8%). Low CD4 count was an independent predictor of fatality (AOR: 3.2, 95%CI: 2.0–5.2). *Conclusions*. HIV-associated CNS disease is common in Douala. CNS symptoms in HIV patients need urgent investigation because of their association with diseases of high case fatality.

IOP

Cognitif/ARV/IRIS



Problématique pré/perHAART

Problématique post HAART

Neurologue et HIV?

- En France
  - IOP, **diminution** de l'incidence annuelle pour 1000 patients/années d'un facteur 10 entre 1995 et 2011
  - Plus trop d'évolution depuis 2000
- PVVIH, manifestations neurologiques
  - **10 fois plus d'événements neurologiques que PnVIH (démence, épilepsie, nerfs périphériques)**
  - **Survenue de 10 ans plus précocément**
  - Présentation **initiale** chez 10% (20%dans le LMIP)
  - 30 à 50% durant l'**évolution**
  - Études **autopsique**: 80% des cas

Neurologie et VIH

- Trois entités
  - Liées à l'**immunodépression**, IOP et Kc
    - Garder la culture des IOP, Kc comme mode d'entrée dans le SIDA
  - Liées au **neurotropisme** du VIH
  - Liées à **l'activation immune chronique**

Complexité des situations = **pluridisciplinarité**

Historique et PVD

Pb moderne

Atteinte centrale

- **IOP**
  - Toxoplasmose
  - LEMP
  - Cryptococcose
  - CMV, HSV, VZV
  - Tuberculose
- **Lymphome**
- Atteinte vasculaire

- **Atteinte directe liée au VIH? Rôle immunité?**
  - Primo Infection
  - Trouble cognitif
  - Myélopathie vacuolaire
  - Encéphalomyélite à CD8

Atteintes périphériques

Tableau I. Prévalences des complications neurologiques les plus fréquentes de l'infection par le VIH. Incidence des complications neurologiques centrales au cours de l'infection par le VIH en 2011.

Pathologie	Incidence/1000 p.a.
Encéphalite due au VIH	1,5
Toxoplasmose cérébrale	0,9
Accidents vasculaires cérébraux	1,1 (H = 1,4, F = 0,5)
Leucoencéphalite multifocale progressive	0,7
Cryptococcose méningée	0,3
Lymphome primitif du SNC	0,1
Tuberculose extrapulmonaire[a]	0,6
Syphilis (toutes formes confondues)[a]	8,0
Lymphome non hodgkinien[a]	1,1

RICE décembre 2012, http://www.ccde.fr/_fold/fl-1356007065-945.pdf.

Orientation diagnostique
PVVIH signes neurologiques centraux

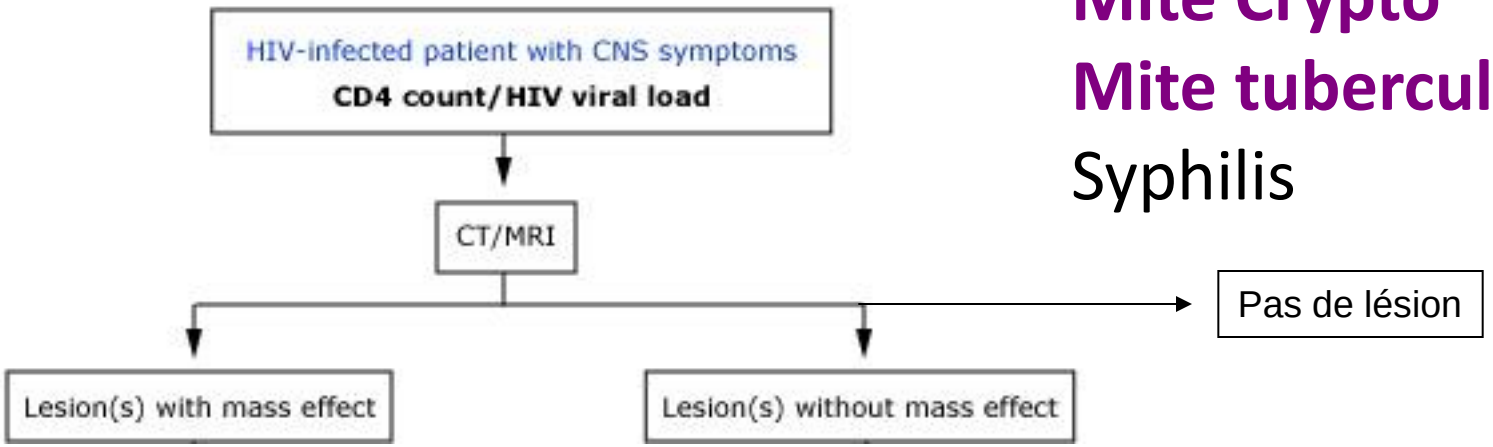
- Si VIH non connu, penser tjs à la **sérologie**, avec l'accord du patient…ou non
- Prise de **prophylaxie** (Utilisation de Bactrim en prophylaxie a diminué de 72,2% à 18,6% la fréquence de la Toxo entre 1991 et 1996)
- Degré d'**immunosuppression**, stade

Fonction immunosuppression

- Si CD4>500: tumeur et métastase comme le patient immunocompétent
- Si 200<CD4<500: pathologie cognitive et motrice sans syndrome focal
- Si CD4<200: syndrome de masse focal, IOP et LM

Orientation diagnostique
PVVIH signes neurologiques centraux

- Si VIH non connu, penser tjs à la **sérologie**, avec l'accord du patient…ou non
- Prise de **prophylaxie** (Utilisation de Bactrim en prophylaxie a diminué de 72,2% à 18,6% la fréquence de la Toxo entre 1991 et 1996)
- Degré d'**immunosuppression**, stade
- Aspect **radiologique** IRM/CT
- **Ponction Lombaire, PCR**
- **Biopsie** cérébrale
- **Traitement d'épreuve**



Mite Crypto

Mite tuberculeuse

Syphilis

Toxoplasmose

Cryptococcome

Tuberculome

Lymphome

Encéphalite VIH

LEMP

Encéphalite CMV

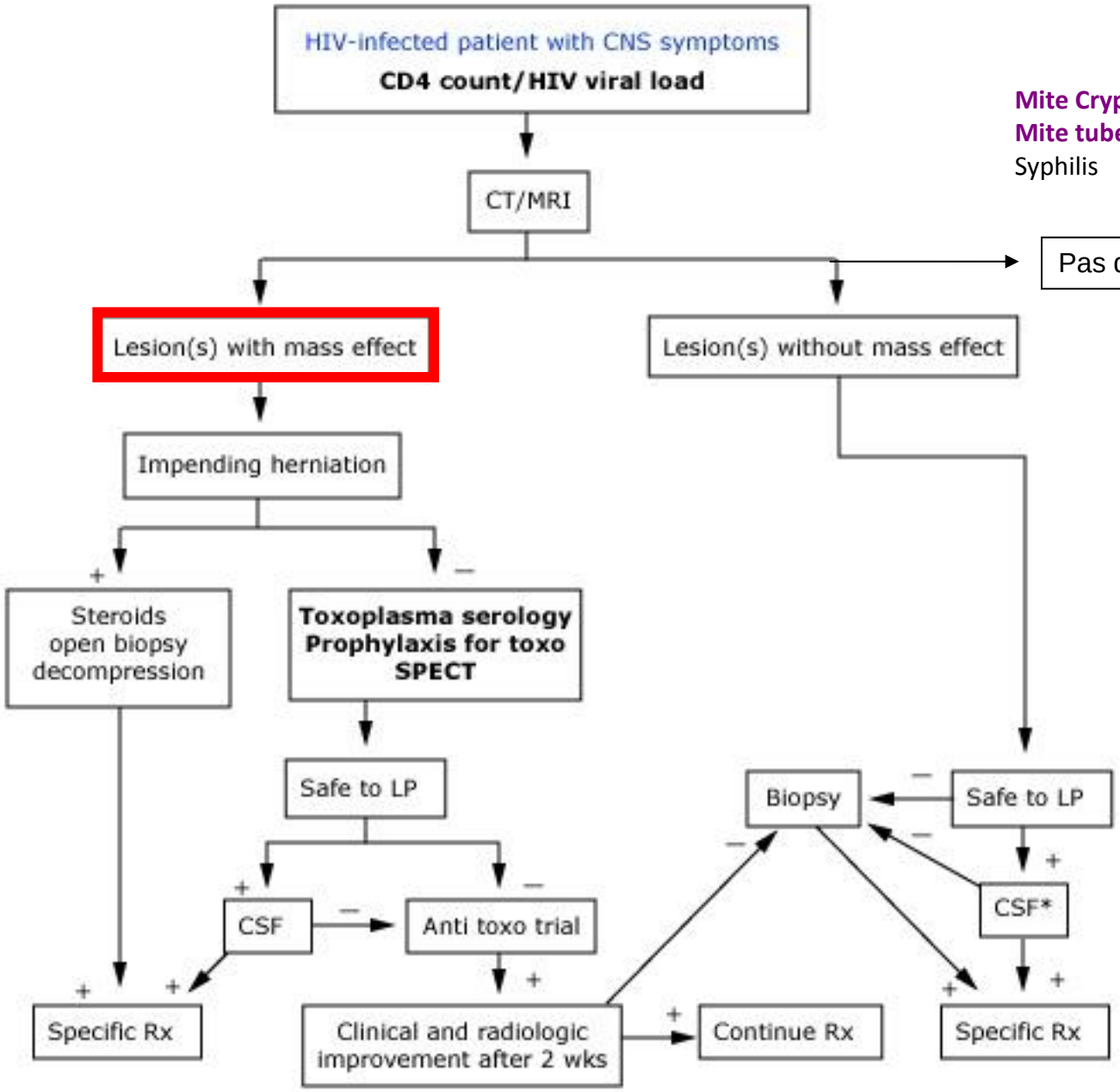
Lésions > 4 cm lymphome?
Lésions multiples = Toxo?

Table 6. Radiological patterns of CNS mass lesions in patients with AIDS.

Imaging technique	Toxoplasmosis	Lymphoma	PML
MRI findings			
Enhancement	Yes	Yes	No
Pattern	Ring	Homogenous or ring	—
Edema	Yes	Yes	No
SPECT thallium-201	Cold	Hot	Cold
PET	Hypometabolic	Hypermetabolic	Hypometabolic[a]

NOTE. PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; SPECT, single-photon emission CT.

[a] Usually hypometabolic, but occasionally hypermetabolic.



Mite Crypto
Mite tuberculeuse
Syphilis

Ponction lombaire

- Pas toujours contributive mais nécessaire si pas de risque d'engagement
- Pléiocytose lymphocytaire, hyperprotéinorrachie….
- PCR: toxoplasma, JC, EBV….CMV
- Encre de chine
- Anapath et immunophénotypage
- Mycobactériologie

PCR dans le LCR

- **JC**
  - Se 74 à 93%, Sp 92 à 100% dans l'ère pré HAART
  - Se 58% depuis HAART, diminution de la réplication par la restauration immunitaire
- **Toxo**
  - Se 52%, Sp 96 à 100%
- **EBV**
  - Se 87%, Sp 80%
- **CMV**
  - Se 80%, Sp 90%

Neurology. 1997 Mar;48(3):687-94.

Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF.

Antinori A, Ammassari A, De Luca A, Cingolani A, Murri R, Scoppettuolo G, Fortini M, Tartaglione T, Larocca LM, Zannoni G, Cattani P, Grillo R, Roselli R, Iacoangeli M, Scerrati M, Ortona L.

Author information

Abstract

OBJECTIVE: To identify disease patterns in AIDS-related focal brain lesions (FBL) and to design a decision-making strategy for differential diagnosis.

DESIGN: Prospective study. Probabilities of CNS disorders were calculated using Bayes' theorem according to clinical variables (mass effect at CT or MRI, Toxoplasma serology, anti-Toxoplasma prophylaxis) and to the results of polymerase chain reaction (PCR) assays.

PRE HAART

The **probability** of TE was 0.87 in **Toxoplasma** seropositive patients with mass effect who were not on trimethoprim-sulfamethoxazole (TMP-SMX),
but only 0.59 for those receiving prophylaxis.

In Toxoplasma seropositive patients receiving TMP-SMX,
the probability of **PCNSL** was 0.36.

In Toxoplasma seronegative patients with mass effect, the probability of PCNSL was 0.74, which increased to 0.96 if EBV PCR was positive in the CSF.

Among focal brain lesions without mass effect, the probability of **PML** was 0.81, which increased to 0.99 if JCV DNA was detected in the CSF.

Rapid diagnostic tests for neurological infections in central Africa

Cedric P Yansouni*, Emmanuel Bottieau*, Pascal Lutumba, Andrea S Winkler, Lut Lynen, Philippe Büscher, Jan Jacobs, Philippe Gillet, Veerle Lejon, Emilie Alirol, Katja Polman, Jürg Utzinger, Michael A Miles, Rosanna W Peeling, Jean-Jacques Muyembe, François Chappuis, Marleen Boelaert

Lancet Infect Dis 2013; 13: 546–58

Published Online April 24, 2013 http://dx.doi.org/10.1016/S1473-3099(13)70004-5

*Contributed equally to this Review

Department of Clinical Sciences (C P Yansouni MD, Prof E Bottieau MD, Prof L Lynen MD, Prof J Jacobs MD, P Gillet PhD, V Lejon PhD), **Department of Biomedical Sciences**

Infections are a leading cause of life-threatening neuropathology worldwide. In central African countries affected by endemic diseases such as human African trypanosomiasis, tuberculosis, HIV/AIDS, and schistosomiasis, delayed diagnosis and treatment often lead to avoidable death or severe sequelae. Confirmatory microbiological and parasitological tests are essential because clinical features of most neurological infections are not specific, brain imaging is seldom feasible, and treatment regimens are often prolonged or toxic. Recognition of this diagnostic bottleneck has yielded major investment in application of advances in biotechnology to clinical microbiology in the past decade. We review the neurological pathogens for which rapid diagnostic tests are most urgently needed in central Africa, detail the state of development of putative rapid diagnostic tests for each, and describe key technical and operational challenges to their development and implementation. Promising field-suitable rapid diagnostic tests exist for the diagnosis of human African trypanosomiasis and cryptococcal meningoencephalitis. For other infections—eg, syphilis and schistosomiasis—highly accurate field-validated rapid diagnostic tests are available, but their role in diagnosis of disease with neurological involvement is still unclear. For others—eg, tuberculosis—advances in research have not yet yielded validated tests for diagnosis of neurological disease.

Tuberculosis	Prevalence in 2011 was 293 (243–347) cases per 100 000 people in Africa (512 [263–842] in DR Congo); incidence in 2011 was 262 (242–283) cases per 100 000 people in Africa (327 [282–375] in DR Congo); mortality in HIV-negative people in 2011 was 26 (21–31) deaths per 100 000 people in Africa (54 [24–96] in DR Congo); proportion of patients with tuberculosis who also had HIV was 39% in Africa and 15% in DR Congo[28]	Neurological involvement in about 1% of all patients with tuberculosis (higher in children and patients with HIV co-infection)[29]
HIV and related opportunistic infections	23 (22–25) million people had HIV in Africa in 2011, of whom 1·2 (1·1–1·3) million died;[30] HIV prevalence in people aged 15–49 years was 4·6% in Africa[30] in 2011 and 1·3% in DR Congo in 2009[31]	>20% of patients with AIDS have neurological complications of various causes, including cryptococcal meningitis, HIV-associated neurological disease, toxoplasmic encephalitis, stroke, and tuberculosis of the CNS[32]

HIV-associated toxoplasmic encephalitis						
None	NA	NA	NA	NA	Good candidate for loop-mediated isothermal amplification process or antigen detection	Compatible brain imaging and response to treatment within 14 days is an acceptable surrogate for histopathology
HIV-associated cryptococcal meningitis						
CrAg LFA (Immuno-Mycologics, Norman, USA)[61,62]	Antigen	CSF, serum, plasma, urine	Confirmed meningitis, and acute respiratory illness	Yes, on CSF	Phase 2, immunochromatographic strip, no boiling of samples is needed	Positive culture or detection of cryptococcal antigen in CSF (using traditional cryptococcal antigen assays) or positive microscopy on CSF, or either positive result from blood (culture or cryptococcal antigen) in conjunction with a clinically compatible illness[63]

Molecular Diagnosis of Central Nervous System Opportunistic Infections in HIV-Infected Zambian Adults

Omar K. Siddiqi,[1,2] Musie Ghebremichael,[3] Xin Dang,[1] Masharip Atadzhanov,[2] Patrick Kaonga,[2] Michael N. Khoury,[1] and Igor J. Koralnik[1]

[1]Division of Neuro-Virology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [2]Department of Internal Medicine, University of Zambia School of Medicine, Lusaka; and [3]Harvard Medical School and Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Boston

Background. Knowledge of central nervous system (CNS) opportunistic infections (OIs) among people living with human immunodeficiency virus (HIV) in sub-Saharan Africa is limited.

Methods. We analyzed 1 cerebrospinal fluid (CSF) sample from each of 331 HIV-infected adults with symptoms suggestive of CNS OI at a tertiary care center in Zambia. We used pathogen-specific primers to detect DNA from JC virus (JCV), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV) types 1 and 2, *Mycobacterium tuberculosis*, and *Toxoplasma gondii* via real-time polymerase chain reaction (PCR).

Results. The patients' median $CD4^+$ T-cell count was 89 cells/μL (interquartile range, 38–191 cells/μL). Of 331 CSF samples, 189 (57.1%) had at least 1 pathogen. PCR detected DNA from EBV in 91 (27.5%) patients, *M. tuberculosis* in 48 (14.5%), JCV in 20 (6.0%), CMV in 20 (6.0%), VZV in 13 (3.9%), HSV-1 in 5 (1.5%), and HSV-2 and *T. gondii* in none. Fungal and bacteriological studies showed *Cryptococcus* in 64 (19.5%) patients, pneumococcus in 8 (2.4%), and meningococcus in 2 (0.6%). Multiple pathogens were found in 68 of 189 (36.0%) samples. One hundred seventeen of 331 (35.3%) inpatients died during their hospitalization. Men were older than women (median, 37 vs 34 years; $P = .01$), more recently diagnosed with HIV (median, 30 vs 63 days; $P = .03$), and tended to have a higher mortality rate (40.2% vs 30.2%; $P = .07$).

Conclusions. CNS OIs are frequent, potentially treatable complications of AIDS in Zambia. Multiple pathogens often coexist in CSF. EBV is the most prevalent CNS organism in isolation and in coinfection. Whether it is associated with CNS disease or a marker of inflammation requires further investigation. More comprehensive testing for CNS pathogens could improve treatment and patient outcomes in Zambia.

Keywords. HIV; Zambia; cerebrospinal fluid; PCR; opportunistic infections.

Biopsie et lésions focales

Table 4. The findings of studies investigating brain biopsy in patients with AIDS who have focal neurological disease.

Reference	No. of subjects	Percentage of patients with				Definitive diagnosis	Major morbidity, %[a]	Mortality, %[b]
		Lymphoma	PML	Toxoplasmosis	Other			
[3]	50	28	28	26	18	96	8	0
[15]	251	33	30	15	16	94	3.2	2.8
[120]	26	42	15	23	12	96	4	4
[121]	13	31	23	38	15	85	8	0
[122]	25	36	24	8	12	80	4	0
[123]	23	39	22	30	4	88	0	8.7
[124]	20	15	35	25	15	70	5	0
[125]	12	50	25	0	17	92	8.3	0
[126]	26	46	23	15	8	92	11.5	0
[127]	25	40	8	40	4	92	0	0
[128]	158	51	17	6	14	86	3.7	3.1

NOTE. PML, progressive multifocal leukoencephalopathy.

[a] Defined as hemorrhage or permanent neurological deficits; does not include death.

[b] Biopsy-related mortality (death related to biopsy complication within 30 days of biopsy).

Skiest, CID, 2002

Biopsie et lésions focales

Table 2. Diagnoses determined by the 250 stereotactic biopsy procedures.

Finding	No. of diagnostic reports
1 diagnosis per patient	225
Multiple diagnoses per patient	16
2	15
3	1
Not diagnostic	5
Total	268

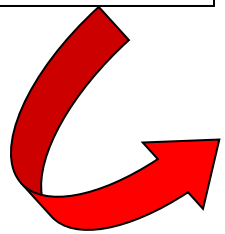


Table 3. Pathological findings in patients with multiple diagnoses.

Patient group, patient no.	Findings
1 lesion on CT/MRI	
11	Thromboembolism, PML
24	HIV encephalitis, PML
51	Lymphoma, *Mycobacterium* isolated
62	HIV encephalitis, anaplastic astrocytoma
79	HIV encephalitis, PML
149	HIV encephalitis, lymphoma
176	Lymphoma, *Mycobacterium* isolated
217	Toxoplasmosis, PML
>1 lesion on CT/MRI	
37	Cryptococcosis, lymphoma
54	HIV encephalitis (frontal), PML (cerebellum)
61	Toxoplasmosis, thromboembolism, PML
72	HIV encephalitis, periventricular inflammation
104	HIV encephalitis, demyelination (PML suspected)
107	Lymphoma, *Histoplasma capsulata* isolated
150	HIV encephalitis, PML
216	Toxoplasmosis, PML
101	Toxoplasmosis, PML, small-vessel vasculitis

NOTE. PML progressive multifocal leukoencephalopathy.

6% avec lésions multiples

30% des cas, histologie diffère du diag prédit

Gildenberg, CID, 1998

Biopsie et lésions focales

Table 4. Complications of stereotactic biopsy and their outcome rates.

Patient group, complication	No. (%) of patients per outcome category		
	Nonfatal	Fatal	Total
Initial (n = 32)			
Bleeding, acute	0	0	0
Bleeding, delayed	1 (3.1)	3 (9.4)	4 (12.5)
Subtotal	1 (3.1)	3 (9.4)	4 (12.5)
Main series[a] (n = 218)			
Bleeding, acute	5 (2.3)	2 (0.9)	7 (3.2)
Cerebral edema	2 (0.9)	1 (0.4))	3 (1.4)
Anesthesia-related (airway)		1 (0.4)	1 (0.4)
Subtotal	7 (3.2)	4 (1.8)	11 (5)
Total (250)	8 (3.2)	7 (2.8)	15 (6)

Gildenberg, CID, 1998

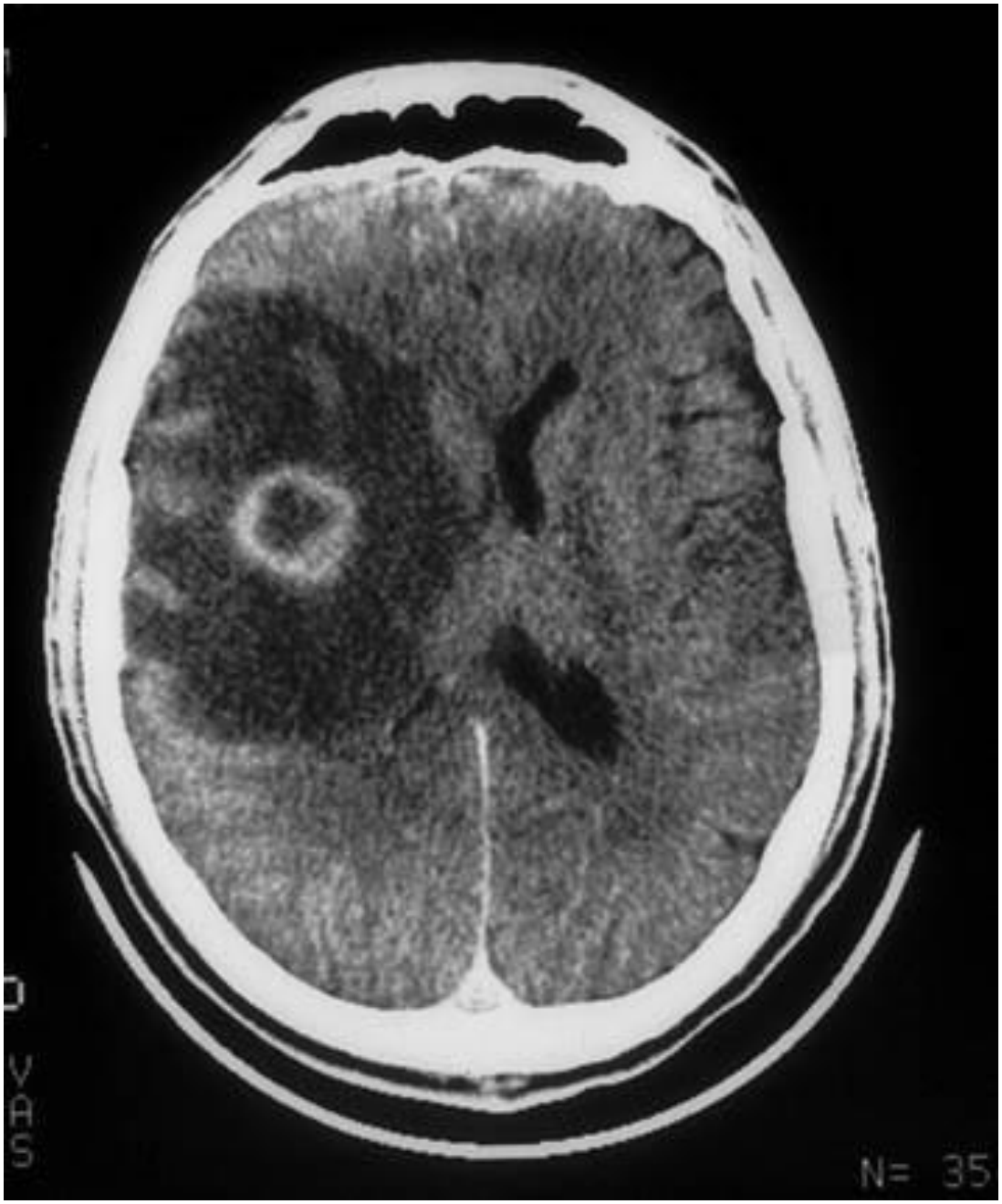
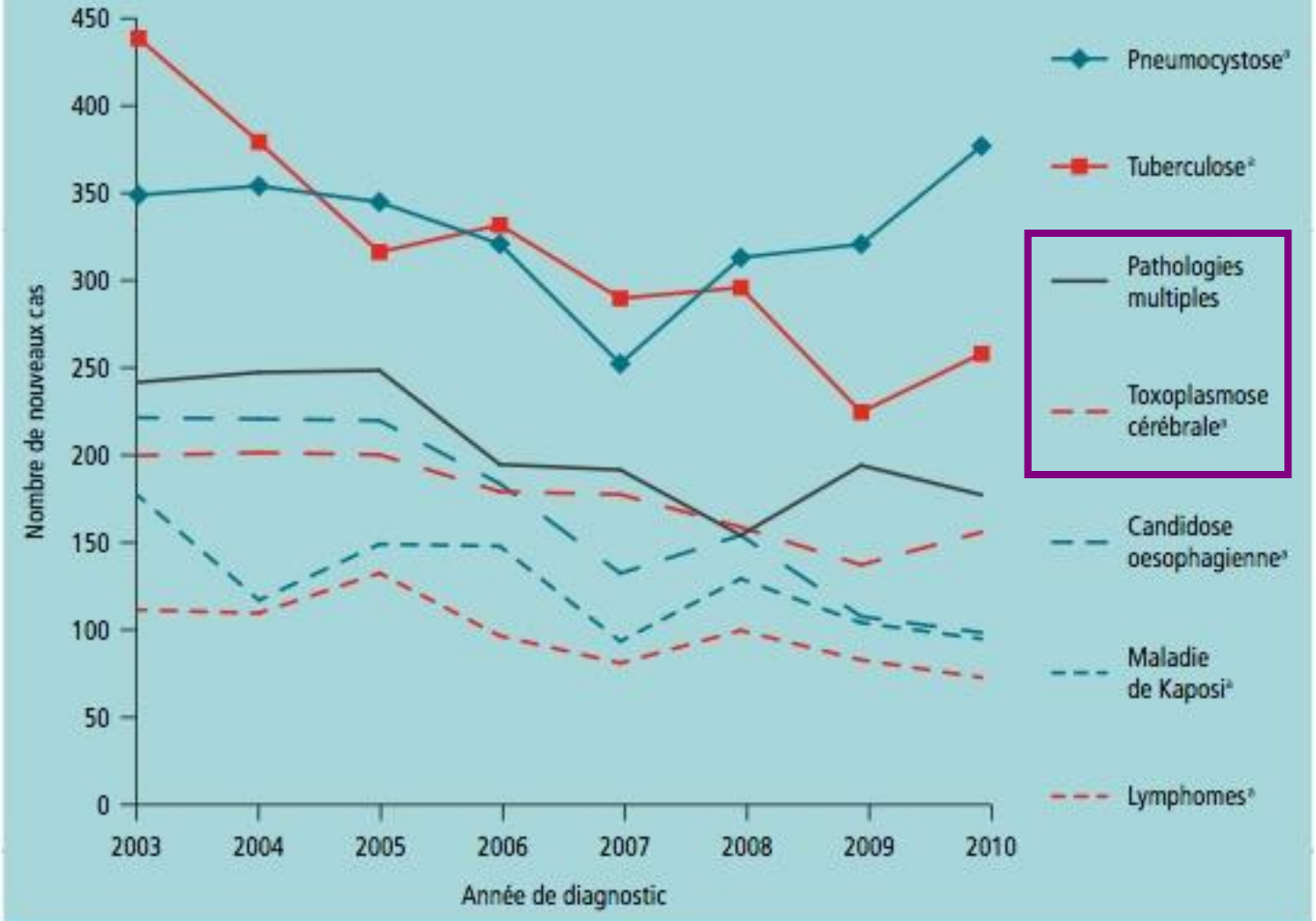
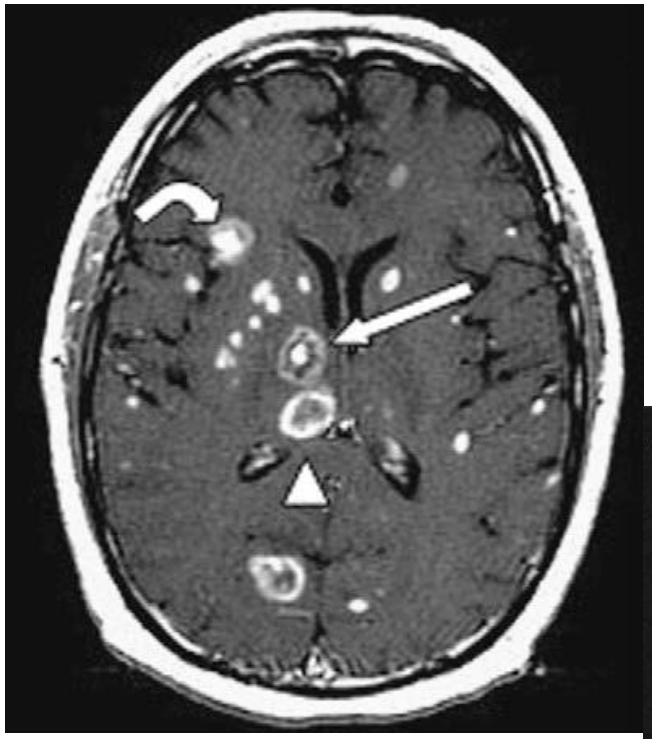

N= 35

Figure 2 **Pathologies inaugurales de sida les plus fréquentes chez les adultes (France - Données au 31/12/2010 corrigées pour les délais de déclaration et la sous-déclaration) /** ***Figure 2 Number of newly diagnosed AIDS indicative diseases in adults (France - Data up to 31/12/2010 adjusted for reporting delays and underreporting)***

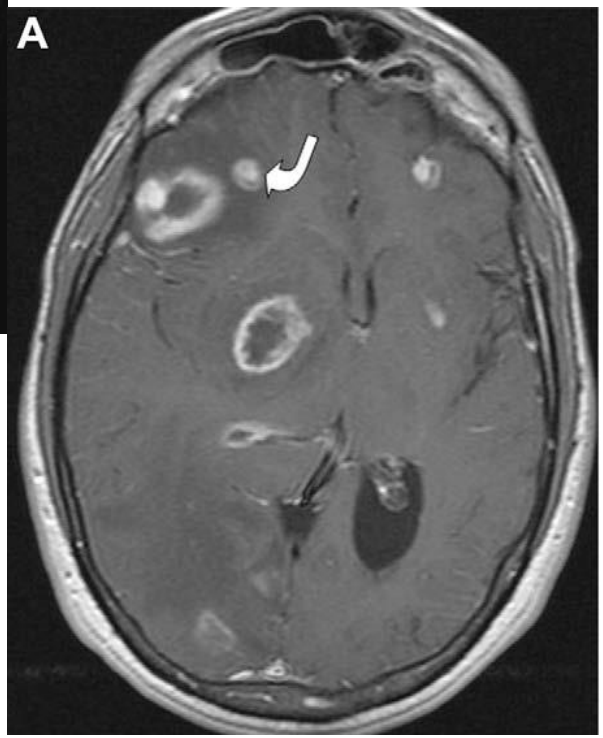


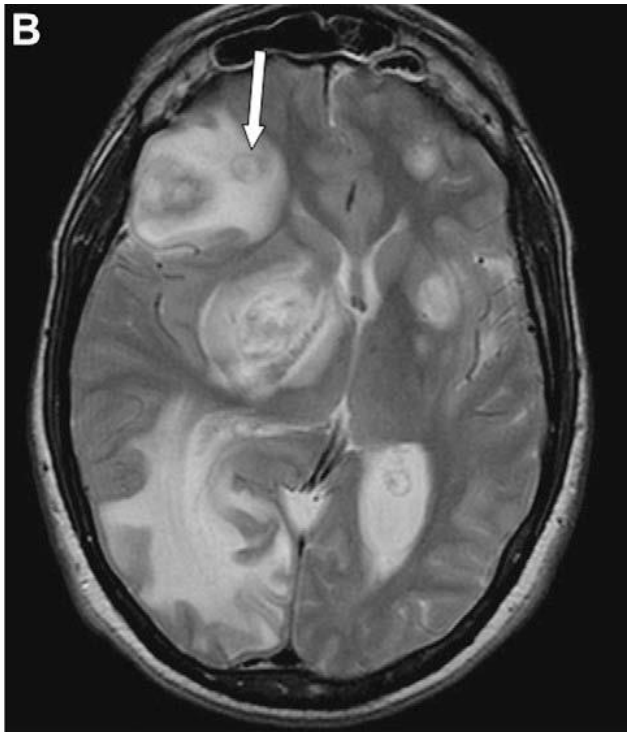
[a] Pathologies isolées.

Toxoplasmose



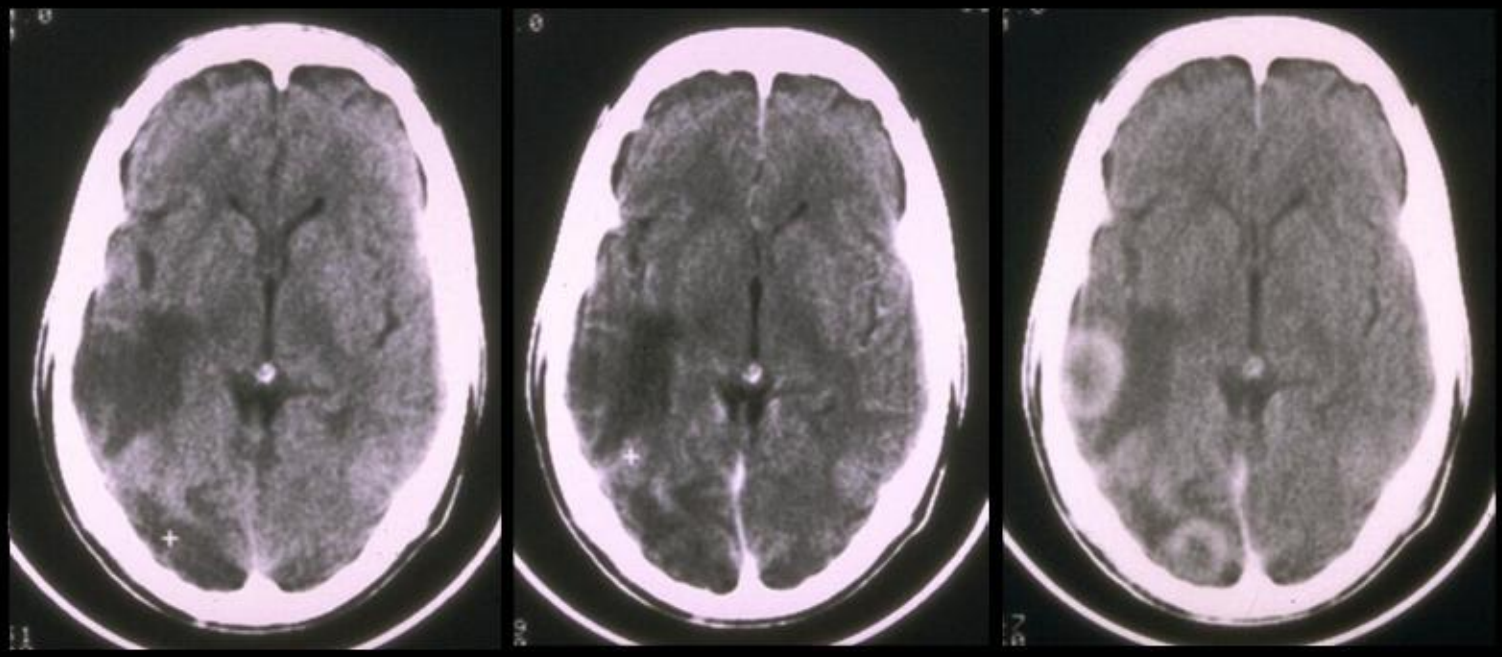
Réactivation endogène de kyste (inactivité des antifolate, controlé par l'immunité) en trophozoite
70% immun
PVVIH < 100 CD4 voire 200
Fièvre dans 50% des cas





Signe de la cible,
atteintes multiples,
Noyaux grix centraux

Toxo Case 4: Delayed uptake of contrast medium

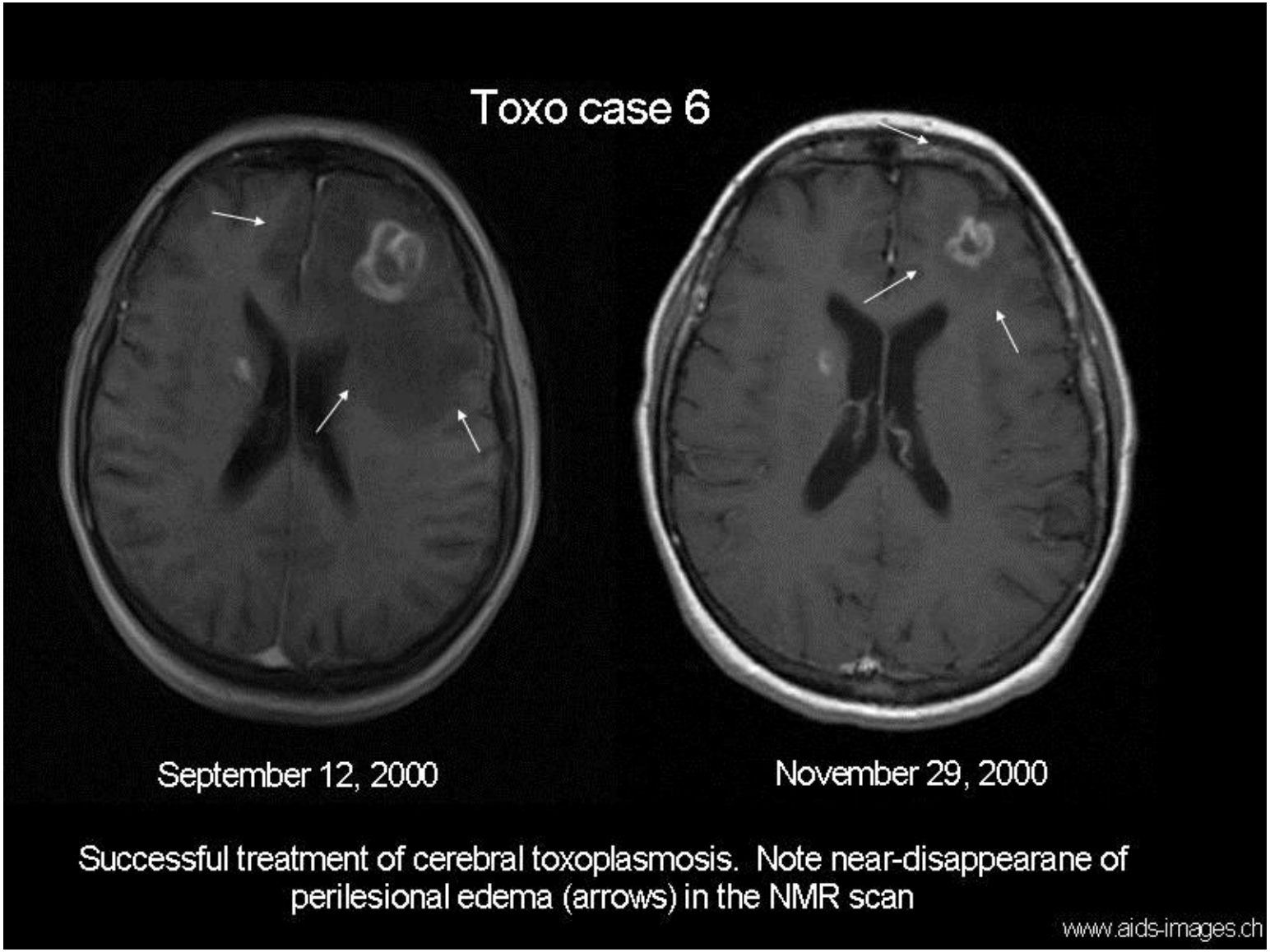


No contrast

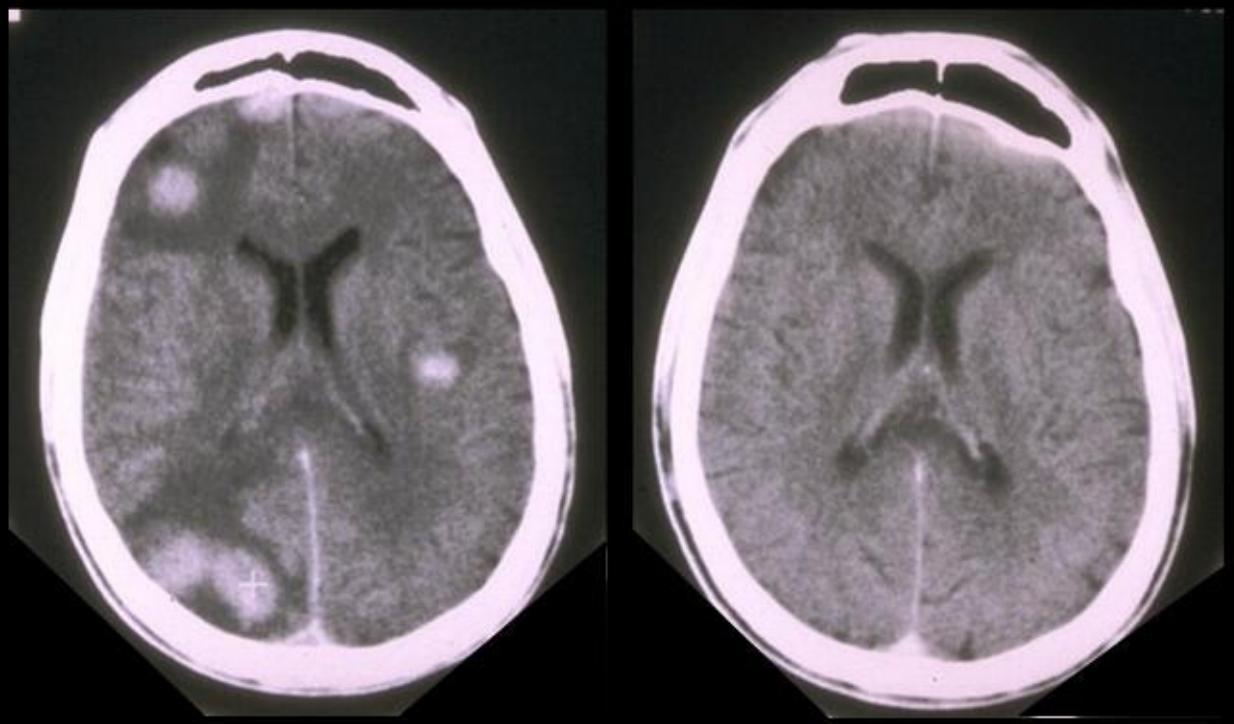
Immediately after injection

Two hours later

www.aids-images.ch


Toxo case 6
September 12, 2000
November 29, 2000
Successful treatment of cerebral toxoplasmosis. Note near-disappearane of perilesional edema (arrows) in the NMR scan
www.aids-images.ch

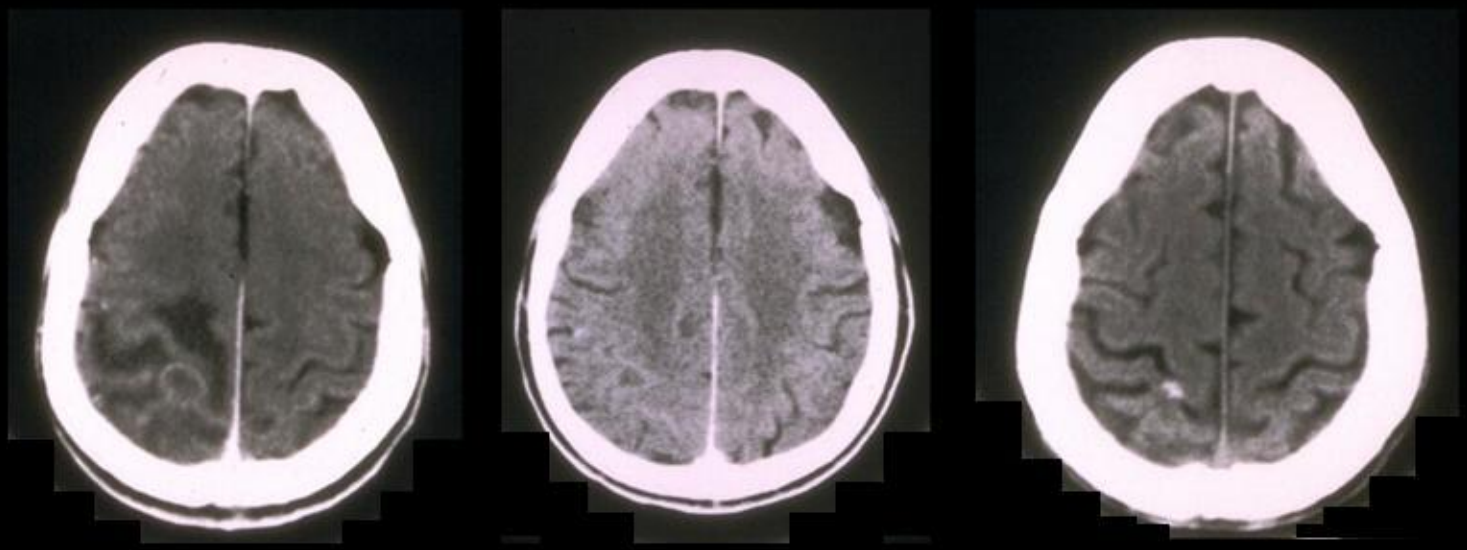
Toxo case 3, slide #2



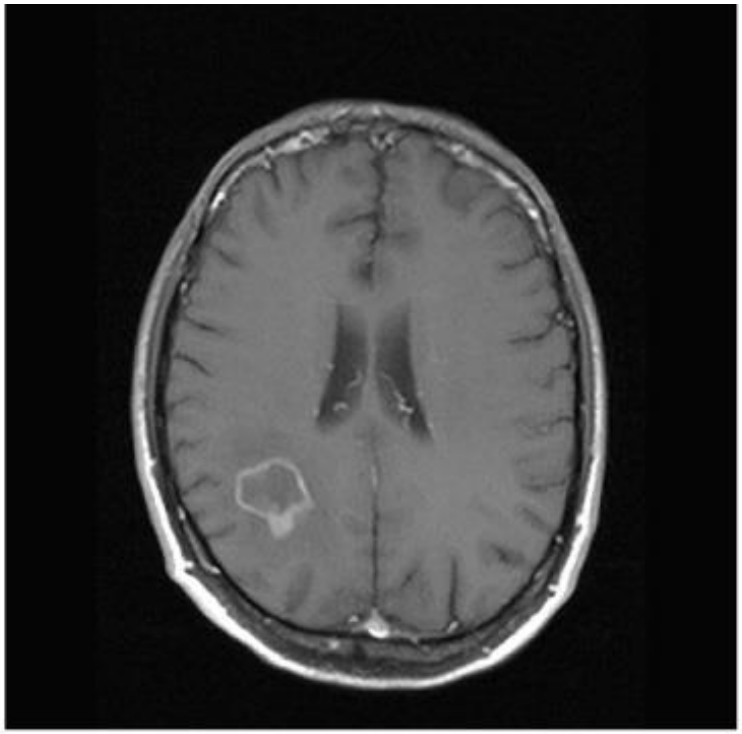
Case 3: One year later (right) the lesions are no longer visible

Toxo case 1, slide #3

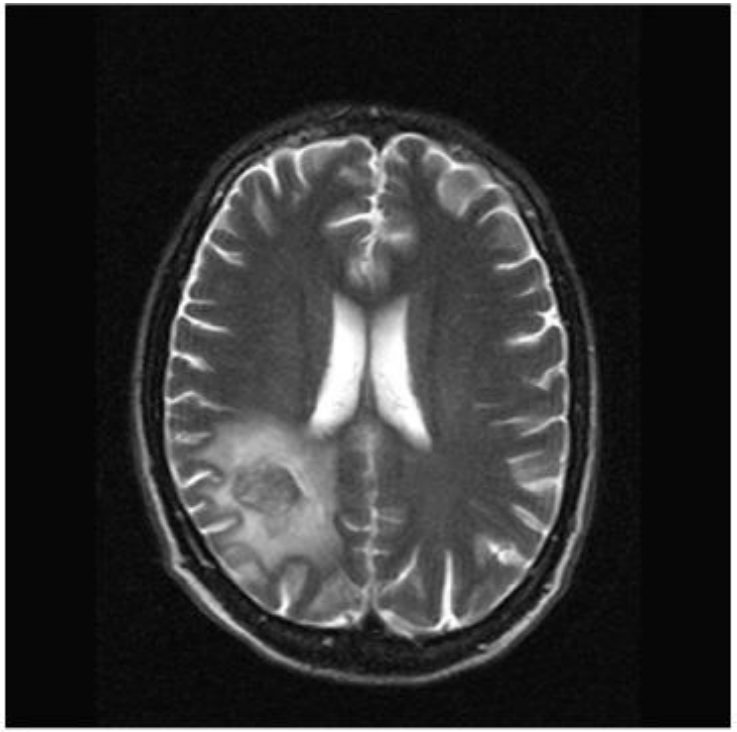
Case 1: 9 months later, only a small calcification remains



Day 0 Day 27 Day 118

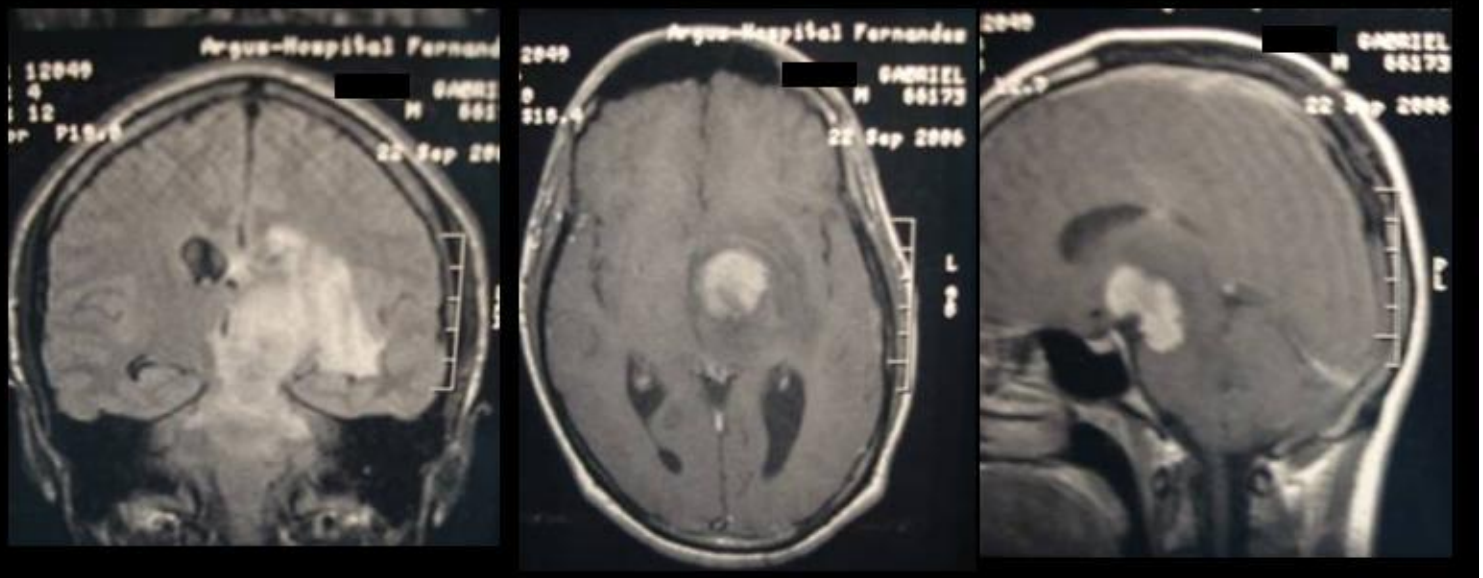


A



B

Mandell, 2005



Case 15b: Primary Brain Lymphoma

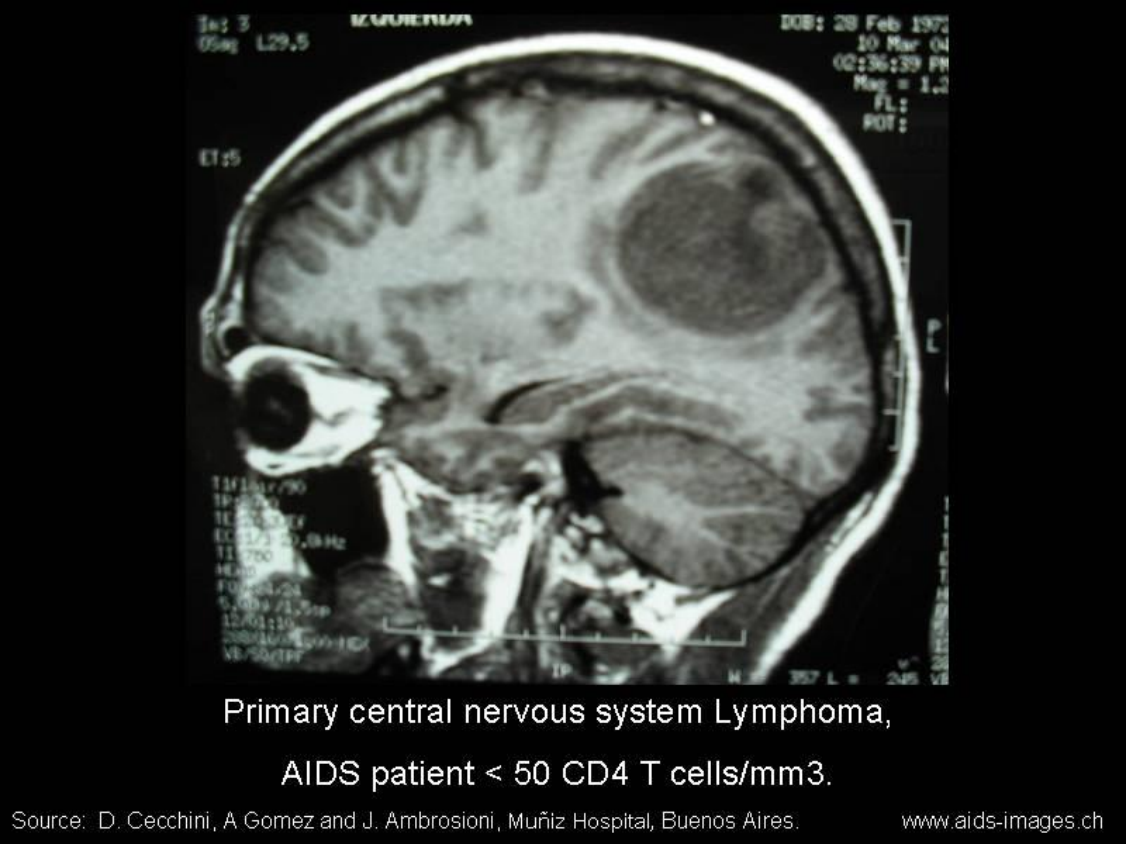
This patient developed III cranial nerve palsy and headache.

Findings suggestive of lymphoma:

- Solitary mass
- Irregular uptake of contrast (left)

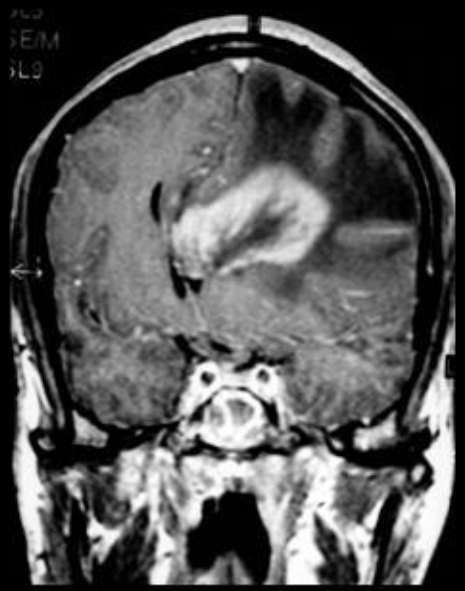
Cerebral biopsy confirmed primary CNS lymphoma

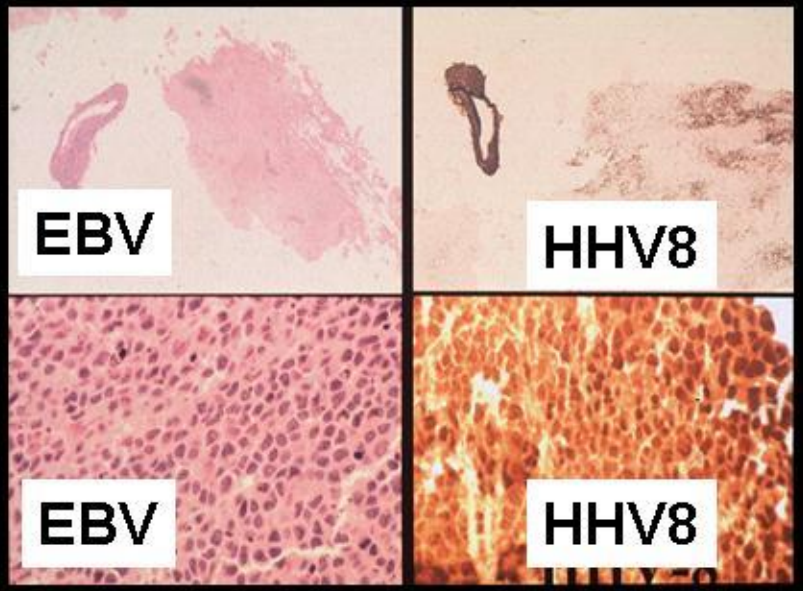
Picture credit: P. Cahn, Buenos Aires



LMNH primitif de type B
CD4 < 50
Et aussi 30% des LMNH systémiques ont des localisations SNC, svt méningées
œdème moins important

Case 13: Brain Lymphoma 23 Months after Multicentric Castleman's Disease





The tumour contained large HHV8+ cells, while staining for EBV was negative

Source: E. Oksenhendler

Table 6. Radiological patterns of CNS mass lesions in patients with AIDS.

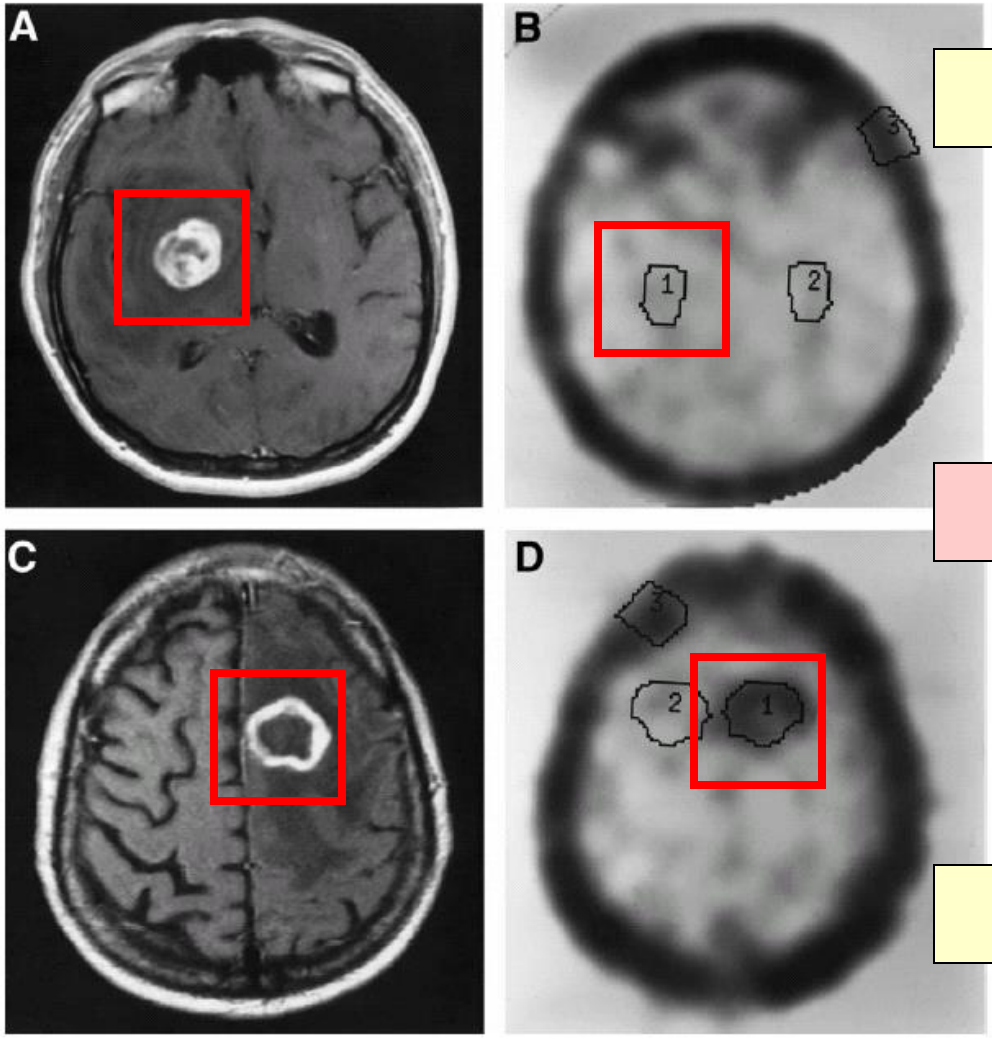
Imaging technique	Toxoplasmosis	Lymphoma	PML
MRI findings			
Enhancement	Yes	Yes	No
Pattern	Ring	Homogenous or ring	—
Edema	Yes	Yes	No
SPECT thallium-201	Cold	Hot	Cold
PET	Hypometabolic	Hypermetabolic	Hypometabolic[a]

NOTE. PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; SPECT, single-photon emission CT.

[a] Usually hypometabolic, but occasionally hypermetabolic.

Skiest, CID, 2002

Single photon emission CT-thallium 201



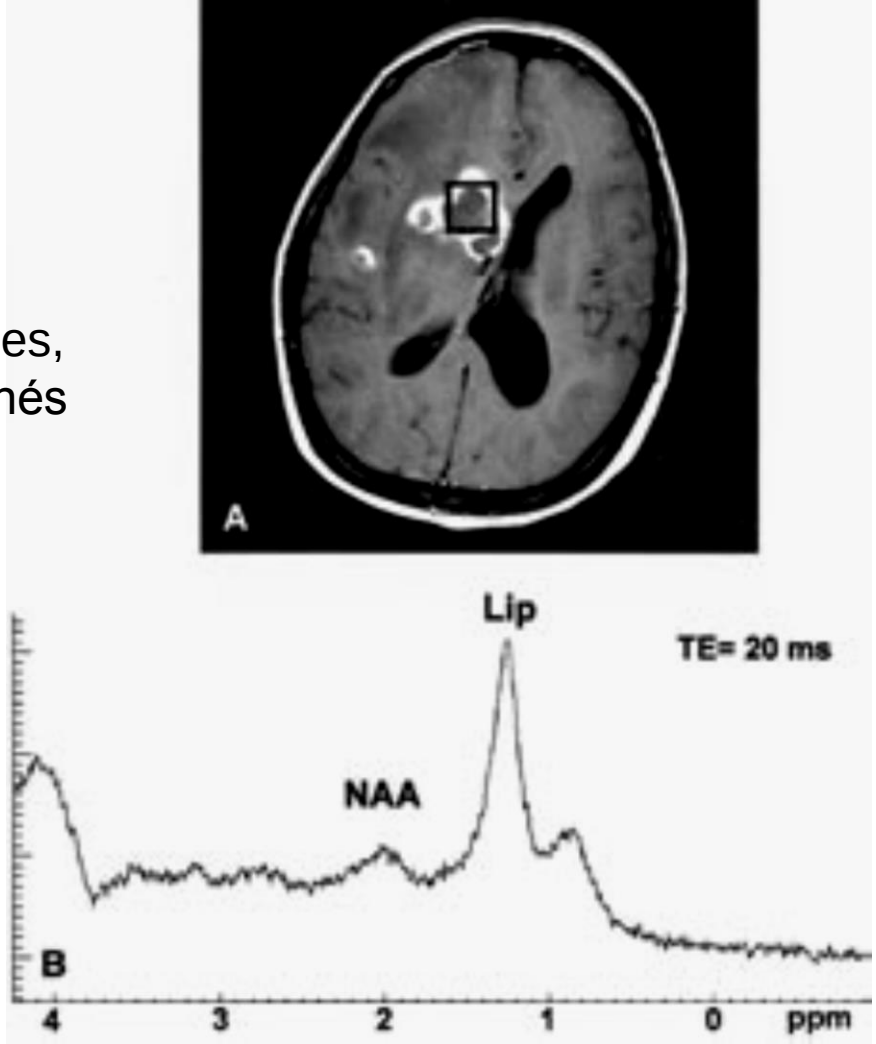
Toxoplasmose

Se 92%, Sp 89%

Lymphome

Germes particuliers

- Toxoplasmose, BK:
  - ADC augmenté
  - Présence de lipides,
  - pas d'acides aminés



Patiente de 33 ans hospitalisée pour céphalées et altération de l'état général. Le scanner et l'IRM retrouvent de multiples lésions kystiques prenant le contraste en périphérie (A). En SRM, les seules espèces métaboliques présentes sont les lipides libres, profil fortement évocateur d'une toxoplasmose cérébrale. Le diagnostic a été confirmé par la découverte d'une séropositivité VIH méconnue et la régression des lésions sous traitement anti-toxoplasmique.

Miller, STI, 1998

IRM…

Toxoplasmose

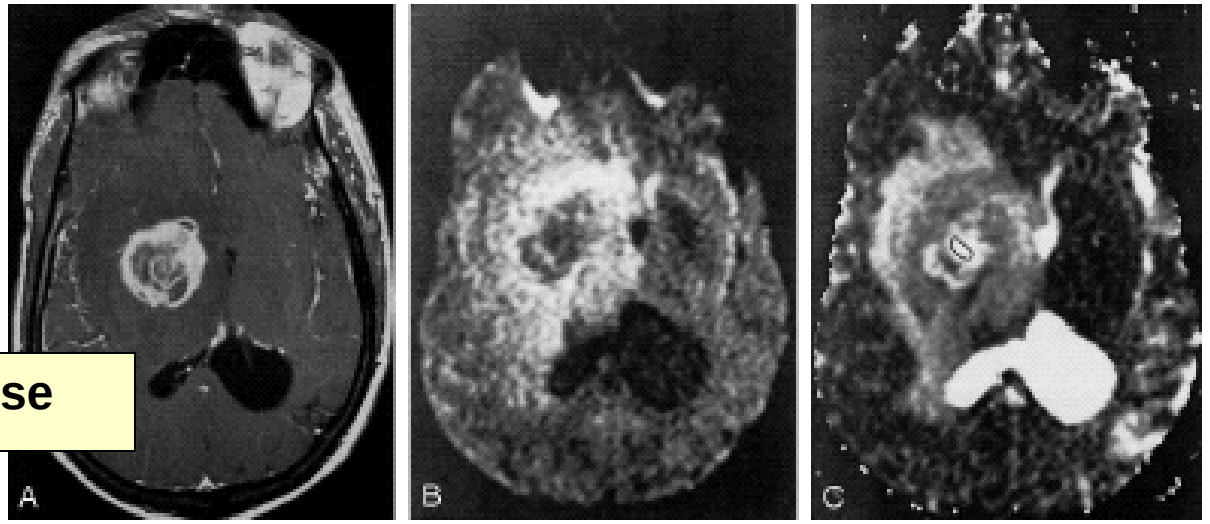


Fig. 2. Axial images in an AIDS patient with toxoplasmosis.
A, Axial T1-weighted gadolinium-enhanced MR image. The lesion in the right basal ganglia has an irregular, enhancing rim.
B, DW image (b = 1000 s/mm²). The core of the lesion demonstrates unrestricted diffusion.
C, ADC map of a toxoplasmosis lesion in the right basal ganglia. The outline indicates the ROI within the lesion used for ADC computation. The core of the lesion has a mean ADC that is increased relative to that in normal white matter (ADC ratio, 2.23).

Lymphome

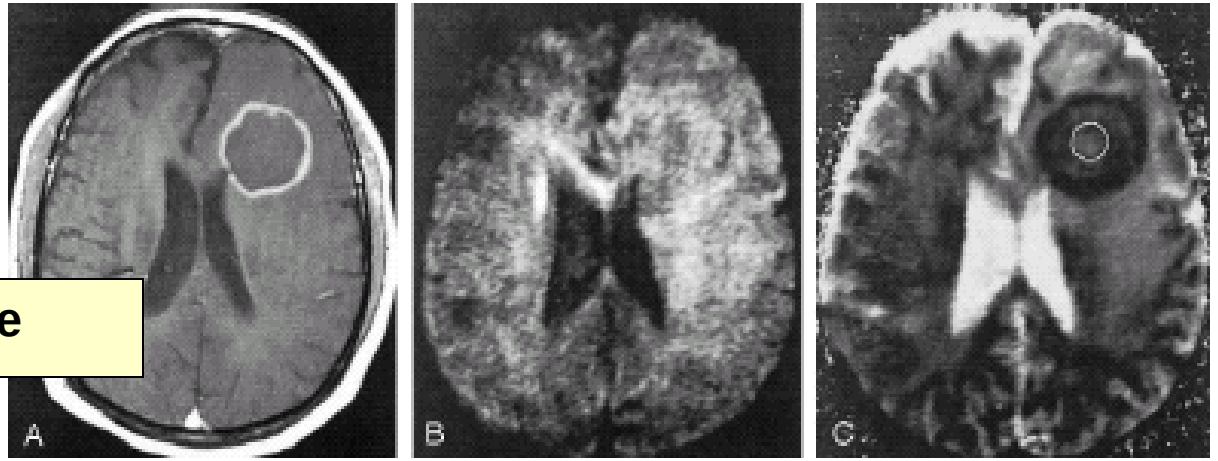
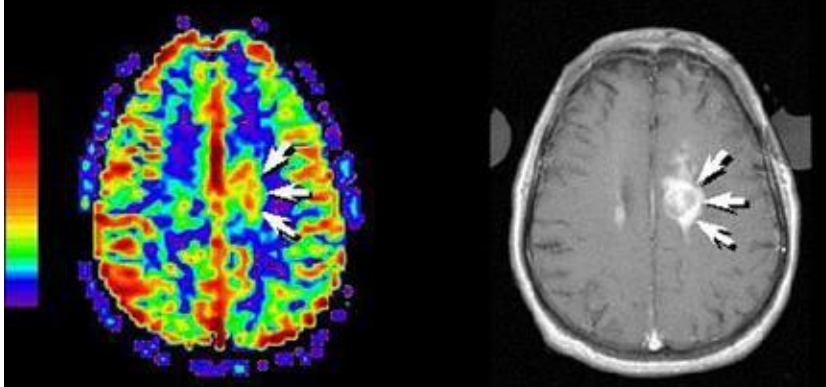
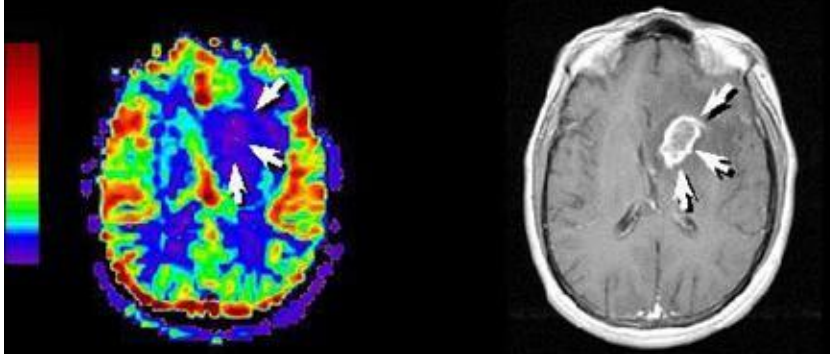


Fig. 3. Axial images in an AIDS patient with lymphoma.
A, Axial T1-weighted gadolinium-enhanced MR image. A lesion with an enhancing rim is present in the left frontal lobe.
B, DW image (b = 1000 s/mm²). The signal intensity of the core of the lesion is similar to that of uninvolved white matter.
C, ADC map of a lymphoma lesion in the left frontal lobe. The outline indicates the ROI within the lesion used for ADC computation. The core of the lesion has a mean ADC that is similar to that of normal white matter (ADC ratio, 1.25).



Primary brain lymphoma (arrows) in a 50-year old man with AIDS. Left: perfusion MR imaging. Right: Gadolinium-enhanced T1-weighted image. The lymphoma lesion shows areas of increased regional cerebral blood volume (rCBV, arrows, left image).



In contrast, the perfusion MR image of a toxoplasma abscess does not show increased rCBV

Cases 11/12: Another method to distinguish toxoplasmosis from lymphoma uses perfusion MR imaging. The metabolically active lymphomas show high blood flow, in contrast to the necrotic centers of toxoplasma abscesses.

Source: Sakaie KE, Gonzales RG. Imaging of Neuro-AIDS. NeuroAids, vol. 2, issue 7, 1999

Table 6. Radiological patterns of CNS mass lesions in patients with AIDS.

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MRI findings			
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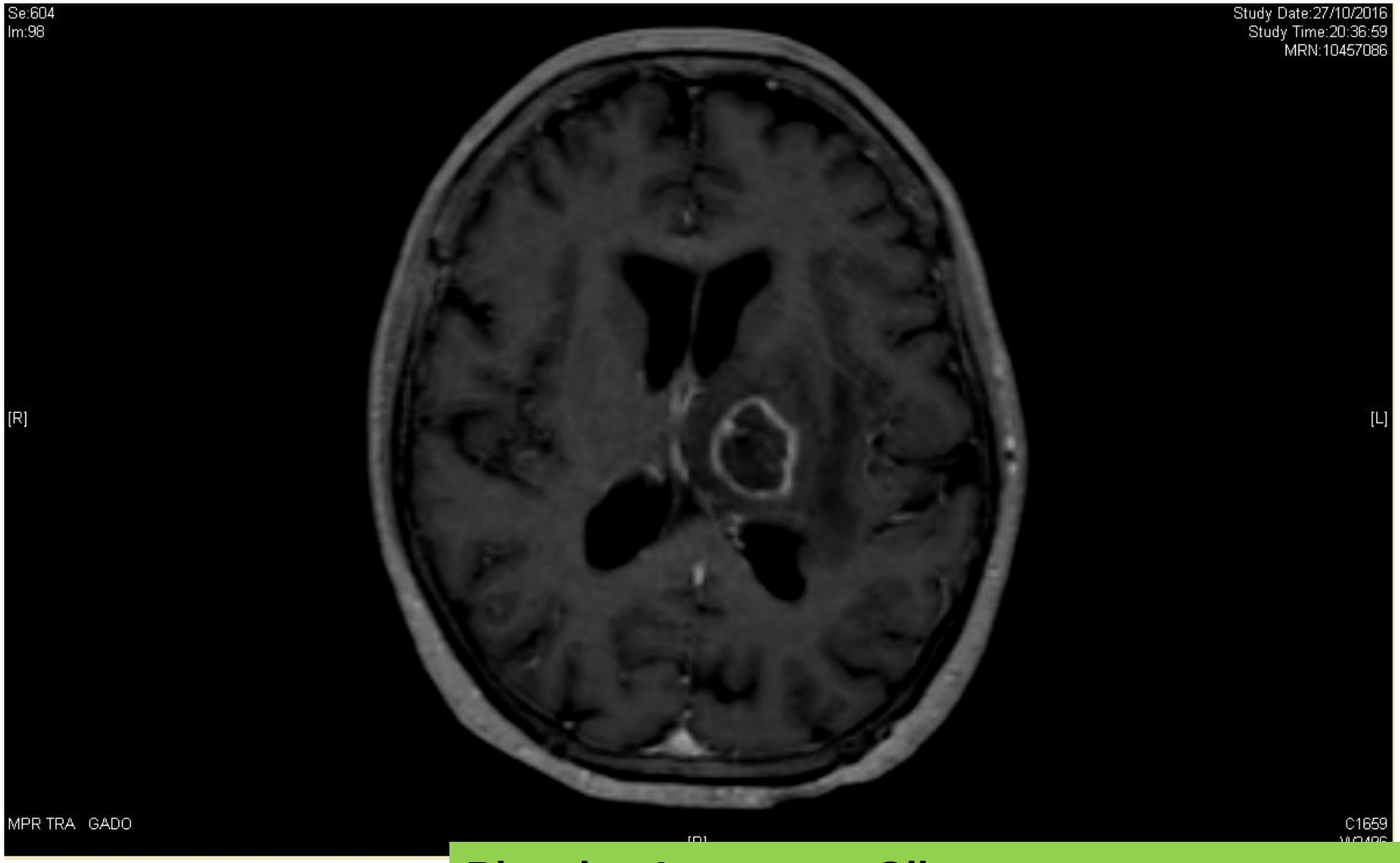
SPECT thallium-201	Cold	Hot	Cold
PET	Hypometabolic	Hypermetabolic	Hypometabolic[a]

NOTE. PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; SPECT, single-photon emission CT.

[a] Usually hypometabolic, but occasionally hypermetabolic.

Thus, their role in helping the clinician establish the cause of a CNS lesion is unclear.

hémiplégie



Biopsie n1: extempo Gliome

Reçu le : 09/11/2016 11:16 | FRANCE

BACTERIOLOGIE

Pr François Vandenesch, Pr Jean Freney, Drs Laetitia Béraud, Coralie Bouchiat, Olivier Dauwalder, Ghislaine Descours, Anne Doléans-Jordheim, Christine Fuhrmann, Pascale Girardo, Sophie Jarraud, Christine Ploton, Anne-Gaëlle Ranc, Waël Salka, Anne Tristan
Tél. secrétariat : 04 72 12 96 21 / 22 / 23 / 24 / 25 - mail : prenom.nom@chu-lyon.fr

Renseignements

38.4 °

EXAMEN BACTERIOLOGIQUE DES HEMOCULTURES

Hémocultures périphérique - échantillon N° 016212679801 prélevé le 09/11/16 à 10:00

Mode de prélèvement	périphérique

Flacon A

Code barre du flacon	ARN10STM Culture aérobie
Statut du flacon	Positif
Délai de positivité	18 H 54 min
Examen direct à partir du flacon	Présence de bacilles à Gram négatif

Culture du flacon A

- *Salmonella spp.*

Identification : par spectrométrie de masse, MALDITOF - VitekMS, bioMérieux

Biopsie n1: extempo Gliome

Biopsie n1: Lésion inflammatoire pour laquelle il est difficile de trancher sur l'étiologie tumorale ou infectieuse en l'absence d'élément vraiment spécifique. Il n'est pas possible de confirmer l'impression extemporannée de gliome. ·L'étude moléculaire est complétée par des PCR universelles à visée microbiologique (Dr O DAUWALDER) et des virus neurotropes (Dr Y Mekki).
L'index de prolifération élevé en périvasculaire et l'aspect parfois atypique des cellules CD20+ soulèvent également la question d'un lymphome B cérébral de présentation inhabituelle. Un avis est demandé au Pr A Glehen Traverse dans le cadre de Lymphopath

?????

Biopsie n2
Sur ces premières techniques, l'aspect observé fait évoquer de façon prioritaire le diagnostic d'Abcès. Colorations spéciales et techniques immunohistochimiques complémentaires en cours de réalisation

Sérologie HIV positive
Lymphocytes CD3+ et CD4+ 3 % 31-63 ** Soit en valeur absolue 19 /µL 314-1270

Biopsie n2
Sur ces premières techniques, l'aspect observé fait évoquer de façon prioritaire le diagnostic d'Abcès. Colorations spéciales et techniques immunohistochimiques complémentaires en cours de réalisation

Sérologie HIV positive
Lymphocytes CD3+ et CD4+ 3 % 31-63 ** Soit en valeur absolue 19 /µL 314-1270

Reçu le : 17/11/2016 16:36

69677 BRON CEDEX
FRANCE

BACTERIOLOGIE

Pr François Vandenesch, Pr Jean Freney, Drs Laetitia Béraud, Coralie Bouchiat, Olivier Dauwalder, Ghislaine Descours, Anne Doléans-Jordheim, Christine Fuhrmann, Pascale Girardo, Claude-Alexandre Gustave, Sophie Jarraud, Anne-Gaëlle Ranc, Waël Salka, Anne Tristan
Tél. secrétariat : 04 72 12 96 21 / 22 / 23 / 24 / 25 - mail : prenom.nom@chu-lyon.fr

EXAMEN BACTERIOLOGIQUE DES ABCES

Abcès - échantillon N° 016218313401 (date et heure de prélèvement non renseignées)

Mode de prélèvement	poudrier
Localisation	non précisée

CULTURE

- Quelques colonies de *Salmonella Enteritidis*

Identification	par spectrométrie de masse, MALDITOF - VitekMS, bioMérieux
Antibiogramme	automate Vitek2 bioMérieux (cf fin du compte-rendu)

Biopsie n2
Sur ces premières techniques, l'aspect observé fait évoquer de façon prioritaire le diagnostic d'Abcès. Colorations spéciales et techniques immunohistochimiques complémentaires en cours de réalisation

Sérologie HIV positive
Lymphocytes CD3+ et CD4+ 3 % 31-63 ** Soit en valeur absolue 19 /µL 314-1270

Reçu le : 17/11/2016 16:36

69677 BRON CEDEX
FRANCE

Ref ext :

Prélevé le : 17/11/2016 16:37
Reçu le : 18/11/2016 18:18

59, boulevard Pinel
69677 BRON CEDEX
FRANCE

BACTERIOLOGIE

Pr François Vandenesch, Pr Jean Freney, Descours, Anne Doléans-Jordheim, Christ Anne-Gaëlle Ranc, Waël Salka, Anne Tris
Tél. secrétariat : 04 72 12 96 21 / 22 / 23 /

EXAME

Abcès - échantillon N° 016218313401 (c

Mode de prélèvement	poudrier
Localisation	non pré

CULTURE

- Quelques colonies de *Salmonella Ente*

Identification	par spectrométrie de masse, MALDITOF - VitekMS, bioMérieux
Antibiogramme	automate Vitek2 bioMérieux (cf fin du compte-rendu)

TOXOPLASMOSE - SERODIAGNOSTIC FONGIQUE ET PARASITAIRE

Pr M. Wallon, Pr S. Picot, Pr F. Peyron, Dr AL. Bienvenu, Dr D. Dupont, Dr F. Persat, Dr M. Rabodonirina, Dr C. Ramade,
Secrétariat : téléphone : 04 72 07 18 72 (37 18 72) - fax : 04 72 07 18 73 (37 18 73).
Email : francois.peyron@chu-lyon.fr; florence.persat@chu-lyon.fr; meja.rabodonirina@chu-lyon.fr; martine.wallon@chu-lyon.fr

DIAGNOSTIC DE LA TOXOPLASMOSE PAR PCR

Nature de prélèvement : biopsie
Résultat : **Positif**
Kit Toxoplasma gondii Bio-Evolution, ABI PRISM 7500

SPECIAL ARTICLE

Evidence-based guideline: Antiepileptic drug selection for people with HIV/AIDS

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy

G.L. Birbeck, MD, MPH, DTMH, FAAN
J.A. French, MD, FAAN
E. Perucca, MD, PhD, FRCP(Edin)
D.M. Simpson, MD
H. Fraimow, MD
J.M. George, PharmD, BCPS
J.F. Okulicz, MD
D.B. Clifford, MD
H. Hachad, PharmD
R.H. Levy, PhD

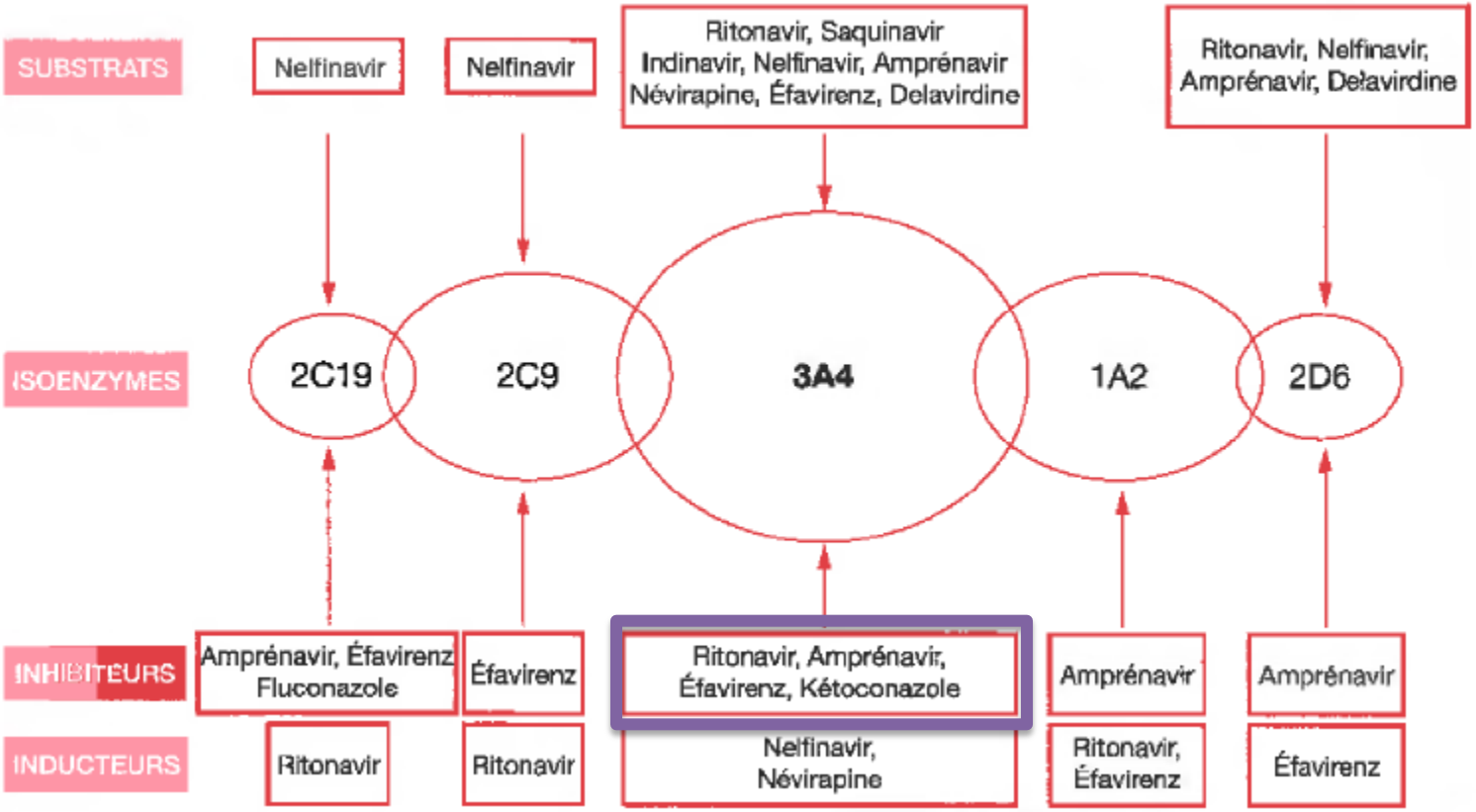
Correspondence & reprint requests to American Academy of Neurology: guidelines@aan.com

ABSTRACT

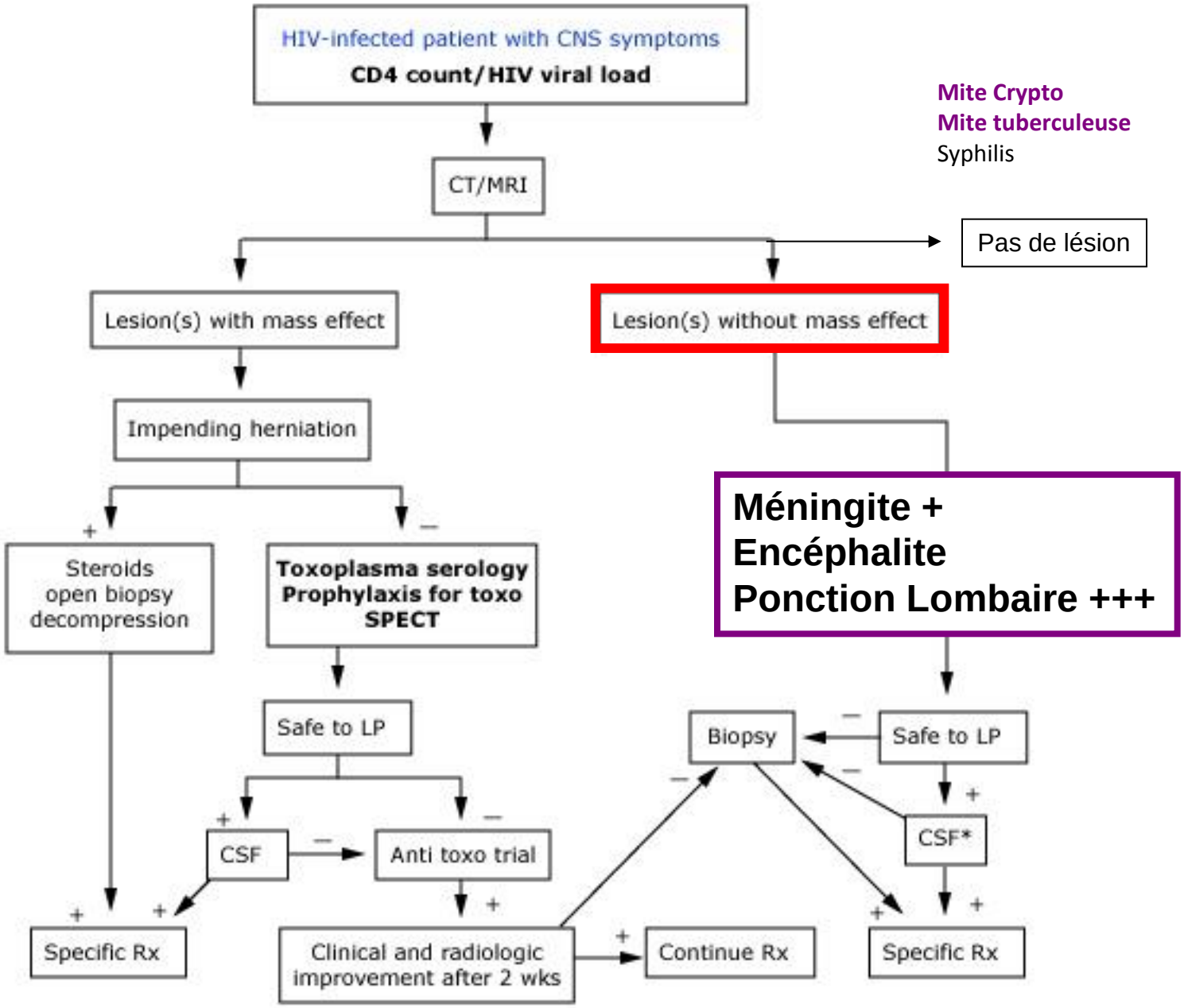
Objective: To develop guidelines for selection of antiepileptic drugs (AEDs) among people with HIV/AIDS.

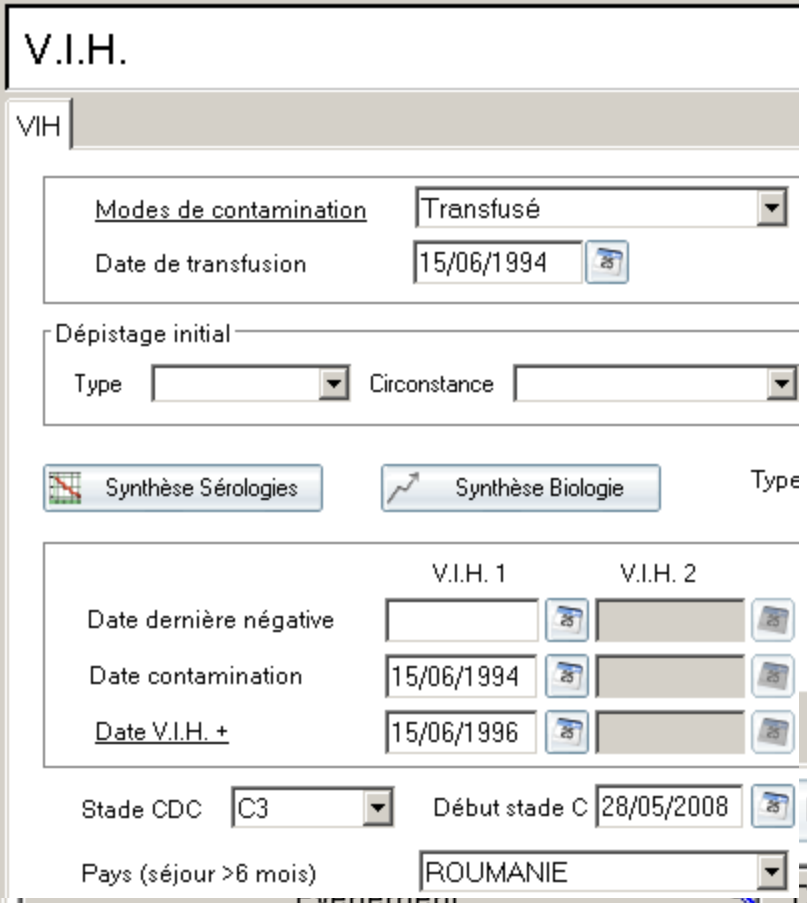
Methods: The literature was systematically reviewed to assess the global burden of relevant comorbid entities, to determine the number of patients who potentially utilize AEDs and antiretroviral agents (ARVs), and to address AED-ARV interactions.

Results and Recommendations: AED-ARV administration may be indicated in up to 55% of people taking ARVs. Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of ~50% to maintain unchanged serum concentrations (Level C). Patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations (Level C). Coadministration of valproic acid and efavirenz may not require efavirenz dosage adjustment (Level C). Patients receiving ritonavir/atazanavir may require a lamotrigine dosage increase of ~50% to maintain unchanged lamotrigine serum concentrations (Level C). Coadministration of raltegravir/atazanavir and lamotrigine may not require lamotrigine dosage adjustment (Level C). Coadministration of raltegravir and midazolam may not require midazolam dosage adjustment (Level C). Patients may be counseled that it is unclear whether dosage adjustment is necessary when other AEDs and ARVs are combined (Level U). It may be important to avoid enzyme-inducing AEDs in people on ARV regimens that include protease inhibitors or nonnucleoside reverse transcriptase inhibitors, as pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen (Level C). *Neurology*® 2012;78:139–145



…..lévétiracétam

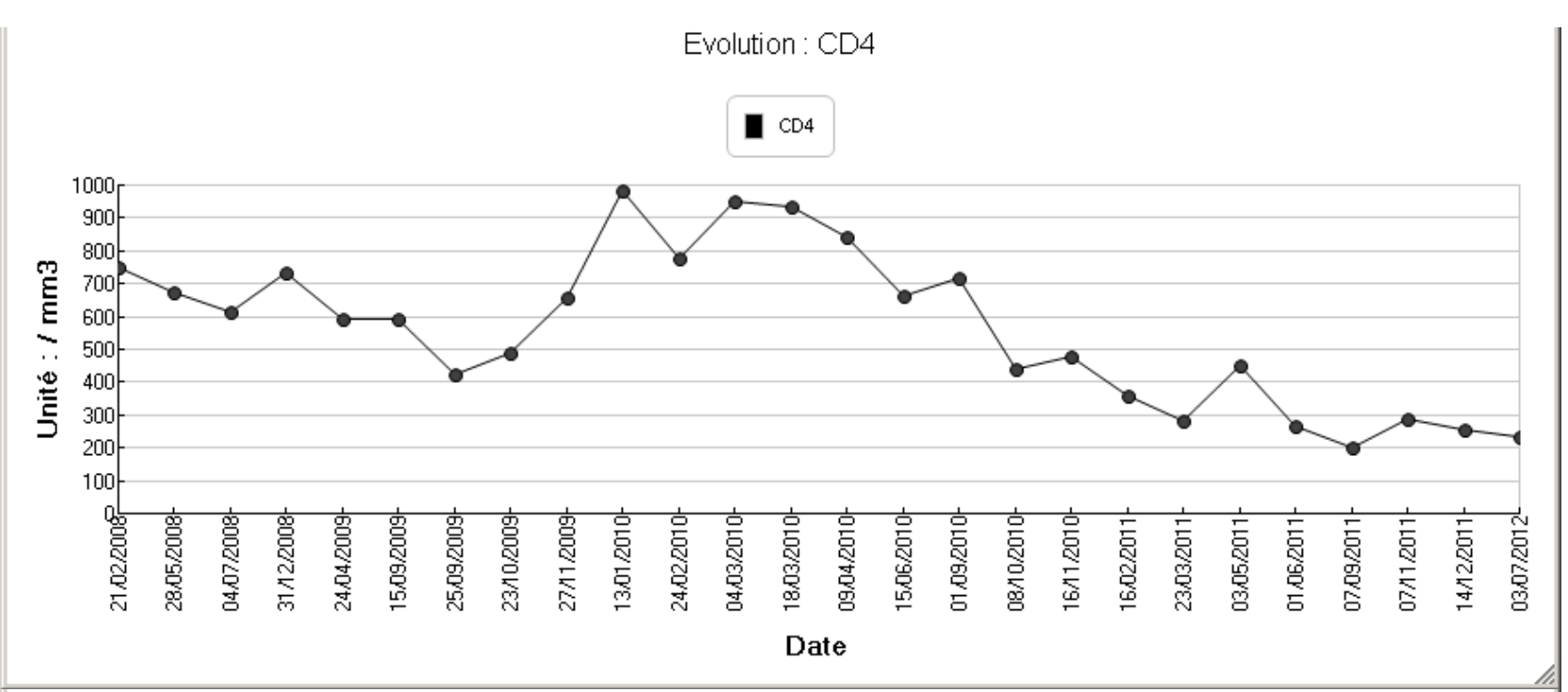

HIV-infected patient with CNS symptoms
CD4 count/HIV viral load
CT/MRI
Pas de lésion
Lesion(s) with mass effect
Lesion(s) without mass effect
Impending herniation
Steroids
open biopsy
decompression
Toxoplasma serology
Prophylaxis for toxo
SPECT
Safe to LP
CSF
Anti toxo trial
Specific Rx
Clinical and radiologic
improvement after 2 wks
Continue Rx
Biopsy
Safe to LP
CSF*
Specific Rx
Mite Crypto
Mite tuberculeuse
Syphilis
Méningite +
Encéphalite
Ponction Lombaire +++

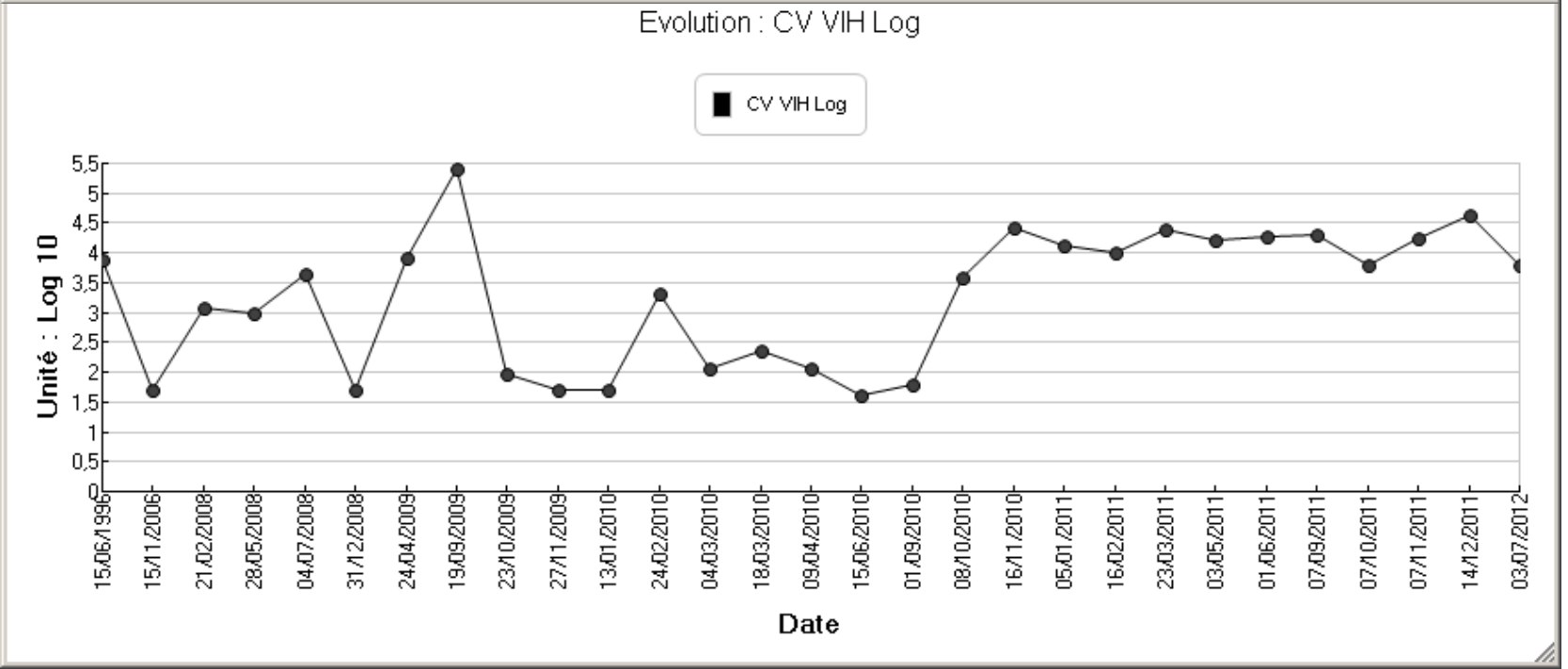


06/11/1989

Modifier | Supprimer | Ajouter un événement

Evénement	Début	Fin	Motif	Type
Aptivus + Fuzeon + Intelence + Isentress + Norvir	09/07/2012			VIH
Kalétra + Truvada	01/06/2011	09/07/2012	Intensification thérapeutique	VIH
Intelence + Invirase + Isentress + Norvir + Truvada	07/04/2010	01/06/2011	Non observance	VIH
Fuzeon + Intelence + Isentress + Norvir + Prezista + Truvada	04/03/2010	07/04/2010	Autres motifs thérapeutiques	VIH
Intelence + Isentress + Norvir + Prezista + Truvada	04/12/2009	04/03/2010	Echec virologique	VIH
Fuzeon + Isentress + Norvir + Prezista + Truvada	05/10/2009	04/12/2009	Simplification thérapeutique	VIH
Truvada + Viramune	31/12/2008	05/10/2009	Echec virologique	VIH
Crixivan + Retrovir + Viread	15/06/2006	31/12/2008	Effets secondaires digestifs	VIH
Agenerase + Videx + Zerit	15/06/1999	15/08/2000	Echec virologique	VIH
Agenerase + Epivir + Zerit	15/06/1998	15/06/1999	Echec virologique	VIH


Evolution : CD4
CD4
Unité : / mm3
1000
900
800
700
600
500
400
300
200
100
0
21/02/2008
28/05/2008
04/07/2008
31/12/2008
24/04/2009
15/09/2009
25/09/2009
23/10/2009
27/11/2009
13/01/2010
24/02/2010
04/03/2010
18/03/2010
09/04/2010
15/06/2010
01/09/2010
08/10/2010
16/11/2010
16/02/2011
23/03/2011
03/05/2011
01/06/2011
07/09/2011
07/11/2011
14/12/2011
03/07/2012
Date


Evolution : CV VIH Log
CV VIH Log
Unité : Log 10
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
15/06/1996
15/11/2006
21/02/2008
28/05/2008
04/07/2008
31/12/2008
24/04/2009
19/09/2009
23/10/2009
27/11/2009
13/01/2010
24/02/2010
04/03/2010
18/03/2010
09/04/2010
15/06/2010
01/09/2010
08/10/2010
16/11/2010
05/01/2011
16/02/2011
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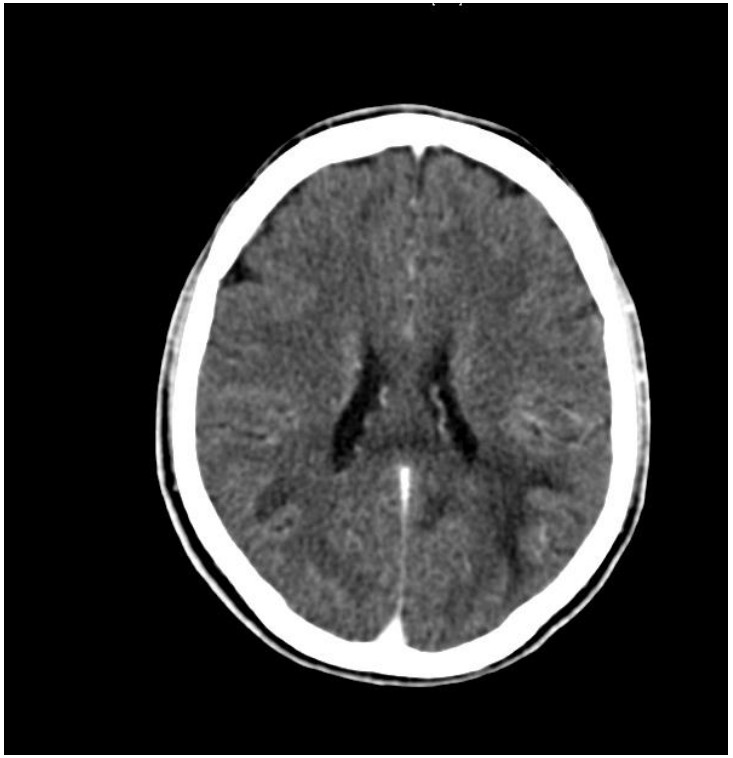
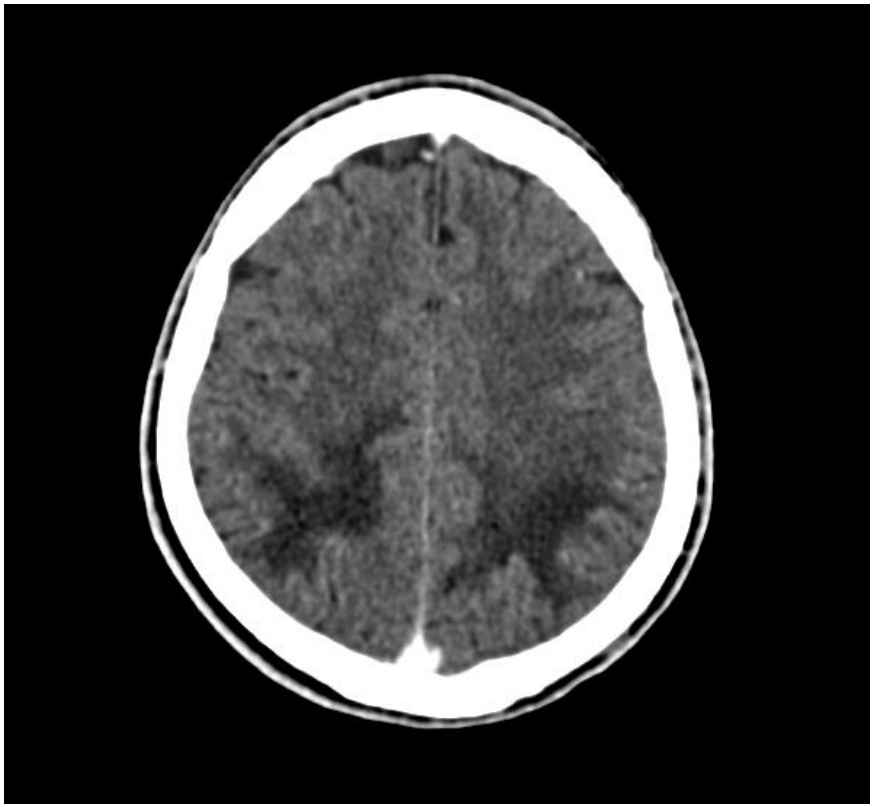
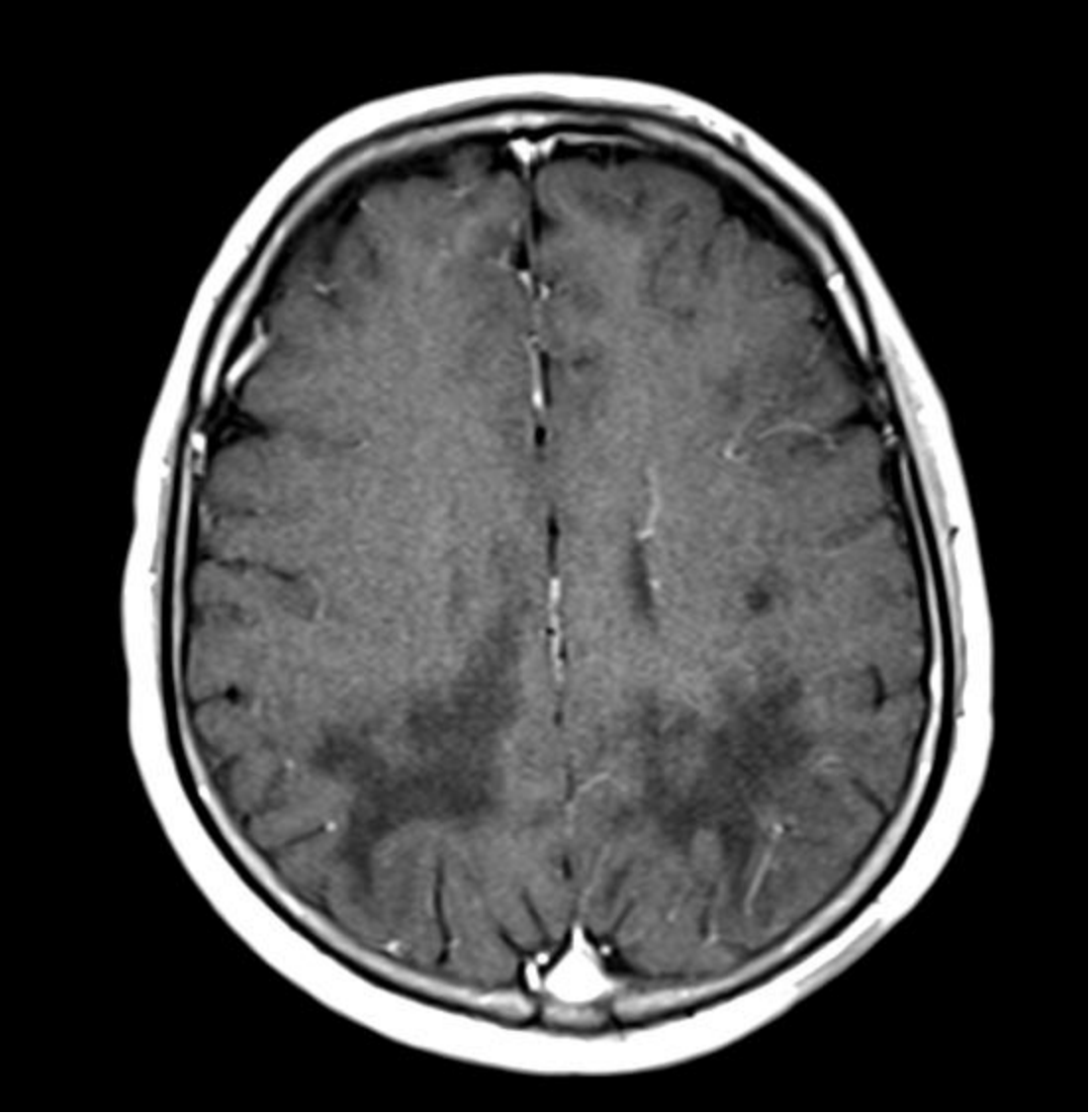
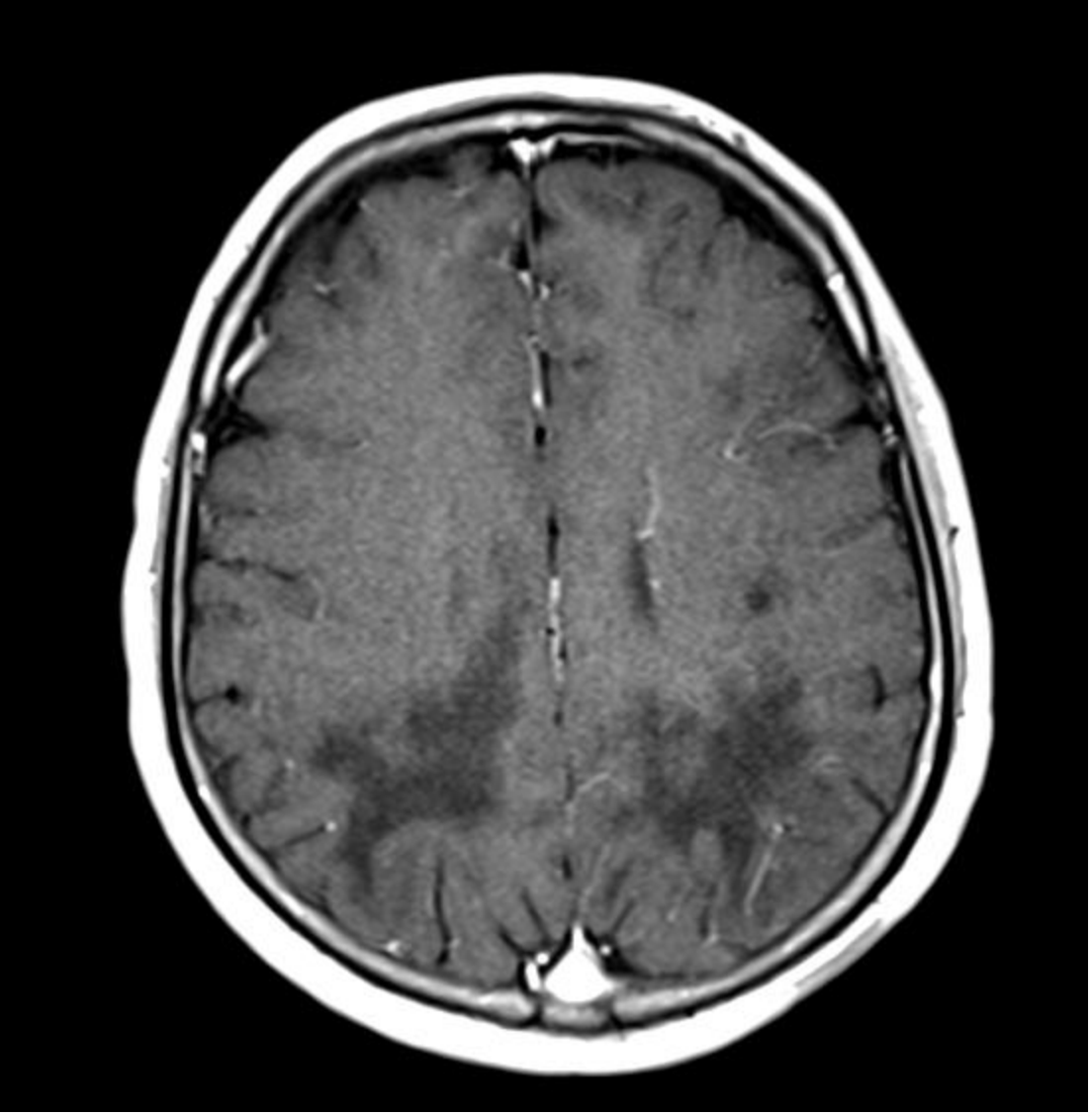
03/07/2012
Date

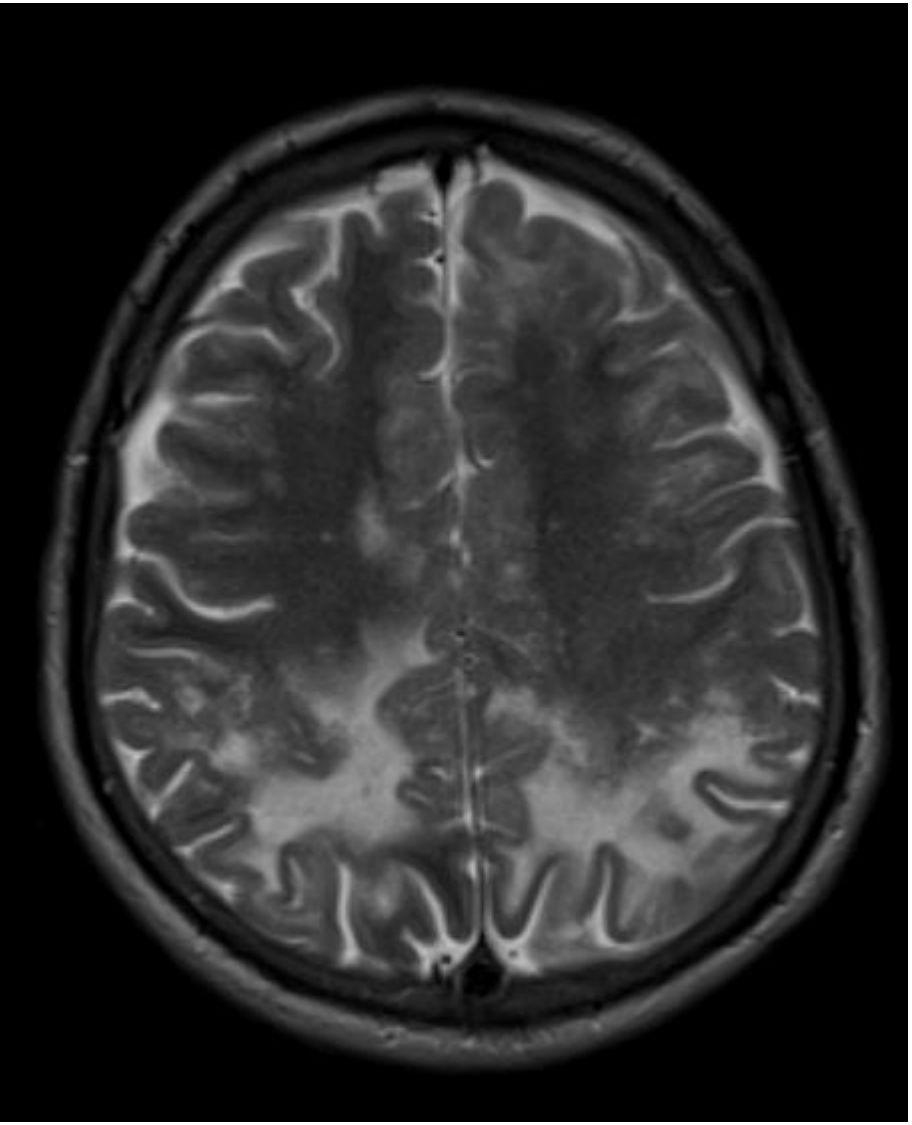








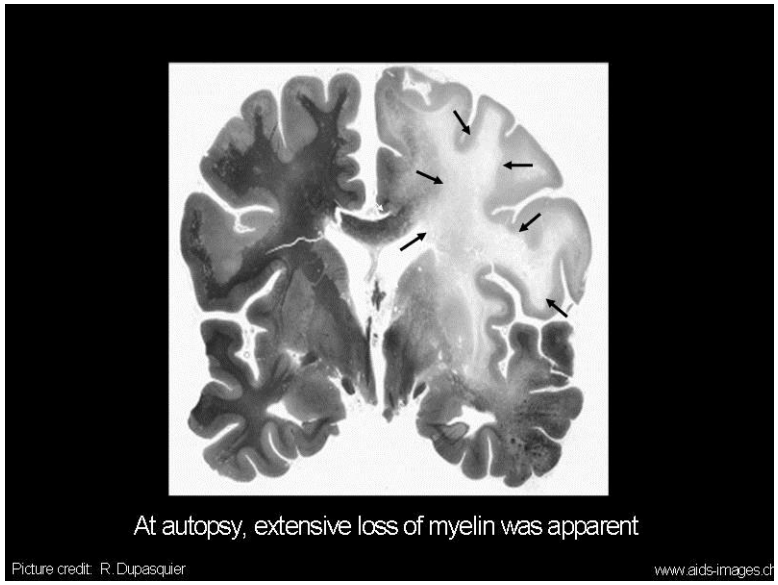
Lésion de la substance blanche pariéto occipitale sous corticale étendue aux fibres en U, à limite très nette suivant le tracé des circonvolutions, sans œdème effets de masse ou prise de contraste en T1, mais en hypoT1

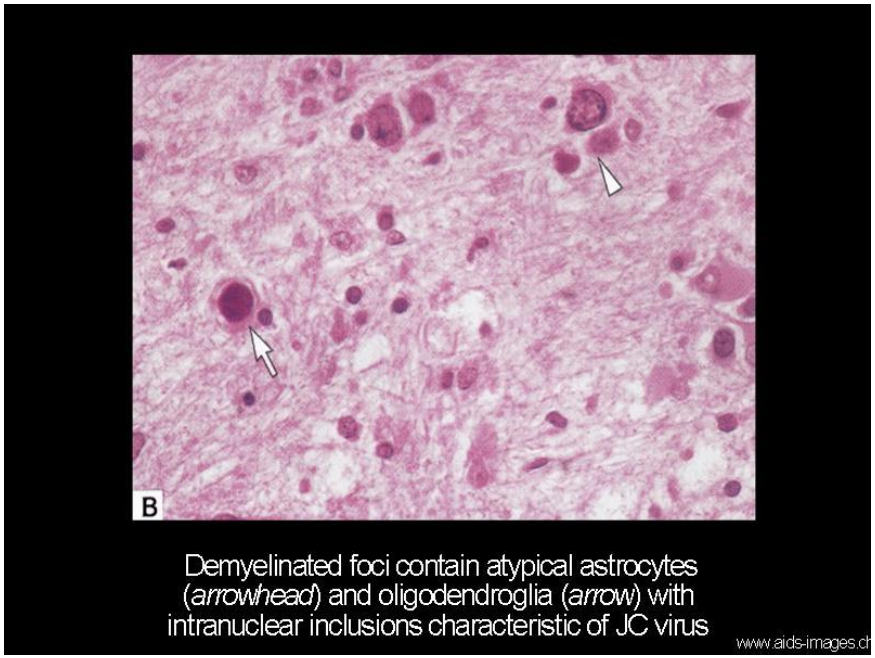


CD4<100, classiquement mais pas tjs
John Cunningham virus (JCV),
polyoma virus,
seroprevalence of 70-90%,
persistance en extra cerebral
Prévalence stable malgré ARV 7%
-car survie augmente
-absence de Lcytotoxiques CD8 spécifique
-protéine Tat VIH augmente la transcription du JC
-altération de la Barrière par le VIH augmente la pénétration des LCB JC+ et du JC libre
Trble moteur fqt

Survie
Valeur prédictive CD8 JC+
CV JC (sang, LCR)

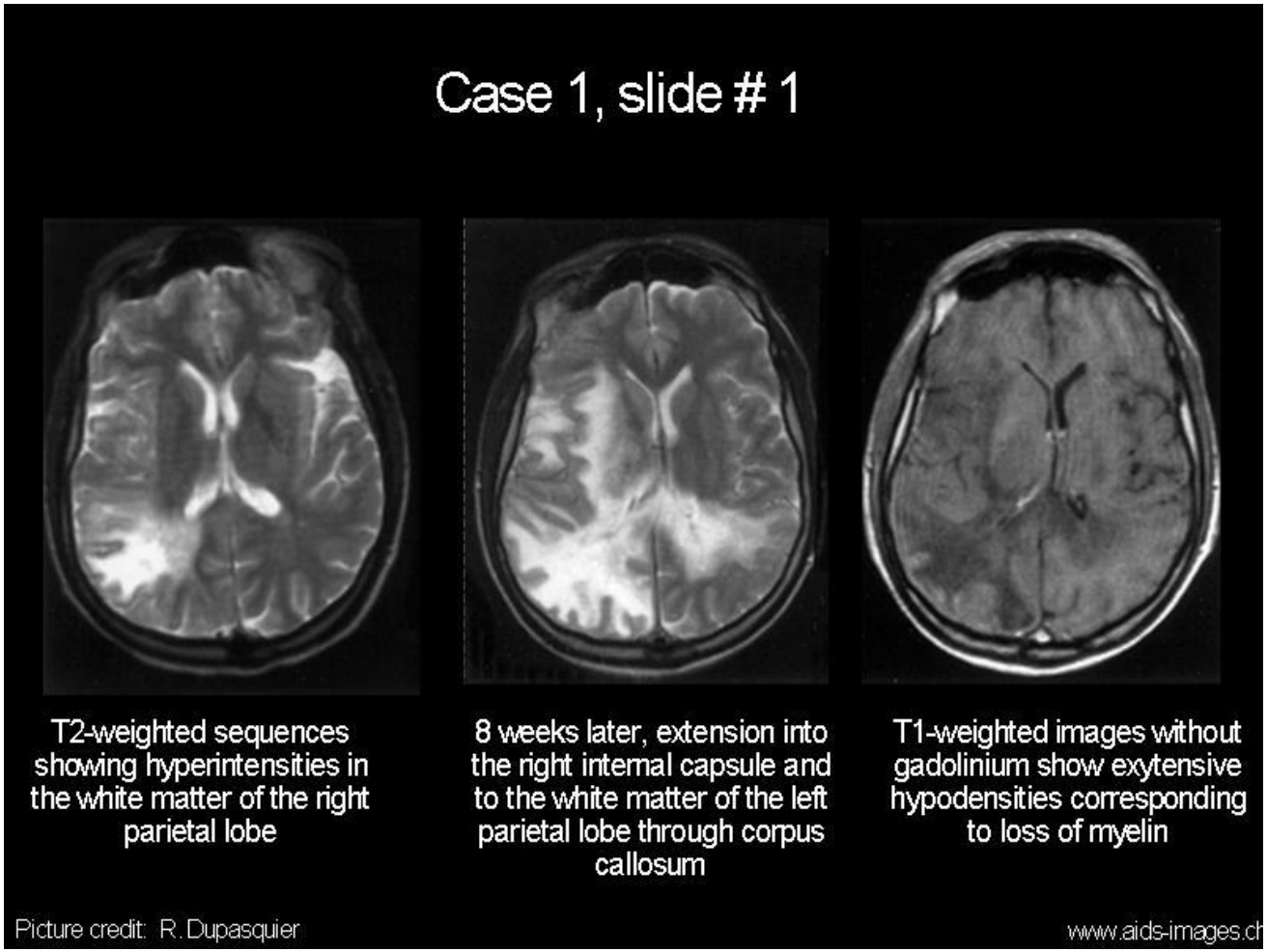
Restauration CD4
Interleukine 7





Sa cellule cible est l'oligodendrocyte, produisant la myéline, ce qui entraîne des lésions de démyélinisation

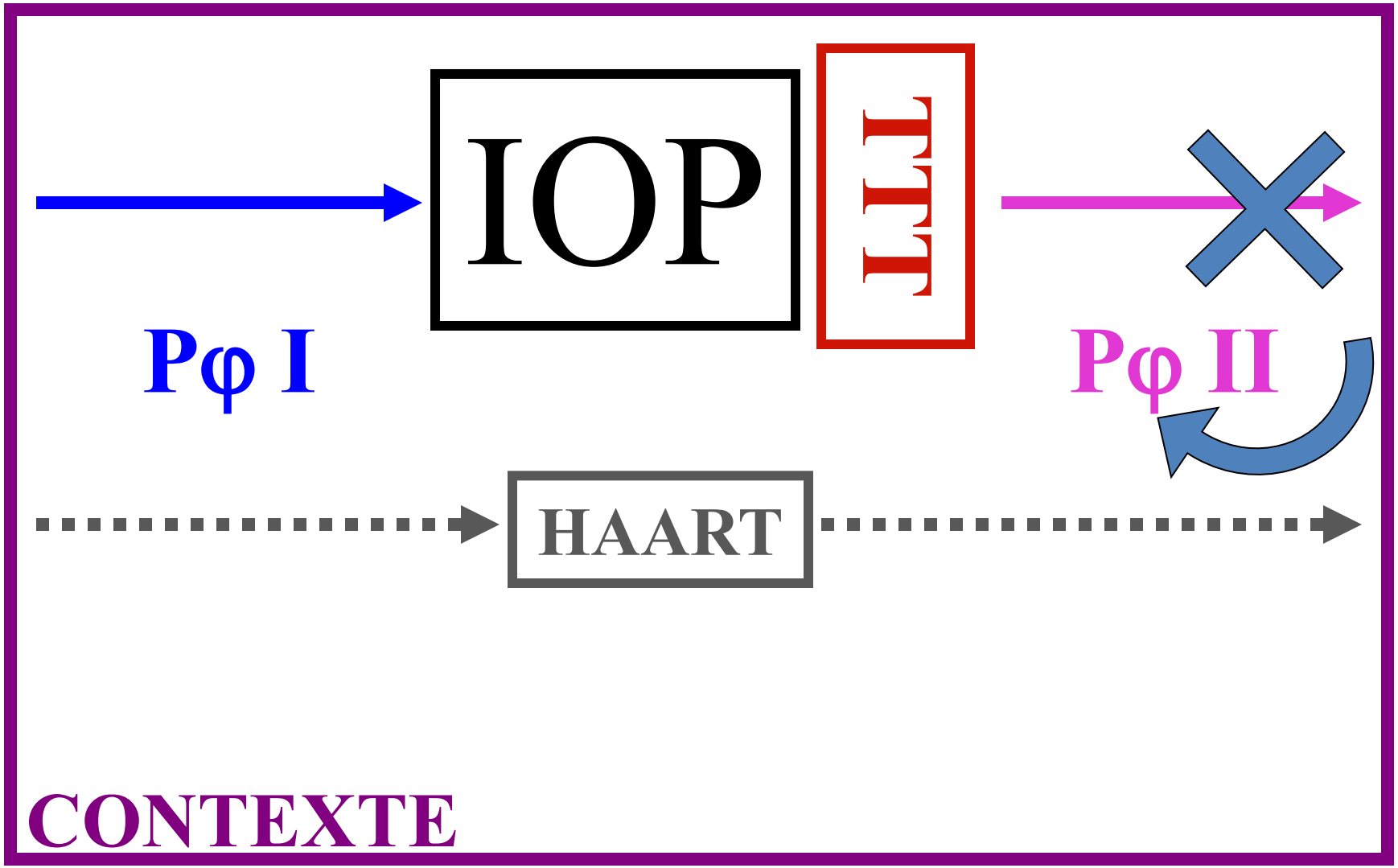
Pronostic, traitement



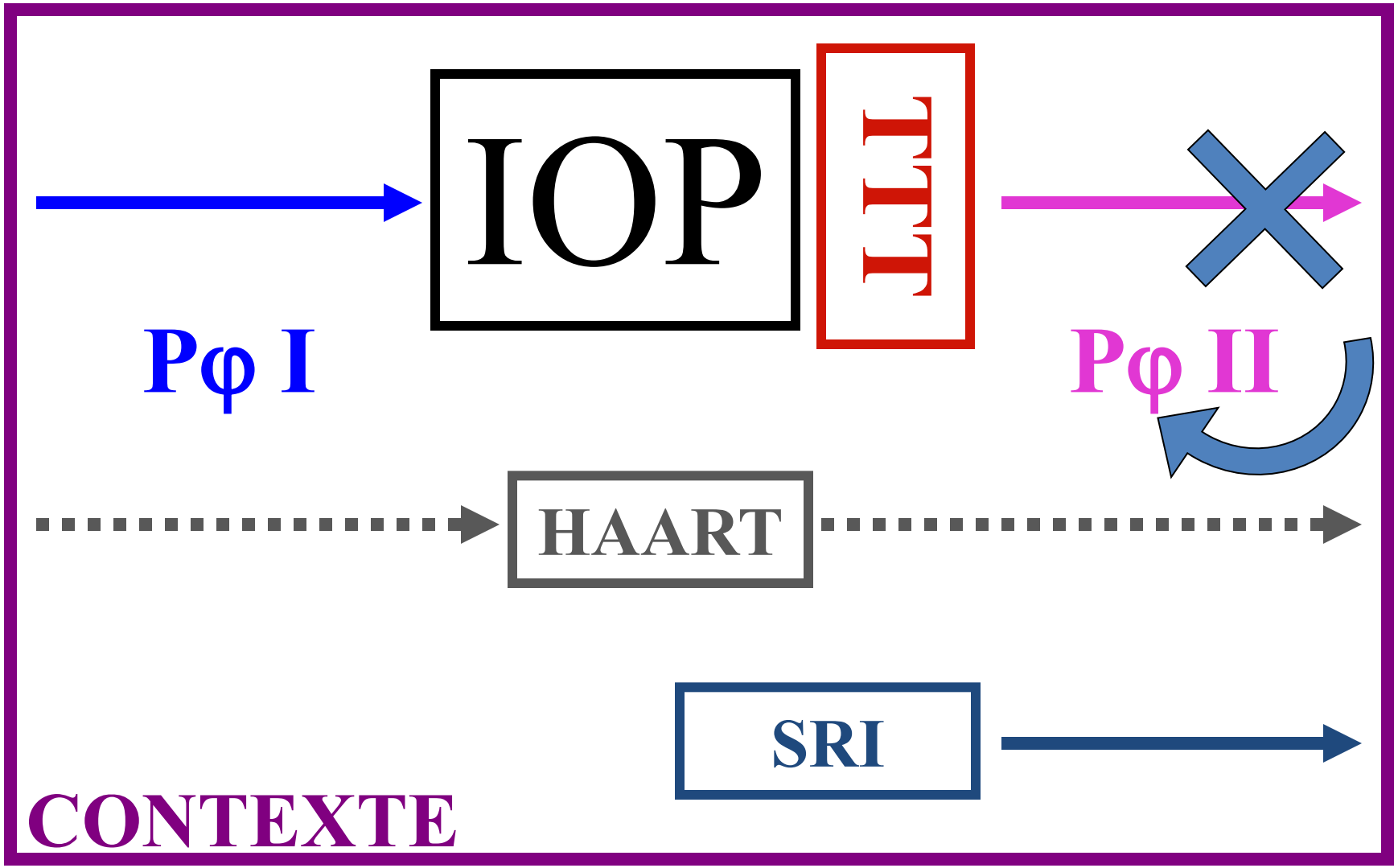
Mefloquine
Mirtazapine
Il7

ARV!

Les acteurs en présence



Les acteurs en présence

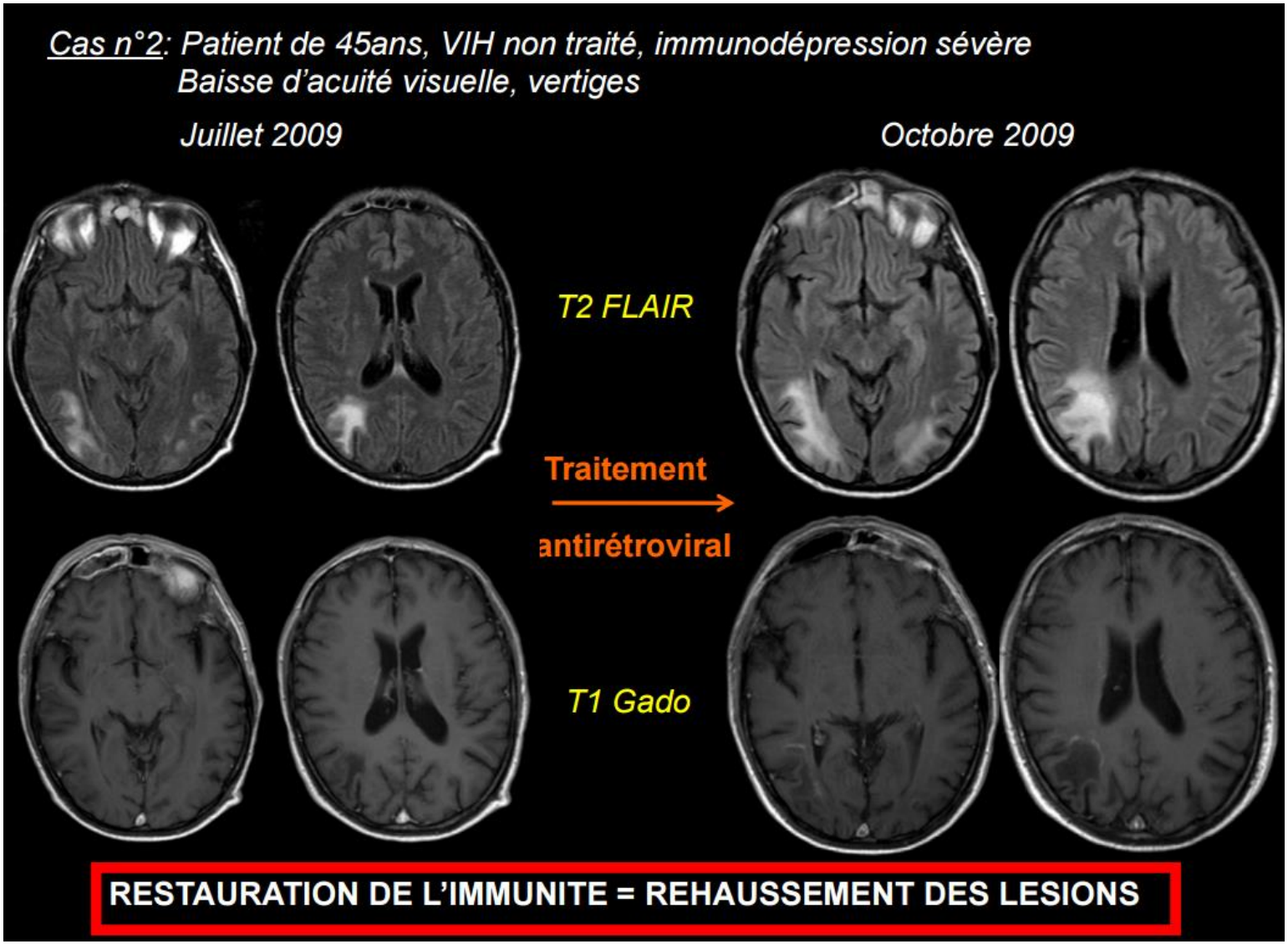


IRS, 30% des patients, CNS 1%

***Panel 1:* Factors to be evaluated in considering whether the presentation or deterioration of an opportunistic mycobacterial infection is due to immune reconstitution disease**

Temporal association between starting HAART regimen and subsequent development of clinical phenomena (the majority within 3 months).
Unusual clinical manifestations.
Unexpected clinical course.
Exclusion of alternative explanations—eg, drug resistance, non-compliance with treatment for the opportunistic infection.
Evidence of preceding immune restoration—eg, a rise in blood CD4 lymphocyte count; restoration of cutaneous hypersensitivity to mycobacterial antigens (PPD or MAC antigen); increased in-vitro T-cell proliferative responses to PPD or MAC antigen.
Histopathological or cytological appearances of unexpectedly florid cell-mediated immune response within tissue samples.
Preceding fall in plasma HIV-1 load, providing evidence of a response to HAART.

Lancet Infect Dis 2005; 5: 361–73


Cas n°2: Patient de 45ans, VIH non traité, immunodépression sévère
Baisse d'acuité visuelle, vertiges
Juillet 2009
Octobre 2009
T2 FLAIR
Traitement
antirétroviral
T1 Gado
RESTAURATION DE L'IMMUNITE = REHAUSSEMENT DES LESIONS

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Medical Imagery

Progressive multifocal leukoencephalopathy with immune reconstitution inflammatory syndrome misdiagnosed as cerebral toxoplasmosis in an HIV-infected woman☆

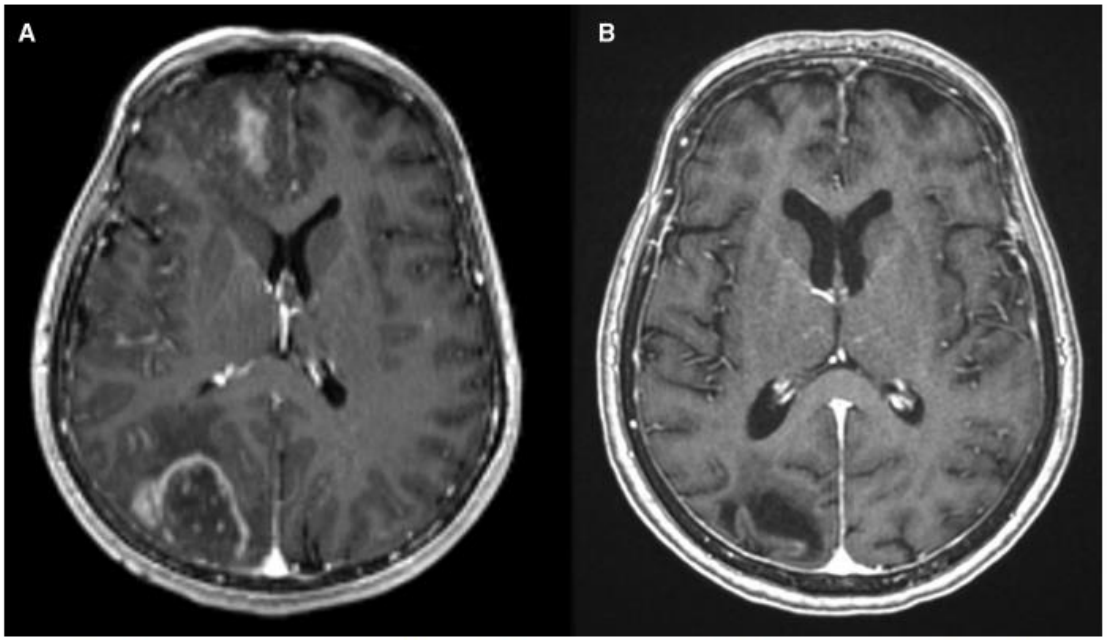
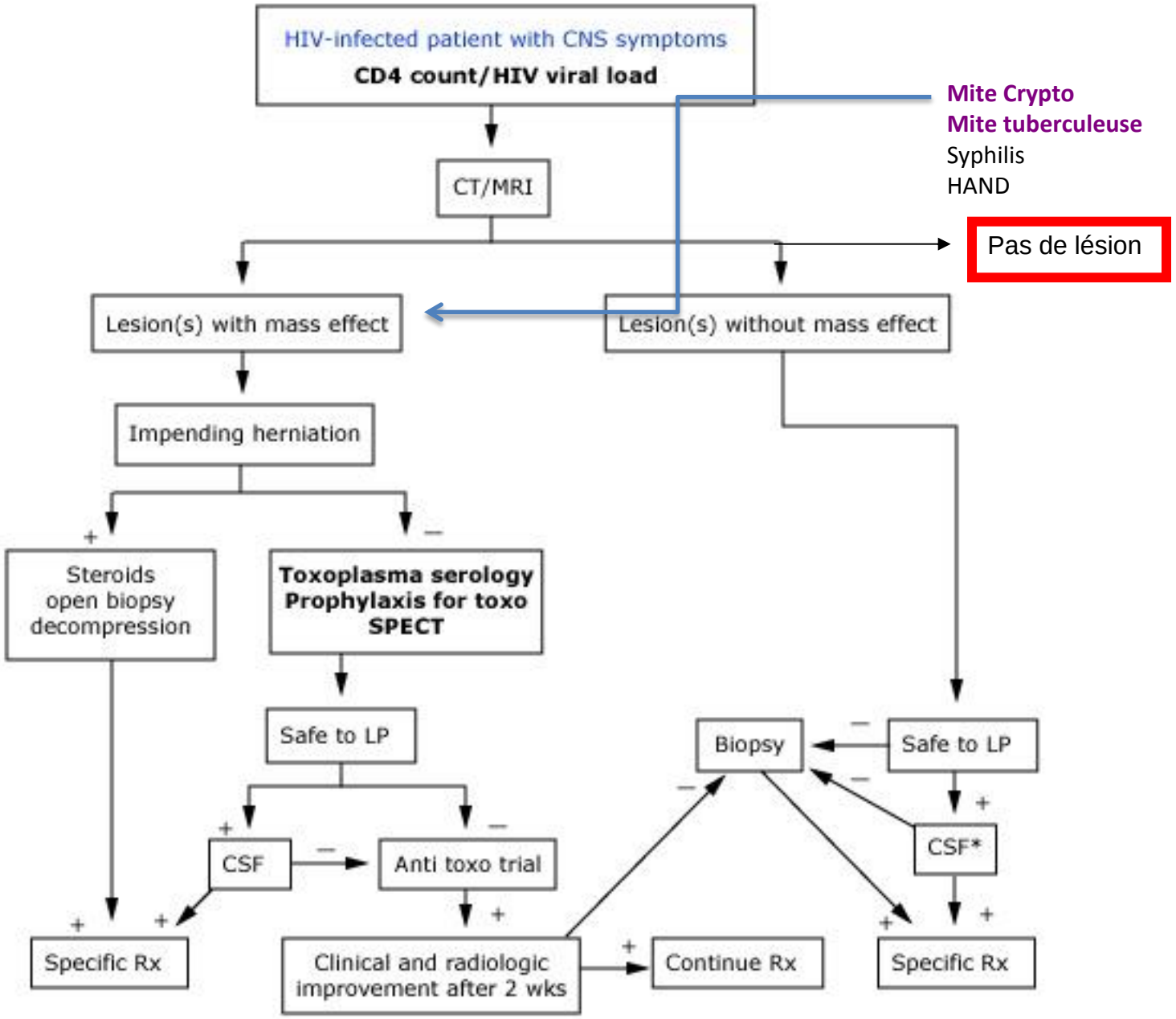
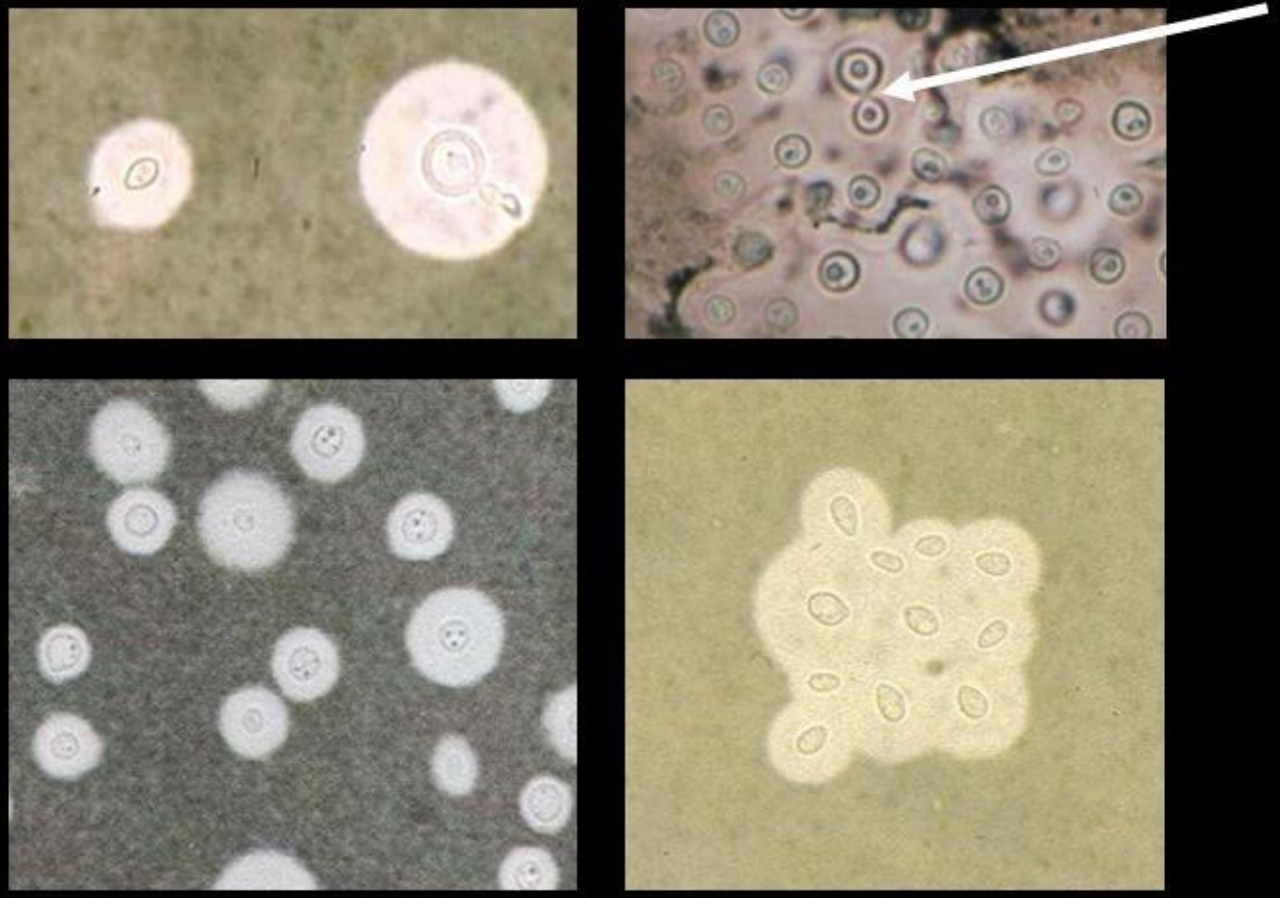


Figure 1. Cerebral magnetic resonance imaging: (A) multifocal ring-enhancing lesions; (B) image enhancement fading within 3 months of oral steroid therapy.

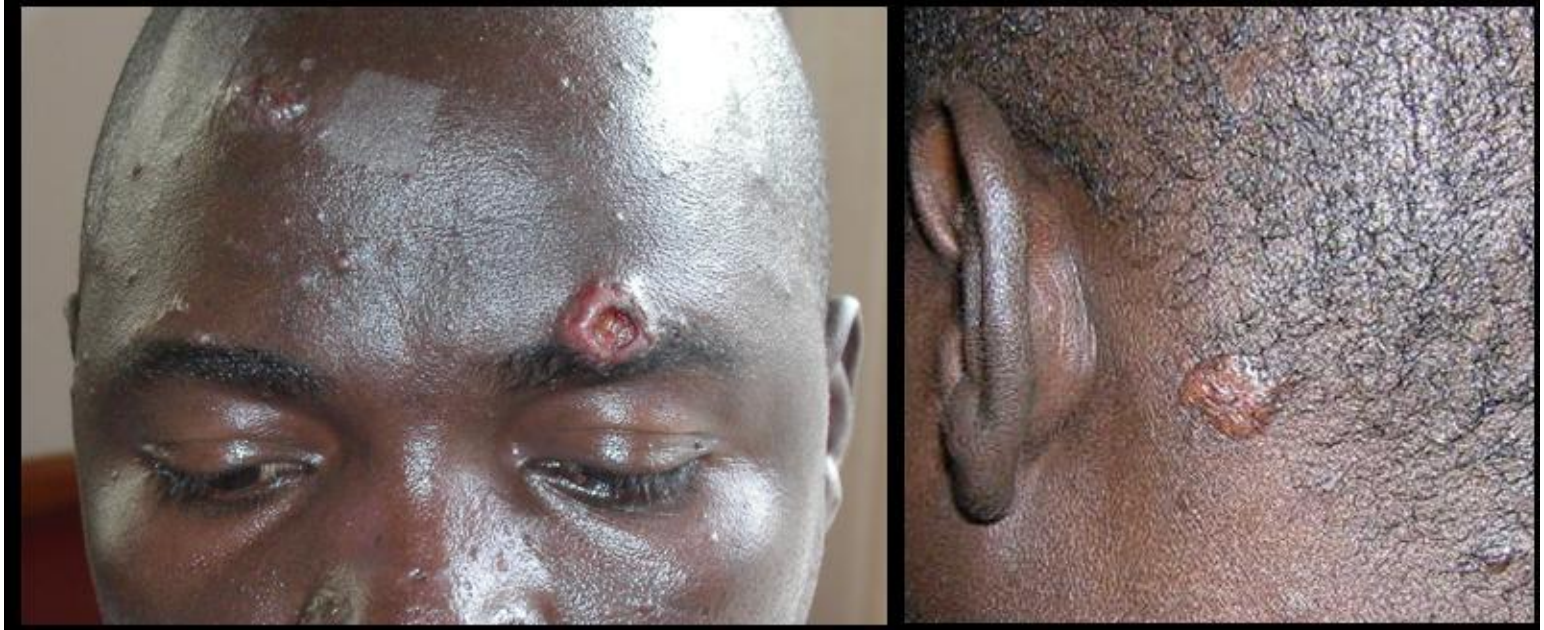
A 53-year-old woman presenting with oral candidiasis was diagnosed with HIV-1 infection. The CD4 cell count nadir was 71 cells/mm^3 (5%) and viral load was 445 000 copies/ml. Treatment was initiated with emtricitabine/tenofovir and boosted darunavir. One month later, she presented seizures with psychomotor slowdown, left upper-limb paresis, cerebellar syndrome, left homonymous hemianopsia, and cortical blindness. Her HIV viral load had decreased dramatically (968 copies/ml); the CD4 count was 57 cells/mm^3 (9%). Cerebral magnetic resonance imaging identified multifocal ring-enhancing lesions (Figure 1A). Although other diagnoses could have been considered, cerebral toxoplasmosis was suspected on the grounds of frequency, and sulfadiazine–pyrimethamine was initiated. Two weeks later, the seizures recurred and progressive multifocal leukoencephalopathy (PML) was finally diagnosed from the presence of JC virus DNA in cerebrospinal fluid, serum, and brain biopsy. Cerebral toxoplasmosis was ruled out by the small mass effect of cerebral lesions and the absence of Toxoplasma DNA in the brain. Despite a moderate

☆ Cécile-Audrey Durel, Thomas Perpoint, and Florent Valour contributed equally to the manuscript. All authors were involved in patient care and approved the final version of the manuscript.


HIV-infected patient with CNS symptoms
CD4 count/HIV viral load
CT/MRI
Lesion(s) with mass effect
Lesion(s) without mass effect
Impending herniation
Steroids
open biopsy
decompression
Toxoplasma serology
Prophylaxis for toxo
SPECT
Safe to LP
CSF
Anti toxo trial
Specific Rx
Clinical and radiologic
improvement after 2 wks
Continue Rx
Biopsy
Safe to LP
CSF*
Specific Rx
Mite Crypto
Mite tuberculeuse
Syphilis
HAND
Pas de lésion



In the cerebrospinal fluid, after staining with « india ink » (in reality, now a synthetic stain), *C. neoformans'* large capsule is clearly visible. Budding forms are typical (arrow)



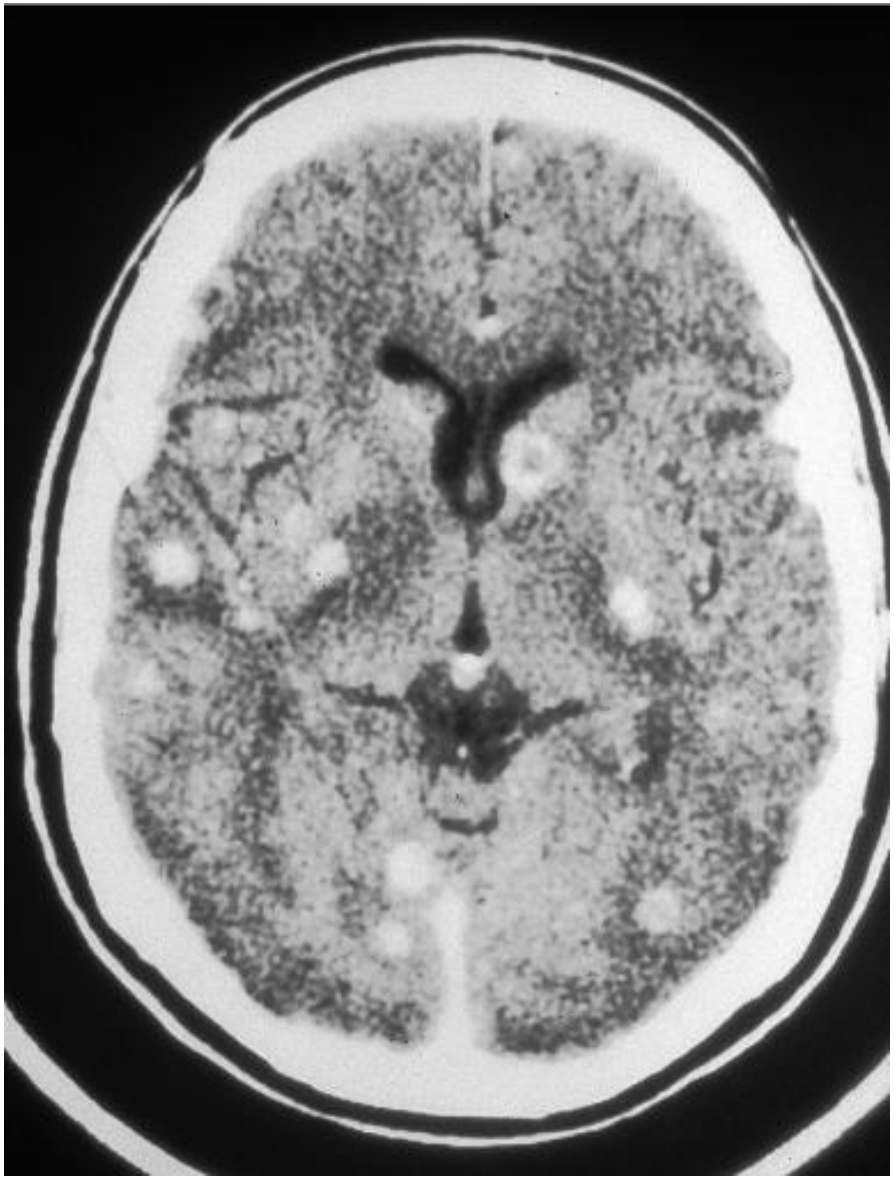
Cutaneous cryptococcosis in a patient from Zimbabwe; cryptococci were isolated from cerebro-spinal fluid

Photograph by R. Lüthy, Harare

www.aids-images.ch

IRIS + cryptococcome

10 à 30 % des MEite Crypto
Récurrence de la méningite ou
Apparition de cryptococcomes



Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis

David R. Boulware, M.D., M.P.H., David B. Meya, M.Med., Conrad Muzoora, M.Med., Melissa A. Rolfes, Ph.D., Katherine Huppler Hullsiek, Ph.D., Abdu Musubire, M.Med., Kabanda Taseera, M.Med., Henry W. Nabeta, M.B., Ch.B., Charlotte Schutz, M.B., Ch.B., M.P.H., Darlisha A. Williams, M.P.H., Radha Rajasingham, M.D., Joshua Rhein, M.D., Friedrich Thienemann, M.D., Ph.D., Melanie W. Lo, M.D., Kirsten Nielsen, Ph.D., Tracy L. Bergemann, Ph.D., Andrew Kambugu, M.Med., Yukari C. Manabe, M.D., Edward N. Janoff, M.D., Paul R. Bohjanen, M.D., Ph.D., Graeme Meintjes, M.B., Ch.B., Ph.D., for the COAT Trial Team*

ABSTRACT

BACKGROUND

Cryptococcal meningitis accounts for 20 to 25% of acquired immunodeficiency syndrome–related deaths in Africa. Antiretroviral therapy (ART) is essential for survival; however, the question of when ART should be initiated after diagnosis of cryptococcal meningitis remains unanswered.

METHODS

We assessed survival at 26 weeks among 177 human immunodeficiency virus–infected adults in Uganda and South Africa who had cryptococcal meningitis and had not previously received ART. We randomly assigned study participants to undergo either earlier ART initiation (1 to 2 weeks after diagnosis) or deferred ART initiation (5 weeks after diagnosis). Participants received amphotericin B (0.7 to 1.0 mg per kilogram of body weight per day) and fluconazole (800 mg per day) for 14 days, followed by consolidation therapy with fluconazole.

RESULTS

The 26-week mortality with earlier ART initiation was significantly higher than with deferred ART initiation (45% [40 of 88 patients] vs. 30% [27 of 89 patients]; hazard ratio for death, 1.73; 95% confidence interval [CI], 1.06 to 2.82; P=0.03). The excess deaths associated with earlier ART initiation occurred 2 to 5 weeks after diagnosis (P=0.007 for the comparison between groups); mortality was similar in the two groups thereafter. Among patients with few white cells in their cerebrospinal fluid (<5 per cubic millimeter) at randomization, mortality was particularly elevated with earlier ART as compared with deferred ART (hazard ratio, 3.87; 95% CI, 1.41 to 10.58; P=0.008). The incidence of recognized cryptococcal immune reconstitution inflammatory syndrome did not differ significantly between the earlier-ART group and the deferred-ART group (20% and 13%, respectively; P=0.32). All other clinical, immunologic, virologic, and microbiologic outcomes, as well as adverse events, were similar between the groups.

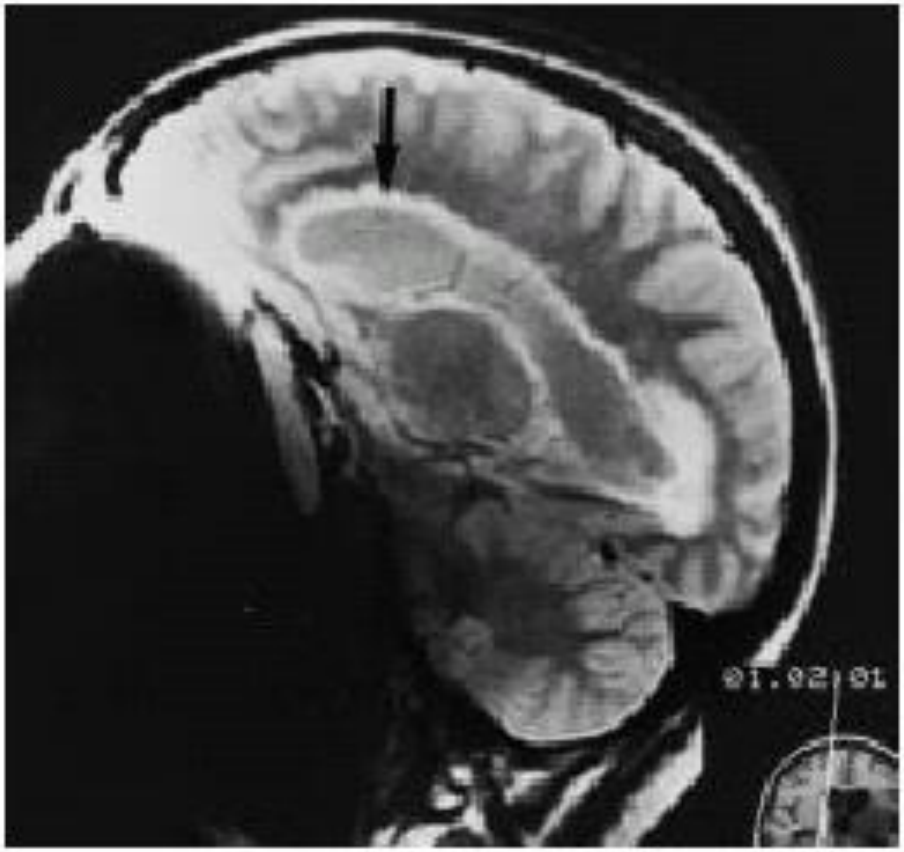
CONCLUSIONS

Deferring ART for 5 weeks after the diagnosis of cryptococcal meningitis was associated with significantly improved survival, as compared with initiating ART at 1 to 2 weeks, especially among patients with a paucity of white cells in cerebrospinal fluid. (Funded by the National Institute of Allergy and Infectious Diseases and others; COAT ClinicalTrials.gov number, NCT01075152.)

From the University of Minnesota, Minneapolis (D.R.B., D.B.M., M.A.R., K.H.H., D.A.W., R.R., J.R., M.W.L., K.N., T.L.B., P.R.B.); the Infectious Disease Institute (D.B.M., A.M., H.W.N., D.A.W., R.R., J.R., M.W.L., A.K., Y.C.M.) and School of Medicine, College of Health Sciences (D.B.M.), Makerere University, Kampala, and Mbarara University of Science and Technology, Mbarara (C.M., K.T.) — both in Uganda; the University of Cape Town, Cape Town, South Africa (C.S., F.T., G.M.); Johns Hopkins School of Medicine, Baltimore (Y.C.M.); the Mucosal and Vaccine Research Program Colorado (MAVRC), University of Colorado Denver, Aurora, and Denver Veterans Affairs Medical Center, Denver (E.N.J.); and Imperial College London, London (G.M.). Address reprint requests to Dr. Boulware at MTRF 3-222, 2001 6th St. SE, Minneapolis, MN 55455, or at boulw001@umn.edu.

*A list of members of the Cryptococcal Optimal ART Timing (COAT) Trial Team is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2014;370:2487-98.
DOI: 10.1056/NEJMoa1312884


01.02.01

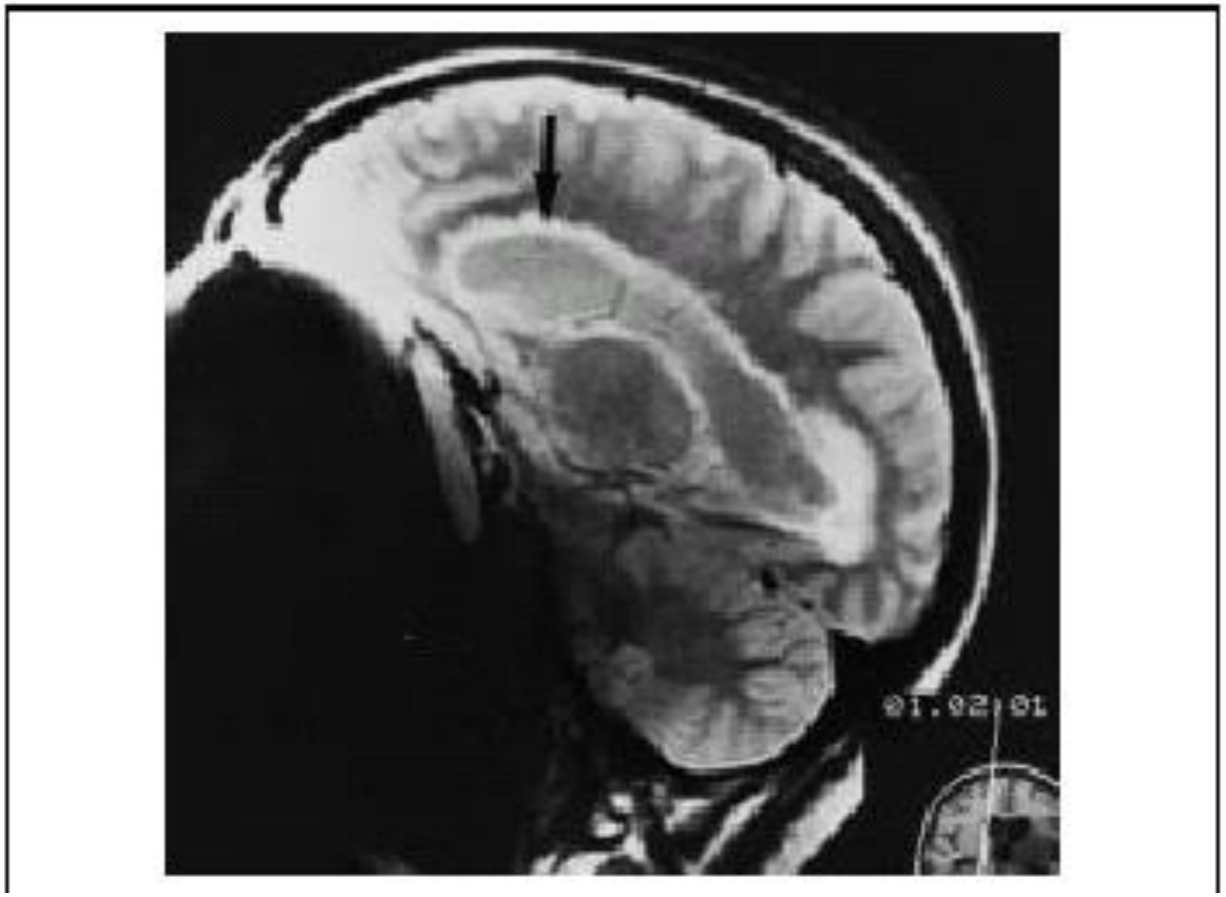
CMV **CD4<50, manifestation très protéiforme, urgence ttt**

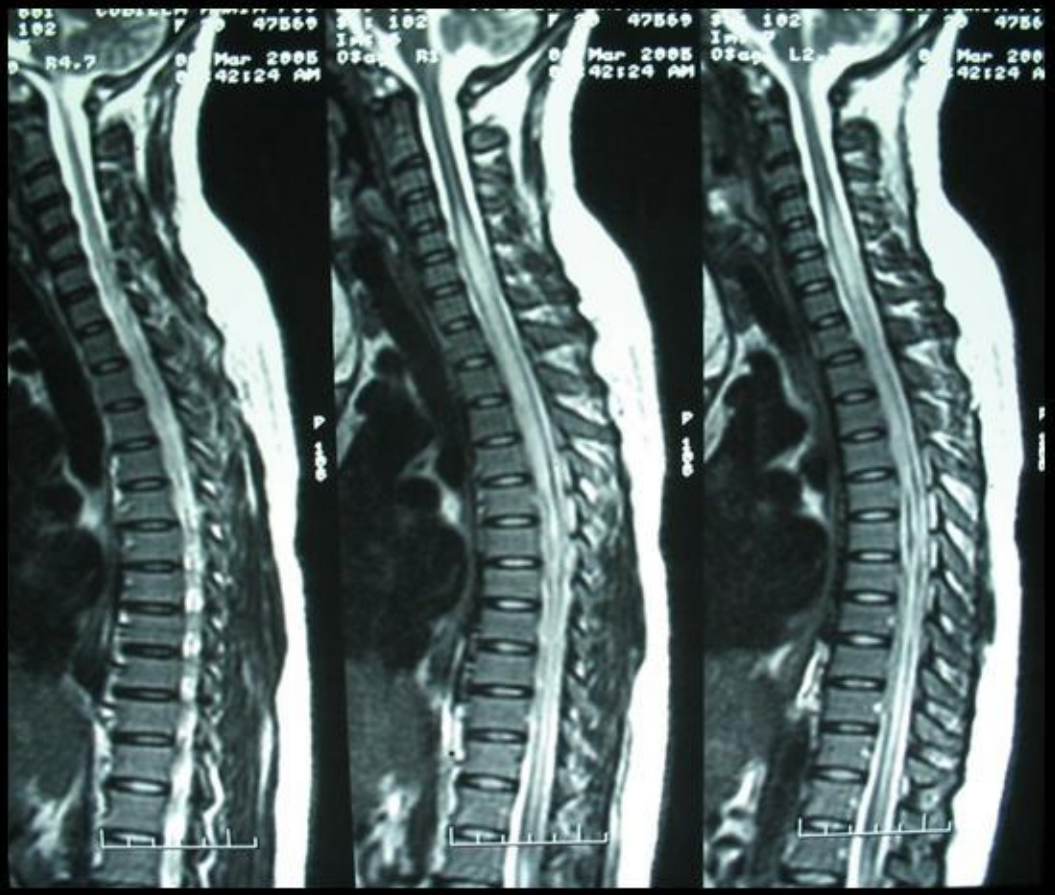
-Ventriculo encéphalite aigue (nécrosante, PNN, hypoG)

-Encéphalite diffuse micronodulaire, forme plus frustre type encéphalite VIH, souvent négligée

-Possibilité d'encéphalites focales nécrosantes (type toxo) ou non (rhombencéphalite)

-Myélites et myéloradiculites nécrosantes ou non



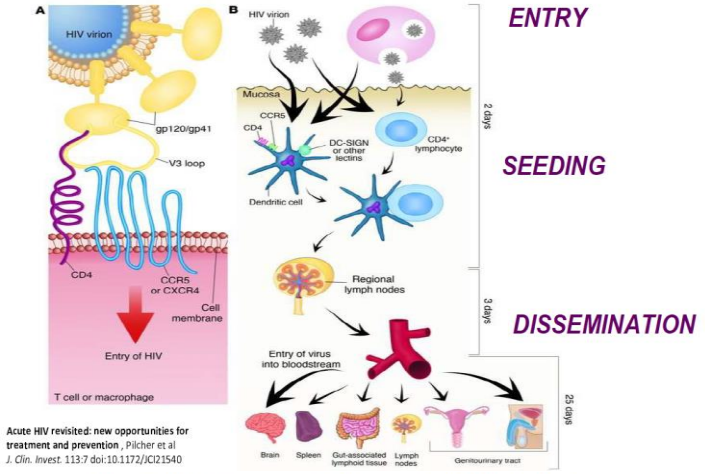


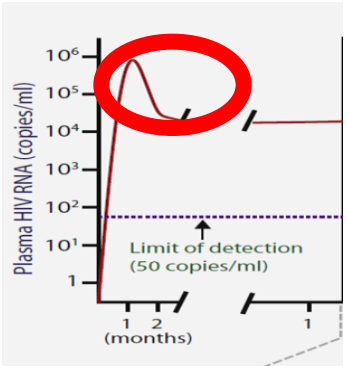
Extensive CMV myelitis, < 50 CD4 cells/mm3

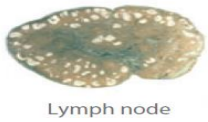
Source: D. Cecchini, A Gomez and J. Ambrosioni, Muñiz Hospital, Buenos Aires.

Rôle du VIH = virus Neurotrope

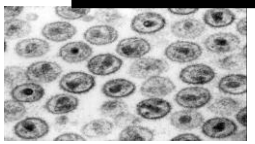
- Connu depuis le début de l'épidémie
- Atteinte réservoir dès le début de l'infection

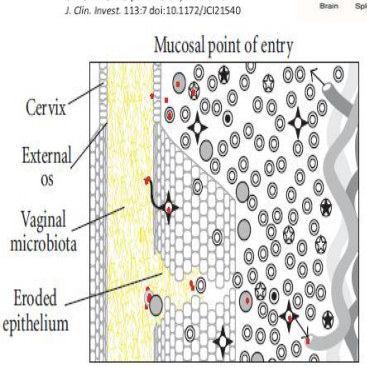


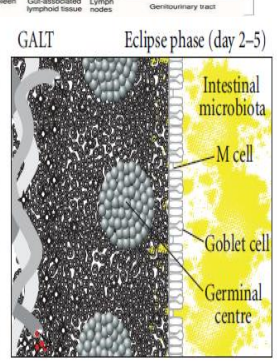


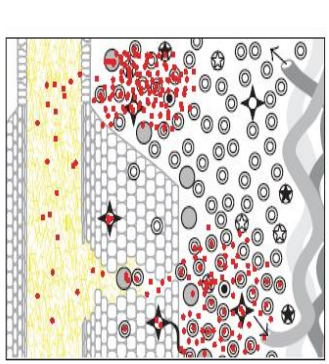


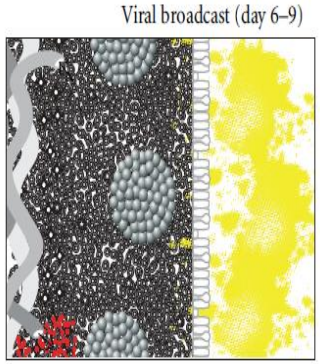
SNC ++++++++++
Microglie et macrophage exprime les CD4

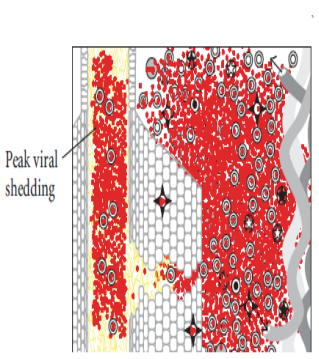


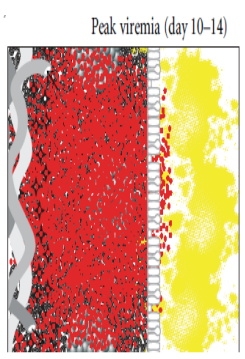












VIH virus Neurotrope

- **Atteinte directe, précoce, tardive**: pb de la compartimentalisation
- **Atteinte indirecte, précoce, tardive**: pb de l'activation immune générale ou cérébrale
- **Atteinte vasculaire associée**

Fatal brain necrosis in primary HIV infection

Wouter Meersseman, Kristel Van Laethem, Katrien Lagrou, Guido Wilms, Raf Sciot, Marc Van Ranst, Annemie Vandamme, Eric Van Wijngaerden

Lancet 2005; 366: 866

Departments of Internal Medicine (W Meersseman MD, E Van Wijngaerden MD), Bacteriology (K Lagrou MD), Pathology (R Sciot MD), Radiology (G Wilms MD), Clinical and Epidemiological Virology (A Vandamme MD), and AIDS Reference Laboratory (K Van Laethem MD, M Van Ranst MD), Rega Institute, Katholieke Universiteit and University Hospitals Leuven, B-3000 Leuven, Belgium

Correspondence to: Eric Van Wijngaerden eric.vanwijngaerden@uz.kuleuven.ac.be

In November, 2004, a 31-year-old man was admitted to our hospital with a prominent morbilliform rash, pharyngitis, and a fever (40°C). He had been well until 2 weeks earlier, when he developed a fever, rash, and diarrhoea. HIV serology from 4 days earlier was negative. Neurological examination on admission was normal. However, 3 days later, he became lethargic and had a tonic-clonic seizure, necessitating intubation and mechanical ventilation. There was no evidence of hypoxia or hypotension. HIV screening tests done on admission were positive, indicating seroconversion. HIV western blot was indeterminate; p24 antigen was more than 200 pg/mL, plasma HIV-1 RNA was greater than 500 000 copies per mL, and peripheral blood lymphocytes were $4{\cdot}6\times10^{9}$/L, with 621 CD4-positive cells per μL, and 2759 CD8-positive cells per μL. CT of the brain without contrast was normal, and lumbar puncture showed 217 cells per mL (96% lymphocytes). Culture of blood and cerebrospinal fluid, serology, and PCR did not demonstrate active infection with herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, JC virus, *Borrelia burgdorferi*, *Treponema pallidum*, mycobacteria, other bacterial pathogens, fungi, or toxoplasma. Cerebrospinal fluid HIV-1 RNA was greater than 500 000 copies per mL. MRI of the brain showed massive diffuse cortical and laminar necrosis (figure). 6 days after admission, the western blot was positive for HIV-1, and p24 antigen had disappeared.

Despite treatment with zidovudine, lopinavir, efavirenz, and dexamethasone, the patient died 11 days

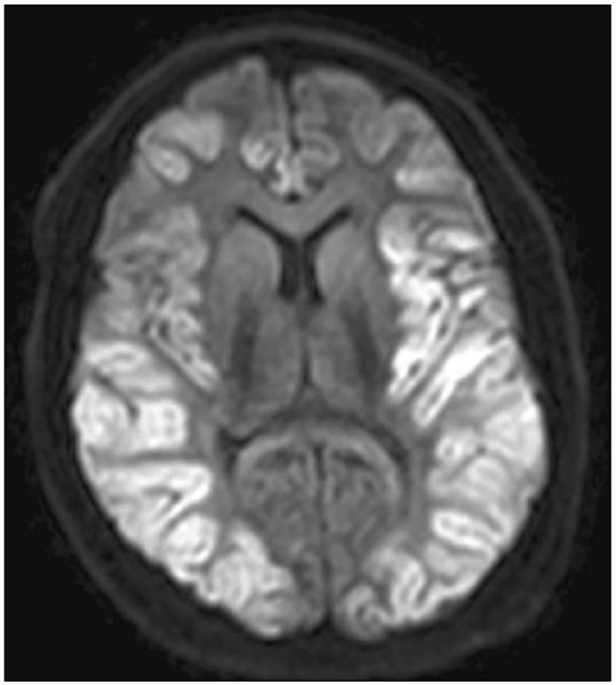


Figure: MRI of the brain (diffusion-weighted image)
The cortex of the brain is diffusely hyperintense, a reflection of the severe disturbance of the diffusion of the protons in the cells, due to cytotoxic oedema.

stimulates cytotoxic T-lymphocytes (CTL) responses in recently infected people. The CTL response initially follows the rise of HIV in the blood, and when that response reaches a peak the virus level falls.[4] In our patient, brain necrosis coincided with the development of CD8-positive lymphocytosis and the disappearance of

Balance Immunitaire
CD8+/CD4+
Macrophages

Usuellement, 10 à 15% des PI ont des manifestations neurologiques
Spontanément régressives: méningite, encéphalopathie, myélopathie

Case 4-1

A 56-year-old man with known HIV infection of 2 years' duration was brought to the hospital by his brother, who reported that the patient was not acting like himself and was quieter than usual. The patient had been lost to follow-up after a prolonged hospitalization in which he was found to have HIV/AIDS (CD4+ T-cell count of 6). His brother stated that they had recently moved to a new apartment and that the patient was unable to determine how to unpack the boxes or put away his belongings. He had little spontaneous speech, inattention, apathy, disorientation to time, and 0/3 recall at 3 minutes. He had mild retropulsion, decreased arm swing, a broad-based gait, and decreased sensation to temperature and vibration in a length-dependent, stocking-glove pattern, with positive sway on Romberg testing.

MRI of the brain showed a symmetric leukoencephalopathy and generalized cerebral atrophy (**Figure 4-1**). Lumbar puncture showed a white blood cell (WBC) count of 2/μL and normal protein and glucose concentration; infectious studies for cryptococcal antigen, JC virus, Epstein-Barr virus, and cytomegalovirus were negative by PCR. Serum antibody testing was negative for hepatitis B and C viruses; vitamin B_{12} level was 650 pg/mL, and rapid plasma reagin was nonreactive. The CD4+ T-cell count was 0 cells/μL, and the HIV viral load was 286,270 RNA copies/μL. HIV genotyping indicated possible resistance to saquinavir and ritonavir, likely consistent with poor medication adherence.

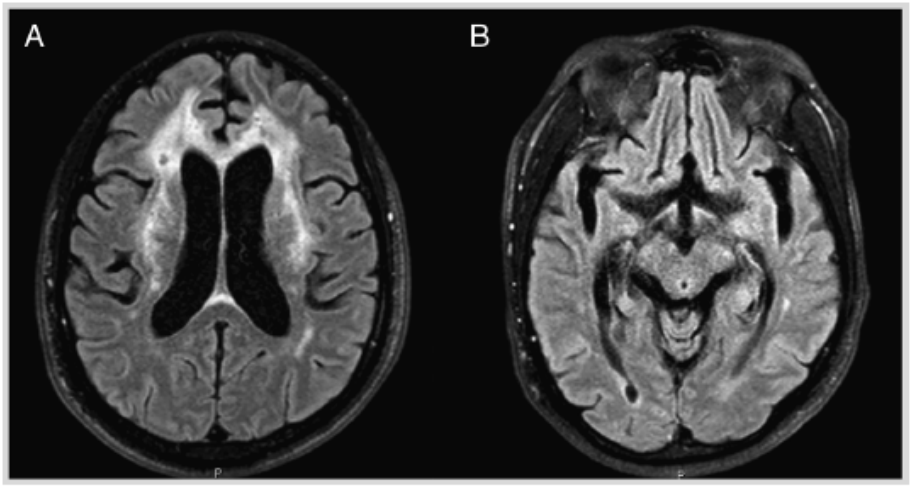
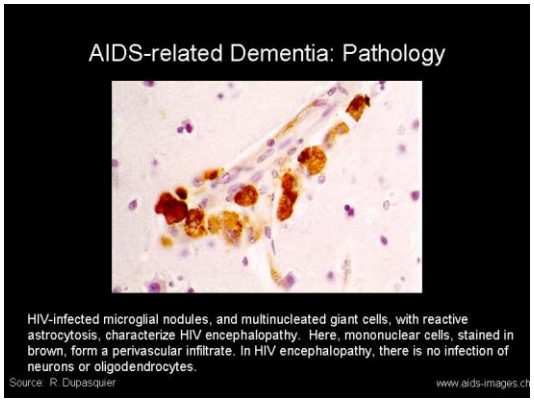
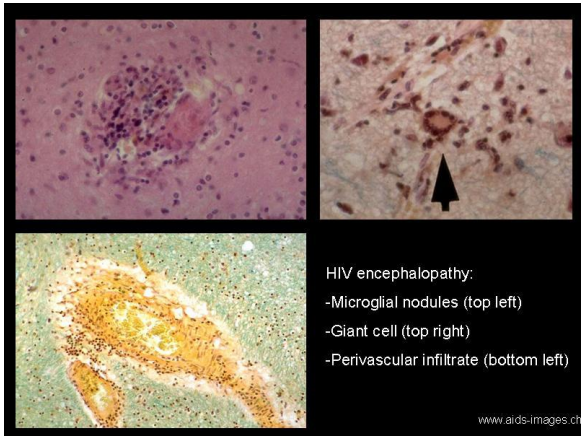


FIGURE 4-1 Fluid-attenuated inversion recovery sequence of MRI shows hydrocephalus *ex vacuo*, diffuse leukoencephalopathy (*A*), and diffuse, generalized atrophy (*B*). This degree of leukoencephalopathy is not a cardinal imaging feature of HIV encephalopathy but is commonly found in patients with advanced HIV infection and likely represents axonal injury.

Comment. At the time of hospitalization for personality change, the patient met criteria for HAD as he had significant cognitive loss with multiple domains affected, particularly psychomotor speed and executive function, and was unable to live independently. While his ventricles were enlarged on MRI, he had no urinary symptoms and a large volume lumbar puncture resulted in no improvement of his gait. After re-initiating treatment with ART and OI prophylaxis, he showed some improvement in his independent function on a visit more than 6 months later, as evidenced by regular checks of his pillboxes to ensure that he was filling them properly and adhering to his regimen.



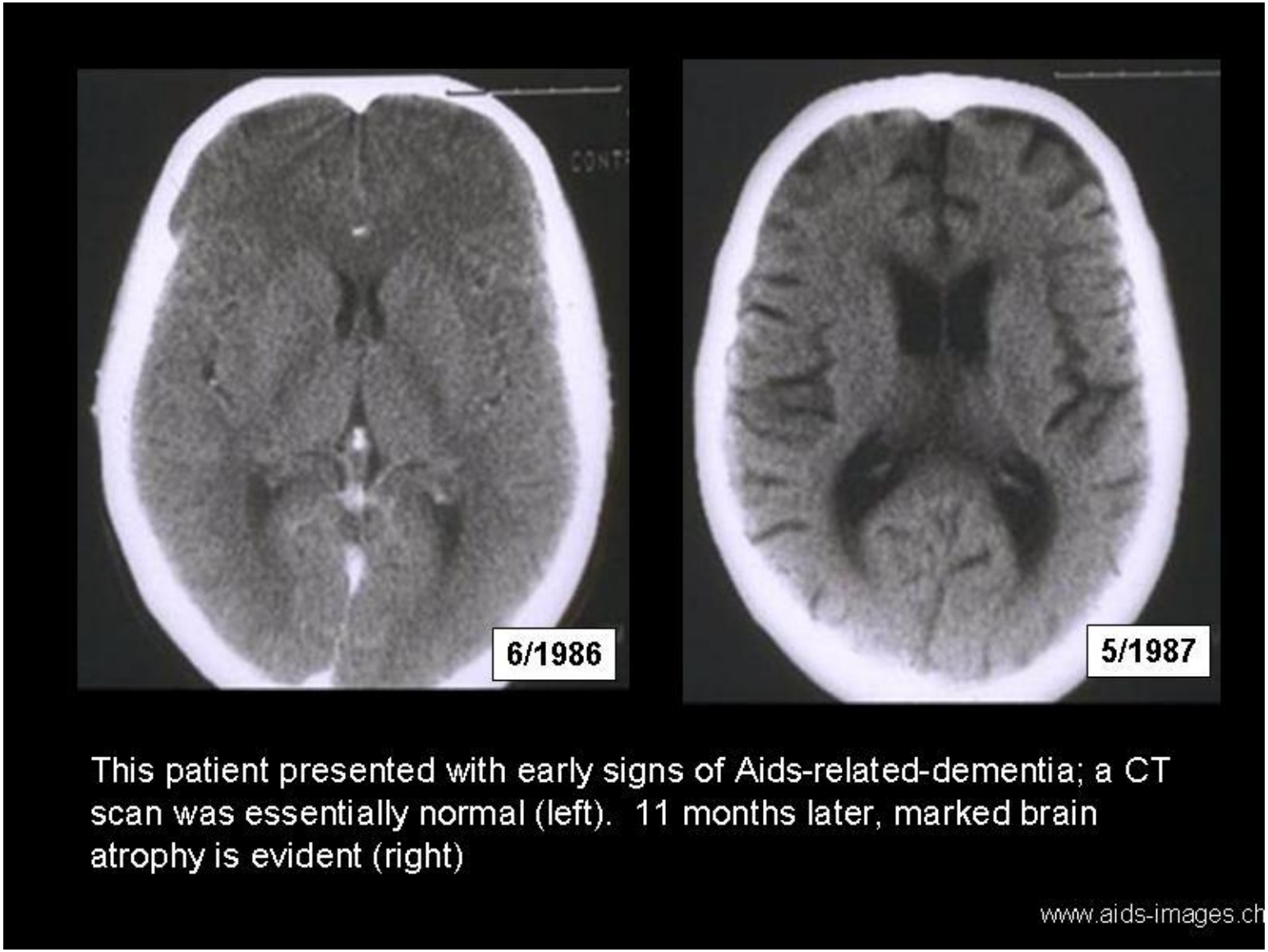


Atrophie
hyperT2
Normo T1

Continuum Lifelong Learning Neurol 2012 18(6):1319–1337.

AIDS Dementia

Trouble cognitif et VIH…



TNC

- Les troubles sévères, (démence sous corticale type PK ou Huuntington) ont drastiquement **diminué** par contrôle de la CV
- 30 à 50% des PVVIH ont des TNC, dont 60% sont des formes **asymptomatiques**, souvent à CV contrôlée
  - Rôle du VIH
  - Rôle du vieillissement, **association aux AVCi**, augmentation de 40% des AVCi pour les moins de 50 ans entre 1997 et 2006
  - Rôle des **comorbidités**, utilisation de statine, femme, fibrose hépatique
- **Corolaire: inobservance, précarisation**

Déclin cognitif / **HAND**

2007 (critères de Frascati), ***HIV-associated neurocognitive disorders***
trois niveaux de gravité croissante en fonction des résultats obtenus lors d'une évaluation neuropsychologique et de l'aptitude dans les activités de la vie quotidienne

1) **Déficit cognitif asymptomatique, *Asymptomatic Neurocognitive Impairment*** (ANI) définis par une diminution de plus d'un écart type dans au moins deux domaines cognitifs, mais sans retentissement sur la vie quotidienne.

2) **Trouble cognitif mineur, *Minor Neurocognitive Disorder*** (MND) répondant aux mêmes critères que l'ANI, mais associés à un retentissement sur la vie quotidienne (tblement mais continu à travailler), sans pour autant remplir les critères de démence.

3) **Démence associée au VIH, *HIV Associated Dementia*** (HAD) définie par une Diminution d'au moins 2 écarts types dans au moins deux domaines cognitifs, avec retentissement marqué sur la vie quotidienne (dépendance). Incidence de 7% en 1989 à 1% en 2000.

-Evolution non linéaire, non prévisible? Risque trois fois plus de ANI vers NMD versus pas de signe CROI 2012
-1 et 2 même si CV controlée
-3 CV haute CD4 bas

Dépistage des TNC

- La question du dépistage, de leur signification et du pronostic reste entière
- Surenchère inquiétante et anxiogène pour les patients et les médecins avec switch trop fréquent de ttt
- Banalisation non souhaitable
- Dépistage en plusieurs temps permettant le plus souvent une réassurance rapide

En CS régulièrement

Questionnaire n°1	
(1) «Vous arrive-t-il de ressentir des troubles de la mémoire par exemple, oubliez-vous des rendez-vous ou la survenue d'évènements récents?»	Une réponse «très souvent» à au moins l'un de ces items témoignerait d'une plainte cognitive
(2) «Vous arrive-t-il d'avoir l'impression d'être plus lent pour raisonner, planifier des activités ou résoudre des problèmes ?»	
(3) «Avez-vous des difficultés pour vous concentrer ou focaliser votre attention? Par exemple, suivre une conversation, lire un livre ou regarder la télévision».	
Questionnaire n°2	
(1) Avez-vous l'impression que votre mémoire fonctionne moins bien ?	Une réponse « Oui » à au moins 4 questions ou à la question (5) témoi-gnerait d'une plainte cognitive.
(2) Avez-vous l'impression d'enregistrer moins bien ?	
(3) Oubliez-vous des rendez-vous importants ?	
(4) Perdez-vous vos affaires plus souvent ou plus longtemps ?	
(5) Rencontrez-vous des difficultés d'orientation (ne pas reconnaître un endroit où vous êtes déjà allé) ?	
(6) Vous arrive-t-il d'oublier complètement des évènements (photo, récit) ?	
(7) Vous arrive-t-il d'avoir des manques du mot ?	
(8) Connaissez-vous une baisse d'activité de peur de vous tromper ?	
(9) Connaissez-vous une modification du caractère (repli, moins d'intérêt) ?	

Qui dépister ?

Pour des raisons pratiques, il ne paraît pas raisonnable de procéder à un dépistage généralisé des TNC chez tous les PVVIH. Il semble préférable de focaliser le dépistage sur les personnes qui présentent des facteurs de risque cognitif avérés (BIII) :

- soit liés à l'infection virale :
  - nadir CD4 < 200/mm³,
  - antécédents d'infections opportunistes du SNC,
  - mauvaise observance des ARV,
  - charge virale plasmatique détectable ;
  - soit liés à l'hôte :
- âge > 50 ans,
  - co-infection par le VHC,
  - facteurs de risque vasculaire ou pathologie cérébrovasculaire avérée,
  - consommation de substances psycho-actives,
  - troubles psychiatriques,
  - syndrome d'apnées du sommeil ;
- ou aux personnes qui ont une plainte cognitive spontanée ou à travers les questionnaires de plainte cognitive.

Rapport Morlat 2013

International HIV Dementia Scale :
Dépistage rapide des troubles neuro-cognitifs chez les pvvih :

Mémoire - Encodage :

Donner 4 items à retenir (chien, chapeau, haricot, rouge), une seconde pour dire chaque item.
Demander au patient les 4 mots juste après les avoir dit.
Répéter les mots si le patient ne s'en souvient plus. Puis l'informer que vous le réinterrogerez sur les 4 mots plus tard.

1°) Vitesse motrice :

Demander au patient de taper avec les deux premiers doigts de la main non dominante aussi amplement et rapidement que possible.
4 = 15 en 5 seconde
3 = entre 11 et 14 en 5 secondes
2 = 7 à 10 en 5 secondes
1 = 3 à 6 en 5 secondes
0 = 0 à 2 en 5 secondes

Toujours associer avec évaluation de l'humeur
Échelle PHQ9

2°) vitesse psychomotrice :

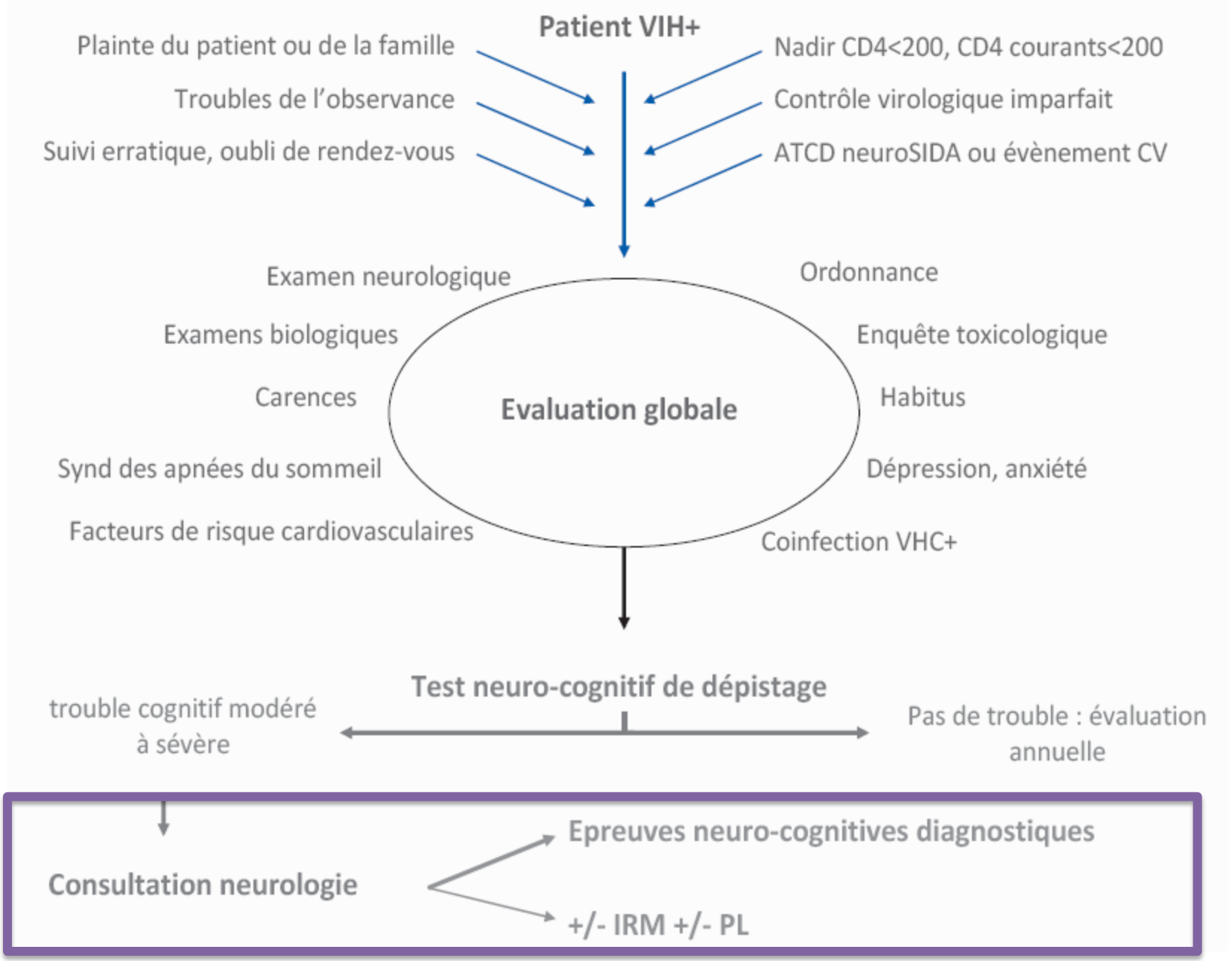
Demander a patient de réaliser les mouvements suivants avec la main non dominante aussi rapidement que possible.

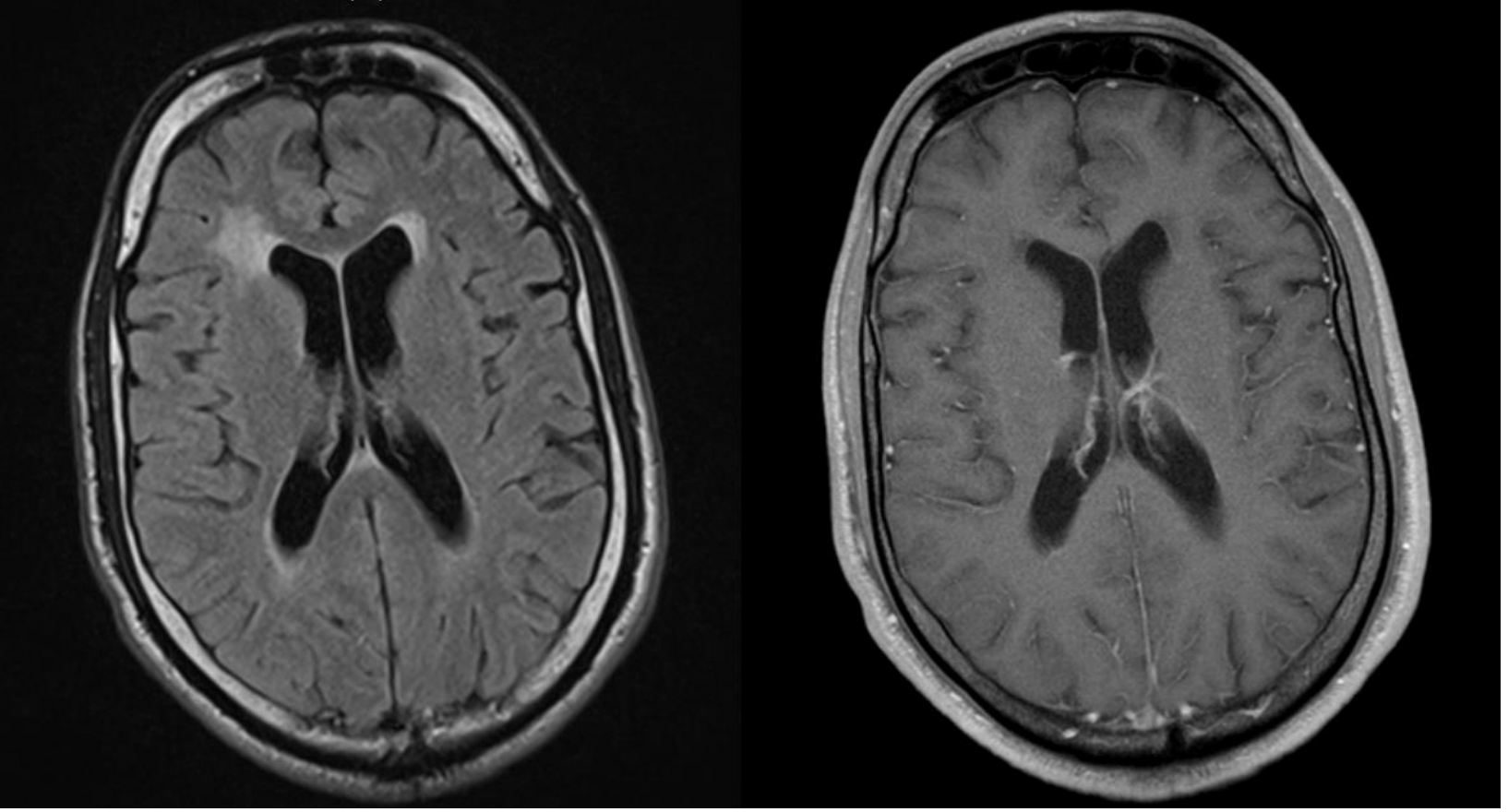
- Poser le poing sur une surface plane
- Poser la main sur une surface plane paume vers le bas
- Poser la main perpendiculairement à une surface plane, sur la tranche du 5ème doigt
- Réaliser la séquence et faite la pratiquer deux fois au patient pour qu'il s'entraine

4 = 4 séquences en 10 secondes
3 = 3 séquences en 10 secondes
2 = 2 séquences en 10 secondes
1 = 1 séquences en 10 secondes
0 = performance impossible

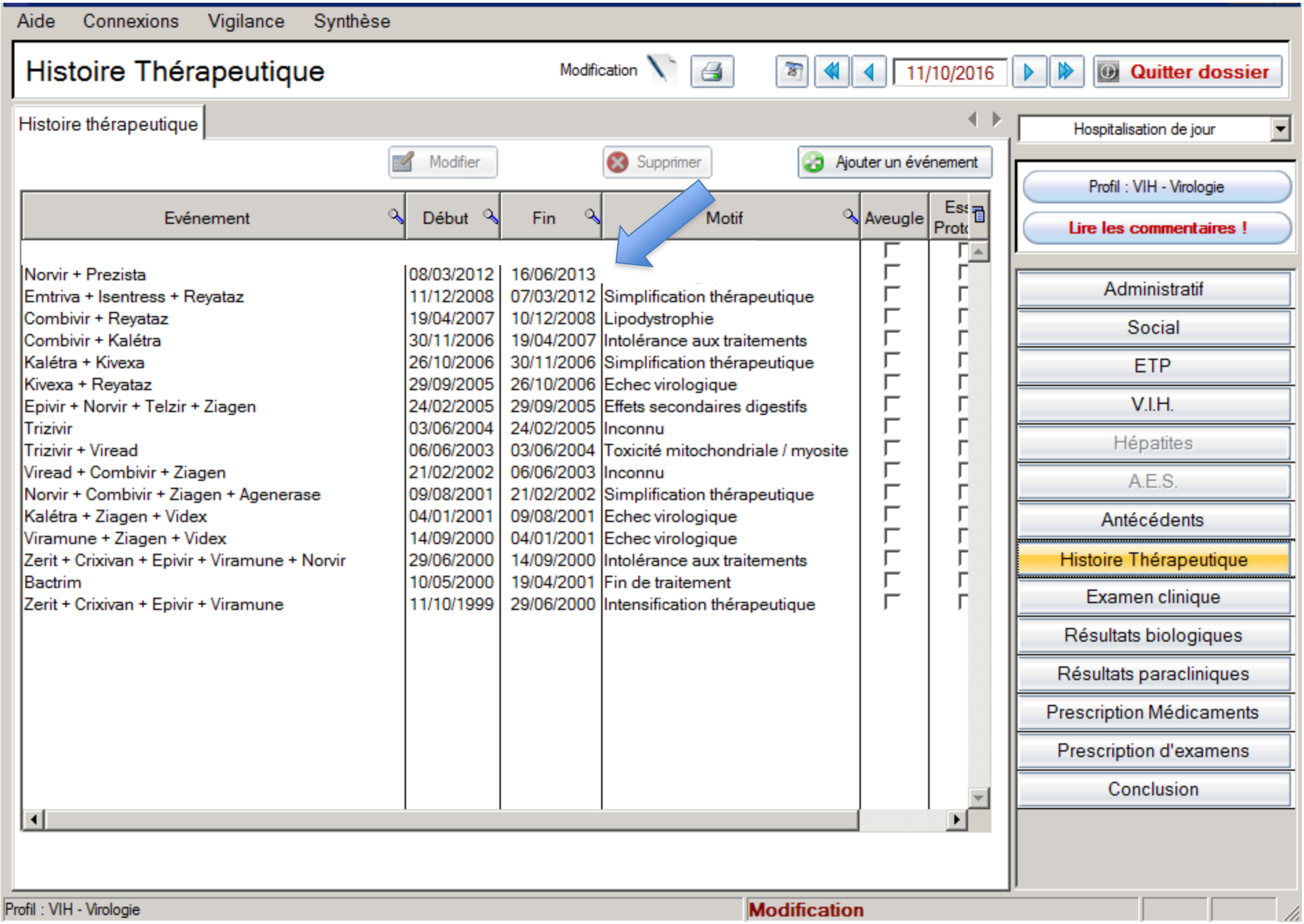
3°) Mémoire – Rappel :
Demander au patient de rappeler les 4 mots. Pour les mots oubliés, aidez avec un indice sémantique tel que animal (chien), vêtement (chapeau), légume (haricot) et couleur (rouge). Donner un point pour chaque mot spontanément énoncé et 0.5 point pour chaque réponse correcte après aide. Maximum 4 points.

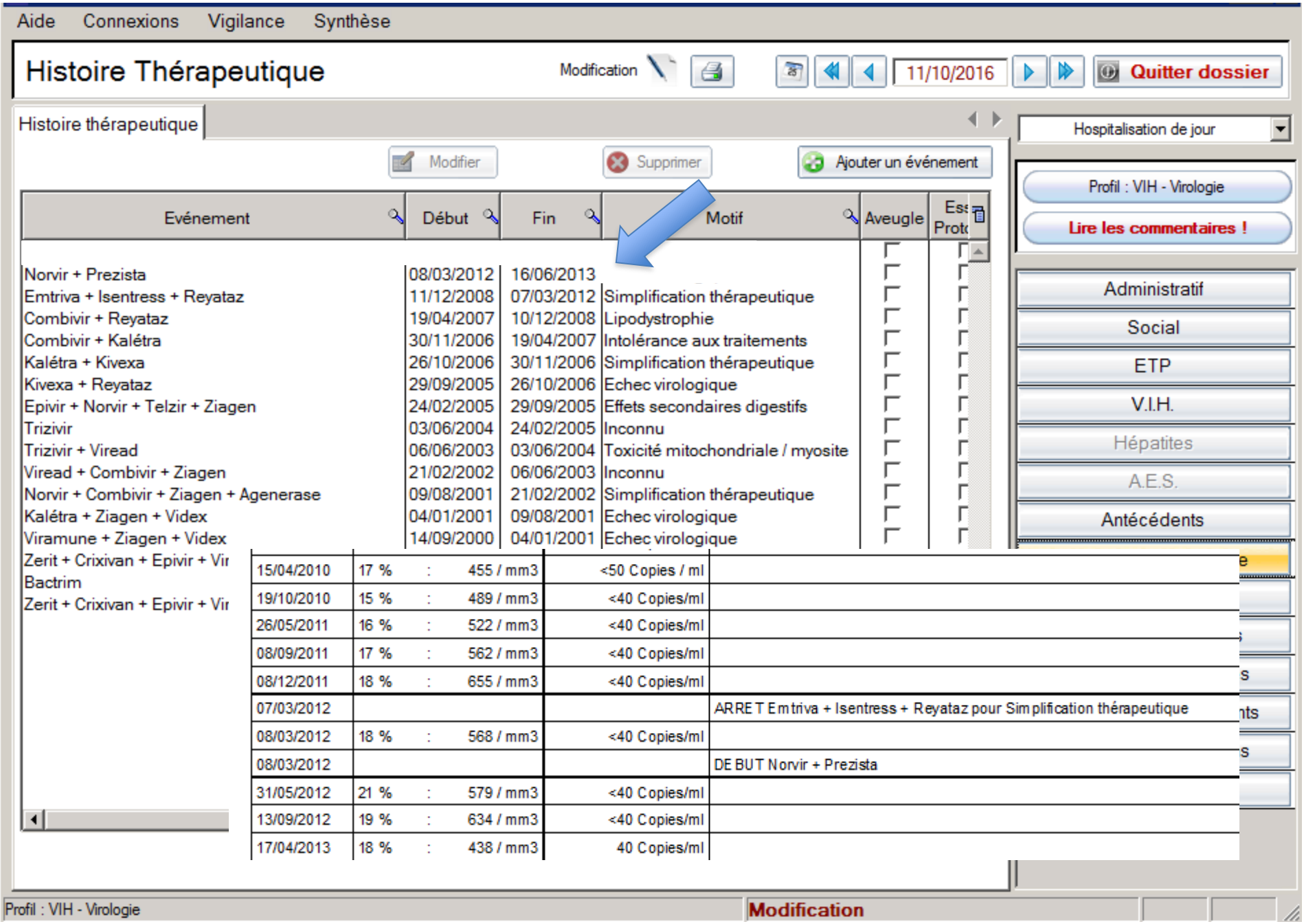
Figure 6. Proposition d'algorithme de PEC cognitive de la PVVIH





Découverte VIH, symptôme neuro atypique
CD4 434, 30%
CV VIH plasmatique 59 cop/ml
CV VIH LCR 22630 cop/ml
Pas de dissociation génotypique
LCR 49 C, 92% lympho, prot 0.80, G normale


Aide
Connexions
Vigilance
Synthèse
Histoire Thérapeutique
Modification
11/10/2016
Quitter dossier
Histoire thérapeutique
Hospitalisation de jour
Modifier
Supprimer
Ajouter un événement
Evénement
Début
Fin
Motif
Aveugle
Norvir + Prezista 08/03/2012 16/06/2013
Emtriva + Isentress + Reyataz 11/12/2008 07/03/2012 Simplification thérapeutique
Combivir + Reyataz 19/04/2007 10/12/2008 Lipodystrophie
Combivir + Kalétra 30/11/2006 19/04/2007 Intolérance aux traitements
Kalétra + Kivexa 26/10/2006 30/11/2006 Simplification thérapeutique
Kivexa + Reyataz 29/09/2005 26/10/2006 Echec virologique
Epivir + Norvir + Telzir + Ziagen 24/02/2005 29/09/2005 Effets secondaires digestifs
Trizivir 03/06/2004 24/02/2005 Inconnu
Trizivir + Viread 06/06/2003 03/06/2004 Toxicité mitochondriale / myosite
Viread + Combivir + Ziagen 21/02/2002 06/06/2003 Inconnu
Norvir + Combivir + Ziagen + Agenerase 09/08/2001 21/02/2002 Simplification thérapeutique
Kalétra + Ziagen + Videx 04/01/2001 09/08/2001 Echec virologique
Viramune + Ziagen + Videx 14/09/2000 04/01/2001 Echec virologique
Zerit + Crixivan + Epivir + Viramune + Norvir 29/06/2000 14/09/2000 Intolérance aux traitements
Bactrim 10/05/2000 19/04/2001 Fin de traitement
Zerit + Crixivan + Epivir + Viramune 11/10/1999 29/06/2000 Intensification thérapeutique
Profil : VIH - Virologie
Lire les commentaires !
Administratif
Social
ETP
V.I.H.
Hépatites
A.E.S.
Antécédents
Histoire Thérapeutique
Examen clinique
Résultats biologiques
Résultats paracliniques
Prescription Médicaments
Prescription d'examens
Conclusion
Profil : VIH - Virologie
Modification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11/10/2016
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Lire les commentaires !
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Norvir + Combivir + Ziagen + Agenerase 09/08/2001 21/02/2002 Simplification thérapeutique
Kalétra + Ziagen + Videx 04/01/2001 09/08/2001 Echec virologique
Viramune + Ziagen + Videx 14/09/2000 04/01/2001 Echec virologique
Zerit + Crixivan + Epivir + Vir
Bactrim
Zerit + Crixivan + Epivir + Vir
15/04/2010 17 % : 455 / mm3 <50 Copies / ml
19/10/2010 15 % : 489 / mm3 <40 Copies/ml
26/05/2011 16 % : 522 / mm3 <40 Copies/ml
08/09/2011 17 % : 562 / mm3 <40 Copies/ml
08/12/2011 18 % : 655 / mm3 <40 Copies/ml
07/03/2012 ARRET Emtriva + Isentress + Reyataz pour Simplification thérapeutique
08/03/2012 18 % : 568 / mm3 <40 Copies/ml
08/03/2012 DEBUT Norvir + Prezista
31/05/2012 21 % : 579 / mm3 <40 Copies/ml
13/09/2012 19 % : 634 / mm3 <40 Copies/ml
17/04/2013 18 % : 438 / mm3 40 Copies/ml
Profil : VIH - Virologie
Modification

Examen du 01/06/13
Appareil utilisé : IRM Avanto Date de mise en service, le 07/03/05

IRM de l'encéphale

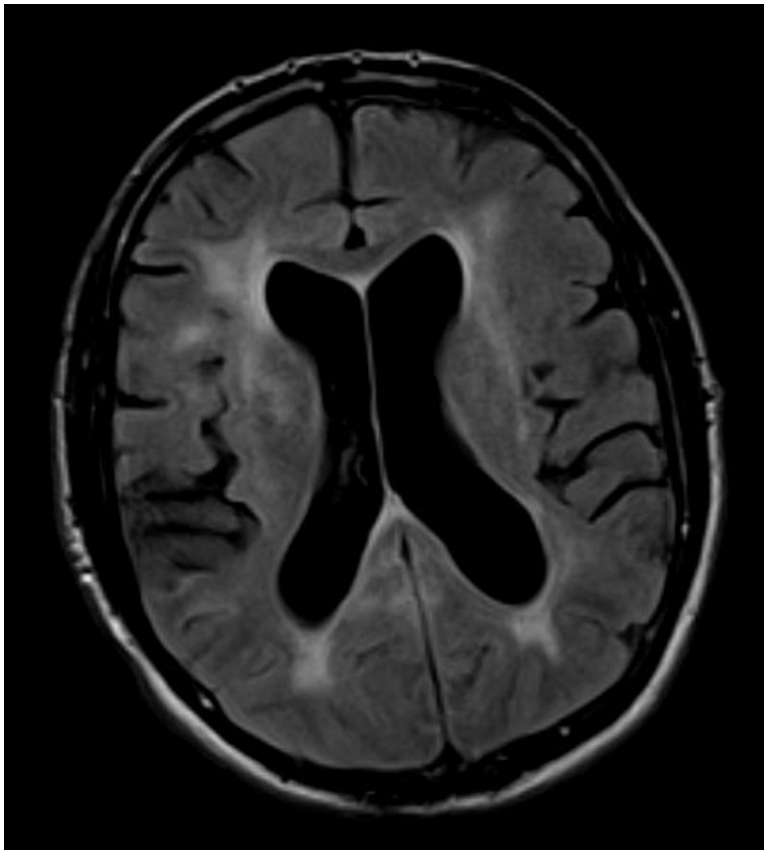
Indication :
Troubles phasiques.

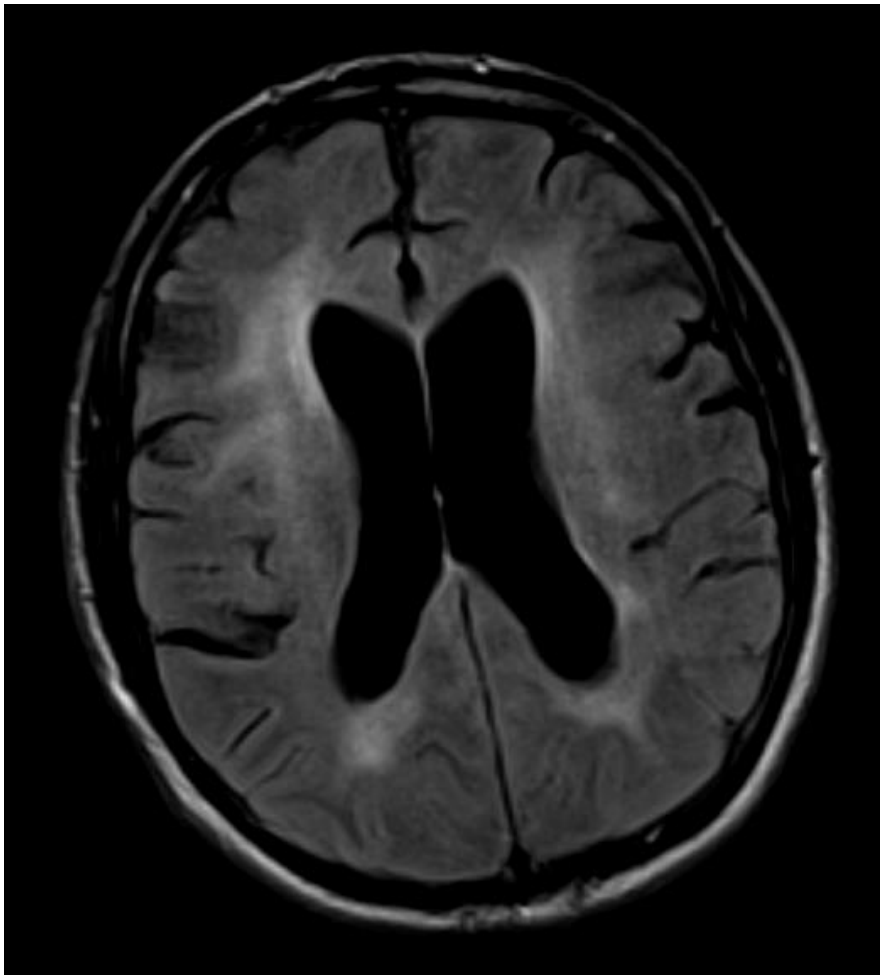
Technique :
Coupes axiales pondérées en diffusion; T2*,T2 FLAIR puis ARM pondérée en TOF sur l
e
polygone de Willis suivie d'une ARM injectée des TSA.
Produit Utilisé : MultiHance FL 15 ml - Quantité : 15 ml - Numéro de lot : s2p107j

Résultat :
En pondération de diffusion, on n'observe pas de lésion ischémique récente.
En pondération T2 FLAIR, on observe une leucoaraïose et un hypersignal T2 FLAIR diffus, anormal qui touche quasi toute la substance blanche.
A noter, une atrophie cérébrale qui se traduit essentiellement par une dilatation ventriculaire prédominante du côté gauche.
En pondération T2*, on n'observe pas de microbleed.
Sur le plan vasculaire, on retient un aspect normal des artères intracrâniennes de gros et moyen calibre.
Au niveau des TSA, on n'observe pas de sténose significative.
A noter tout de même un aspect un peu irrégulier des bulbes carotidiens qui présentent aussi un discret rétrécissement (complétez avec un écho-doppler).
On retient aussi un aspect très irrégulier de l'artère vertébrale droite qui est grêle (aspect normal de l'artère vertébrale gauche qui est dominante).

Conclusion :
Absence de lésion ischémique récente.
Atrophie cérébrale diffuse avec hypersignal diffus de la substance blanche.

-Absence de lésions ischémiques
-Atrophie cérébrale diffuse avec hypersignal T2 diffus de la substance blanche





Edité le : 04/06/13 à 20h37m

LIQUIDE CEPHALORACHIDIEN : CYTOLOGIE ET BIOCHIMIE

			Valeurs usuelles	Antériorité
Indication spécifiée :	Formule leucocytaire NON prescrite.			
Lieu de la ponction :	Ponction lombaire			
Volume d'échantillon :	2,0	ml		
ASPECT				
Avant centrifugation :	Clair			
Après centrifugation, surnageant :	Clair			
Après centrifugation, culot :				
NUMERATION DES ELEMENTS				
Leucocytes ..... :	* 23	Méga é ts/L	<3	
Erythrocytes..... :	<100	Méga é ts/L	<100	
CYTOLOGIE				
Frottis obtenu par concentration, cyt centrifugation et oloration MGG				
Frottis de densité cellulaire corr cte				
- Lymphocytes	91	%		
- Monocytes	9	%		
- Polynucléaires neutrophiles	0	%		
Présence de lymphoplasmocytes.				
BIOCHIMIE				
Protéinorachie ..... :	* 0,63	g/L	0,20 - 0,40	
Cl Benzéthonium Architect Abbott	résultats non maj rés par l'aspect coloré du LCR.			
Glycorachie ..... :	3,7	mmol/L	2,3 - 4,0	
Glucose hexokinase				

Vincent GAZZANO Interne en biologie

*** Edition Finale ***

Edité le : 04/06/13 à 20h37m

LIQUIDE CEPHALORACHIDIEN : CYTOLOGIE ET BIOCHIMIE

		Valeurs usuelles	Antériorité
Indication spécifiée :	Formule leucocytaire NON prescrite.		
Lieu de la ponction :	Ponction lombaire		
Volume d'échantillon :	2,0 ml		

ASPECT

Avant centrifugation :	Clair
Après centrifugation, surnageant :	Clair
Après centrifugation, culot :	

NUMERATION DES ELEMENTS

Leucocytes .....:	* 23	Méga élts/L	<3
Erythrocytes.....:	<100	Méga élts/L	<100

CYTOLOGIE

Frottis obtenu par concentration, cytocentrifugation et coloration MGG

Frottis de densité cellulaire correcte

- Lymphocytes	91 %
- Monocytes	9
- Polynucléaires neutrophiles	0

Présence de lymphoplasmocytes.

BIOCHIMIE

Protéinorachie .....:	* 0
Cl Benzéthonium Architect Abbott : résu	

LCR.

Glycorachie .....:	3
Glucose hexokinase	

Vincent GAZZANO Interne en biologi

*** Edition Finale ***

--- Prél. 130605506401 du 04/06/2013 00:00 (Liquide Céphalo-Rachidien) - ---

-- VIRUS de l'Immunodéficience huma

Quantification de l'ARN du VIH1 (RealTime PCR)	: 1417 copies/ml

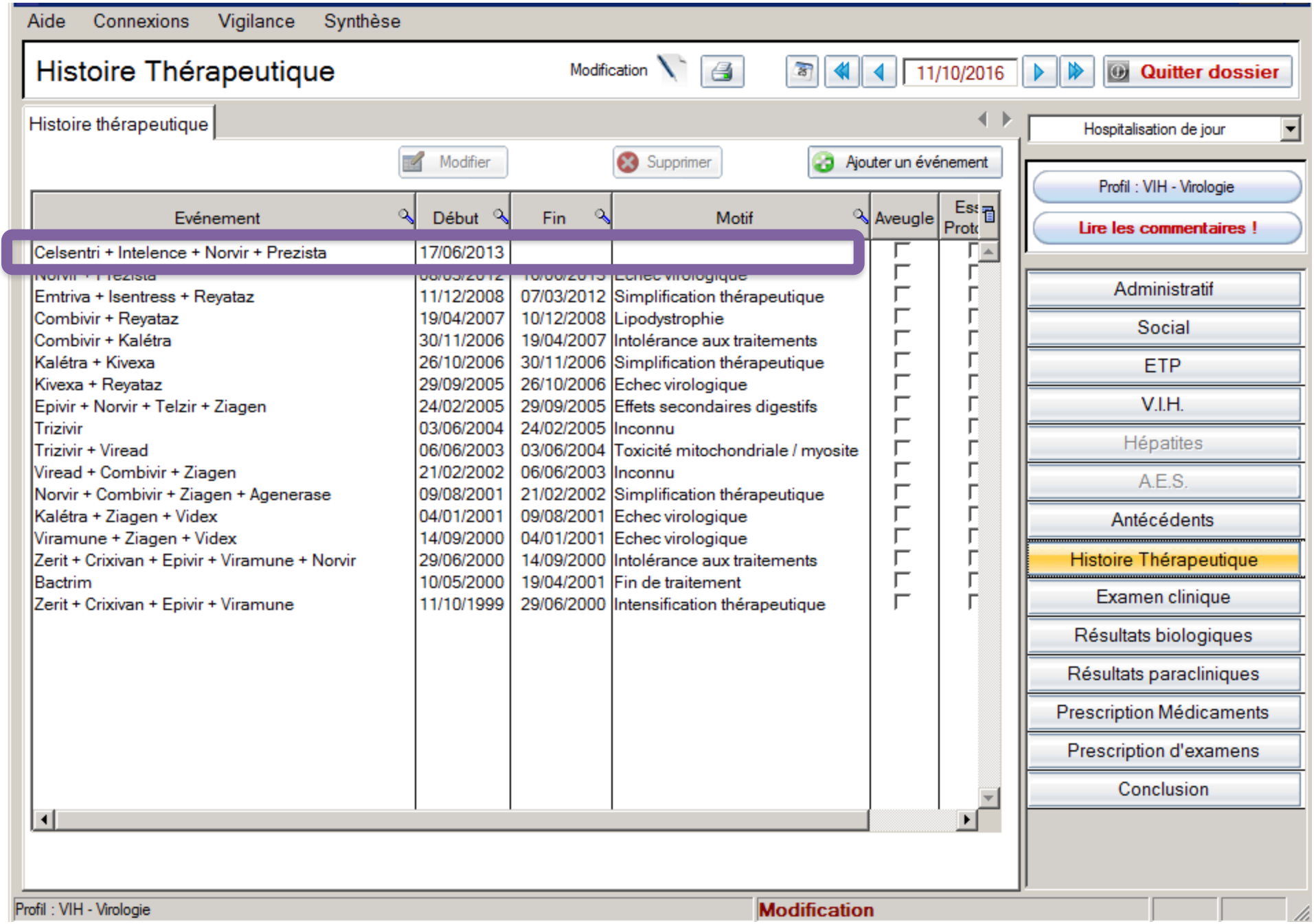
-- RealTime HIV-1, ABBOTT

PCR temps réel dans le gène de l'intégrase du VIH-1, avec controle interne

Seuil de détection : 40 copies/ml (1 copie = 1.72 UI/ml) --

Génotypage du VIH 1

Séquence de la réverse transcriptase du VIH1	: Génome non amplifiable
Séquence de la protéase du VIH 1	: Séquence jointe
Séquence de l'intégrase du VIH1	: RESISTANCE AU RALTEGRAVIR


Aide
Connexions
Vigilance
Synthèse
Histoire Thérapeutique
Modification
11/10/2016
Quitter dossier
Histoire thérapeutique
Hospitalisation de jour
Modifier
Supprimer
Ajouter un événement
Profil : VIH - Virologie
Lire les commentaires !
Evénement
Début
Fin
Motif
Aveugle
Celsentri + Intelence + Norvir + Prezista 17/06/2013
Emtriva + Isentress + Reyataz 11/12/2008 07/03/2012 Simplification thérapeutique
Combivir + Reyataz 19/04/2007 10/12/2008 Lipodystrophie
Combivir + Kalétra 30/11/2006 19/04/2007 Intolérance aux traitements
Kalétra + Kivexa 26/10/2006 30/11/2006 Simplification thérapeutique
Kivexa + Reyataz 29/09/2005 26/10/2006 Echec virologique
Epivir + Norvir + Telzir + Ziagen 24/02/2005 29/09/2005 Effets secondaires digestifs
Trizivir 03/06/2004 24/02/2005 Inconnu
Trizivir + Viread 06/06/2003 03/06/2004 Toxicité mitochondriale / myosite
Viread + Combivir + Ziagen 21/02/2002 06/06/2003 Inconnu
Norvir + Combivir + Ziagen + Agenerase 09/08/2001 21/02/2002 Simplification thérapeutique
Kalétra + Ziagen + Videx 04/01/2001 09/08/2001 Echec virologique
Viramune + Ziagen + Videx 14/09/2000 04/01/2001 Echec virologique
Zerit + Crixivan + Epivir + Viramune + Norvir 29/06/2000 14/09/2000 Intolérance aux traitements
Bactrim 10/05/2000 19/04/2001 Fin de traitement
Zerit + Crixivan + Epivir + Viramune 11/10/1999 29/06/2000 Intensification thérapeutique
Administratif
Social
ETP
V.I.H.
Hépatites
A.E.S.
Antécédents
Histoire Thérapeutique
Examen clinique
Résultats biologiques
Résultats paracliniques
Prescription Médicaments
Prescription d'examens
Conclusion
Profil : VIH - Virologie
Modification

DDN : 09/01/1962 SEXE : Homme
N° venue : 6649582018

DEMANDE N° **0140950658**

Prélevé le : 07/10/2014 16:00
Reçu le : 07/10/2014 16:42

24817 HS H SEMAINE MALADIES INFECTIEUSES

HOPITAUX DU NORD

103, grande rue de la Croix-Rousse
69317 LYON CEDEX 04
FRANCE

BIOCHIMIE

Biochimie Proximité - Tél : 0472071855 - Fax : 0472001574
Dr P.J. BONDON, Dr B. POGGI

CYTOCHIMIE DE LIQUIDE CEPH

Lacticodéshydrogénase *Technique IFCC L→P 37°C SIEMENS*	10	UI/L
Ponction	Lombaire	
Aspect	Clair	
Surnageant	Clair	
Protéines *Technique Rouge Pyrogallol SIEMENS*	↑0.52	g/L
Glucose *Technique Hexokinase SIEMENS*	↑4.3	mmol/L
Lactates *Technique LDH-UV SIEMENS*	2.2	mmol/L
Erythrocytes	↑8	Méga é
Leucocytes	2	Méga é

Pharmacologie spécialisée

Dr M-C Gagnieu - Dr F Parant
Secrétariat : 04-72-11-06-32 - Laboratoire : 04-72-11-06-49

Dosage d'ANTIRÉTROVIRAUX

Contexte de la demande : réplication virale dans le LCR - CV indétectable dans le plasma - dosages plasmatiques voir dossier N° 0140949577 du 7/10/14

Dosage d'ANTIRÉTROVIRAUX dans le LCR

	Résultats	*Unités*	*Valeurs de référence*	*Antériorités*
Darunavir/PREZISTA Concentration dans le LCR :	0.027	mg/L		
Etravirine/INTELLENCE Concentration dans le LCR :	0.002	mg/L		
Maraviroc/CELSENTRI Concentration dans le LCR :	0.003	mg/L		

Interprétation

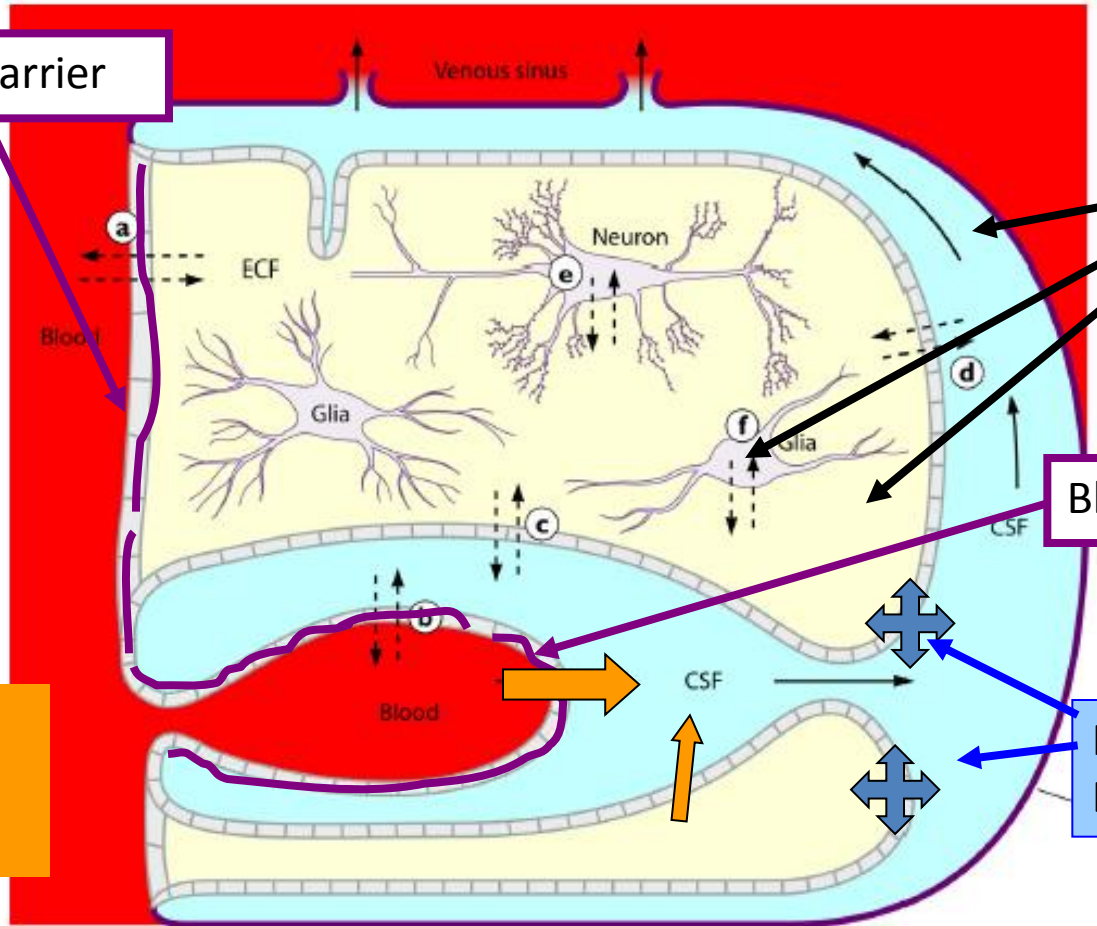
DARUNAVIR :
rapport LCR/plasma attendu = 1,4% - médiane attendue : 0,057 mg/L (IQR: 0,040 à 0,081 mg/L)
concentration plasmatique moyenne = 3,8 mg/L
-> concentration attendue dans le LCR à 0,053 mg/L
-> petite sous-exposition qui justifierait le passage à 600mg x2/J (cf dossier 0140948577 pour dosages plasmatiques)

ETRAVIRINE :
fixation protéique plasmatique = 99,9%
concentration plasmatique moyenne = 0,52 mg/L
-> concentration attendue dans le LCR < 0,001 mg/L

MARAVIROC :
médiane attendue : 0,004 mg/L (IQR: 0,002 à 0,012 mg/L)
-> concentration située en limite inférieure

Clinical Microbiology Reviews, Oct. 2010, p. 858–883
0893-8512/10/$12.00 doi:10.1128/CMR.00007-10

Blood Brain Barrier



3 espaces

Blood CSF Barrier

Synthèse LCR
66% Ple. Cho.
33% diffusion

Pas de Barrière
Diffusion permanente

La présence de tigh junctions entre les cellules endothéliales empêche la pénétration des molécules hydrophiles. Elles sont cependant absentes sur 1/5000 du total de la surface capillaire du cerveau.

BBB + BCB = Barrière de diffusion faite d'une membrane lipidique avec qq zones de faiblesse ou peuvent passer les molécules hydrophiles

Facteur influençant la Concentration d'ARV dans le SNC

- **Taille** de la molécule
- **Lipophilie**
- Fixation **protéique**
- **Transport actif, efflux du CSF vers le sang dans les plexus choroïdes Pgp (IP)**, Oat3 (organic anion transporter 3)et PEPT2 (peptide transporter 2)
- **Dégradation** dans CNS
- **Inactivation** en milieu acide

CNS Drugs (2013) 27:31–55
DOI 10.1007/s40263-012-0018-x

REVIEW ARTICLE

CSF Penetration by Antiretroviral Drugs

Christine Eisfeld · Doris Reichelt · Stefan Evers · Ingo Husstedt

Le score CPE ou score de Charter classe les ARV en quatre niveaux en fonction de leur capacité **présumée à traverser la barrière hémato-encéphalique et à être actifs dans le SNC**.
Le score repose sur des données d'efficacité clinique et/ou virologique au niveau du SNC, de **dosages pharmacologiques dans le LCR** et des propriétés **pharmacochimiques**.

Table 1 Revised CNS penetration-effectiveness (CPE) ranking (reprinted with permission from IAS–USA. Letendre et al. [18]. Updates available at: http://www.iasusa.org)

Antiretroviral drug class[a]	4	3	2	1
NRTI	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTI	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PI	Indinavir/ritonavir	Darunavir/ritonavir	Atazanavir	Nelfinavir
		Fosamprenavir/ritonavir	Atazanavir/ritonavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir/ritonavir		Saquinavir/ritonavir
				Tipranavir/ritonavir
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

NNRTI non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor

[a] Larger numbers reflect estimates of better penetration or effectiveness in the CNS

Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions

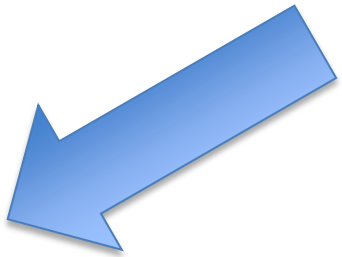
ABSTRACT

Objective: The link between CNS penetration of antiretrovirals and AIDS-defining neurologic disorders remains largely unknown.

Methods: HIV-infected, antiretroviral therapy–naive individuals in the HIV-CAUSAL Collaboration who started an antiretroviral regimen were classified according to the CNS Penetration Effectiveness (CPE) score of their initial regimen into low (<8), medium (8–9), or high (>9) CPE score. We estimated "intention-to-treat" hazard ratios of 4 neuroAIDS conditions for baseline regimens with high and medium CPE scores compared with regimens with a low score. We used inverse probability weighting to adjust for potential bias due to infrequent follow-up.

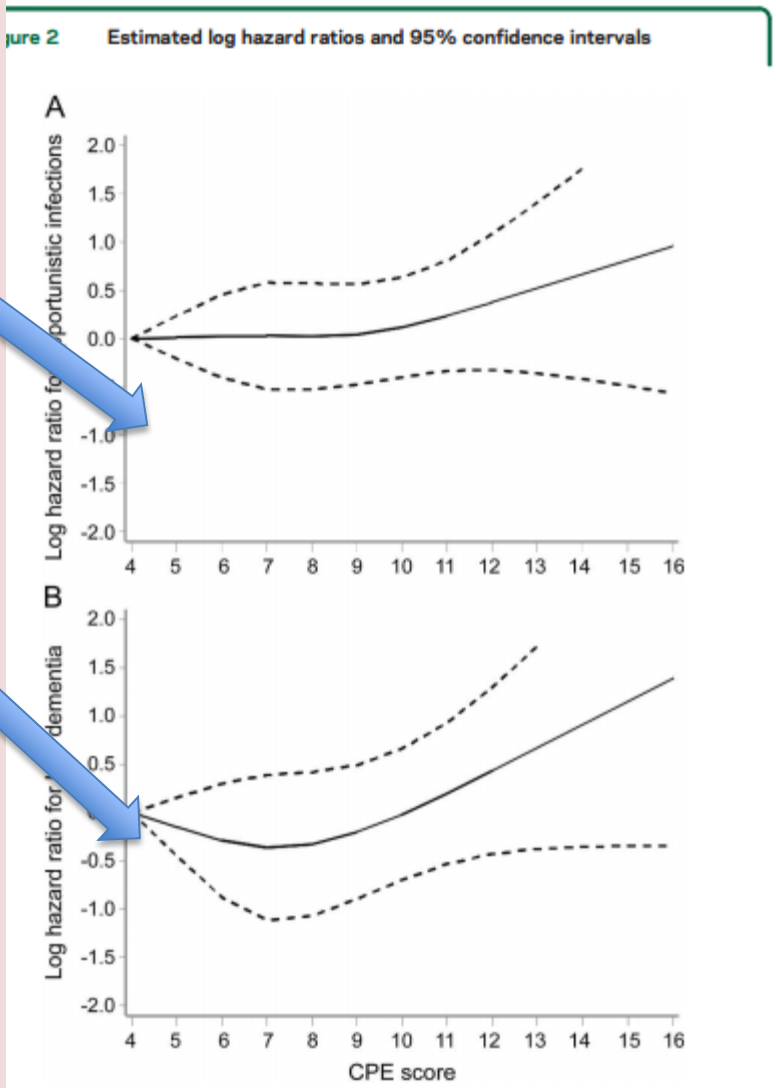
Results: A total of 61,938 individuals were followed for a median (interquartile range) of 37 (18, 70) months. During follow-up, there were 235 cases of HIV dementia, 169 cases of toxoplasmosis, 128 cases of cryptococcal meningitis, and 141 cases of progressive multifocal leukoencephalopathy. The hazard ratio (95% confidence interval) for initiating a combined antiretroviral therapy regimen with a high vs low CPE score was 1.74 (1.15, 2.65) for HIV dementia, 0.90 (0.50, 1.62) for toxoplasmosis, 1.13 (0.61, 2.11) for cryptococcal meningitis, and 1.32 (0.71, 2.47) for progressive multifocal leukoencephalopathy. The respective hazard ratios (95% confidence intervals) for a medium vs low CPE score were 1.01 (0.73, 1.39), 0.80 (0.56, 1.15), 1.08 (0.73, 1.62), and 1.08 (0.73, 1.58).

Conclusions: We estimated that initiation of a combined antiretroviral therapy regimen with a high CPE score increases the risk of HIV dementia, but not of other neuroAIDS conditions. ***Neurology®*** **2014;83:134–141**



We found little change in the incidence of toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy.
Normal = lié à la restauration immune plus qu'à l'indice de pénétration

We estimated that the **incidence of HIV dementia increases by more than 70% after initiating an antiretroviral regimen with a high CPE score compared with a low score**.
Toxicité directe, mitochondriale ou indirecte ARV: dépôt de plaques ExtraC Bamyloïdes et réaction inflammatoire secondaire
Observance?



ated log hazard ratios and 95% confidence intervals for opportunistic infections (A) plasmosis, cryptococcal meningitis, or progressive multifocal leukoencephalopathy) IV dementia (B) comparing each CNS Penetration Effectiveness (CPE) score with a score of 4 (lowest), HIV-CAUSAL Collaboration, 1998–2013.

CD8 Encephalitis in HIV-Infected Patients Receiving cART: A Treatable Entity

François-Xavier Lescure,[1,9] Antoine Moulignier,[1,2] Julien Savatovsky,[3] Corinne Amiel,[4] Guislaine Carcelain,[5] Jean-Michel Molina,[6] Sébastien Gallien,[6] Jérôme Pacanovski,[7] Gilles Pialoux,[1] Homa Adle-Biassette,[8,a] and Françoise Gray[8,a]

[1]Service des Maladies Infectieuses et Tropicales, AP-HP, Hôpital Tenon; [2]Service de Neurologie, and [3]Service d'Imagerie Médicale, Fondation Adolphe de Rothschild; [4]Service de Virologie, AP-HP, Hôpital Tenon; [5]Service d'Immunologie, AP-HP, Groupe Hospitalier Pitié-Salpêtrière; [6]Service des Maladies Infectieuses et Tropicales, AP-HP, Hôpital Saint Louis; [7]Service des Maladies Infectieuses et Tropicales, AP-HP, Hôpital Saint Antoine; [8]Service Central d'Anatomie et de Cytologie Pathologiques, APHP, Hôpital Lariboisière–Université Paris 7; and [9]CDR Saint-Antoine, Inserm U938, Université Paris 6-UPMC, Paris, France

(See the Editorial Commentary by Langford and Letendre on pages 109–11.)

Background. Despite its overall efficacy, combined antiretroviral therapy (cART) has failed to control human immunodeficiency virus (HIV) infection of the central nervous system (CNS). New acute and chronic neurological complications continue to be reported.

Methods. We conducted a retrospective study of 14 HIV-infected patients with documented encephalitis, which was initially attributed to an undetermined origin. Brain magnetic resonance imaging (MRI) uniformly revealed unusual, multiple linear gadolinium-enhanced perivascular lesions.

Results. All patients had manifested acute or subacute neurological symptoms; the brain MRIs indicating diffuse brain damage. The mean duration of HIV infection was approximately 10 years, and 8 patients were immunovirologically stable. Cerebrospinal fluid abnormalities with mildly elevated protein and pleocytosis with >90% lymphocytes, predominantly CD8, were found in all but 1 patient. The mean cerebral spinal fluid HIV load was 5949 copies/mL. Six patients reported a minor infection a few days prior to neurological symptoms, 2 patients presented criteria for the immune reconstitution inflammatory syndrome of the CNS, 2 were in virological escape, and 1 developed encephalitis after interruption of cART. Brain biopsies revealed inflammatory encephalitis associated with astrocytic and microglial activation as well as massive perivascular infiltration by polyclonal $CD8^+$ lymphocytes. All patients had been treated with glucocorticosteroids. The long-term therapeutic response varied from excellent, with no sequalae (n = 5), to moderate, with cognitive disorders (n = 4). The mean survival time was 8 years; however, 5 patients died within 13 months of initiation of treatment.

Conclusions. CD8 encephalitis in HIV-infected patients receiving cART is a clinical entity that should be added to the list of HIV complications.

Patient Characteristic																	Evolution			
Age Sex	Nadir CD4	CD4 ≥6 (mo)	Immu Viral Stable	Entry Way	Onset Year	Onset CD4	pVL ≥6 m (cp/mL)	Onset pVL (cp/mL)	Neurological Symptoms	cART	CSF Prot (g/L)	CSF Cells (μL)	CD8 (%)	CSF VL (cp/mL)	Typical Brain MRI	BB p24* CD4*	Cortico-steroids	pVL (cp/mL)	CSF VL (cp/mL)	Outcome
46 M	190	400	Yes	Minor infection	2001	121	0	4500	Cognitive impairment	DDI 3TC IDVr	1.47	100	85	NA	+	+ –	Yes	<50	<200	Death 9 mo after onset
41 M	. . .	400	Yes	Stop ARV	2002	120	0	35 561	Cognitive impairment	STOP	1.10	9	NA	NA	+	+ +	Yes	62	<200	Total recovery
36 M	10	10	No	IRIS	2003	93	0	0	Headaches, seizures, facial palsy	DDI 3TC LPVr	0.63	40	NA	0	+	+ +	Yes	<50	<200	Total recovery
47 F	140	586	Yes	Minor infection	2005	275	117	692	Headaches, confusion, seizures	LPV fAPVr T20	0.9	80	76	2236	+	+/– –	Yes	<50	<200	Death 3 mo after onset
39 F	15	145	No	IRIS	2005	NA	1120	NA	Comatose	DDI ABC ATVr	0.9	26	68	1120	+	– +	Yes	<50	<200	Death 9 mo after onset
33 F	NA	NA	NA	ND	2005	283	NA	2660	Headaches, cognitive impairment	FTC TDF ATVr	1.13	20	NA	10300	+	– +	Yes	<50	<200	Death 12 mo after onset
37 F	NA	384	Yes	Minor infection	2007	495	0	65 800	Headaches, status epilepticus	ABC 3TC LPVr	0.79	220	69	NA	+	– +/–	Yes	<50	<200	Alive, cognitive impairment
54 F	516	509	No	Minor infection	2007	402	1468	NA	Dizziness, headaches	None	0.8	220	78	672	+	– ++	Yes	<20	<40	Total recovery
33 M	4	244	Yes	Escape	2007	210	216	2379	Confusion, status epilepticus	FTC TDF ATVr	0.42	1	. . .	1230	+	++ +	Yes	<50	<200	Alive, cognitive impairment
43 M	82	169	No	Escape	2007	84	1271	2765	Headaches, dizziness, seizures	3TC ABC ATVr	1.1	46	87	36242	+	– ++	Yes	<50	<40	Alive, cognitive impairment
35 M	NA	450	Yes	Minor infection	1999	214	0	21 700	Dementia	AZT 3TC IDVr	0.8	80	NA	1200	+	ND	Yes	<50	<50	Total recovery
59 F	NA	NA	NA	ND	NA	NA	30	NA	Confusion, seizures	ABC 3TC LPVr	0.52	30	78	NA	+	ND	Yes	NA	NA	Death 1 mo after onset
49 M	NA	230	Yes	Minor infection	2008	114	0	200	Confusion	LPV ABV 3TC	1.57	19	68	3200	+	ND	Yes	<50	<40	Alive, cognitive impairment
39 M	198	900	Yes	ND	2008	742	70	201	Dizziness, memory disorders	3TC ABC ATVr	1.1	26	65	3294	+	ND	Yes	<50	<40	Total recovery

eviations: ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; ATVr, atazanavir boosted with ritonavir; AZT, zidovudine; BB, brain biopsy; cART, combined antiretroviral therapy; CSF, cerebrospinal fluid; DDI, didanosine; IRIS, immune reconstitutio
nmatory syndrome; F, female; fAPVr, fosamprenavir boosted with ritonavir; FTC, emtricitabine; IDV, indinavir; IDVr, indinavir boosted with ritonavir; Immu, immunological; LPV, lopinavir; LPVr, lopinavir boosted with ritonavir; M, male; MRI, magnet
hance imaging; NA, not available; ND, not determined; pVL, plasma viral load; TDF, tenofovir; T20, enfuvirtide; 3TC, lamivudine.

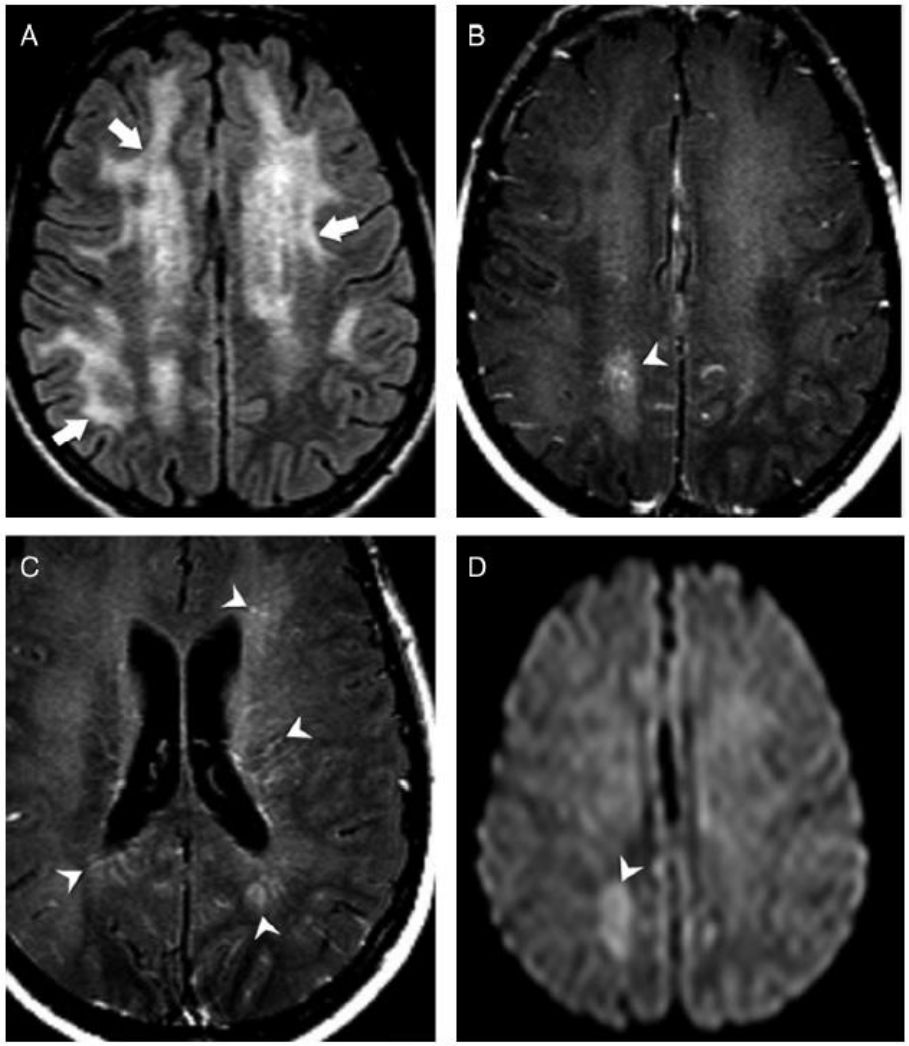


Figure 1. Bilateral and diffuse T2 and fluid-attenuation inversion recovery (FLAIR) high-signal intensities on brain magnetic resonance imaging. *A*, Bilateral and diffuse FLAIR high-signal intensities (arrow). *B* and *C*, Postgadolinium T1-weighted spin-echo imaging combined with magnetization transfer reveals multiple punctate or linear gadolinium-enhanced lesions (arrowheads). *D*, Restricted diffusion lesion at the same perivascular locations (arrowhead).

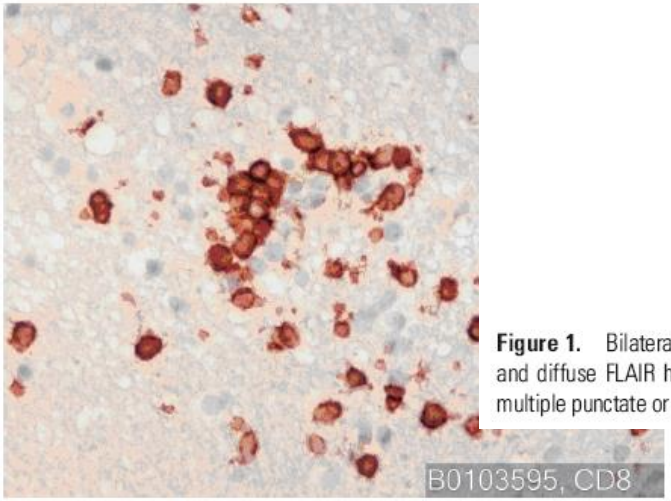


Figure 2. Diffuse brain parenchymal infiltration by $CD8^+$ lymphocytes (abacavir peroxidase method, Diaminobenzidine revelation with a monoclonal antibody raised against CD8 lymphocytes, Dako; patient 1).

Equilibre stable

Patients asymptomatiques

Equilibre instable

Neuro inflammation persistante ?

TNC

EVIH dissociée

Phénomènes aigus ou subaigus

Théorie domino, trebuchet, « hit and run » ou « push and pull »

ET8

Wang et al. 2006, Scaravilli et al. 2007, McCrossan et al. 2006, Price et al. 2000, Tsunoda et al. 2005, Shacklett et al. 2004

INTERNAL MEDICINE

□ CASE REPORT □

CD8 Encephalitis Caused by Persistently Detectable Drug-resistant HIV

Hiroshi Morioka[1,2], Naoki Yanagisawa[2], Shugo Sasaki[2], Noritaka Sekiya[3], Akihiko Suganuma[2], Akifumi Imamura[2], Atsushi Ajisawa[2,4] and Shuji Kishida[5]

Abstract

We herein report a 52-year-old man infected with human immunodeficiency virus (HIV) who was referred to our hospital due to the development of severe neurocognitive disorders and bilateral leukoencephalopathy. He has been treated with antiretroviral agents for 17 years, but low-level viremia has been detected consistently prior to admission. Drug resistant testing of the serum and the cerebrospinal fluid (CSF) both demonstrated a M184V mutation. A brain biopsy revealed perivascular $CD8^+$ T-lymphocyte infiltration, leading to the diagnosis of CD8 encephalitis. The clinical symptoms improved drastically after changing to a nucleoside reverse transcriptase inhibitor sparing regimen, which subsequently decreased the HIV viral load to an undetectable level in both the serum and CSF.

Key words: HIV, CD8 encephalitis, HIV-associated neurocognitive disorder (HAND)

(Intern Med 55: 1383-1386, 2016)
(DOI: 10.2169/internalmedicine.55.5783)

INTERNAL MEDICINE

□ CASE REPORT □

CD8 Encephalitis Caused by Drug-resistar

Hiroshi Morioka[1,2], Naoki Yanagisawa[2], Sh
Akihiko Suganuma[2], Akifumi Imamura[2], Ats

Abstract

We herein report a 52-year-old man infected with human
to our hospital due to the development of severe neurocogni
He has been treated with antiretroviral agents for 17 years,
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the diagnosis of CD8 encephalitis. The clinical symptoms im
reverse transcriptase inhibitor sparing regimen, which subsec
tectable level in both the serum and CSF.

Key words: HIV, CD8 encephalitis, HIV-associated neurocog

(Intern Med 55: 1383-1386, 2016)
(DOI: 10.2169/internalmedicine.55.5783)

Intern Med 55: 1383-1386, 2016 DOI: 10.2169/internalmedicine.55.5783

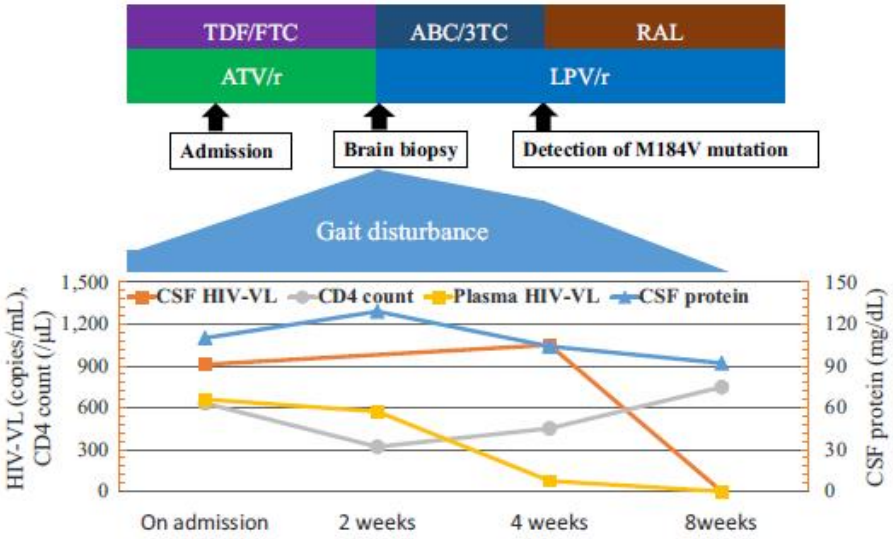


Figure 2. Clinical course. HIV: human immunodeficiency virus, VL: viral load, CSF: cerebrospinal fluid, TDF/FTC: tenofovir/emtricitabine, ATV/r: atazanavir/ritonavir, ABC/3TC: abacavir/lamivudine, LPV/r: lopinavir/ritonavir, RAL: raltegravir

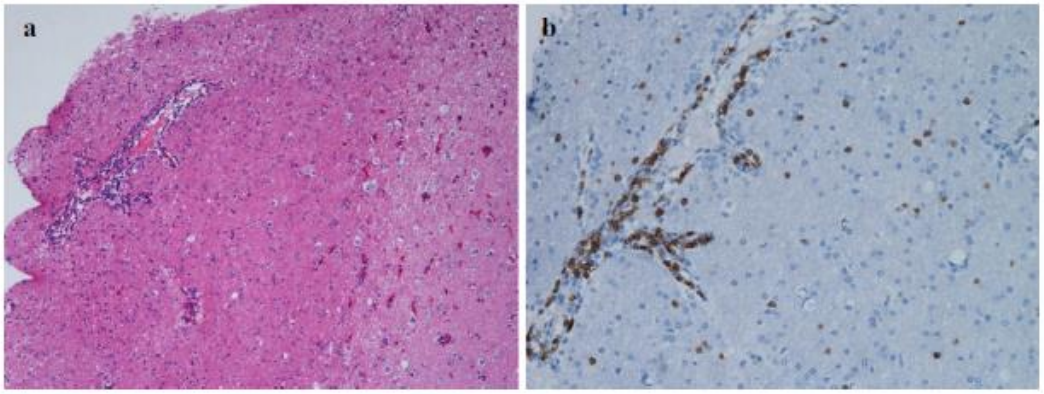


Figure 3. A brain biopsy specimen consist mainly cortical and subcortical layers and partial abnormal white matter. CD8 immunostaining revealed marked perivascular $CD8^+$ T-lymphocyte infiltration (a: Hematoxylin and Eosin staining, b: CD8 immuno-stain).

CROI 2016 Highlights: Neurologic Complications Volume 24 Issue 1 May/June 2016

I. CNS as an HIV reservoir, describing the emergence of CNS compartmentalization of HIV before the initiation of antiretroviral Therapy

In a complementary longitudinal study, Bowman and colleagues (Abstract 401) confirmed a relationship between HIV compartmentalization in the CNS and neurocognitive response to antiretroviral therapy. Using single-genome amplification or deep sequencing of HIV env in CSF and blood, the investigators detected HIV compartmentalization in the CNS in 35% of 28 study participants before the initiation of antiretroviral therapy at CD4+ cell counts below 400 copies/μL. The effect of HIV compartmentalization was examined with respect to performance on a detailed neuropsychologic testing battery at baseline and at 6 months and 12 months after starting treatment. At the baseline visit, no laboratory parameters differed between the compartmentalized and noncompartmentalized groups, and neurocognitive impairment was not statistically significantly higher in the group with compartmentalization than in the group without. However, at 6 months and 12 months after initiation of antiretroviral treatment, the overall global deficit score, a measure of neurocognitive impairment, was statistically significantly lower in the noncompartmentalized than in the compartmentalized group. An interpretation of this finding may be that measurable HIV compartmentalization in the CNS before the initiation of antiretroviral therapy reflects a robust site of HIV replication in the CNS that is less responsive to therapy due to reduced antiretroviral exposure in CNS tissues or cells of replication. Additionally, or alternately, compartmentalized HIV replication in the CNS before antiretroviral treatment may result in more severe inflammatory and neural injuries that are irreversible or slower to reverse with therapy.

CROI 2016 Highlights: Neurologic Complications
Volume 24 Issue 1 May/June 2016

II. Viral escape with evidence of HIV replication
in the CNS despite systemically suppressive therapy

In a related analysis, Evering and colleagues (Abstract 406) used single-genome amplification to assess the relationship between drug resistance mutations in blood and CSF and the presence of HAND in 12 participants with virologic failure during antiretroviral therapy in the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study. Five participants had normal neurocognitive function and 7 had HAND. The presence of drug resistance mutations in CSF and blood was statistically significantly higher among individuals with HAND, and compartmentalization of HIV-1 pol in the CNS was more frequent among individuals with HAND. Moreover, 43% of the participants with HAND had drug resistance mutations detected in CSF that were not detected in the blood. These findings may contribute to an understanding of the pathogenesis of HAND and, particularly, the development of viral escape in CSF among individuals without prolonged effective plasma viral suppression.

Activation microgliale cérébrale chez des patients VIH+ neuro-asymptomatiques (1)

- Etude cas-témoins
  - cas (n = 7) : VIH+ > 18 ans, sous ARV, CV < 50 c/ml > 6 mois
  - témoins (n = 9) : adultes VIH- ne recevant aucun traitement
  - dans les 2 groupes, exclusion syphilis, hépatite B, C, signes neurologiques ou troubles neurocognitifs, usage de drogues récréatives, d'alcool

- Méthode : réalisation le même jour d'IRM séquences T1 et T2, PET scan cérébral avec injection du ligand ^{11}C-(R)-PK11195, tests neurocognitifs sur programme informatique

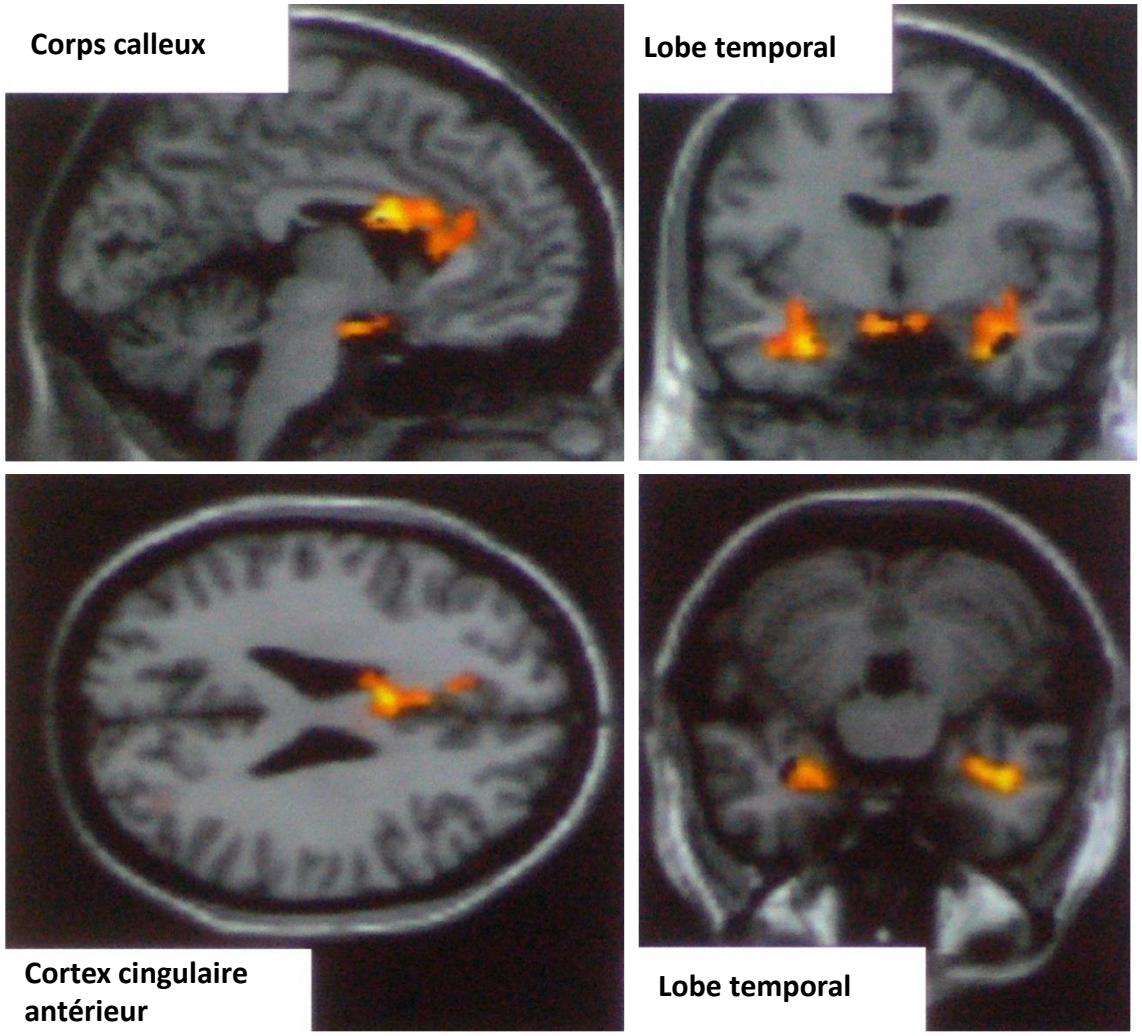
  Le PK11195 se fixe avec une haute affinité sur les cellules microgliales activées
  Le PK11195 peut être radiomarqué avec C11 et utilisé comme traceur avec un PET scan pour identifier et quantifier l'activation microgliale

- Résultats
  - **chez les patients VIH+, virologiquement contrôlés, parfaitement asymptomatiques sur le plan neurologique, l'activation microgliale (fixation du PK11195) est significativement plus importante que chez les sujets VIH- dans le corps calleux, le lobe frontal et temporal, le cortex cingulaire antérieur et postérieur**
  - l'activation microgliale n'est pas corrélée au nadir de CD4 ni à la durée infection VIH

Garvey L, CROI 2012, Abs. 78LB

Activation microgliale cérébrale chez des patients VIH+ neuro-asymptomatiques (2)

Activation microgliale (PET Scan PK11195)



Association très significative entre activation microgliale (fixation PK11195) dans le corps calleux (p = 0,001) et le cortex cingulaire antérieur (p = 0,031)

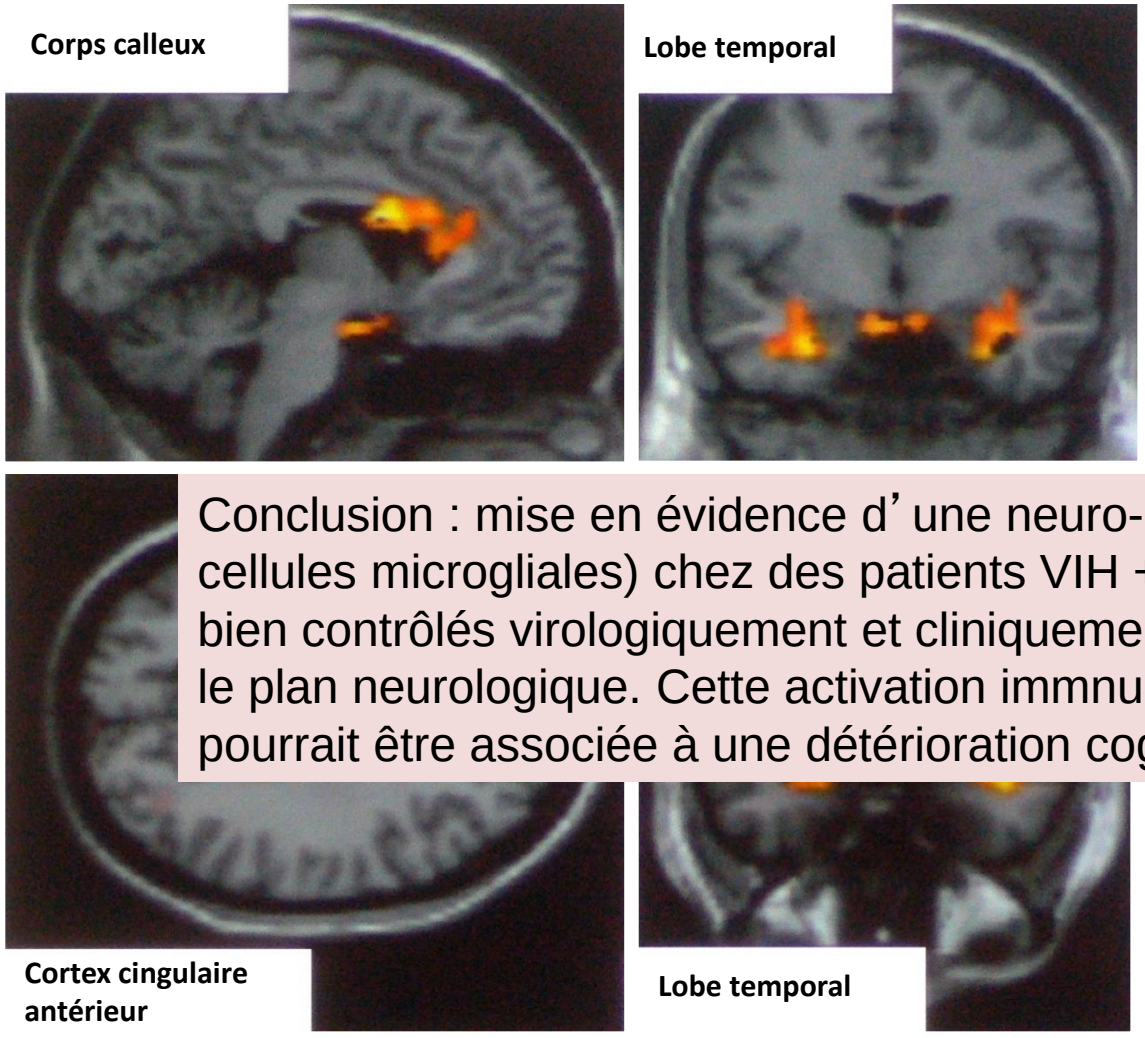
et

un défaut de fonction exécutive, chez les patients VIH+

Garvey L, CROI 2012, Abs. 78LB

Activation microgliale cérébrale chez des patients VIH+ neuro-asymptomatiques (2)

Activation microgliale (PET Scan PK11195)



Association très significative entre activation microgliale (fixation PK11195) dans le corps calleux (p = 0,001) et le cortex cingulaire antérieur (p = 0,031)

Conclusion : mise en évidence d'une neuro-inflammation (activation cellules microgliales) chez des patients VIH + sous traitement ARV, bien contrôlés virologiquement et cliniquement asymptomatiques sur le plan neurologique. Cette activation immnunitaire persistante pourrait être associée à une détérioration cognitive progressive.

VIH+

Garvey L, CROI 2012, Abs. 78LB

CROI 2016 Highlights: Neurologic Complications
Volume 24 Issue 1 May/June 2016

III. Evolution of macrophage-tropic HIV Env presumed to facilitate productive infection of resident CNS macrophages and microglial cells

To better define the virologic basis of CSF viral escape, Joseph and colleagues (Abstract 402) described the virologic features of HIV env derived from individuals with asymptomatic CSF viral escape identified in a cohort study of 96 individuals receiving more than 1 year of antiretroviral therapy with plasma viral suppression. Six of these individuals were identified as having asymptomatic CSF viral escape. Of these 6 individuals, 2 had longitudinal sampling that revealed resolution of viral escape at 9 months, with 1 participant having continued persistence of viral escape (HIV RNA level 356 copies/mL in CSF, with undetectable plasma HIV RNA) at 8 months. Single-genome amplification sequencing of HIV env from CSF-derived samples in the participant with transient viral escape revealed a purely T-cell tropic, clonally expanded population. Similar examination of samples with persistent CSF viral escape revealed a genetically diverse HIV population with enhanced ability to infect cells with low CD4 receptor density, suggesting adaptation to a macrophage-tropic virus. These data suggest that HIV detected in CSF in individuals receiving systemically suppressive antiretroviral treatment can in some cases reflect low-level viral replication within macrophages or microglial cells.

Prise en Charge

- Rendre la charge virale indétectable, plasma et LCR
- Traiter les comorbidités
- Stratégie de renforcement cognitif collectif…type alzheimer?
- Ttt ARV à haut **CPE CNS** penetration efficiency score = score de Charter?
  - Association neuro active si > ou = à 8 ?
- **Rôle des ttt ARV dans les troubles** (efavirenz)
- **Paroxétine** (CROI 2016)

SYSTEMIQUE

HIV

immunosuppression

Activation Immune systémique

ARV

IOP

Restauration immunitaire

COMPARTIMENTATION VIRALE, IMMUNE, THERAPEUTIQUE

CEREBRAL

HIV

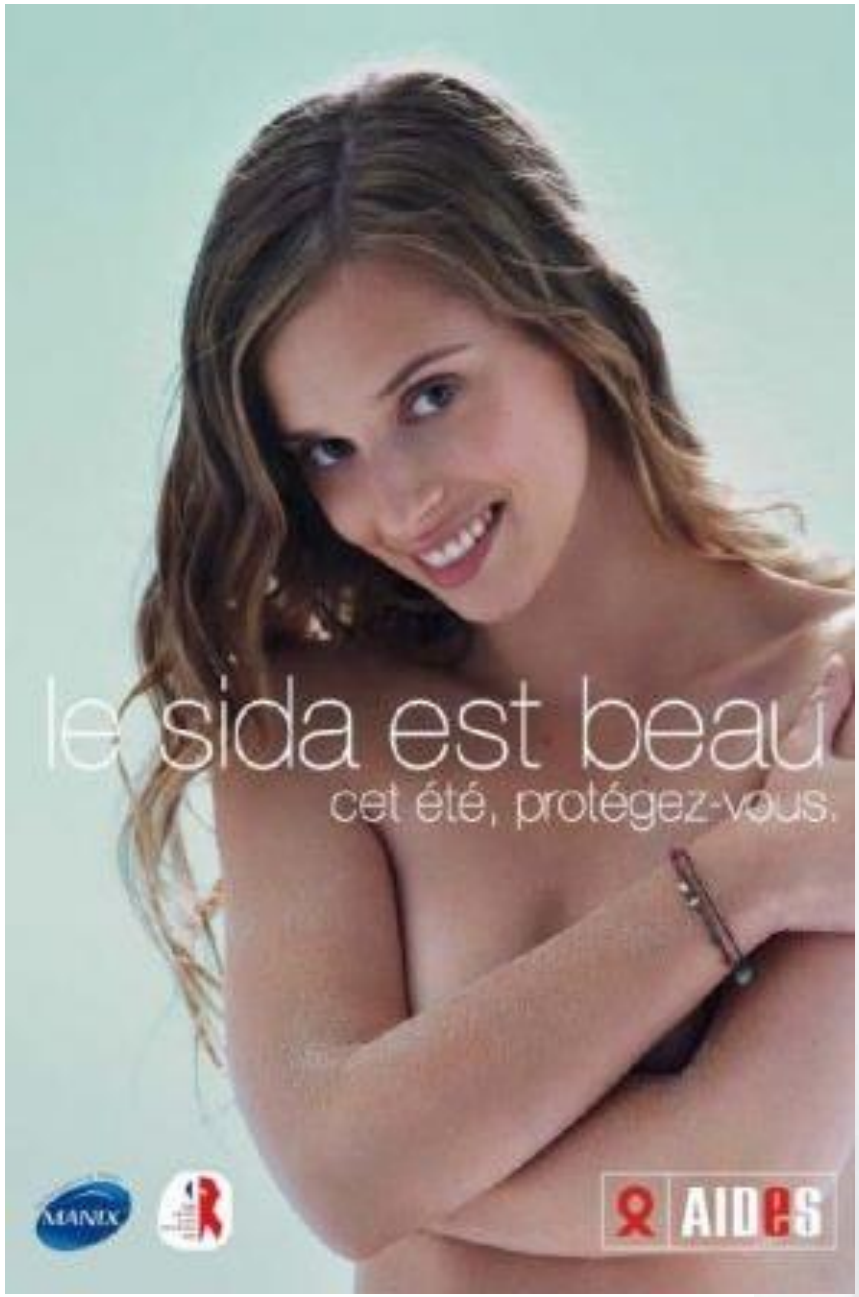
IOP

Activation Immune/HIV cérébrale

Pénétration
Drug résistance
Toxicité directe

HAND
ENCEPHALITE CD8

IRIS


le sida est beau
cet été, protégez-vous.
MANIX
AIDES


Dick dit : "Les préservatifs, c'est comme le papier-toilette,il faut toujours en avoir d'avance."
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Atteintes périphériques

- Polyneuropathies
  - Iatrogène
  - VIH
- Multineuropathies
- PRN
- Dysautonomie

- Atteintes musculaires
  - Liées au VIH
  - Médicamenteuses

HIV/AIDS – Research and Palliative Care

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REVIEW

HIV-related neuropathy: current perspectives

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Sonja G Schütz
Jessica Robinson-Papp

Department of Neurology, Mount Sinai School of Medicine, New York, NY, USA

Abstract: Distal symmetric polyneuropathy (DSP) related to human immunodeficiency virus (HIV) is one of the most common neurologic complications of HIV, possibly affecting as many as 50% of all individuals infected with HIV. Two potentially neurotoxic mechanisms have been proposed to play a crucial role in the pathogenesis of HIV DSP: neurotoxicity resulting from the virus and its products; as well as adverse neurotoxic effects of medications used in the treatment of