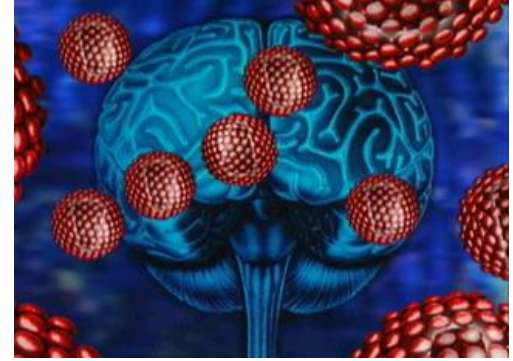


SNC *et* VIH

Dr Antoine MOULIGNIER

Service de Neurologie et UNV

Fondation Ophtalmologique
Adolphe de Rothschild

Données épidémiologiques

Global summary of the AIDS epidemic | 2009

Number of people living with HIV	Total	**33.3 million** [31.4 million–35.3 million]
	Adults	**30.8 million** [29.2 million–32.6 million]
	Women	**15.9 million** [14.8 million–17.2 million]
	Children (<15 years)	**2.5 million** [1.6 million–3.4 million]
People newly infected with HIV in 2009	Total	**2.6 million** [2.3 million–2.8 million]
	Adults	**2.2 million** [2.0 million–2.4 million]
	Children (<15 years)	**370 000** [230 000–510 000]
AIDS deaths in 2009	Total	**1.8 million** [1.6 million–2.1 million]
	Adults	**1.6 million** [1.4 million–1.8 million]
	Children (<15 years)	**260 000** [150 000–360 000]

7000 infections par jour

World Health Organization

UNAIDS

Adults and children estimated to be living with HIV | 2009

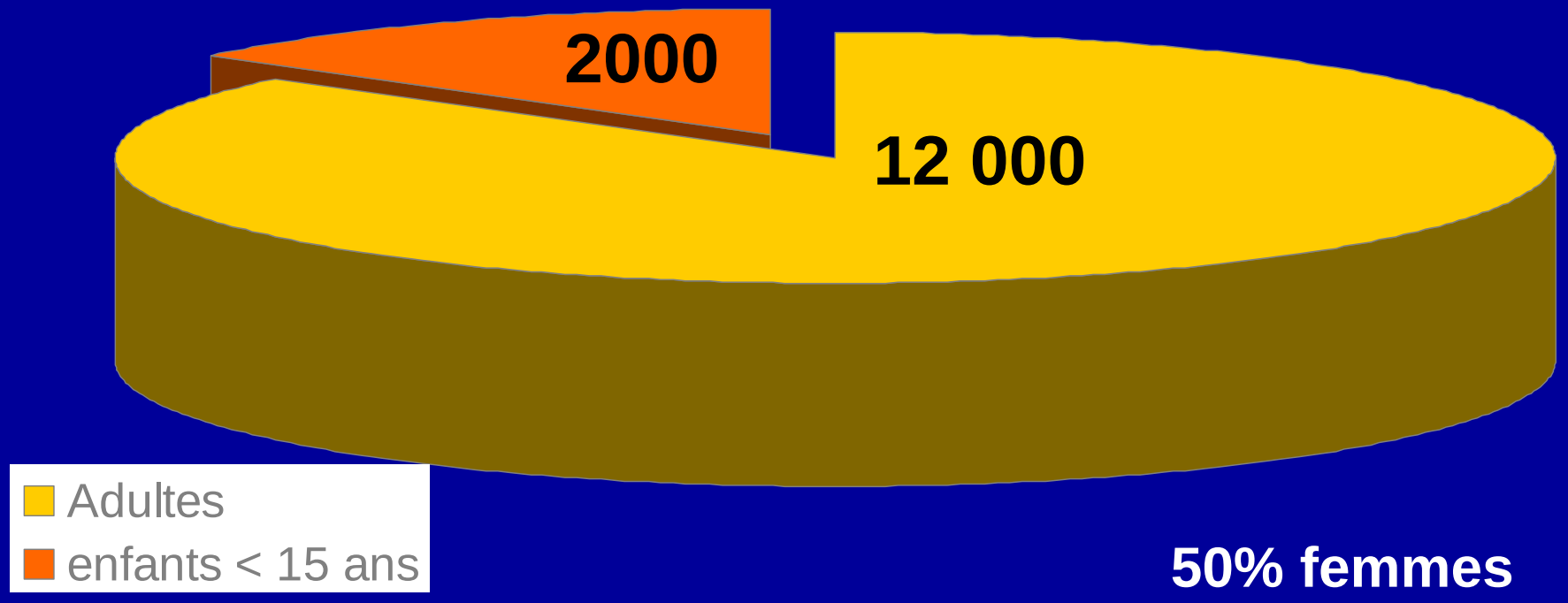
Total: 33.3 million [31.4 million – 35.3 million]

World Health Organization

UNAIDS

Nouveaux cas d'infection à VIH par jour en 2004

14 000 nouveaux cas / j

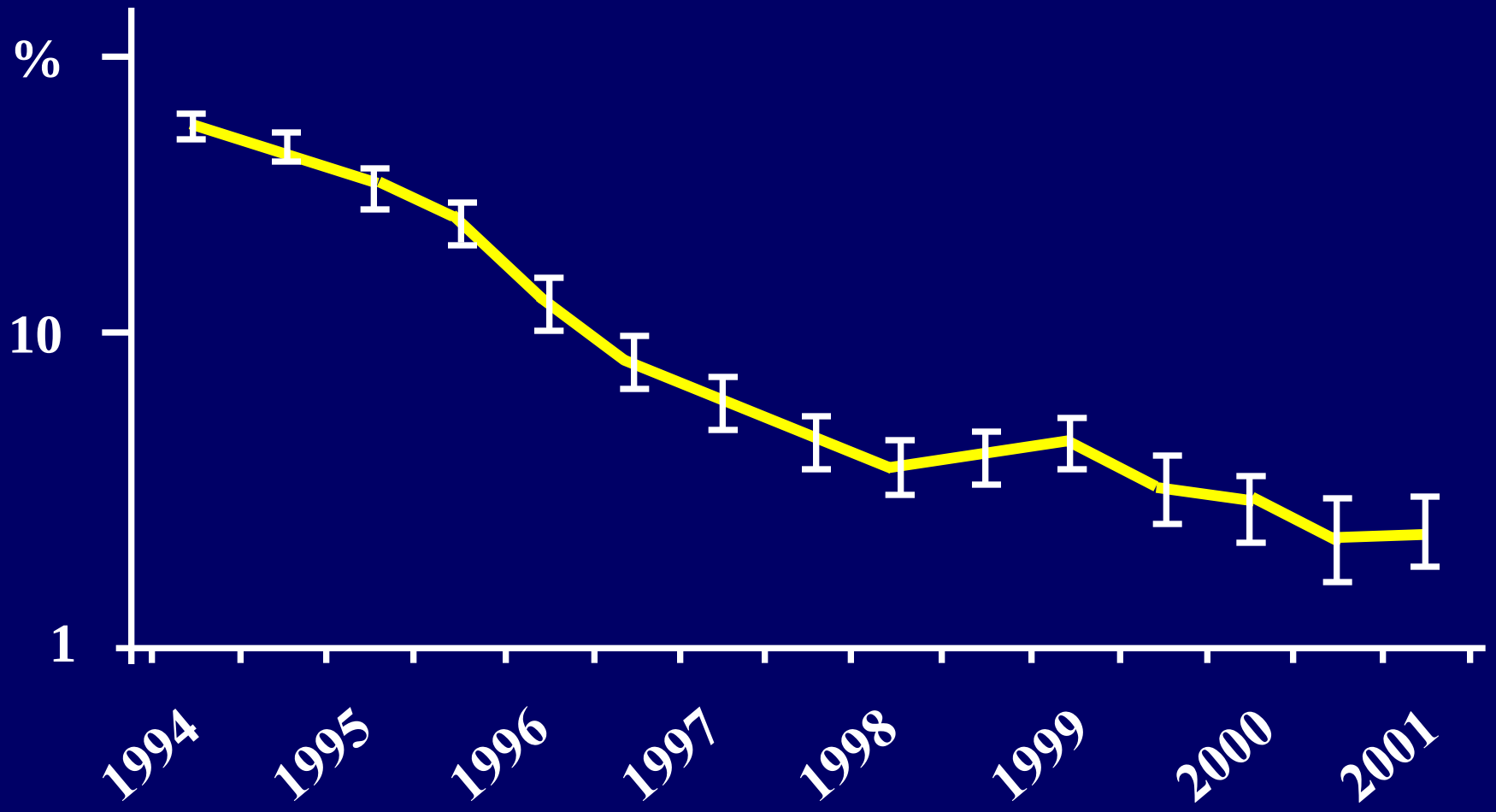


50% femmes
50% 15-24 ans

SITUATION DANS LE MONDE

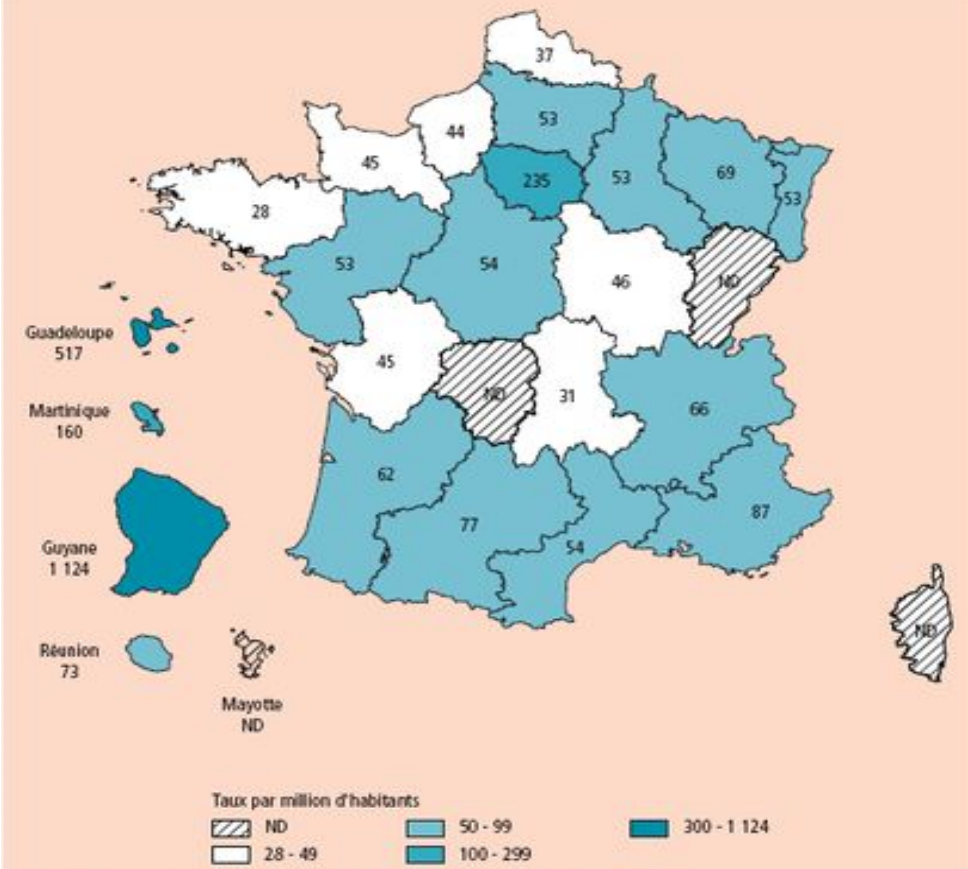
- **70% : contamination hétérosexuelle**
- **90% : pas d ’accès aux traitements**
- **1998 : SIDA avant paludisme et tuberculose**
- **Espérance de vie 59 ans ↘ 45 ans en 2005**

Décès et SIDA
EuroSIDA study group



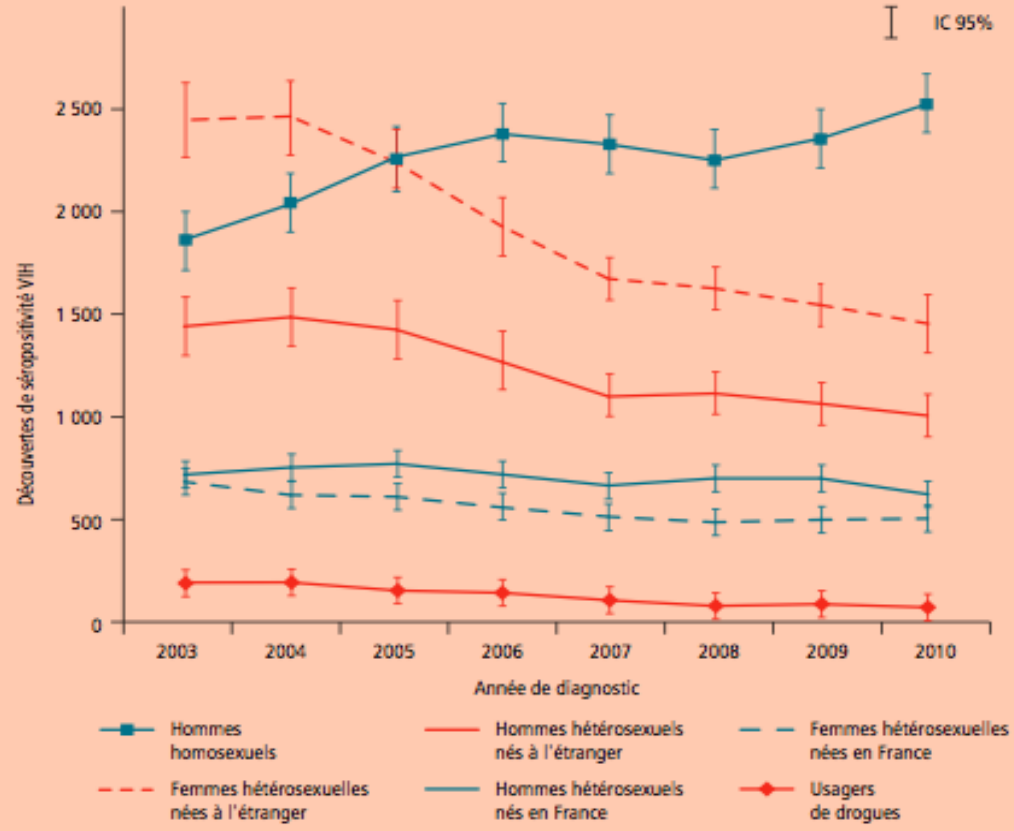
150 000 personnes VIH+ en France

Figure 5 Taux de découvertes de séropositivité VIH par million d'habitants, par région, France, 2010 / *Figure 5 Rate of new HIV diagnoses by million inhabitants, by region, France, 2010*



Données au 31/12/2010 corrigées pour les délais de déclaration et la sous-déclaration
ND = correction 2010 non disponible : les calculs de correction ne sont pas possibles pour certaines régions, en général du fait de délais de transmission trop irréguliers des déclarations.

Figure 4 Découvertes de séropositivité VIH par mode de contamination, sexe, lieu de naissance et année de diagnostic, France (données au 31/12/2010 corrigées pour les délais de déclaration, la sous-déclaration et les valeurs manquantes) / *Figure 4 New diagnoses of HIV infection by transmission group, sex, place of birth and year of diagnosis, France (data reported by 31/12/2010 adjusted for reporting delays underreporting and missing values)*



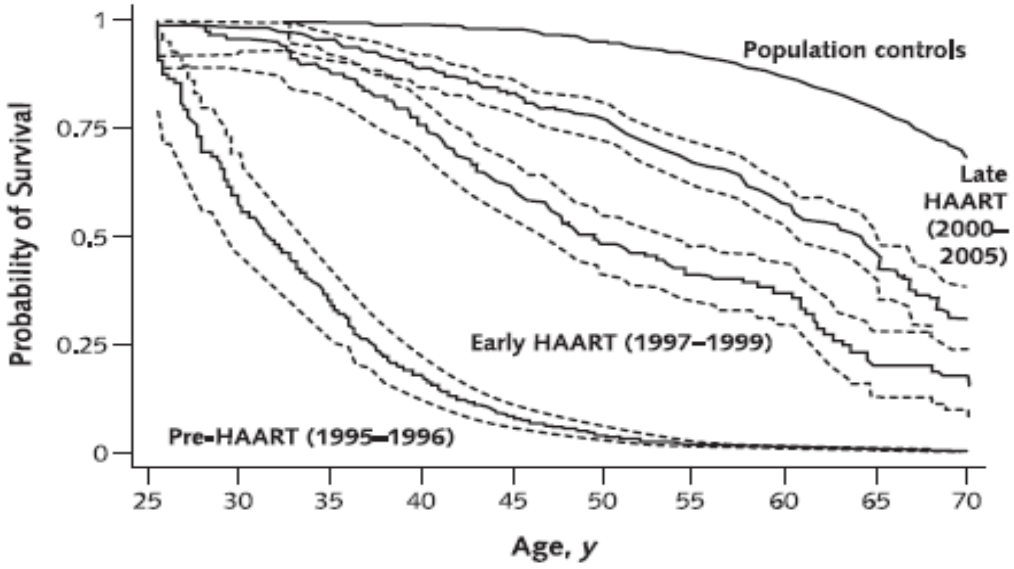
BEH 2011

Actualités épidémiologiques

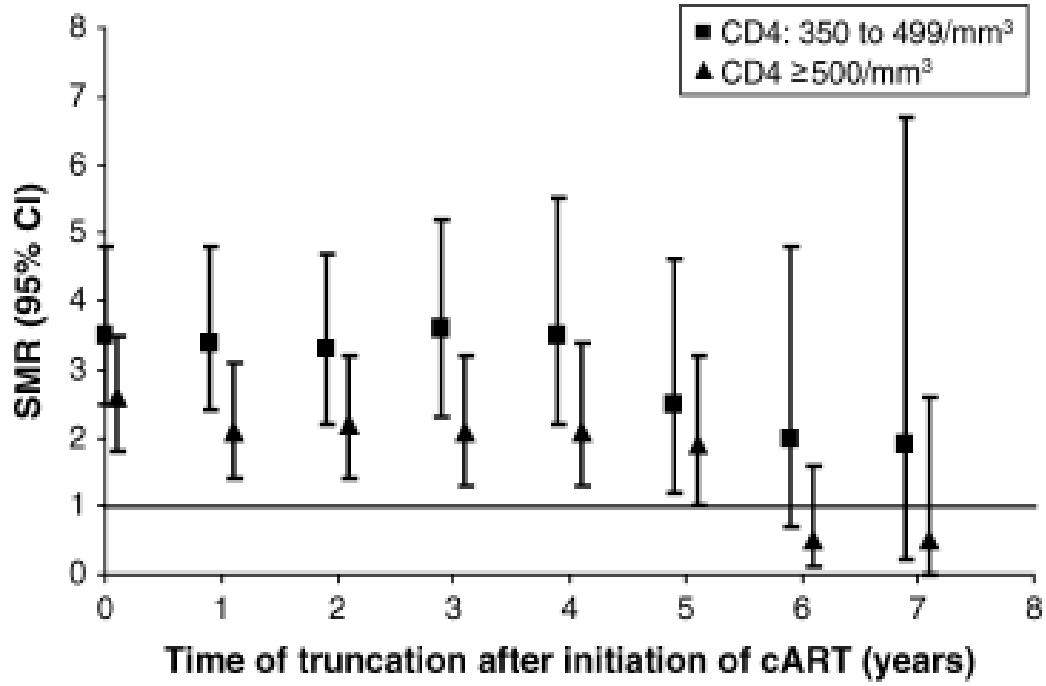
- **Environ 30 000 personnes non dépistées qui s'ignorent VIH+ en France**
- **Encore 7000 à 8000 nvelles contaminations /an**
- **30% de diagnostics trop tardifs (SIDA ou CD4 < 200/mm^3)**
- **Incidence élevée dans la communauté gay accompagnée d'attitudes addictives dures**

Pronostic global : données 10 ans après les HAART

Figure. Survival from age 25 years.



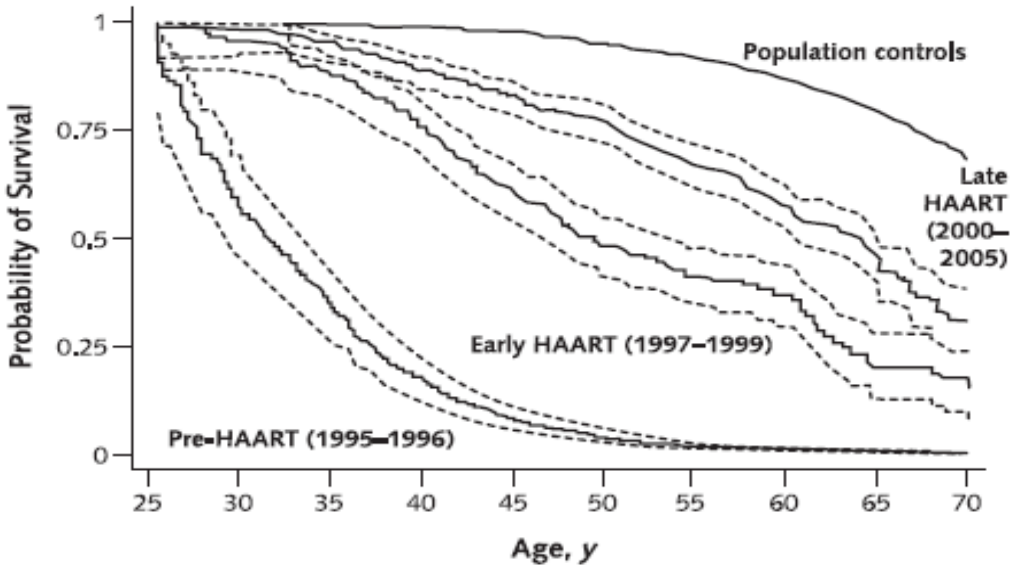
Lhose et al. Ann Intern Med 2007



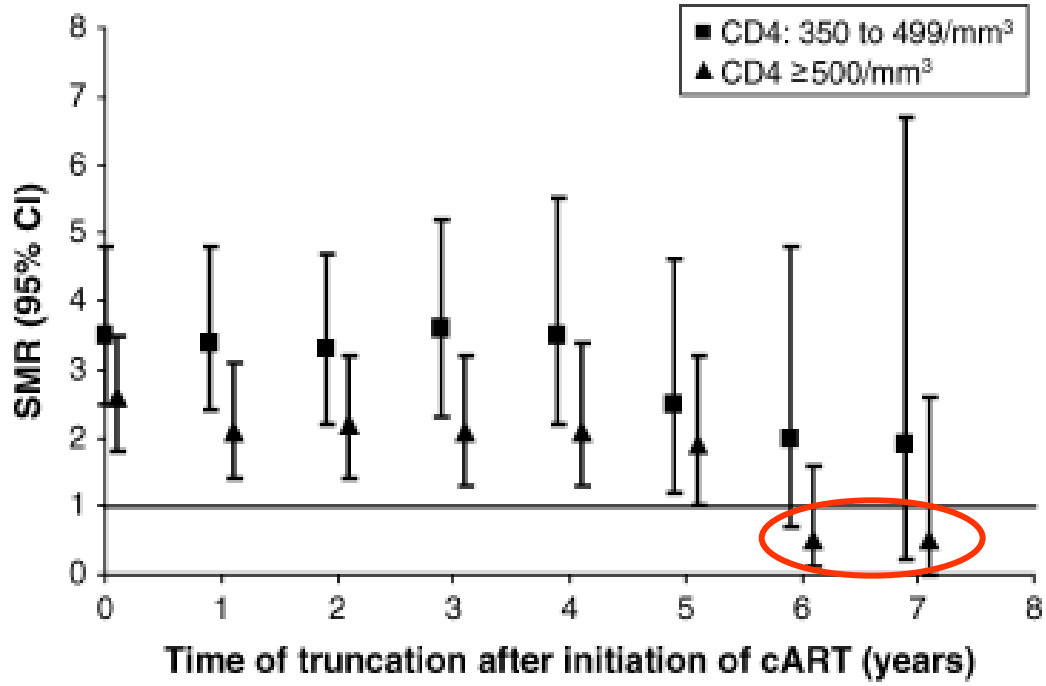
Leyden et al. JAIDS 2007

Pronostic global : nouvelle équation dans le VIH

Figure. Survival from age 25 years.



Lhose et al. Ann Intern Med 2007



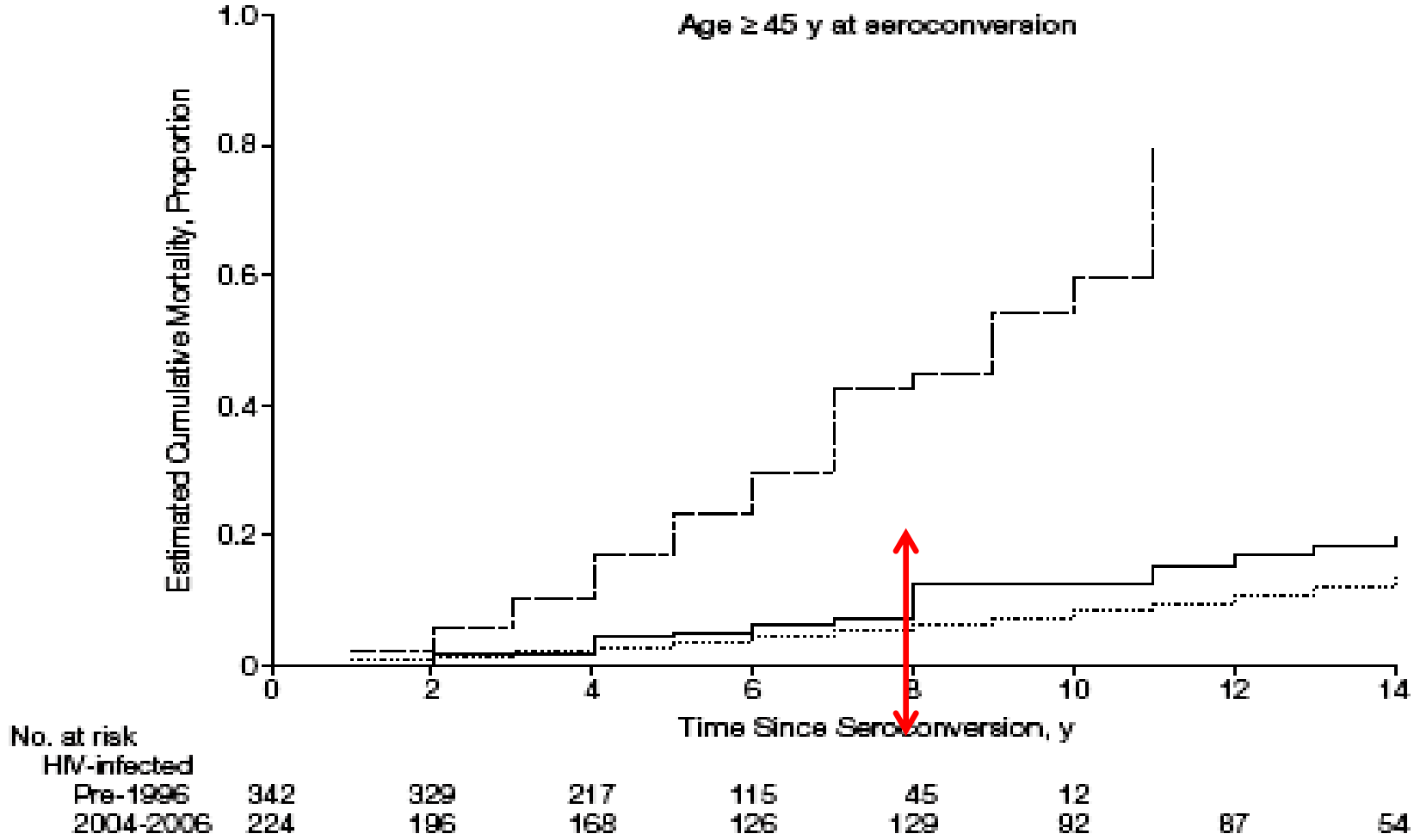
Leyden et al. JAIDS 2007

CV VIH indétectable + CD4>500 CD4/mm3

≥ 6 années consécutives

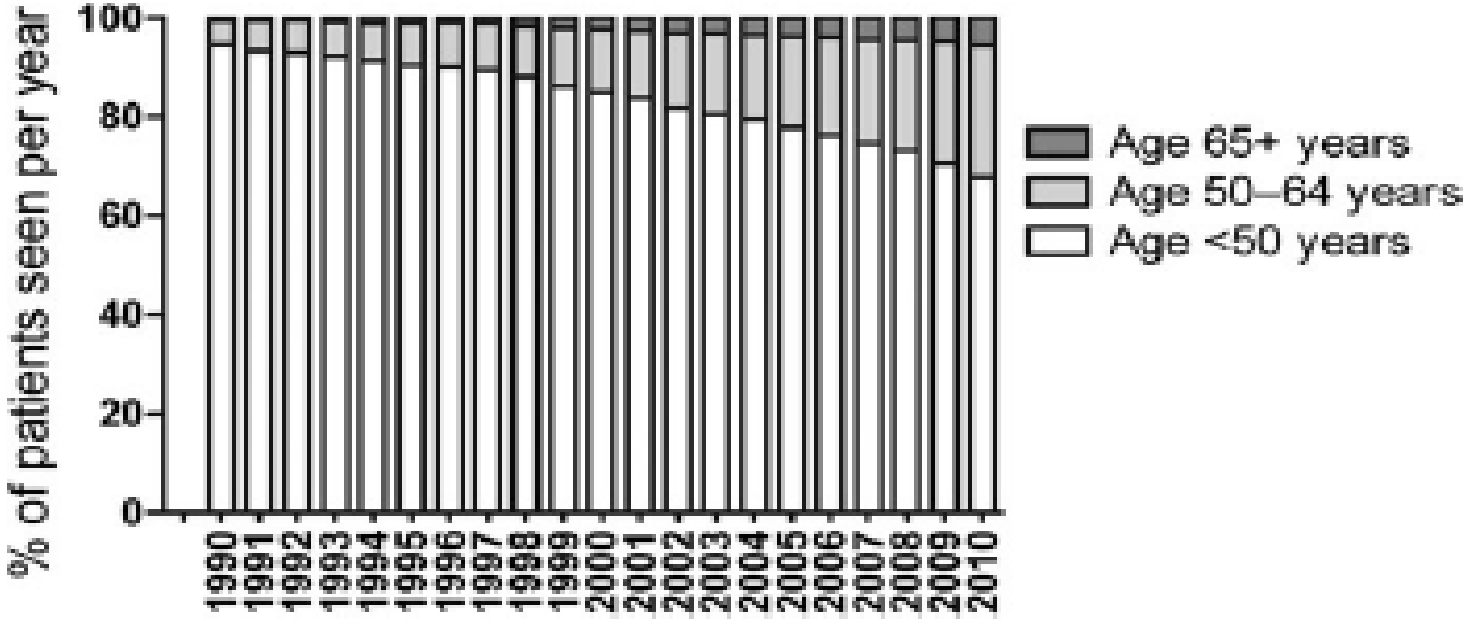
 # PC global VIH-

Mais équation fragile dans le temps

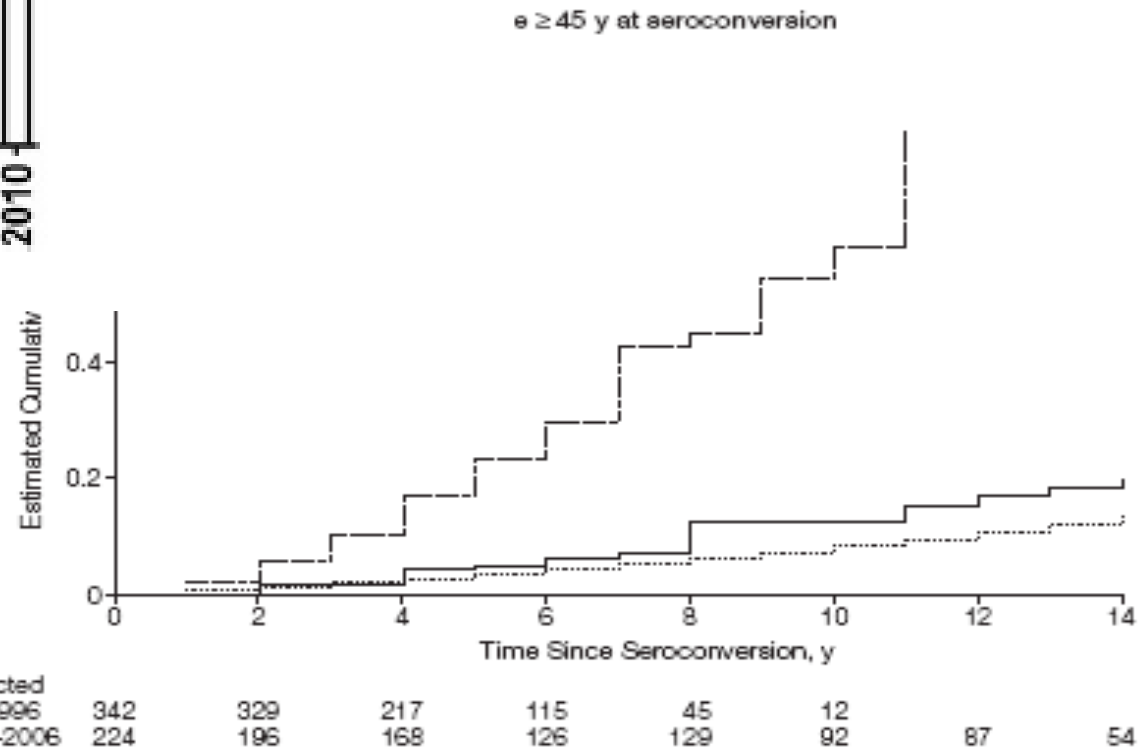


Bhaskaran K et al. JAMA 2008

Mais équation fragile dans le temps
Et le temps passe…



Hasse B et al. CID 2011



Age médian COREVIH : 48 ans
41% ≥ 50 ans
Ancienneté médiane : 12 ans

Bhaskaran K et al. JAMA 2008

Répercussions par organes

- **Sur-risque cardiovasculaire**
  - VIH et ARV
- **Cancers**
  - Classant sida et non classant
- **Maladie hépatique**
  - Surtout / co-infection HBV HCV
- **Maladie rénale**
  - VIH, ARV et autres
- **Déminéralisation osseuse**
  - VIH et ARV
- **Vieillissement cérébral**
  - Déclin cognitif
  - Neuro-vasculaire

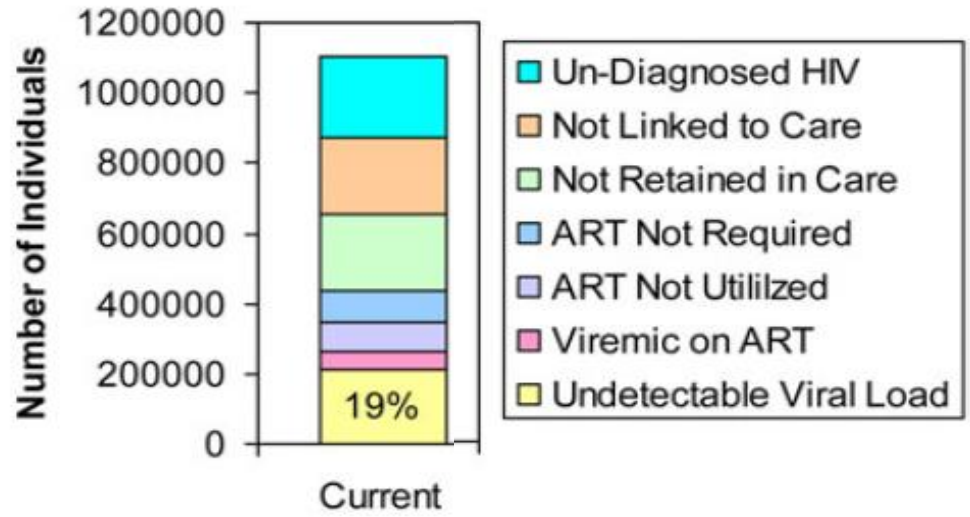
La population VIH en 2012.

VIH+

CV +

Morbidité liée au VIH/sida

Morbidité liée aux comorbidités



Gardner EM et al. CID 2011

La population VIH en 2012
50% « *contrôlée* »

VIH+
CV +

Morbidité liée au VIH/sida

Morbidité liée aux comorbidités

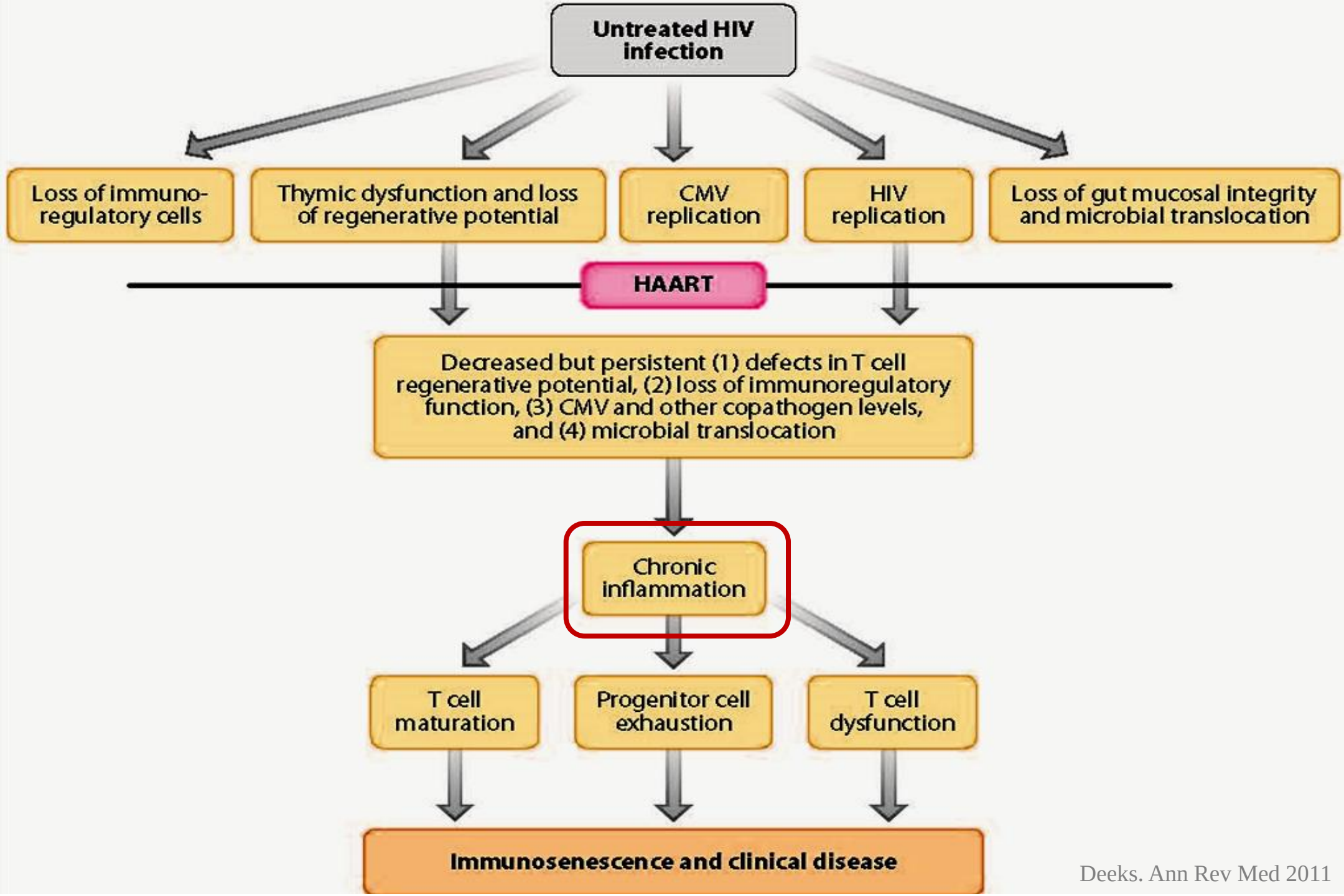
VIH+
CV –

Iatrogénie des ARV Syndrome métabolique

Krishnan S et al. JAIDS 2012

Activation immune persistante

Deeks SG. Ann Rev Med 2011



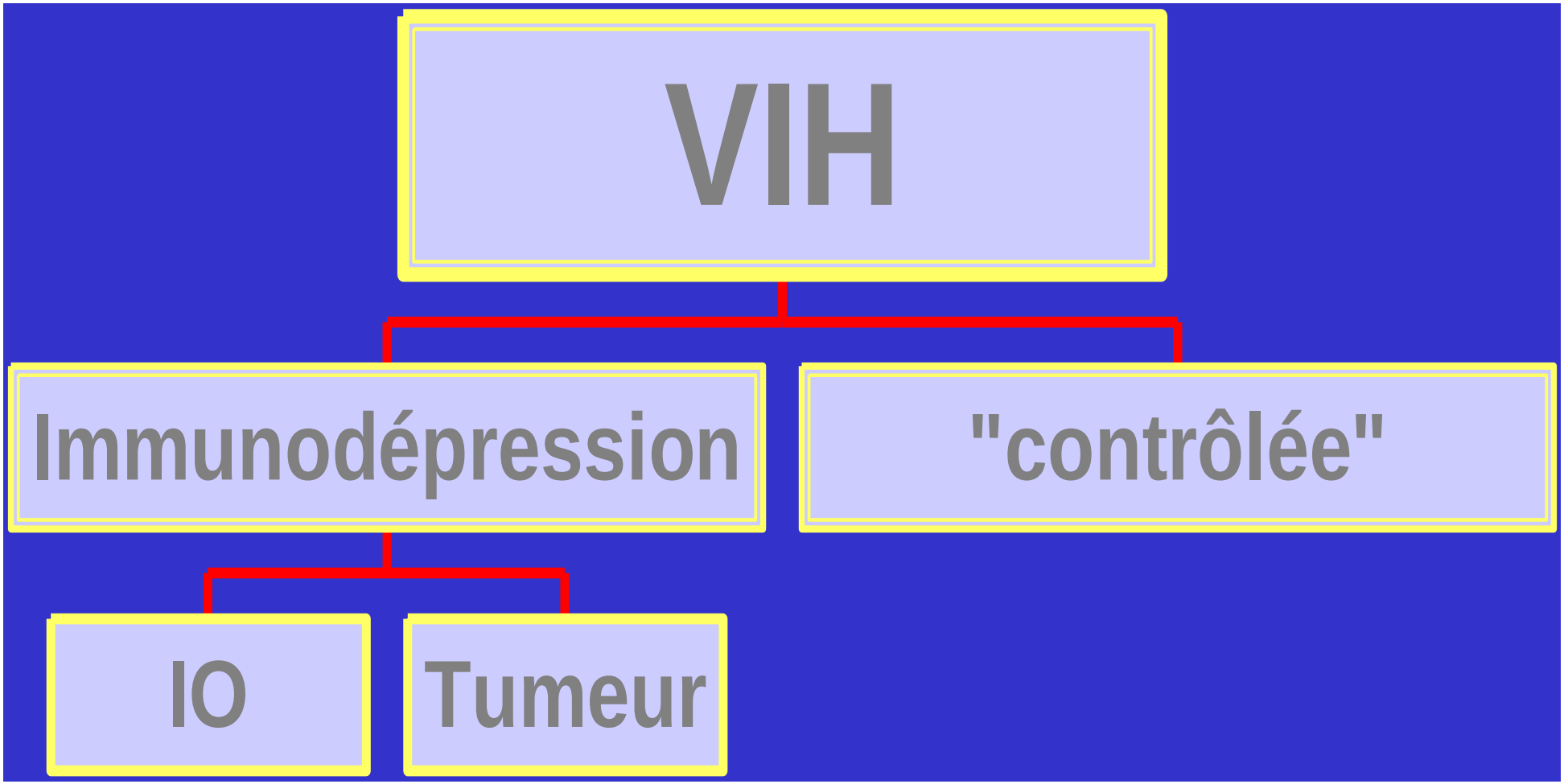
Deeks. Ann Rev Med 2011

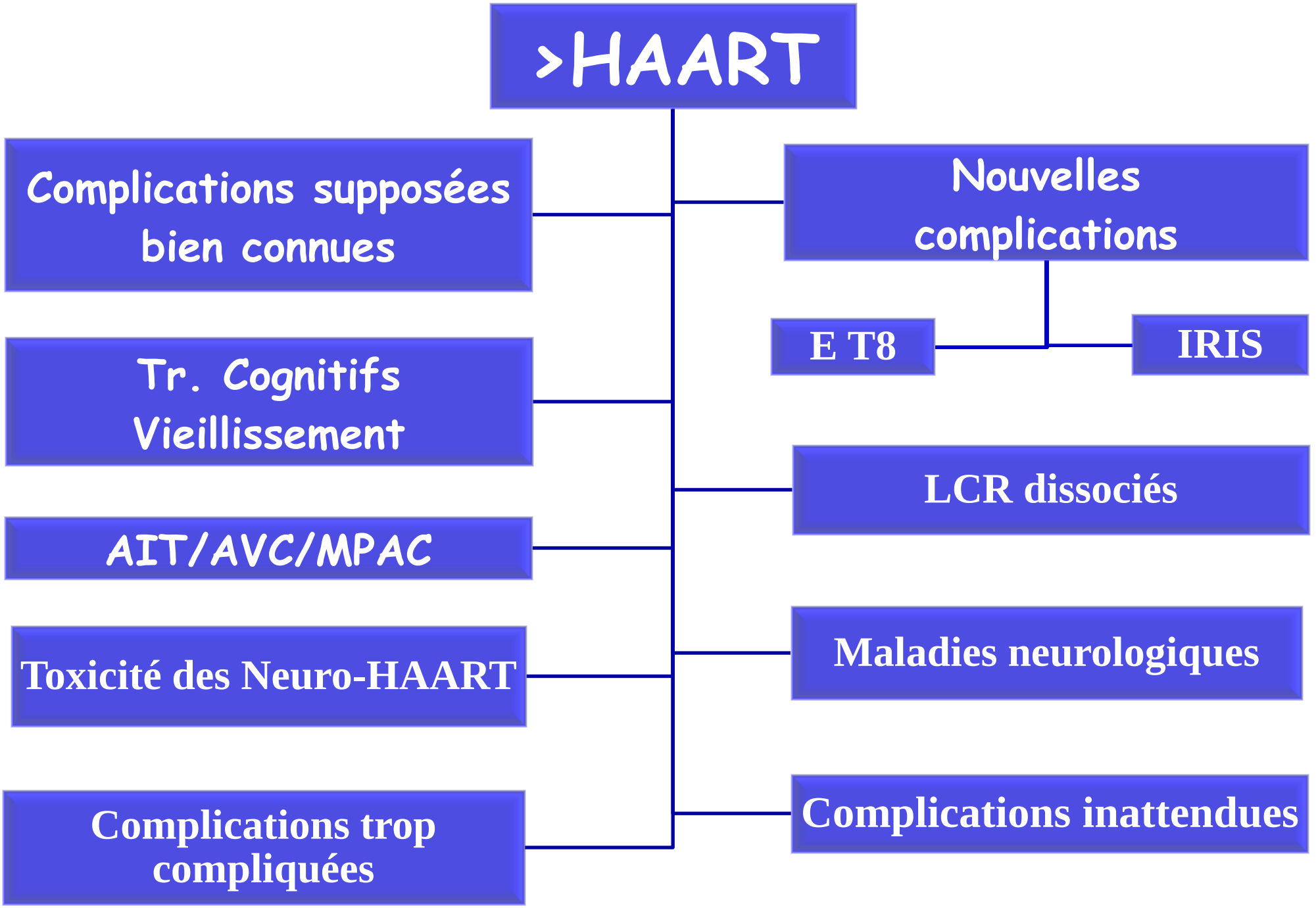
Tableau 1. Proportion de patients traités en succès virologique et en succès immunologique dans l'étude VESPA 2 en 2011

	Métropole	Martinique	Guadeloupe	Saint-Martin	Guyane	Réunion
	(N=3022)	(N=129)	(N=168)	(N=56)	(N=136)	(N=108)
% de patients traités	93	89	96	92	93	92
% des patients traités avec charge virale < 50 copies/mL	86	82	80	78	68	80
% des patients traités avec nombre de CD4 > 500/mm³	57	51	51	25	24	54

80-90% des patients des SMIT sont bien contrôlés

Atteinte du SNC



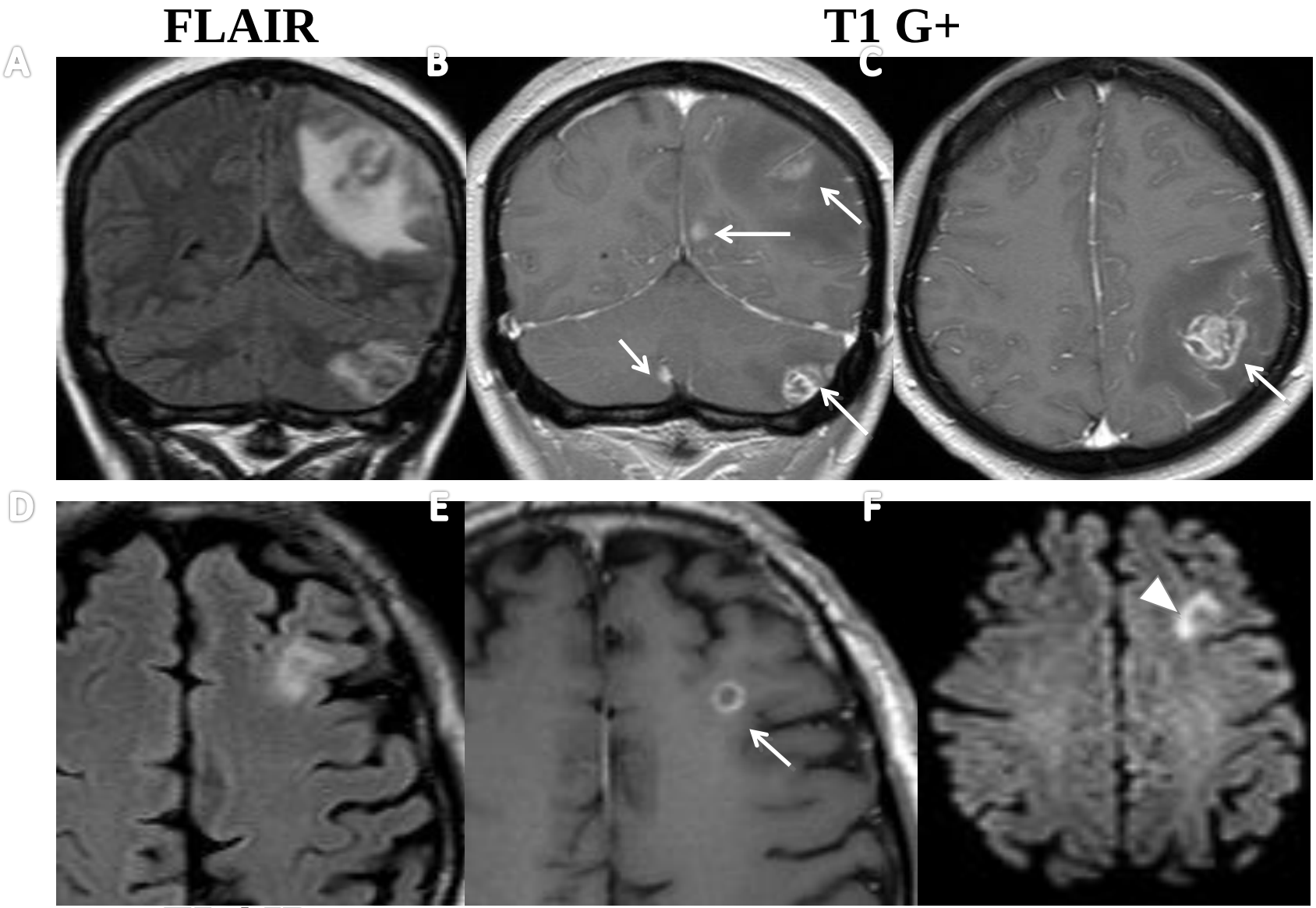

>HAART
Complications supposées bien connues
Tr. Cognitifs Vieillissement
AIT/AVC/MPAC
Toxicité des Neuro-HAART
Complications trop compliquées
Nouvelles complications
E T8
IRIS
LCR dissociés
Maladies neurologiques
Complications inattendues

Les infections opportunistes

- **VIH non connu ou patient non suivi, en rupture de traitement**
- **Immunodépression : CD4 < 200/mm^3**
- **Toxoplasmose, LEMP, BK/MAI, Syphilis, Cryptococcose,**

- ***CMV, VZV, HSV, EBV, HHV-6, HHV-8, entérovirus***
- ***Listériose, nocardiose,***
- ***Candidose, aspergillose, histoplasmose, coccidioïdomycose, blastomycose , mucormycose***
- ***Trypanosomiase, amibiase, cysticercose…***

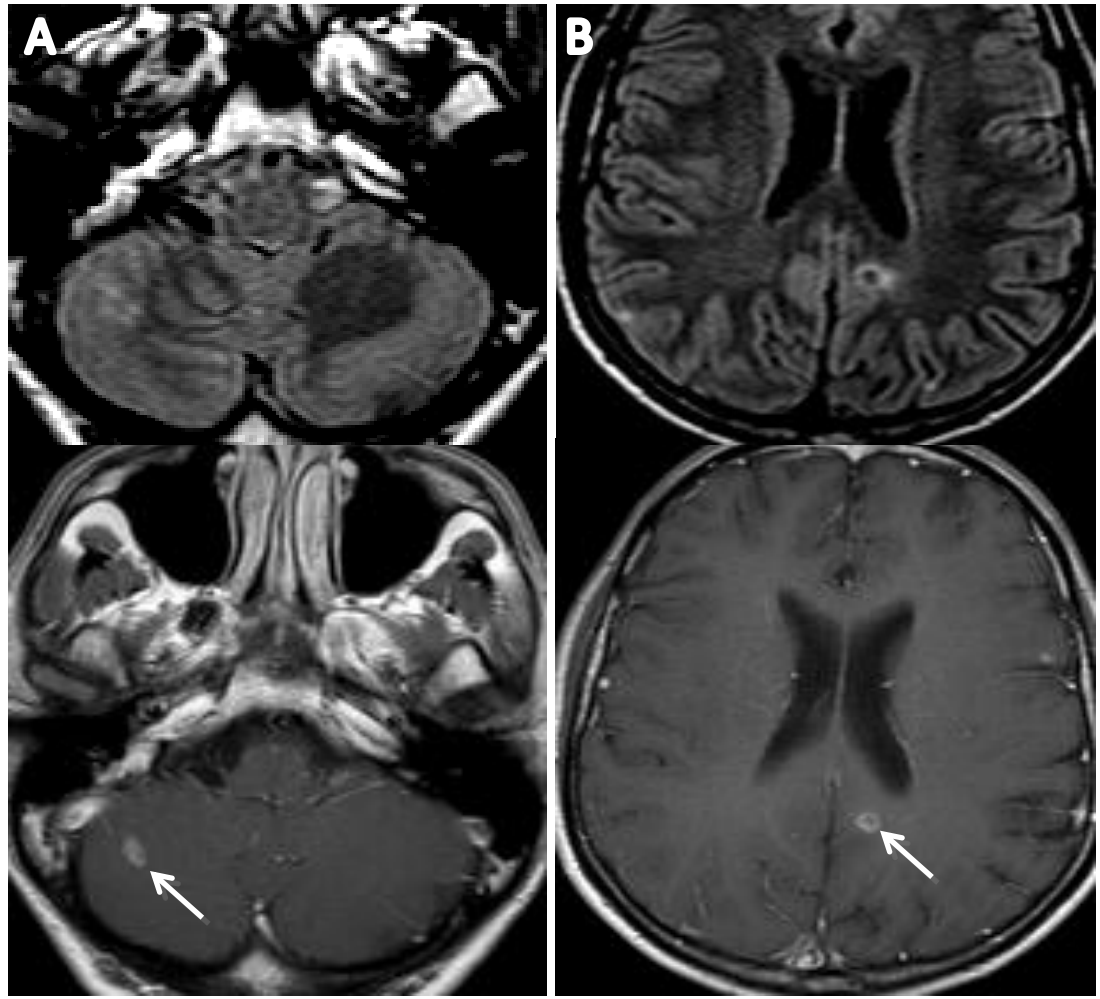
Toxoplasmose



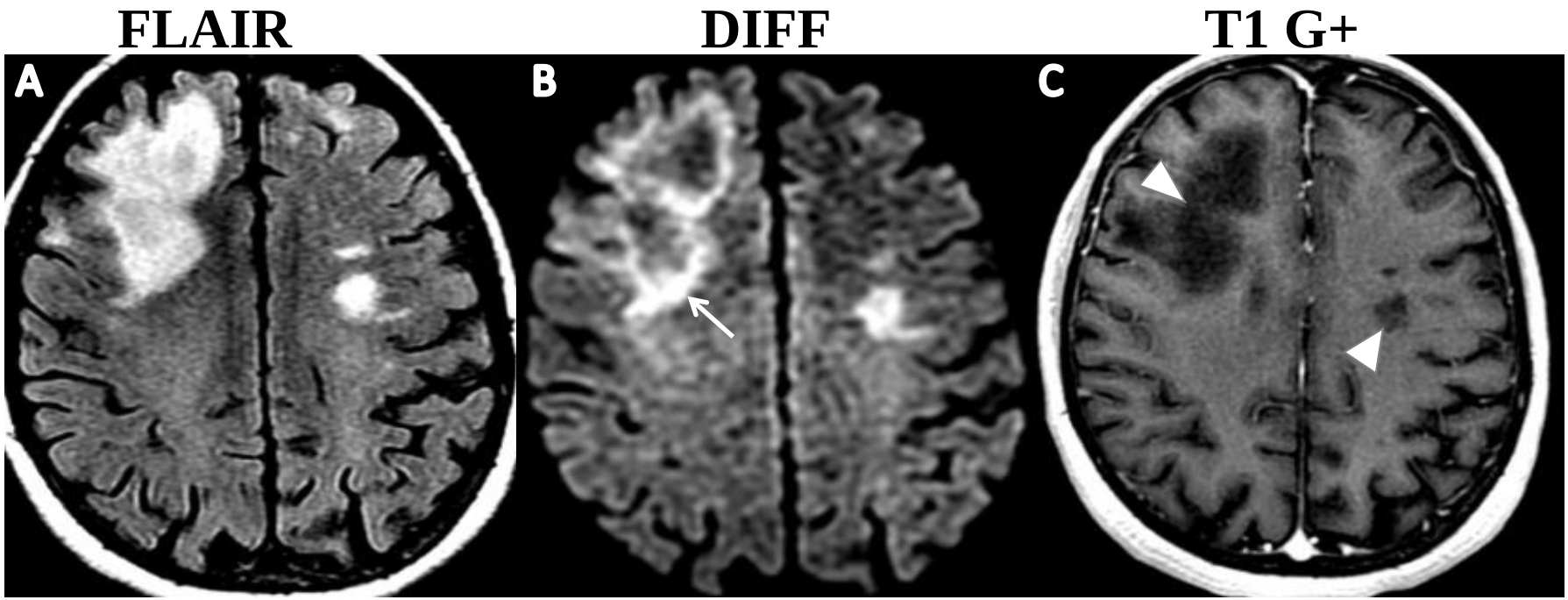
Toxoplasmose, évolution

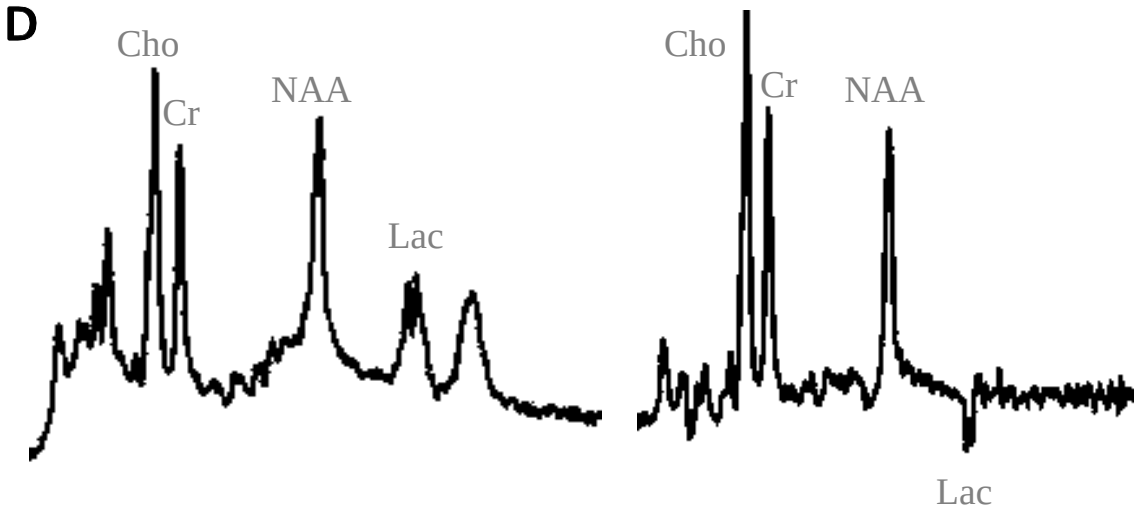
FLAIR

T1 G+

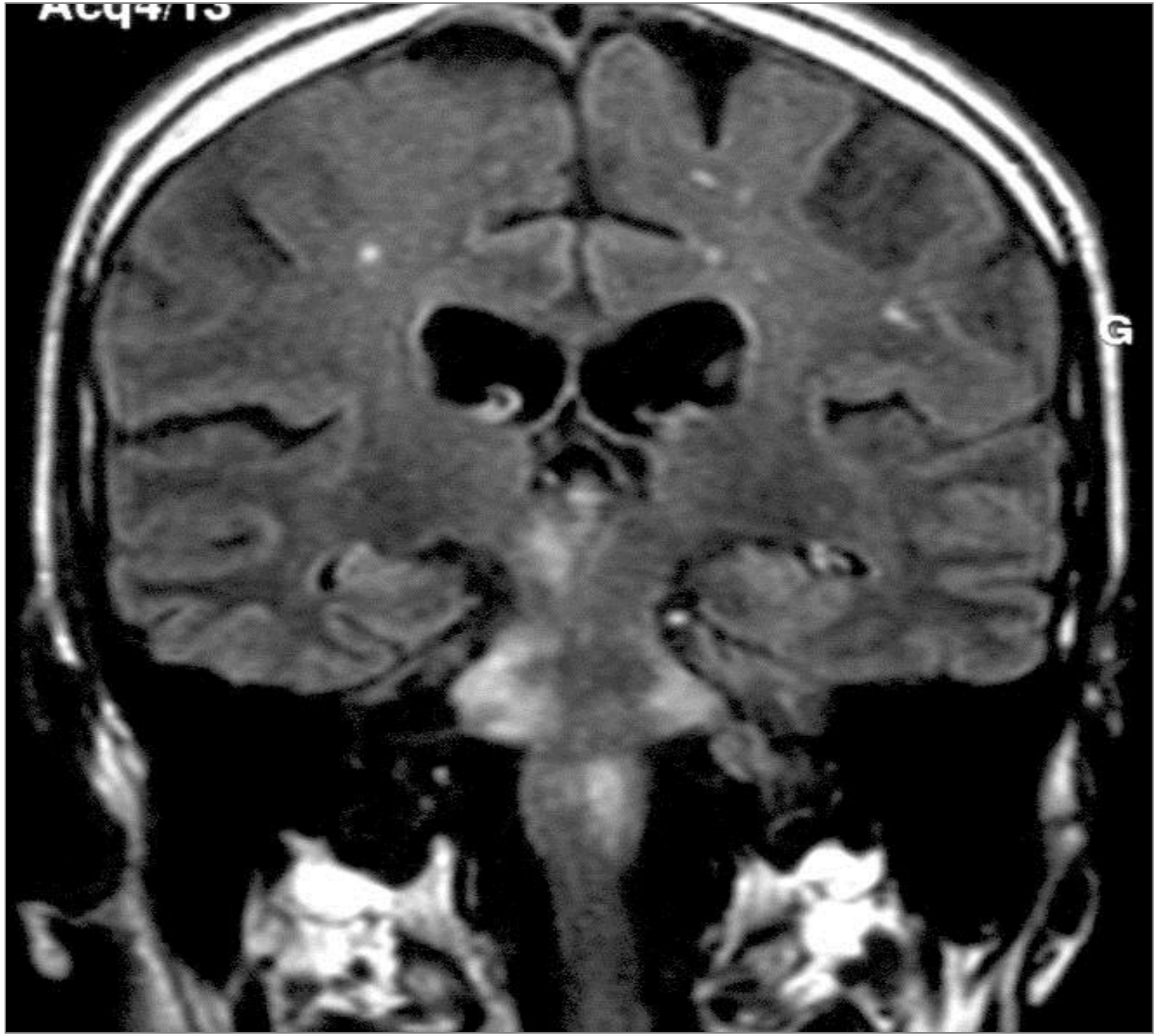


LEMP



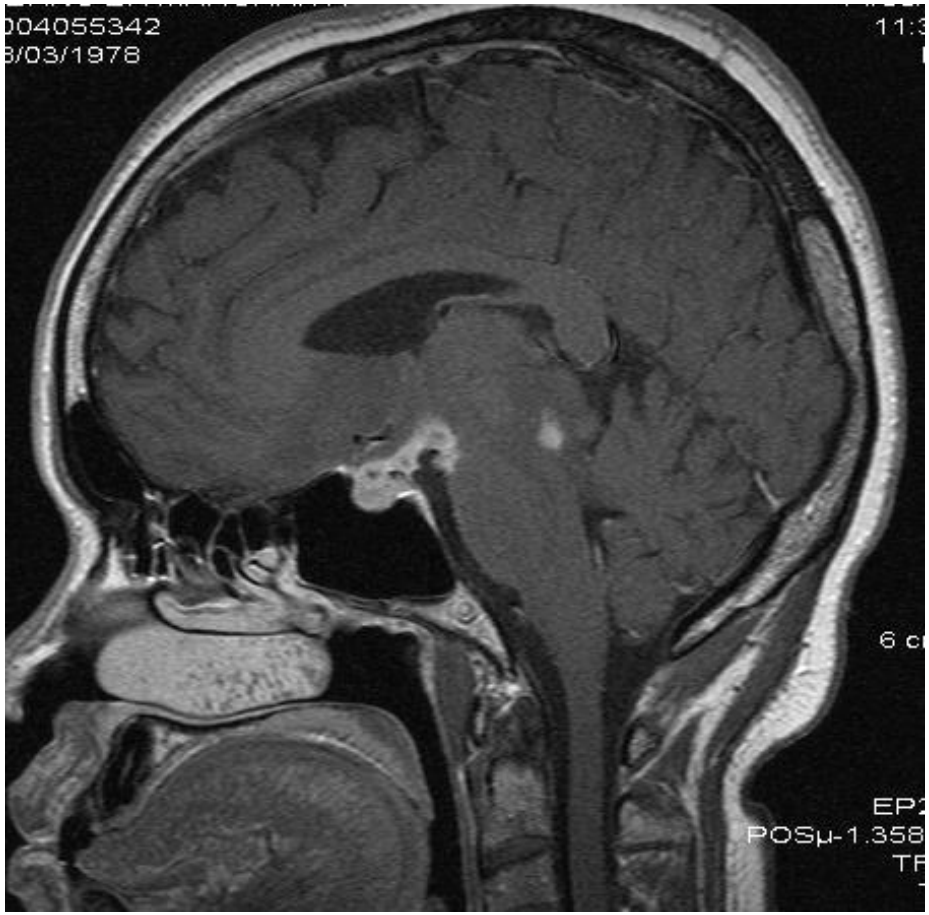


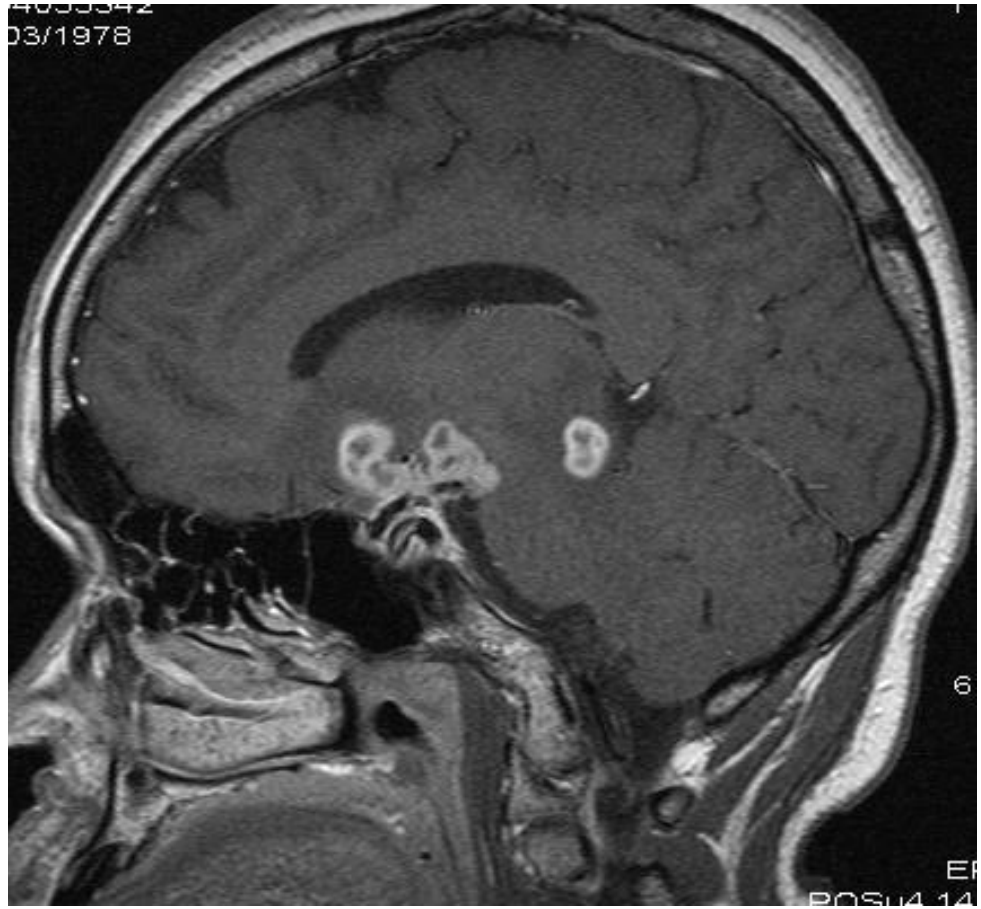
Choline ↑↑
Lactates +
NAA ↓



LEMP

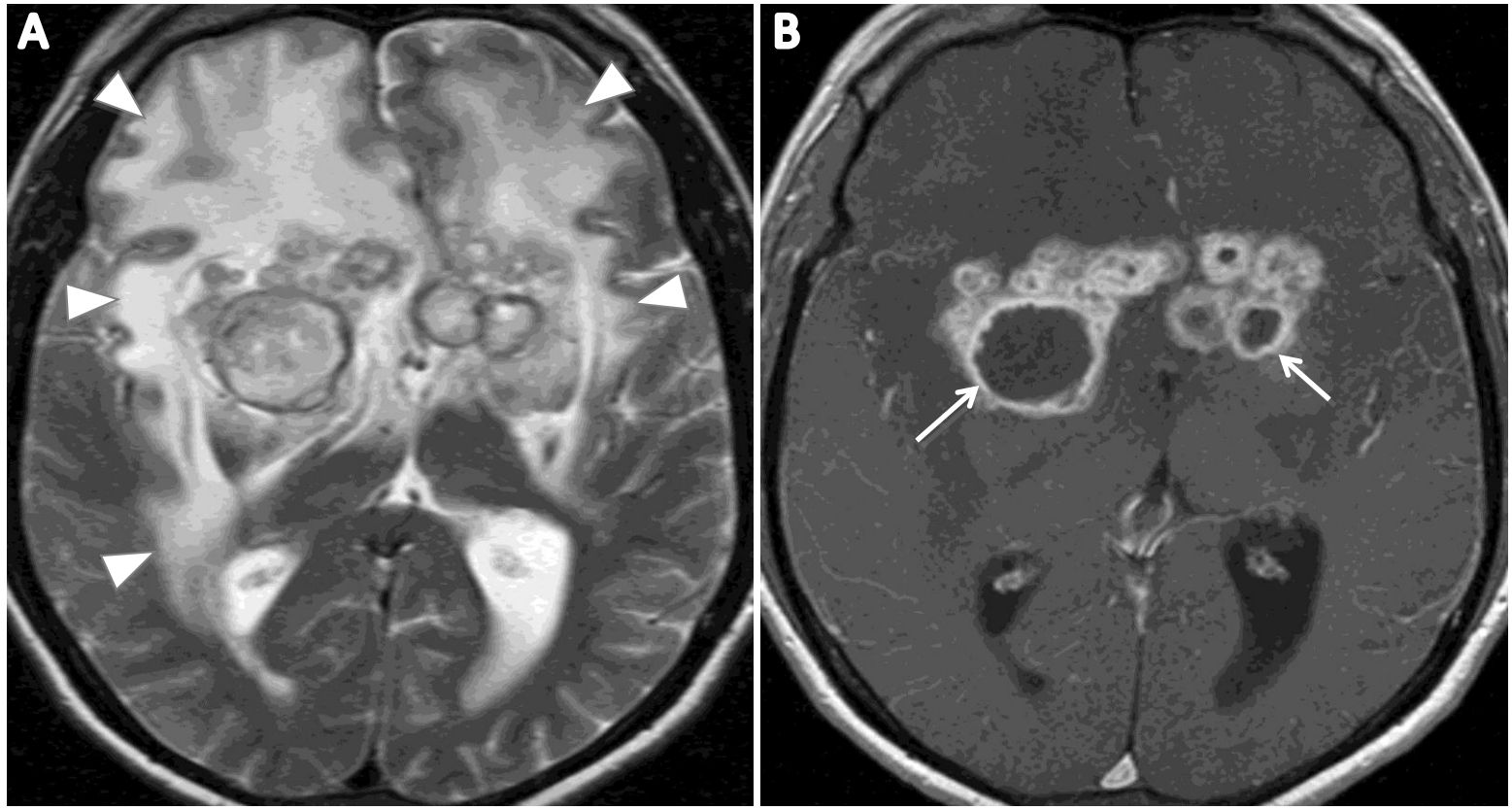
BK





T1 G+

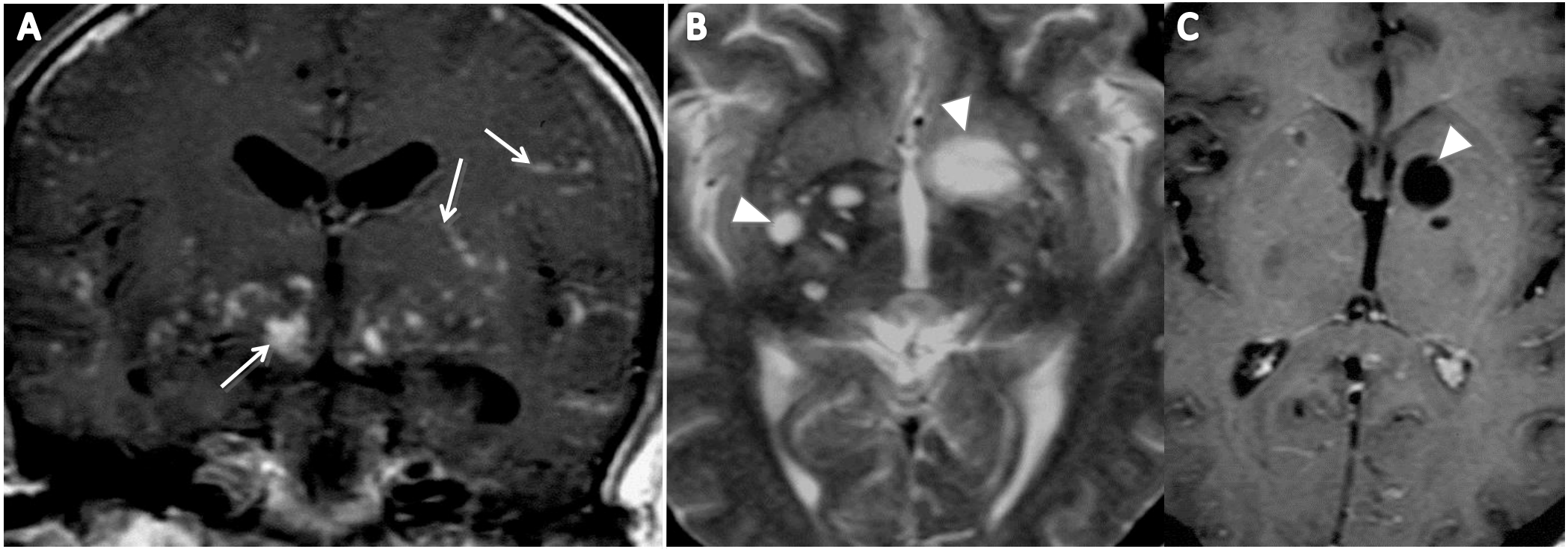
Mycobactérie atypique



T2

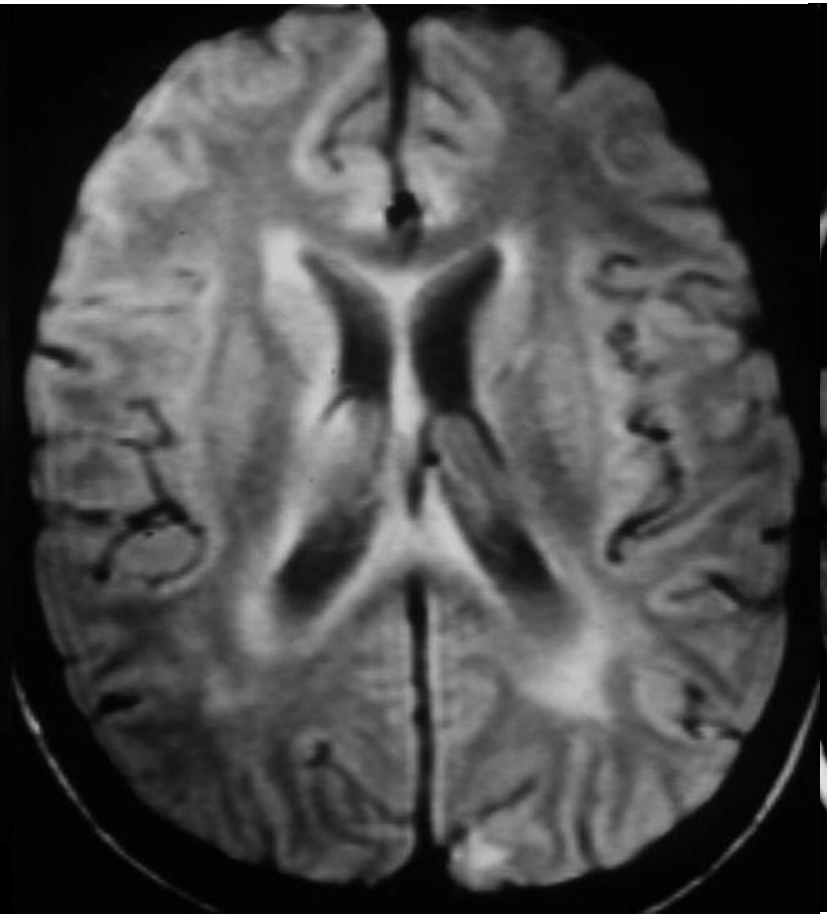
T1 G+

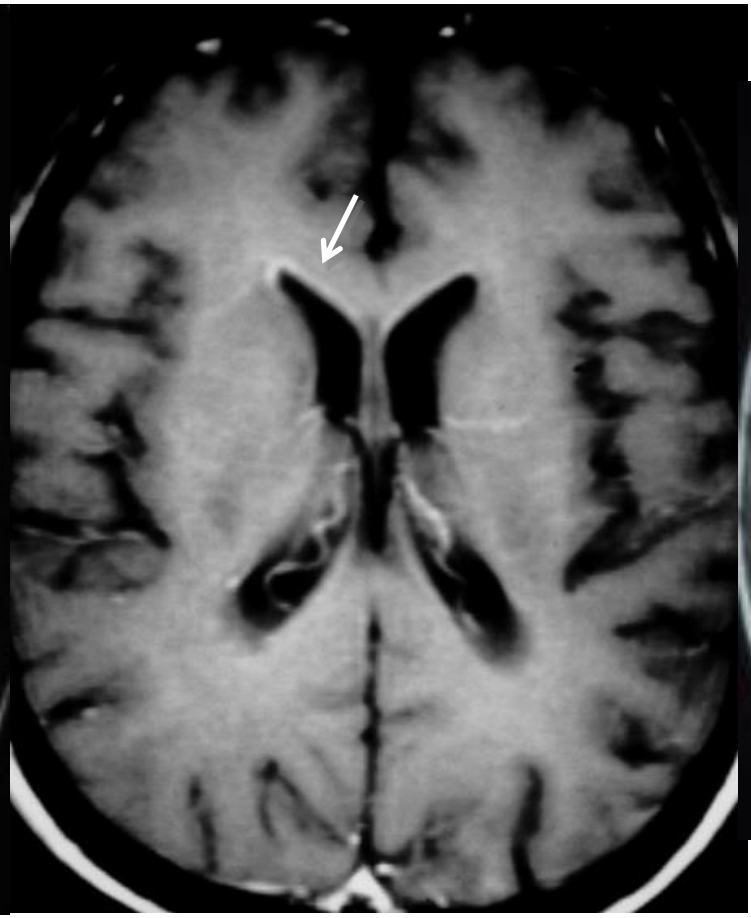
Cryptococcose

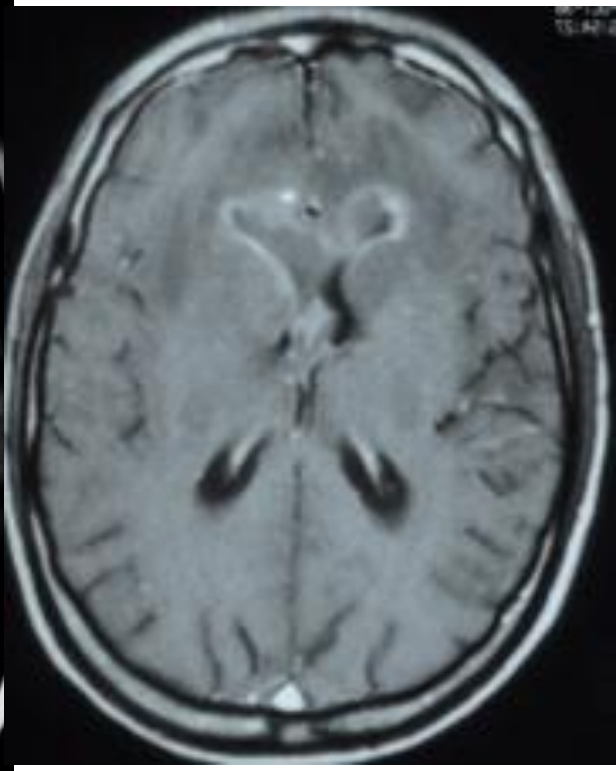


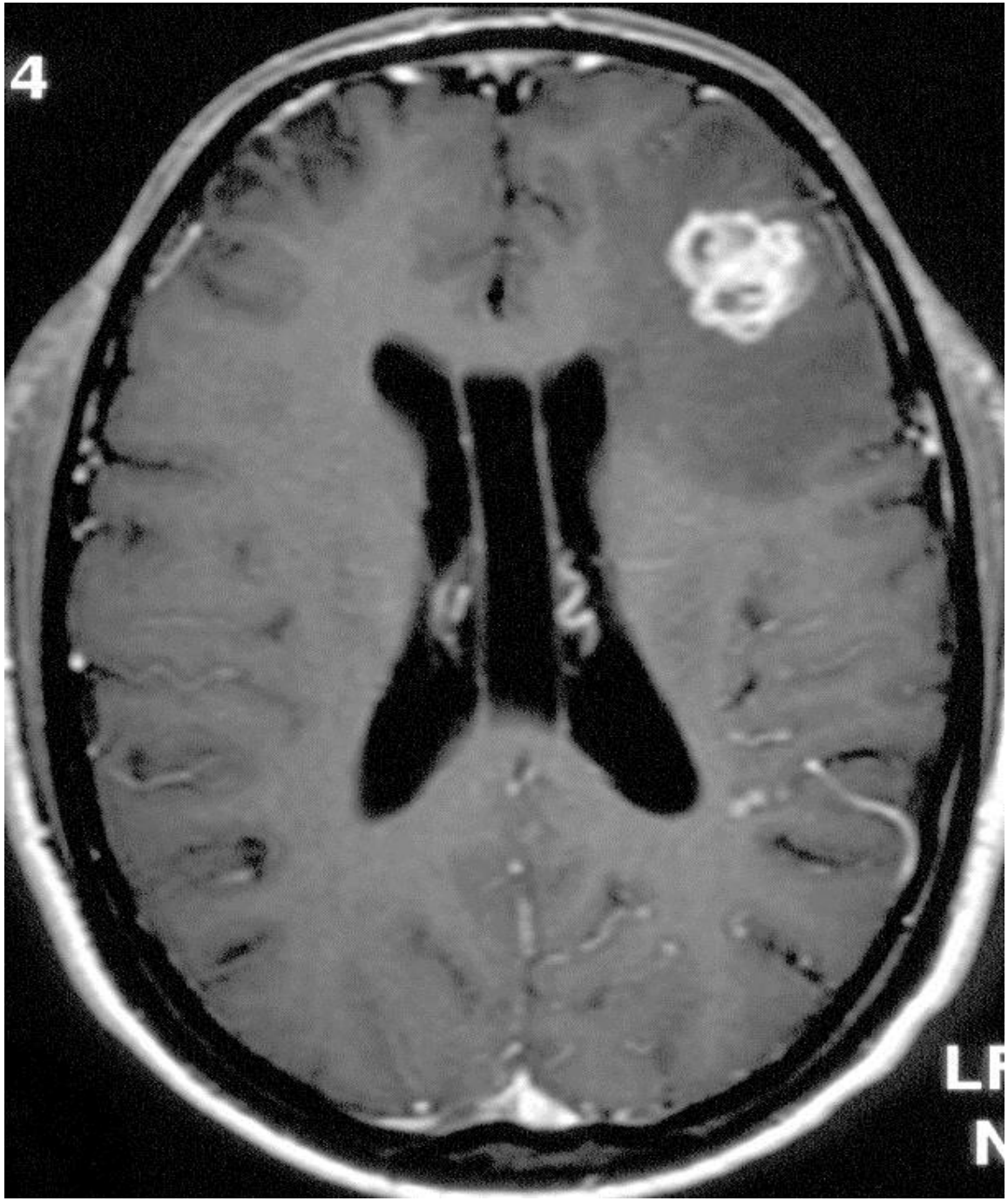
T1 G+ T2 T1 G+

Ventriculite à CMV









T4 = 4/mm^3
plCV = 10^6 c/ml

TOXOPLASMOSE

LNH

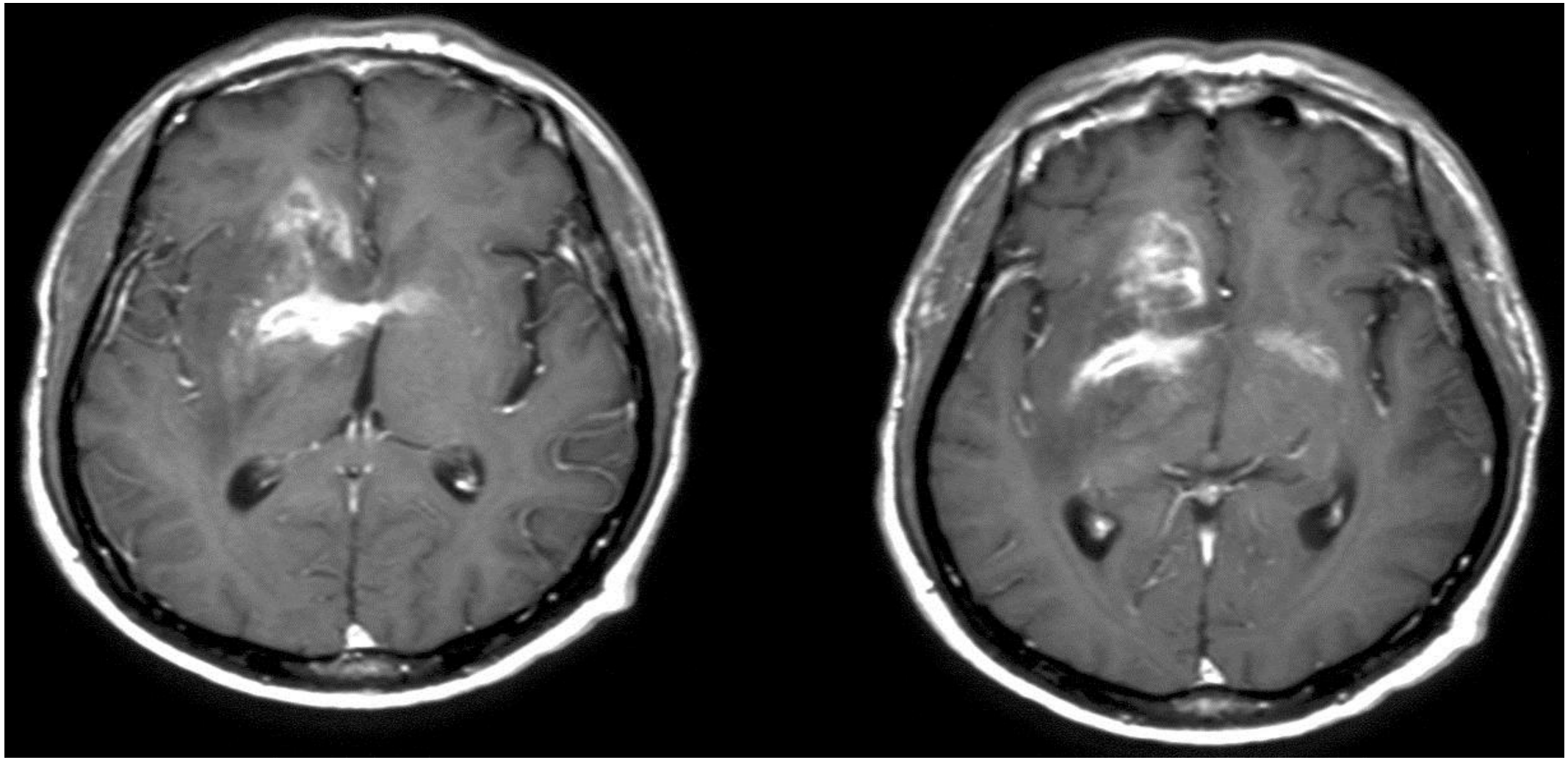
TUBERCULOSE

CRYPTOCOCCOSE

CMV

ABCES

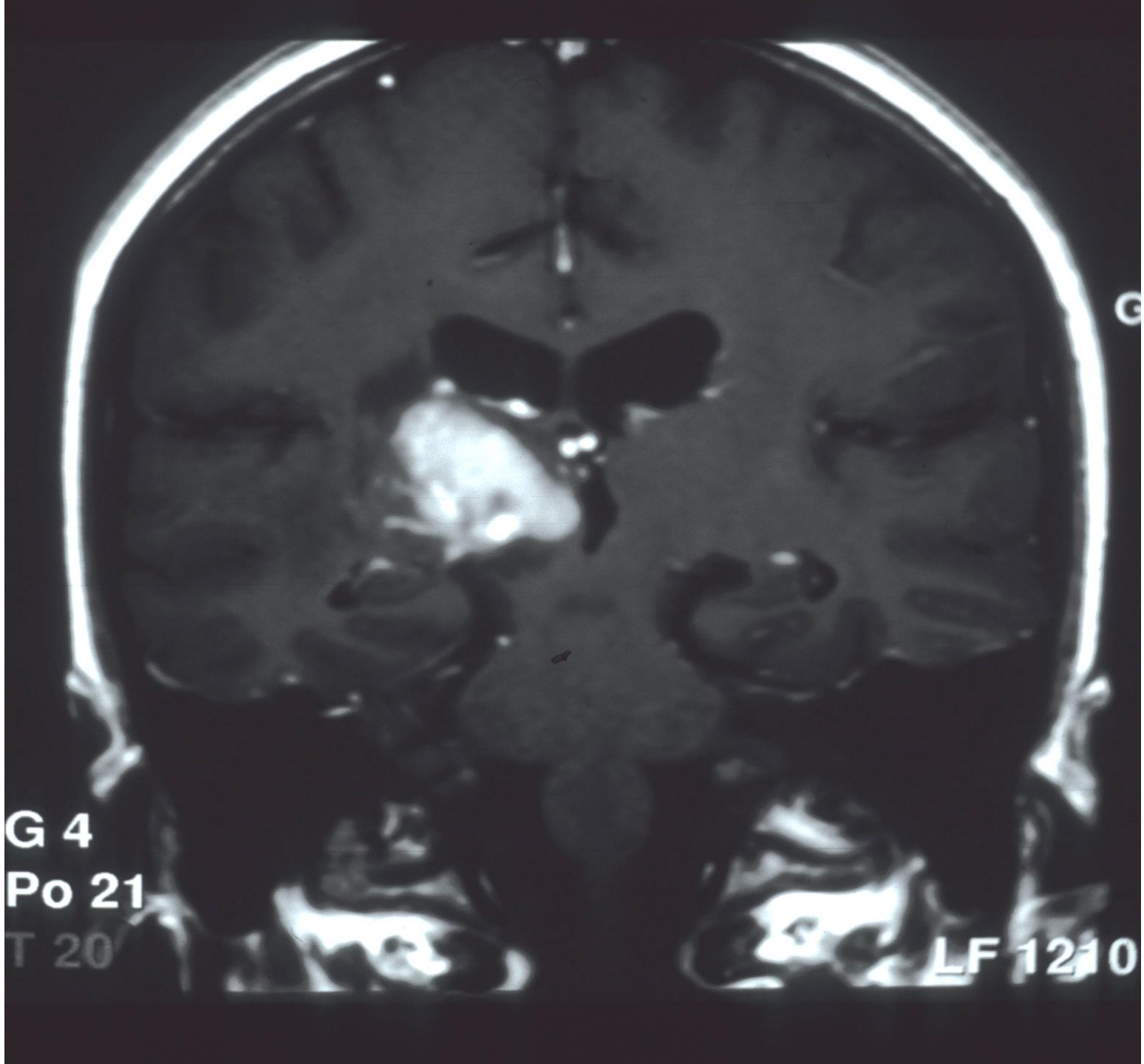
TOXOPLASMOSE ATYPIQUE



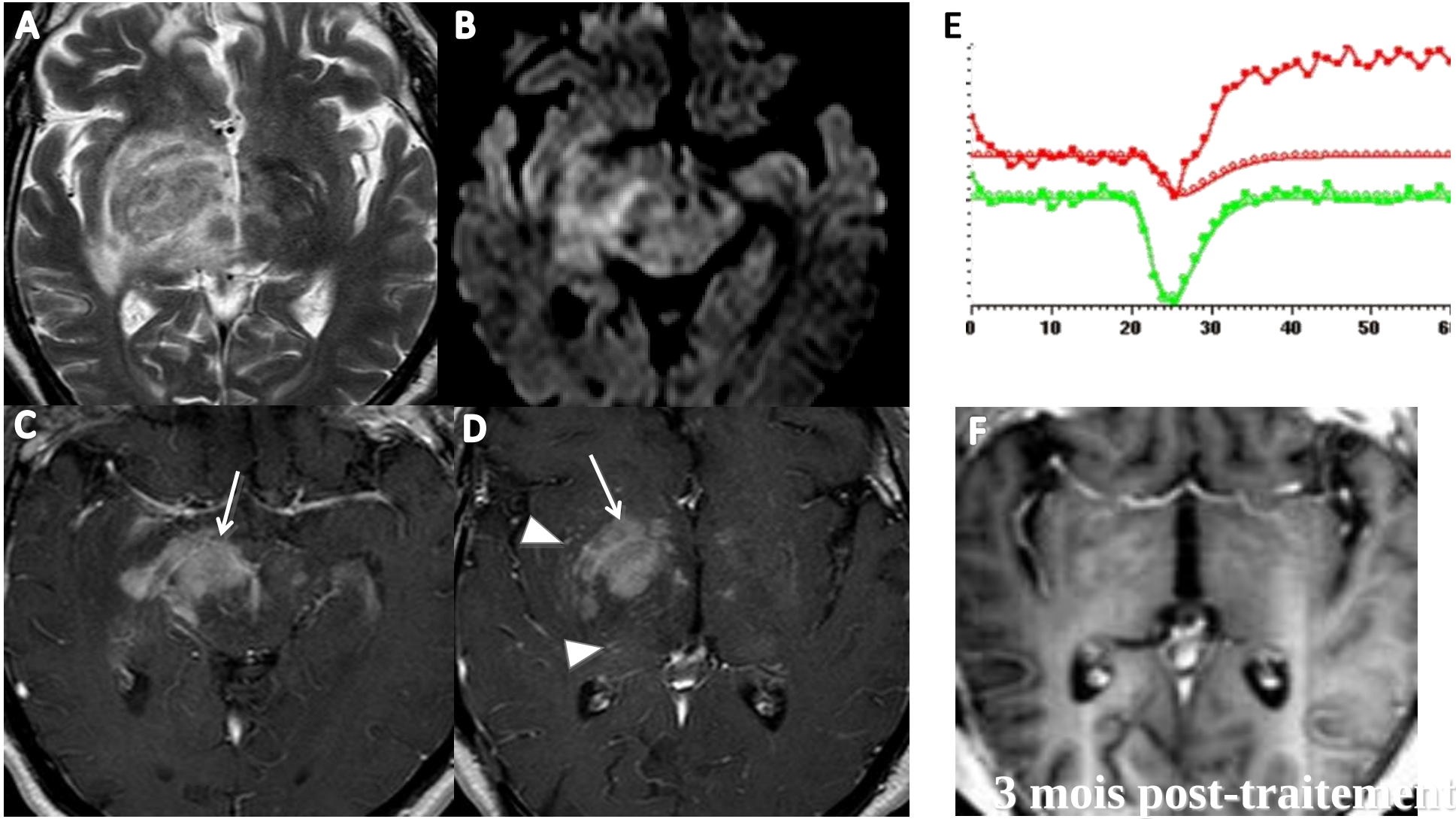
Tumeurs = LNH

- **LCP ou LNH avec atteinte du SNC**
  - **Centro- et immuno- blastiques (WF ou Kiel)**
  - **LNH diffus à grandes cellules (REAL ou OMS)**
- **Toujours EBV +**
- **IRM + PCR EBV +**
- **Biopsie cérébrale (jamais de corticoïdes)**
- **Traitement : MTX *ou CHOP***

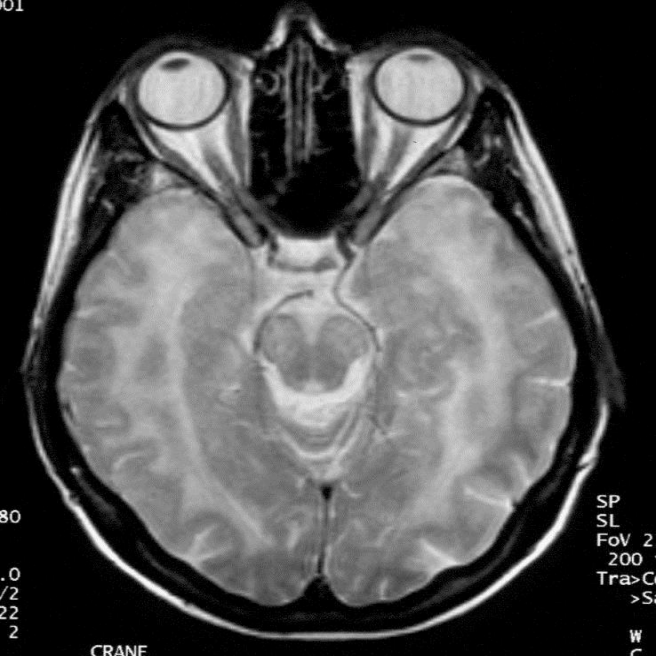
LNH

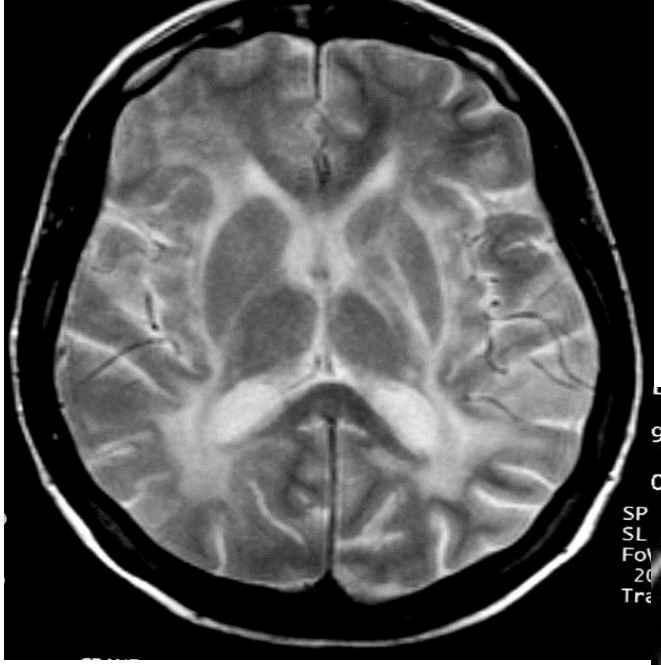


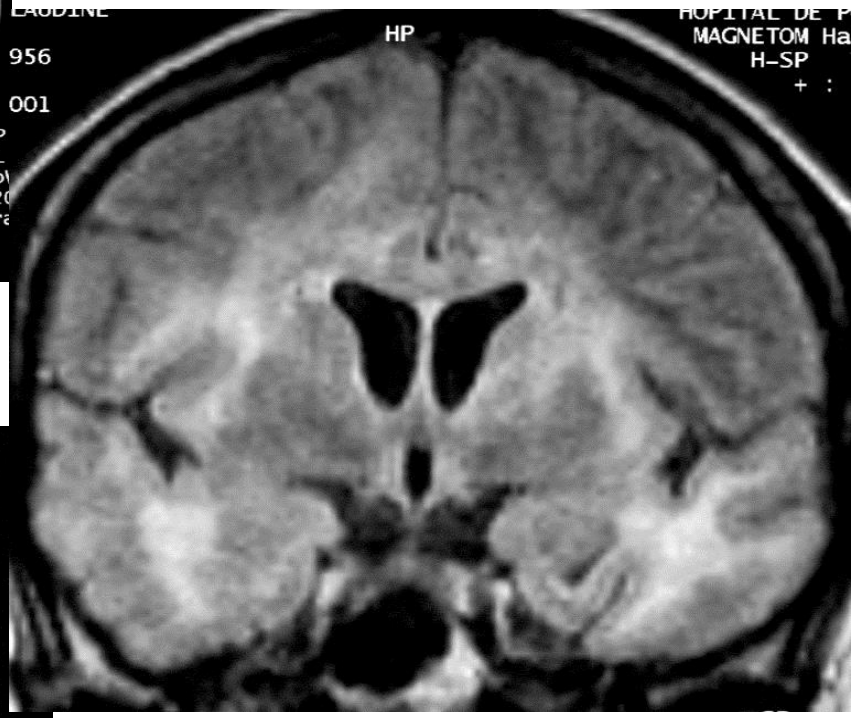
Lymphome

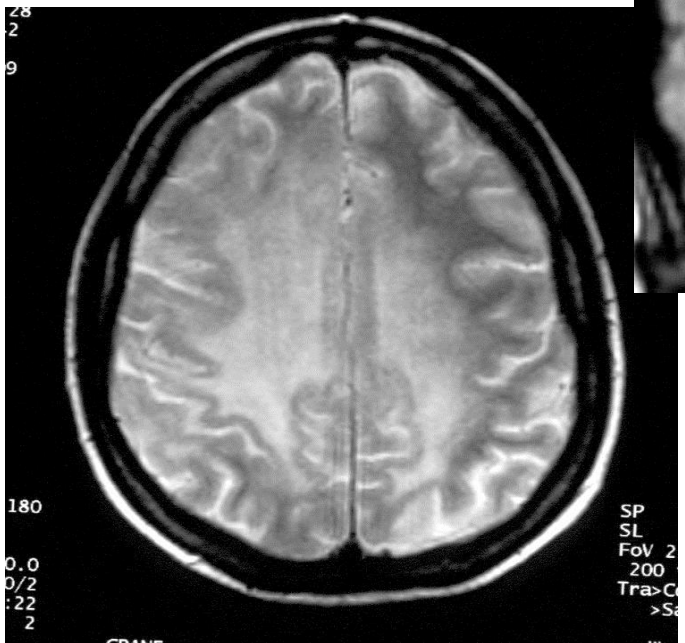


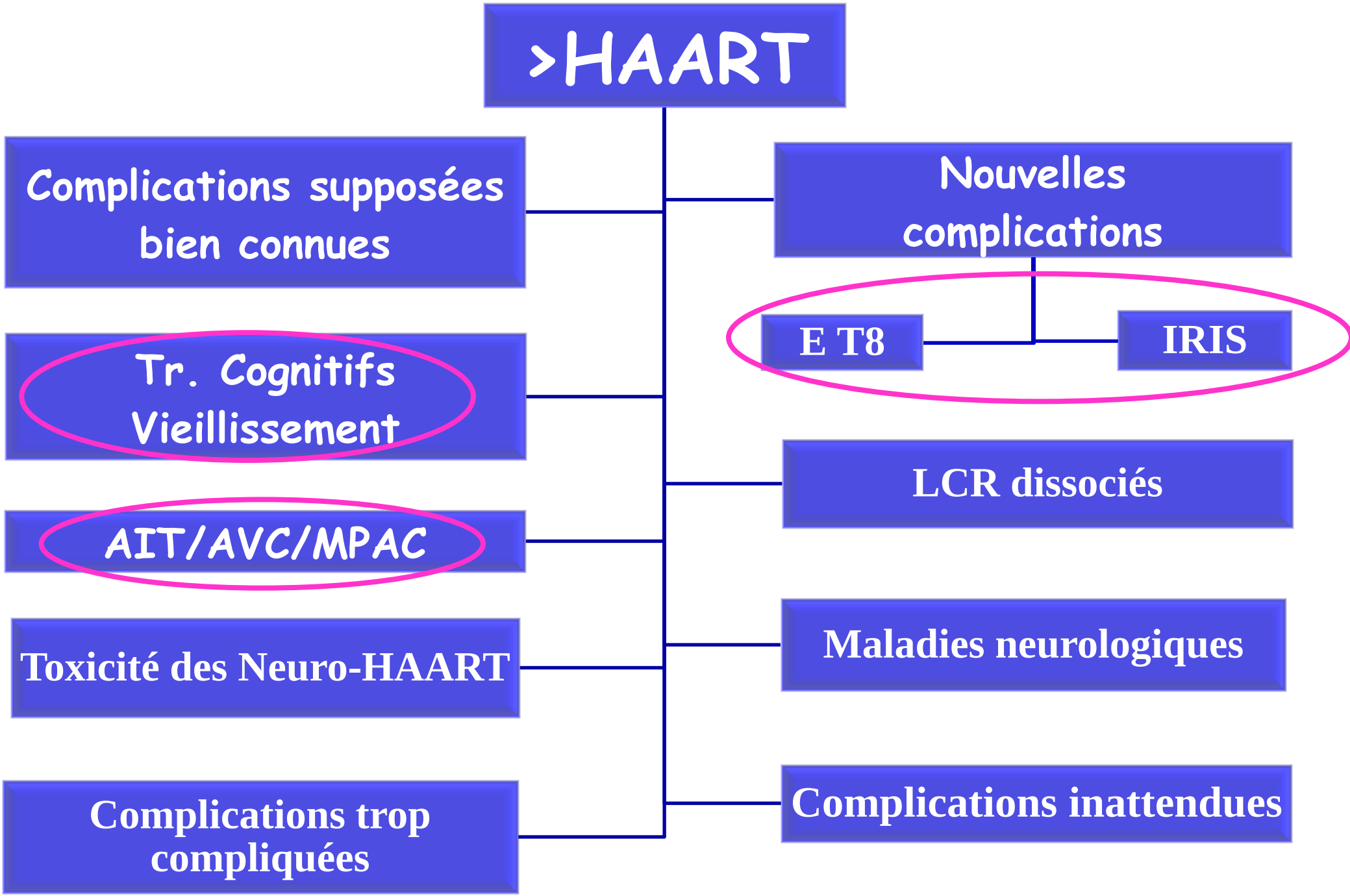
LCP







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AIT/AVC/MPAC
Toxicité des Neuro-HAART
Complications trop compliquées
Nouvelles complications
E T8
IRIS
LCR dissociés
Maladies neurologiques
Complications inattendues

Les situations aiguës

- **Autres que**
  - **infections**
  - **Carences/métaboliques**
  - **AIT/AVC**
  - **…**
- **IRIS**
- **CD8**

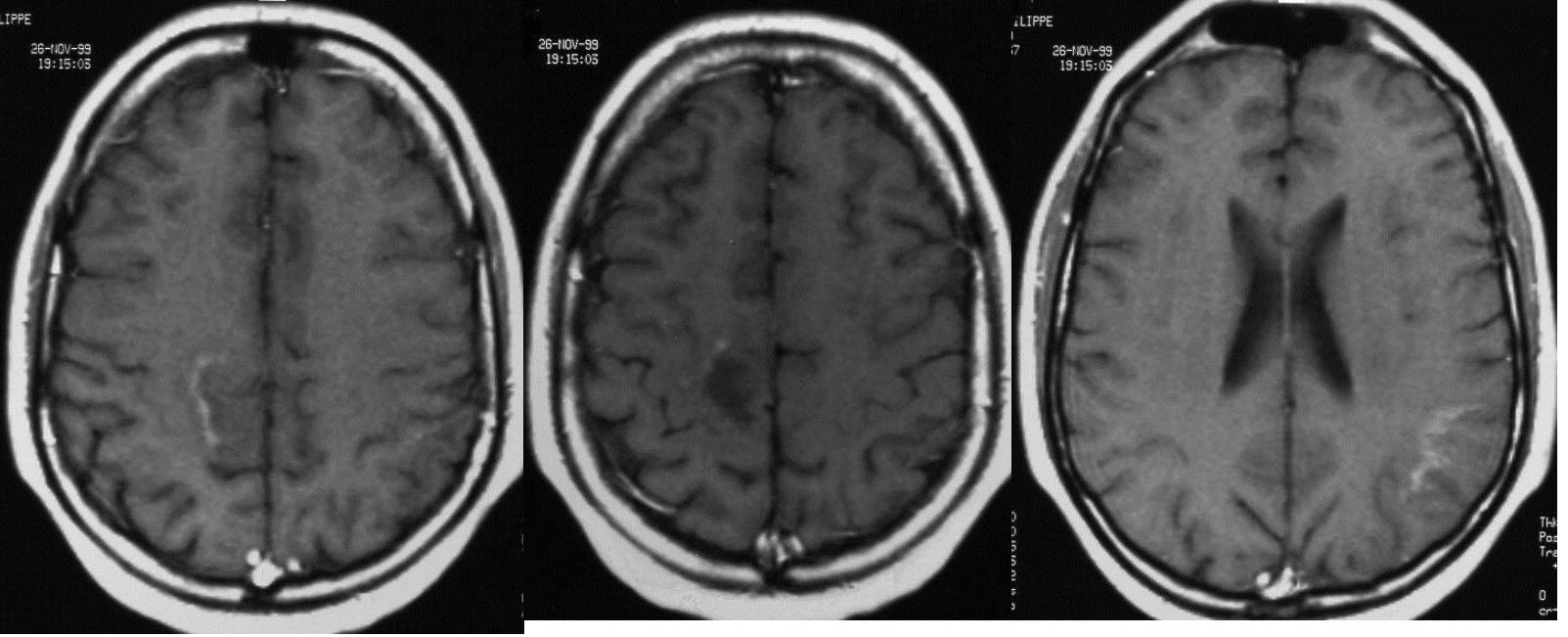
Table 1. Defining features of CNS-IRIS

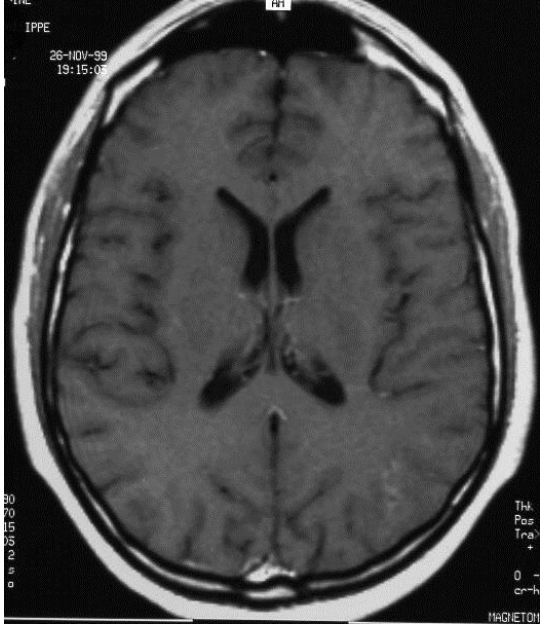
1. Worsening of neurological status after initiation of HAART
2. Deterioration of or new neuroradiological findings suggestive of inflammation
3. A decrease in plasma HIV viral load of ≥ 1 $\log_{10}$
4. Symptoms not explained by a newly acquired disease or by usual course of previously acquired illness
5. Histopathology demonstrating T cell infiltration

Nath 2010

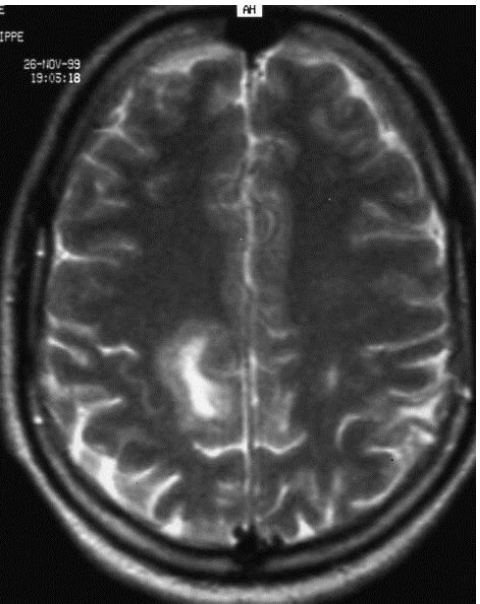
3 formes d'IRIS

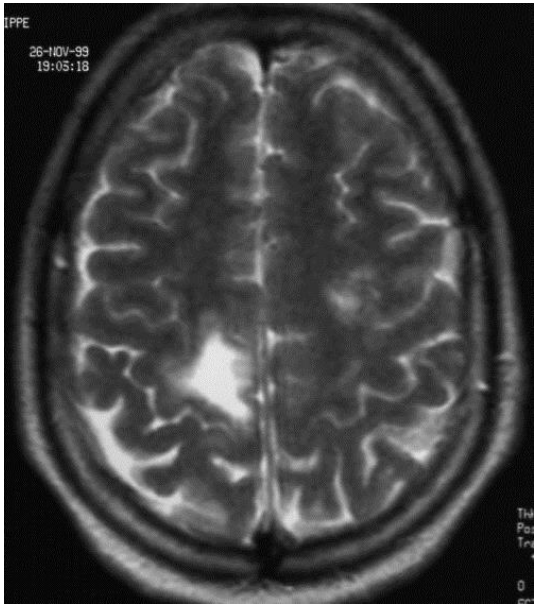
1) **IRIS paradoxal : amélioration initiale d'une infection sous traitement et aggravation 2ndaire après reconstitution immune**
2) **IRIS infectieux : reconstitution d'une réponse immune contre un agent infectieux quiescent mais viable, démasquant une infection jusque là asymptomatique**
3) **IRIS auto-immun : pathologies AI ou inflammatoires déclenchées ou aggravées par la modification de la réponse immune**

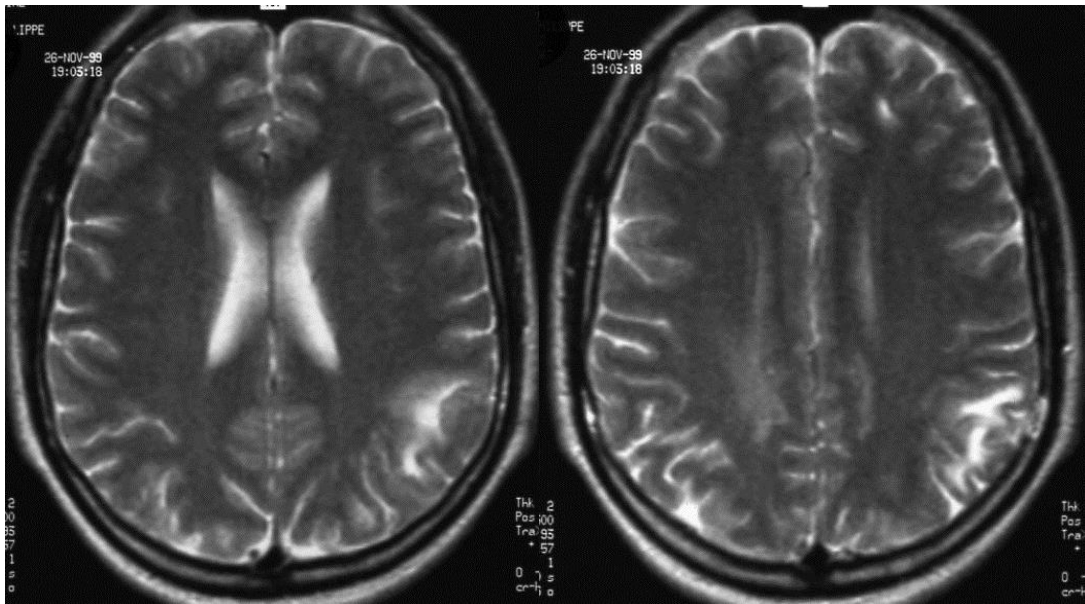




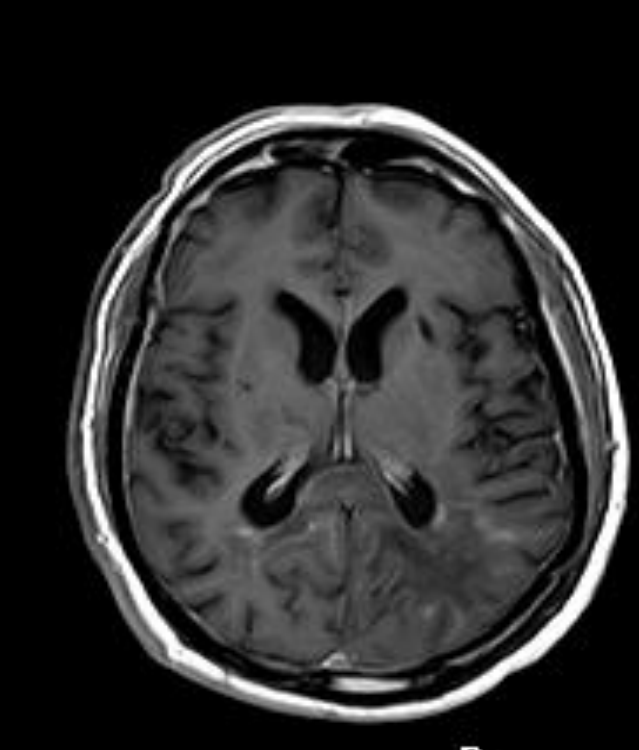
Juillet 50 T4/plCV 326000 c/ml **LEMP IRIS** **Nov 325T4/plCV < 40c/ml**

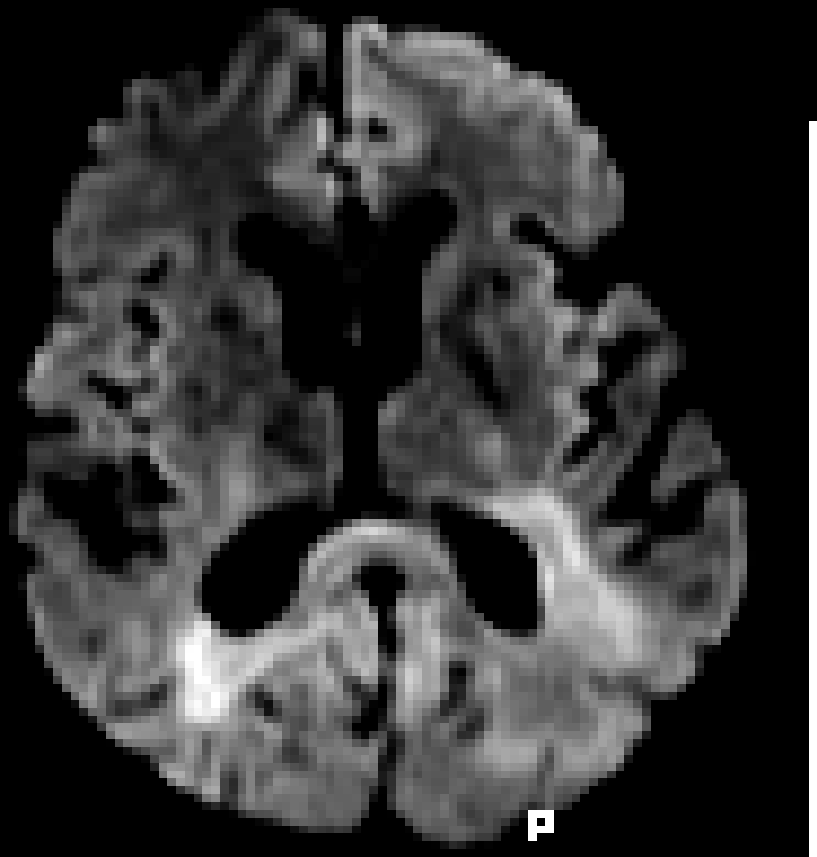


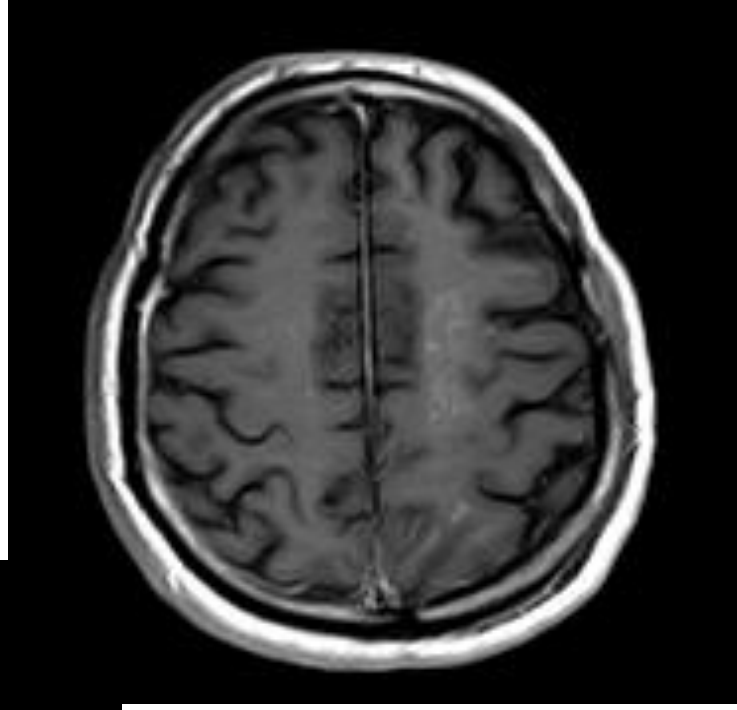


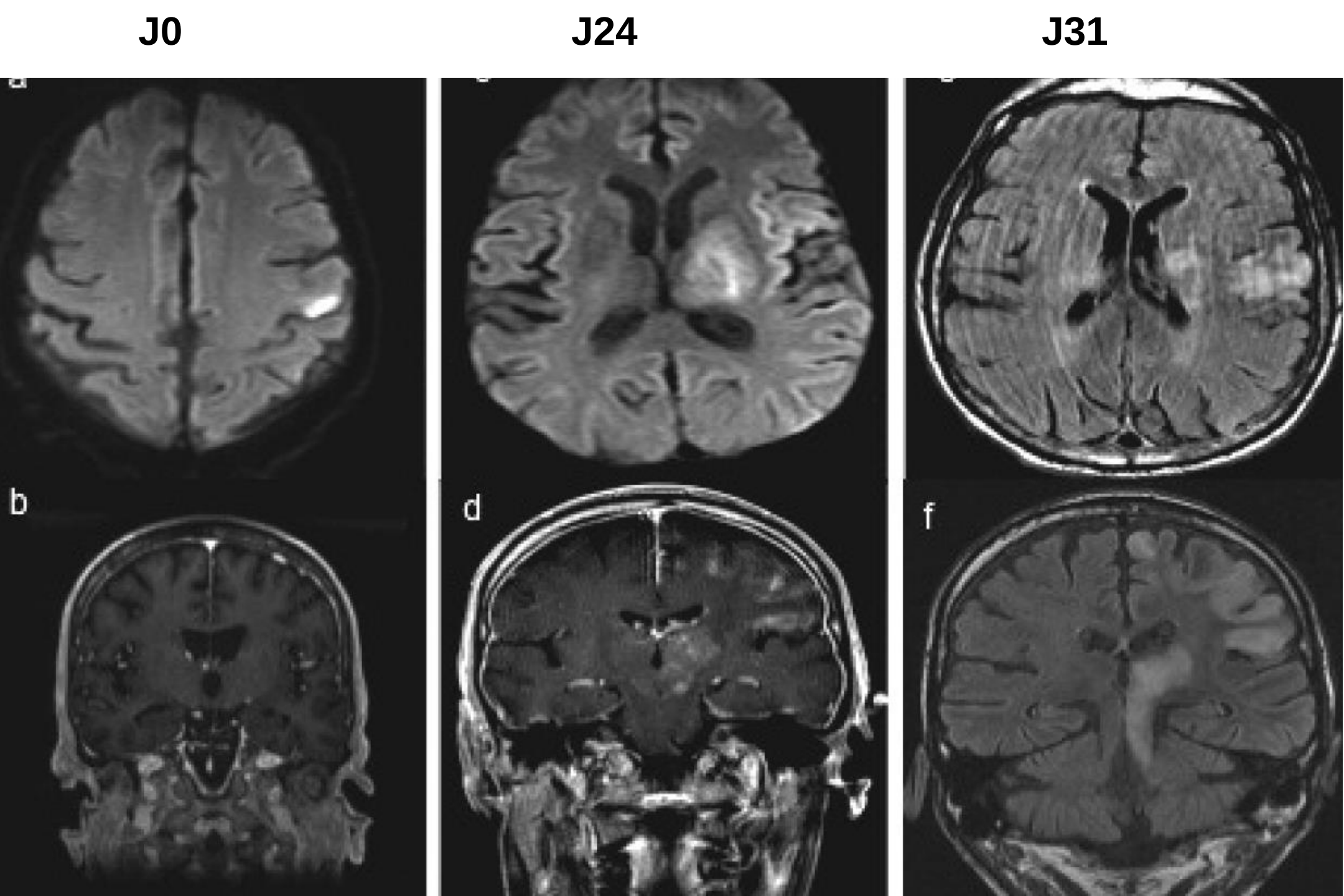


LEMP IRIS








J0
J24
J31
a
b
d
f

« Poussée » inflammatoire

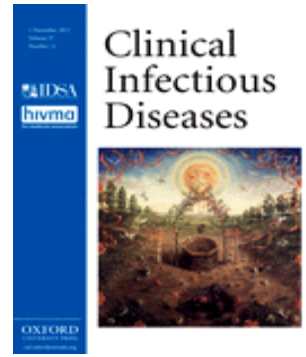
Severe HIV-Associated CD8$^+$ T-Cell Encephalitis: Is It the Tip of the Iceberg?

Dianne Langford[1] and Scott Letendre[2]

[1]Department of Neuroscience, Temple University School of Medicine, Philadelphia, Pennsylvania; and [2]Department of Medicine, University of California, San Diego

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]



Encephalitis with Infiltration by CD8+ Lymphocytes in HIV Patients Receiving Combination Antiretroviral Treatment

Françoise Gray[1]; François Xavier Lescure[2,3]; Homa Adle-Biassette[1]; Marc Polivka[1]; Sébastien Gallien[4]; Gilles Pialoux[2]; Antoine Moulignier[2,5]

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

	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
1	46 M	19	400	Yes	Minor infection	2001	121	0	4600	Cognitive impairment	DDI 3TC IDVr	1.47	100	85	NA	+	+ –	Yes	<50	<200	Death 9 mo after onset
2	41 M	..	400	Yes	StopARV	2002	120	0	35 561	Cognitive impairment	STOP	1.10	9	NA	NA	+	+ +	Yes	62	<200	Total recovery
3	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
4	47 F	14	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
5	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
6	33 F	NA	NA	NA	ND	2005	283	NA	2660	Headaches, cognitive impairment	FTC TDF ATVr	1.13	20	NA	10 300	+	– +	Yes	<50	<200	Death 12 mo after onset
7	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
8	54 F	51	509	No	Minor infection	2007	402	1468	NA	Dizziness, headaches	None	0.8	220	78	672	+	– ++	Yes	<20	<40	Total recovery
9	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
10	43 M	82	169	No	Escape	2007	84	1271	2765	Headaches, dizziness, seizures	3TC ABC ATVr	1.1	46	87	36 242	+	– ++	Yes	<50	<40	Alive, cognitive impairment
11	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
12	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
13	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
14	39 M	19	900	Yes	ND	2008	742	70	201	Dizziness, memory disorders	3TC ABC ATVr	1.1	26	65	3294	+	ND	Yes	<50	<40	Total recovery

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400	Yes	Stop ARV	2002	120	0	35 561	Cognitive impairment
10	No	IRIS	2003	93	0	0	Headaches, seizures, facial palsy
586	Yes	Minor infection	2005	275	117	692	Headaches, confusion, seizures
145	No	IRIS	2005	NA	1120	NA	Comatose
NA	NA	ND	2005	283	NA	2660	Headaches, cognitive impairment
384	Yes	Minor infection	2007	495	0	65 800	Headaches, status epilepticus
509	No	Minor infection	2007	402	1468	NA	Dizziness, headaches
244	Yes	Escape	2007	210	216	2379	Confusion, status epilepticus
169	No	Escape	2007	84	1271	2765	Headaches, dizziness, seizures
450	Yes	Minor infection	1999	214	0	21 700	Dementia
NA	NA	ND	NA	NA	30	NA	Confusion, seizures
230	Yes	Minor infection	2008	114	0	200	Confusion
900	Yes	ND	2008	742	70	201	Dizziness, memory disorders

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

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2	41 M	. . .	400	Yes	StopARV	2002	120	0	35 561	Cognitive impairment	STOP	1.10	9	NA	NA	+	+ +	Yes	62	<200	Total recovery
3	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
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6	33 F	NA	NA	NA	ND	2005	283	NA	2660	Headaches, cognitive impairment	FTC TDF ATVr	1.13	20	NA	10 300	+	– +	Yes	<50	<200	Death 12 mo after onset
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8	54 F	516	509	No	Minor infection	2007	402	1468	NA	Dizziness, headaches	None	0.8	220	78	672	+	– ++	Yes	<20	<40	Total recovery
9	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
10	43 M	82	169	No	Escape	2007	84	1271	2765	Headaches, dizziness, seizures	3TC ABC ATVr	1.1	46	87	36 242	+	– ++	Yes	<50	<40	Alive, cognitive impairment
11	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
12	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
13	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
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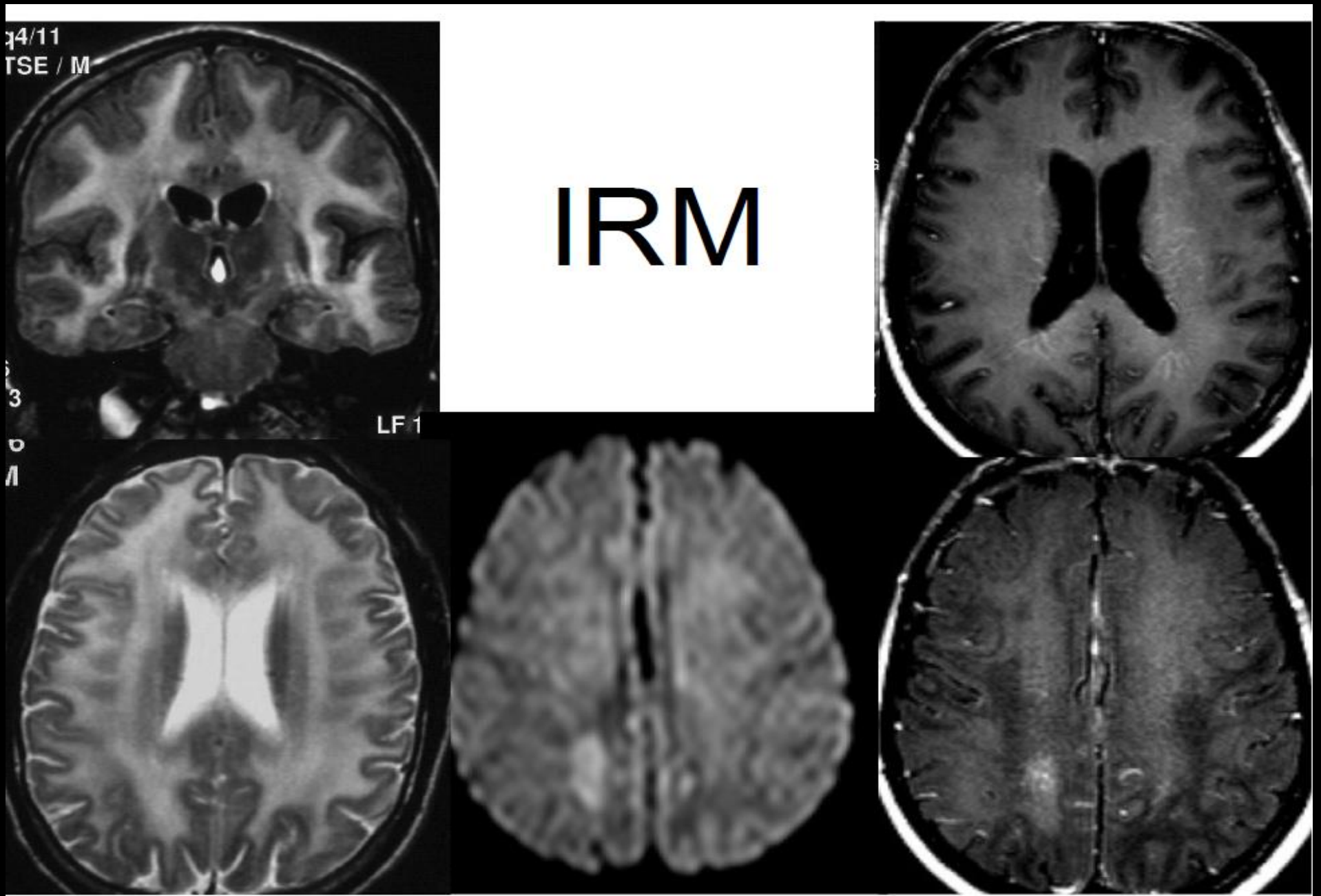
Neurological Symptoms
Cognitive impairment
Cognitive impairment
Headaches, seizures, facial palsy
Headaches, confusion, seizures
Comatose
Headaches, cognitive impairment
Headaches, status epilepticus
Dizziness, headaches
Confusion, status epilepticus
Headaches, dizziness, seizures
Dementia
Confusion, seizures
Confusion
Dizziness, memory disorders

- **Subaigu**
- **Tr cognitifs**
- **Sd confusionnel**
- **Céphalées**
- **Comitialité**
- **Status epilepticus**
- **Tr de la vigilance**
- **Tr de la conscience**
- **Coma**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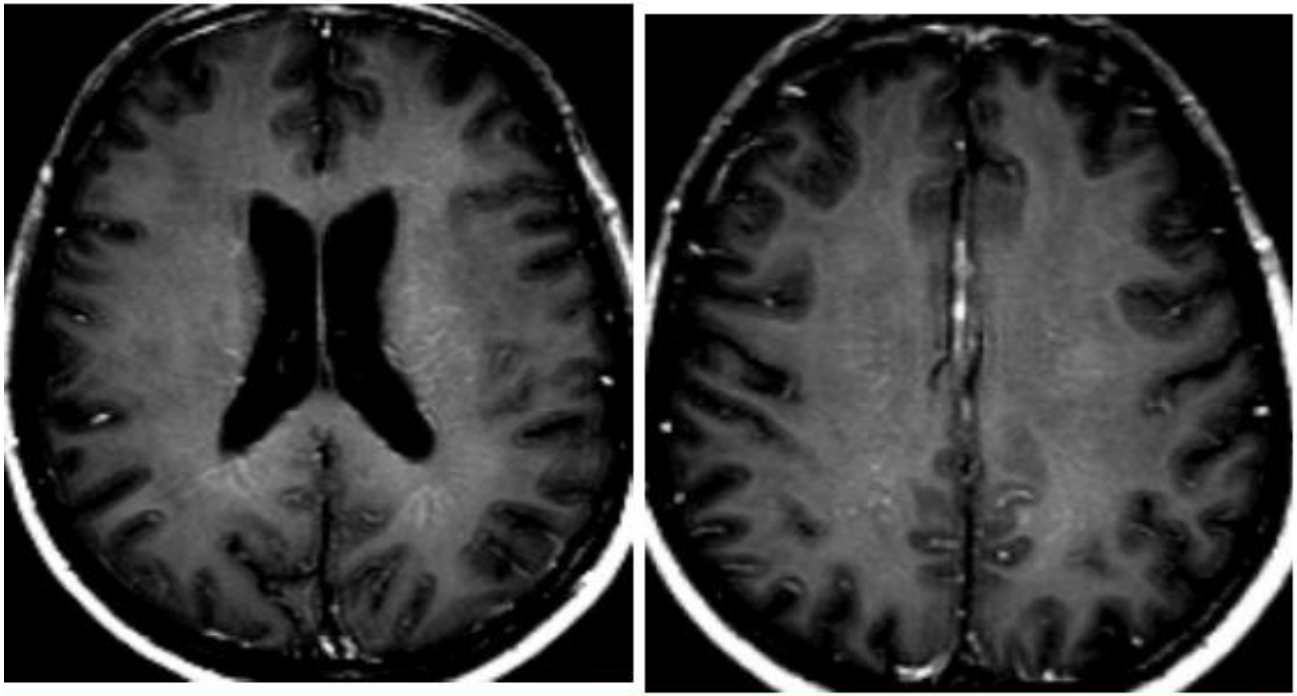
TSE / M
LF 1
IRM

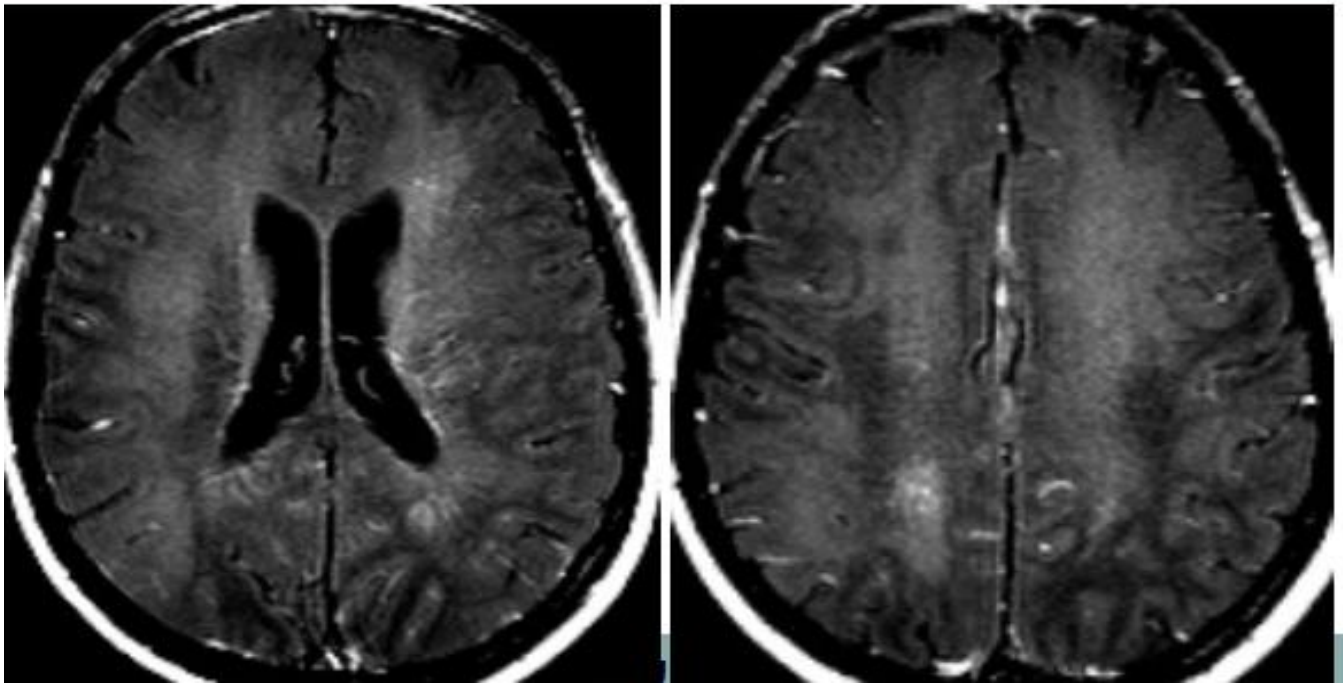


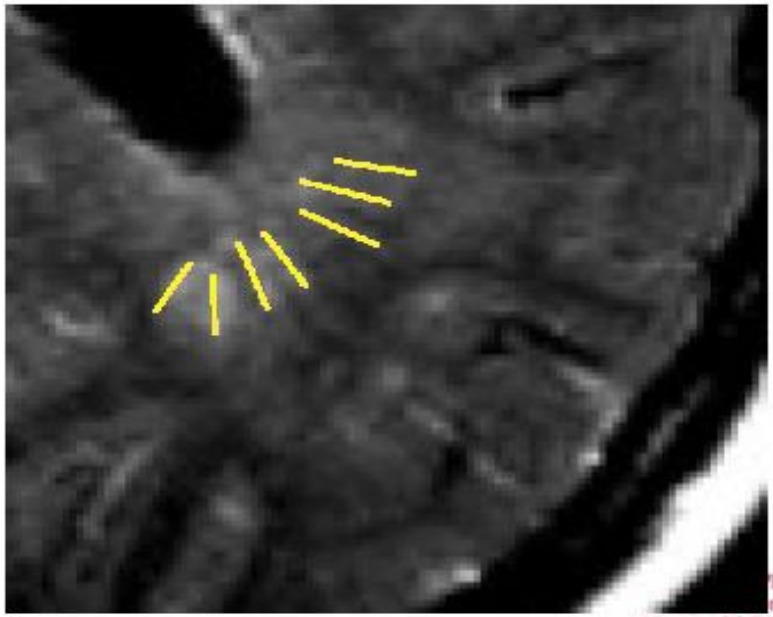
PDC radiaires suivant les espaces périvasculaires distaux (images linéaires ou punctiformes).

Peuvent être non vues si mauvaise technique IRM pour la séquence injecté (par exemple 3D T1 fait dans la plupart des centres : très peu sensible)

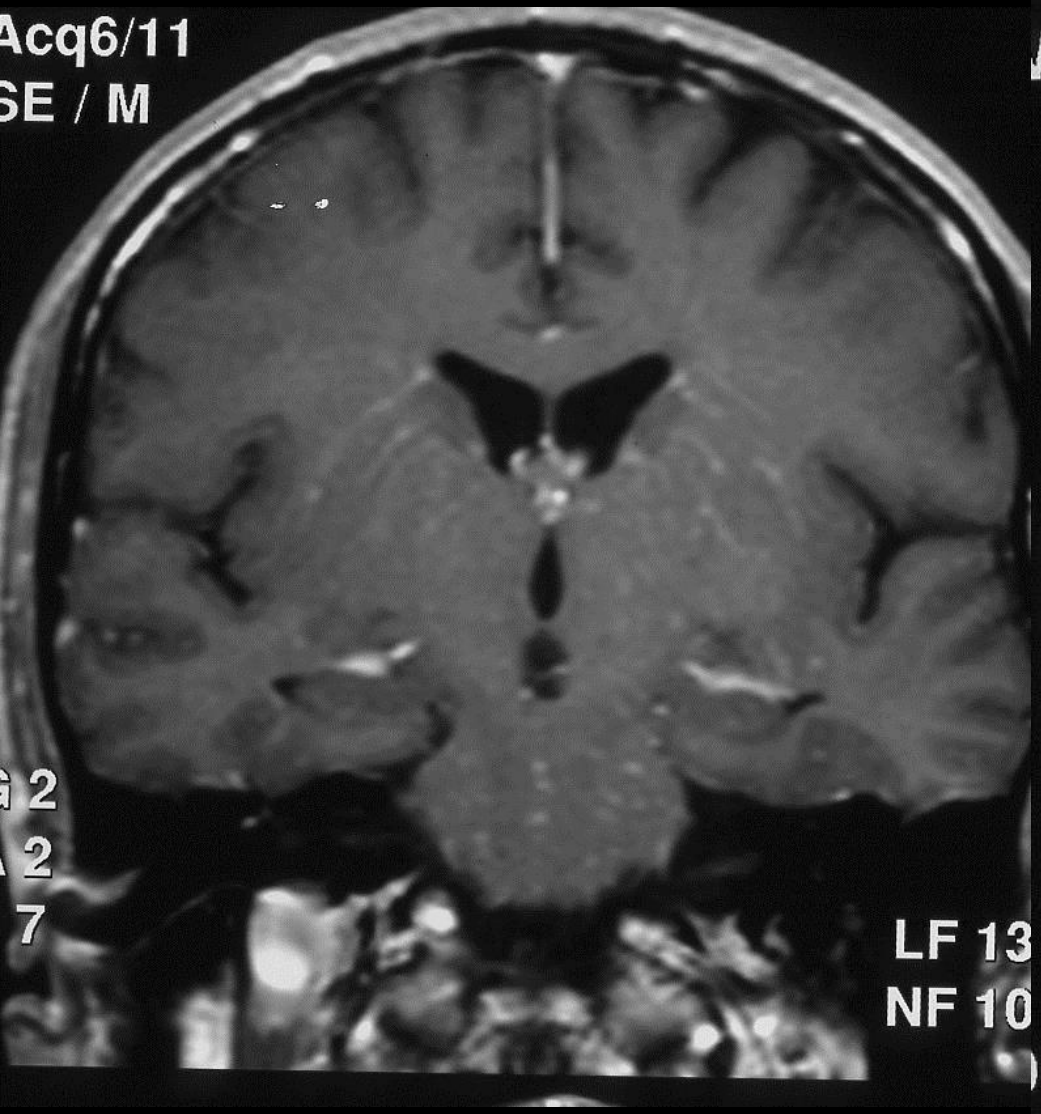
Idéalement : demander un T1 echo de spin avec transfert d'aimantation

T1 Gado





T1 Gado + Transfert d'aimantation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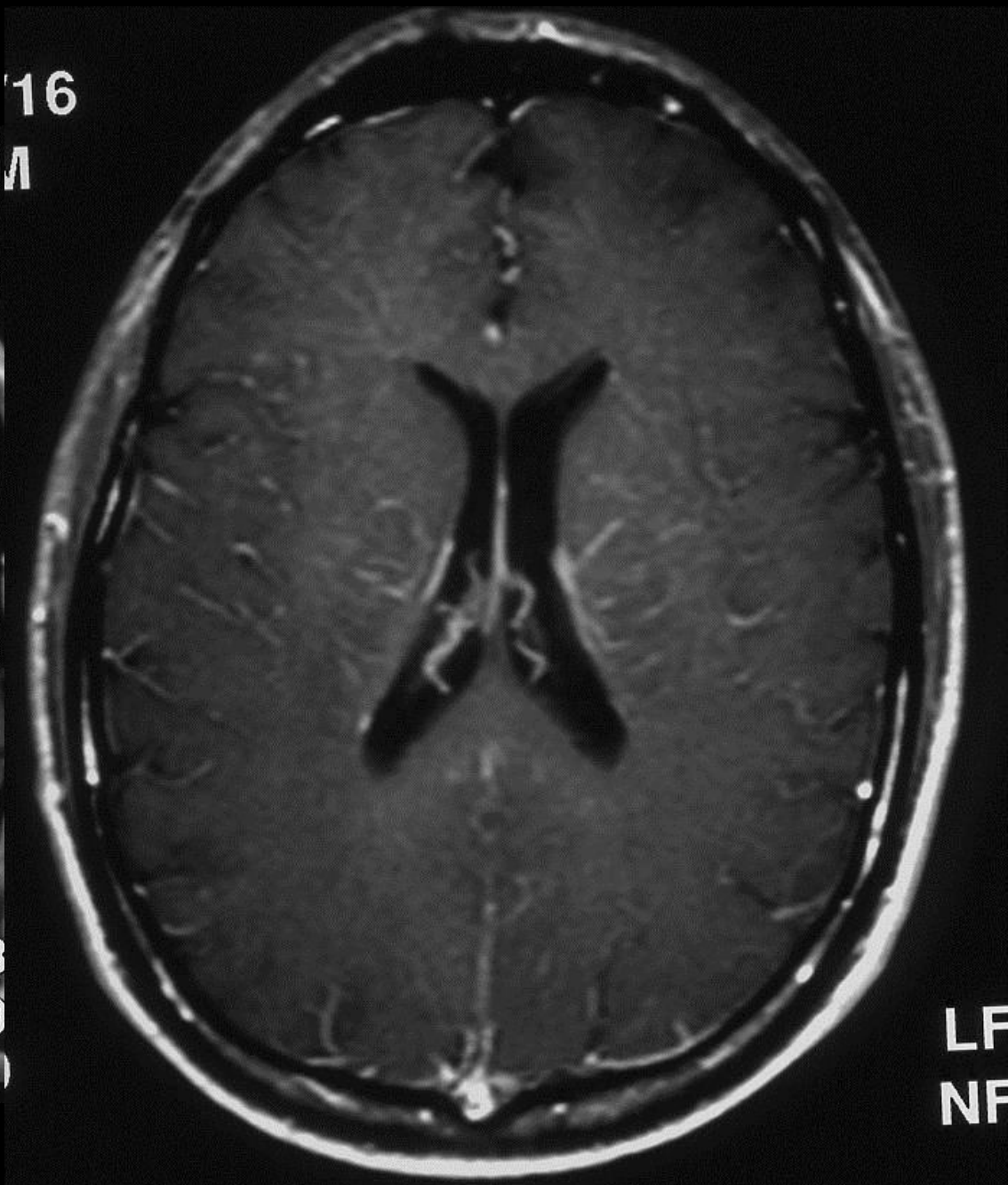
SE / M
LF 13
NF 10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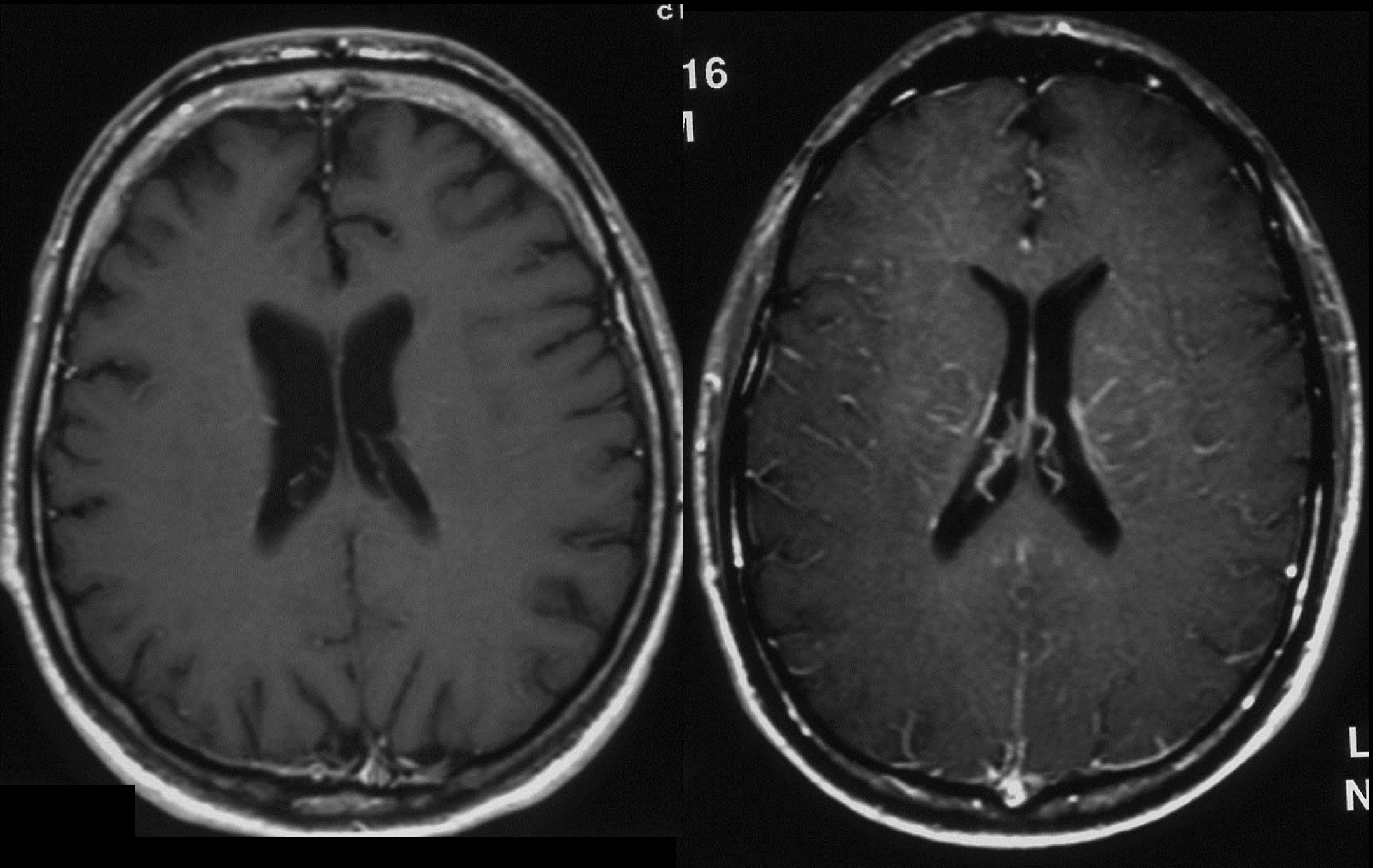
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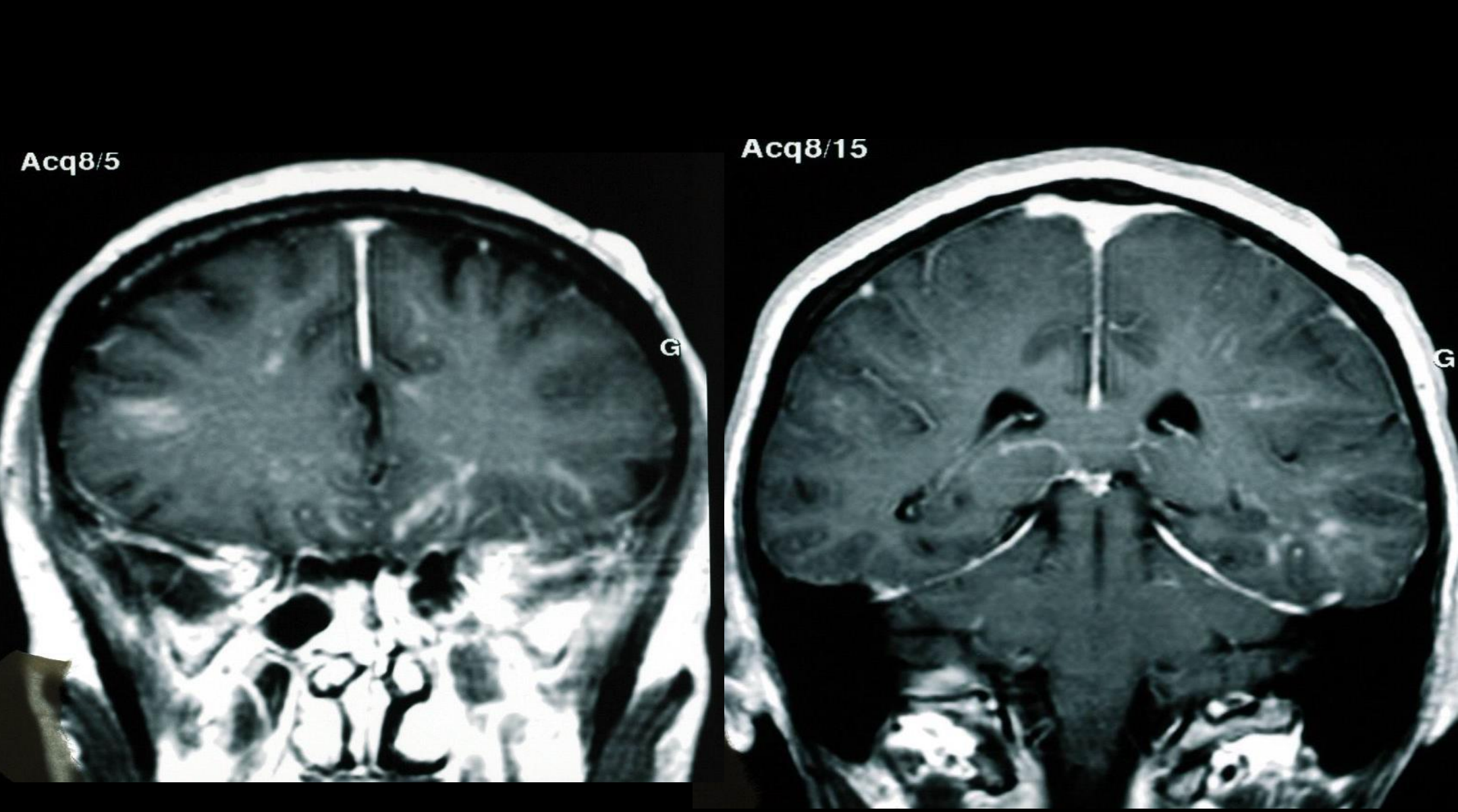
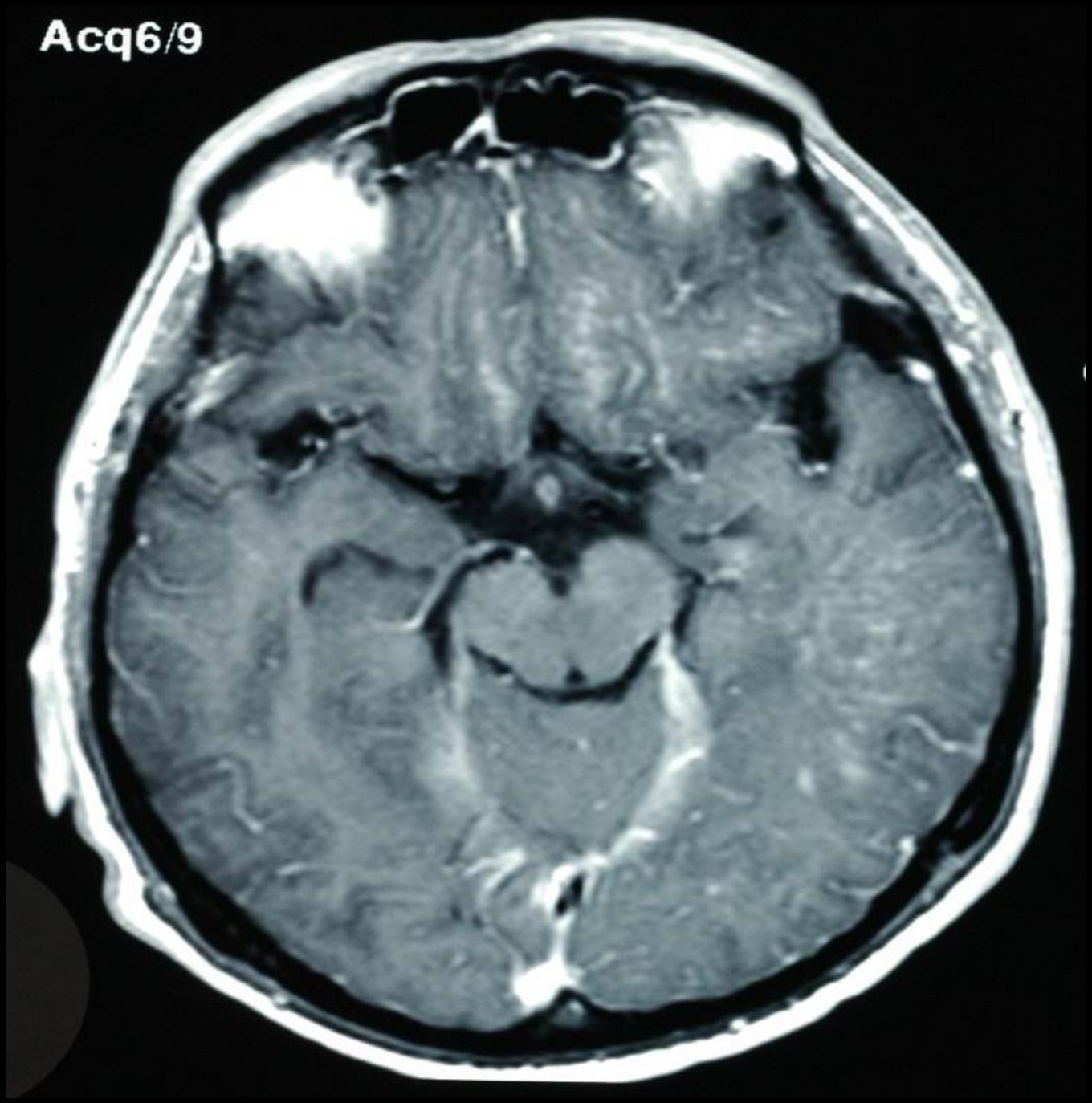

Acq8/5
G
Acq8/15
G


Acq6/9

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

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11	35 M	NA	450	Yes	Minor infection	1999	214	0	21 700	Dementia	ZT 3TC IDVr	0.8	80	NA	1200	+	ND	Yes	<50	<50	Total recovery
12	59 F	NA	NA	NA	ND	NA	NA	30	NA	Confusion, seizures	BC 3TC LPVr	0.52	30	78	NA	+	ND	Yes	NA	NA	Death 1 mo after onset
13	49 M	NA	230	Yes	Minor infection	2008	114	0	200	Confusion	PV ABV 3TC	1.57	19	68	3200	+	ND	Yes	<50	<40	Alive, cognitive impairment
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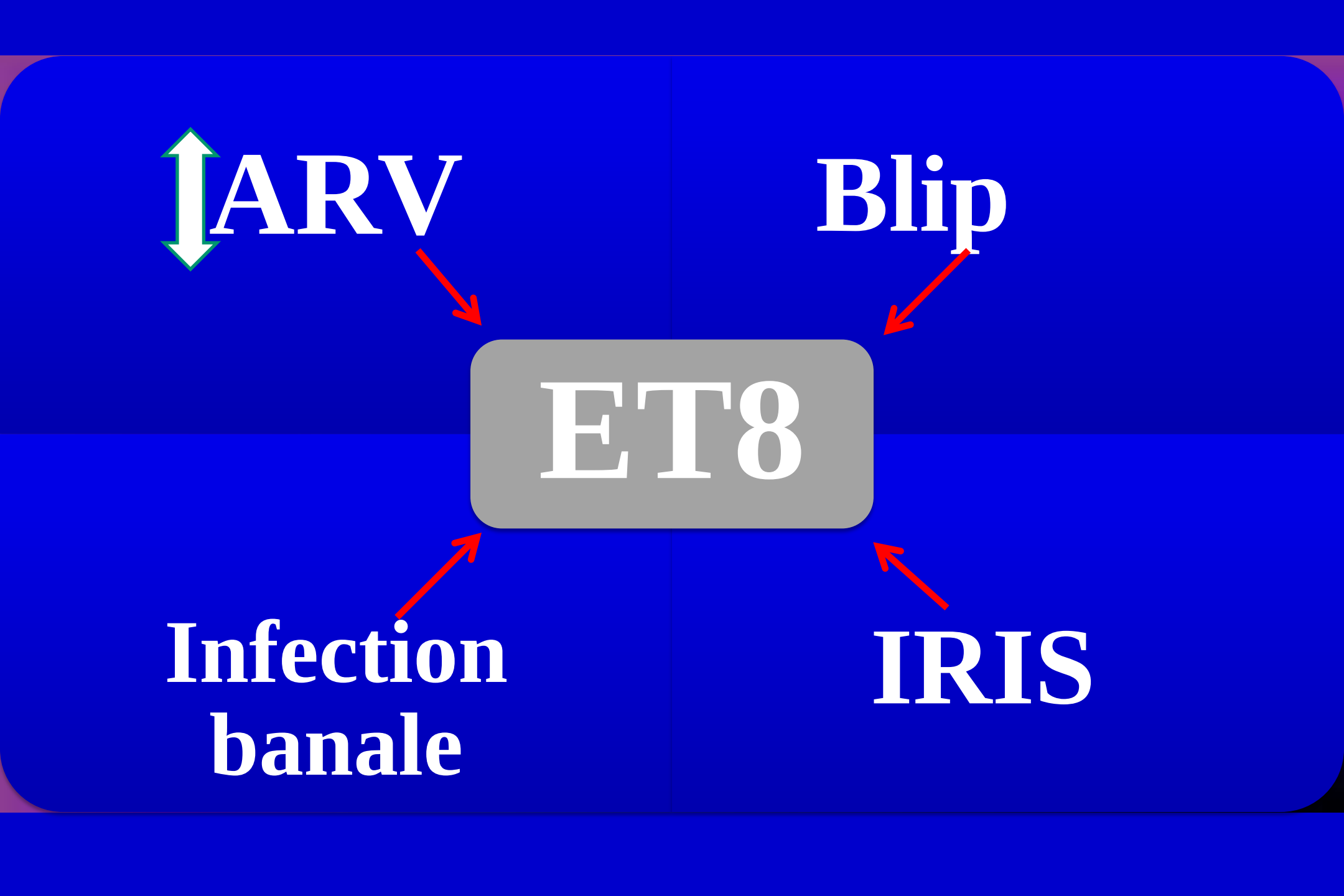
ARV
Blip
ET8
Infection banale
IRIS

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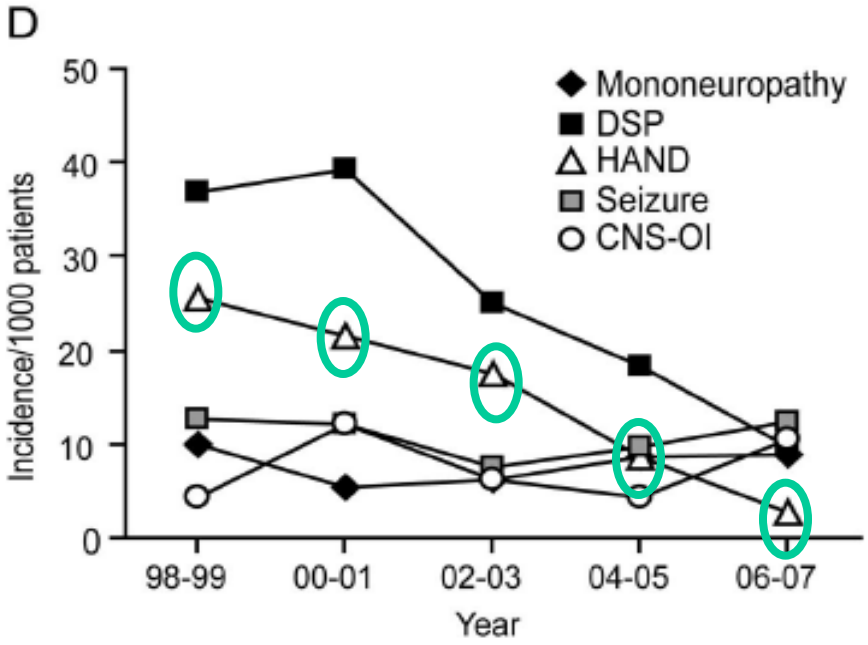
CSF Prot (g/L)	CSF Cells (µL)	CD8 (%)	CSF VL (cp/mL)	Typical Brain MRI	BB p24+ CD4+	Cortico-steroids	PlVL (cp/mL)	CSF VL (cp/mL)
1.47	100	85	NA	+	+ –	Yes	<50	<200
1.10	9	NA	NA	+	+ +	Yes	62	<200
0.63	40	NA	0	+	+ +	Yes	<50	<200
0.9	80	76	2236	+	+/– –	Yes	<50	<200
0.9	26	68	1120	+	– +	Yes	<50	<200
1.13	20	NA	10 300	+	– +	Yes	<50	<200
0.79	220	69	NA	+	– +/–	Yes	<50	<200
0.8	220	78	672	+	– ++	Yes	<20	<40
0.42	1	-	1230	+	++ +	Yes	<50	<200
1.1	46	87	36 242	+	– ++	Yes	<50	<40
0.8	80	NA	1200	+	ND	Yes	<50	<50
0.52	30	78	NA	+	ND	Yes	NA	NA
1.57	19	68	3200	+	ND	Yes	<50	<40
1.1	26	65	3294	+	ND	Yes	<50	<40

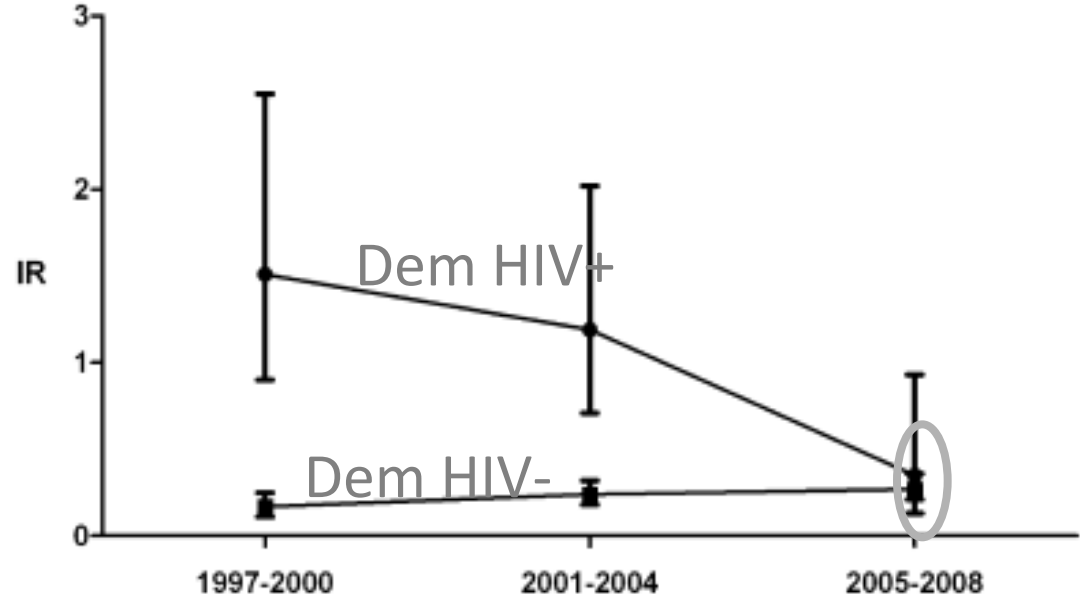
+	Cortico-steroids	PlVL (cp/mL)	CSF VL (cp/mL)	Outcome
	Yes	<50	<200	Death 9 mo after onset
	Yes	62	<200	Total recovery
	Yes	<50	<200	Total recovery
	Yes	<50	<200	Death 3 mo after onset
	Yes	<50	<200	Death 9 mo after onset
	Yes	<50	<200	Death 12 mo after onset
	Yes	<50	<200	Alive, cognitive impairment
	Yes	<20	<40	Total recovery
	Yes	<50	<200	Alive, cognitive impairment
	Yes	<50	<40	Alive, cognitive impairment
	Yes	<50	<50	Total recovery
	Yes	NA	NA	Death 1 mo after onset
	Yes	<50	<40	Alive, cognitive impairment
	Yes	<50	<40	Total recovery

Les troubles cognitifs

L'incidence des tr. cognitifs/HAD diminue



Vivithanaporn et al, Neurology 2010



Lescure et al, CID 2011

Minor Cognitive-Motor Disorder

- Au moins 2/6 symptômes > 1 mois
  - Tr. d'attention ou de concentration
  - Ralentissement idéique
  - Tr. de la mémoire

  } Cog

  - Ralentissement moteur
  - Tr de la coordination

  } Moteur

  - Tr de la personnalité/irritabilité/labilité émotionnelle } Ψ
- +/- retentissement sur ADL
- 2nd^mnt 2 tests < 1,5 DS valeurs normatives
- Dg « clinique » même sans σ. cognitifs !

Critères HNRC

Frascati Conference, 2007

ANI *(asymptomatic NP impairment)*

≥ 2 domaines ≤ 1DS sans R. fonctionnel

Plainte possible : « infra-clinique »

MND *(mild neurocognitive disorder)*

≥ 2 domaines ≤ 1DS + R. fonctionnel ≤ 1DS

HAD

≥ 2 domaines ≤ 2DS ou 1 domaine < 2,5 + 1 domaine < 1 + R. fonctionnel ≤ 1DS

Mais la prévalence est-elle réellement de 50%?

P %	N	Loc	
6	1651	Canada	*Vivithanaporn et al, Neurology 2010*
6-13	345	MACS	*Cole et al, Neurology 2007*
14	292	SMART	*Wright et al, Neurology 2010*
23	158	Neuradapt	*Vassalo et al, CROI 2009*
39	1660	ALLRT	*Robertson et al, AIDS 2007*
49	37	SIGMA	*Dulioust et al, CROI 2009*
52	1555	HNRC	*Heaton et al, Neurology 2010*
59	400	Coh. Aquitaine	*Bonnet et al, AIDS 2012*
69	200	Suisse	*Simioni et al, AIDS 2010*

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Google scholar beta

Octobre 2013

Vivithanaporn et al, Neurology 2010

Cole et al, Neurology 2007 ***37 citations***

Wright et al, Neurology 2010

Vassalo et al, CROI 2009

Robertson et al, AIDS 2007

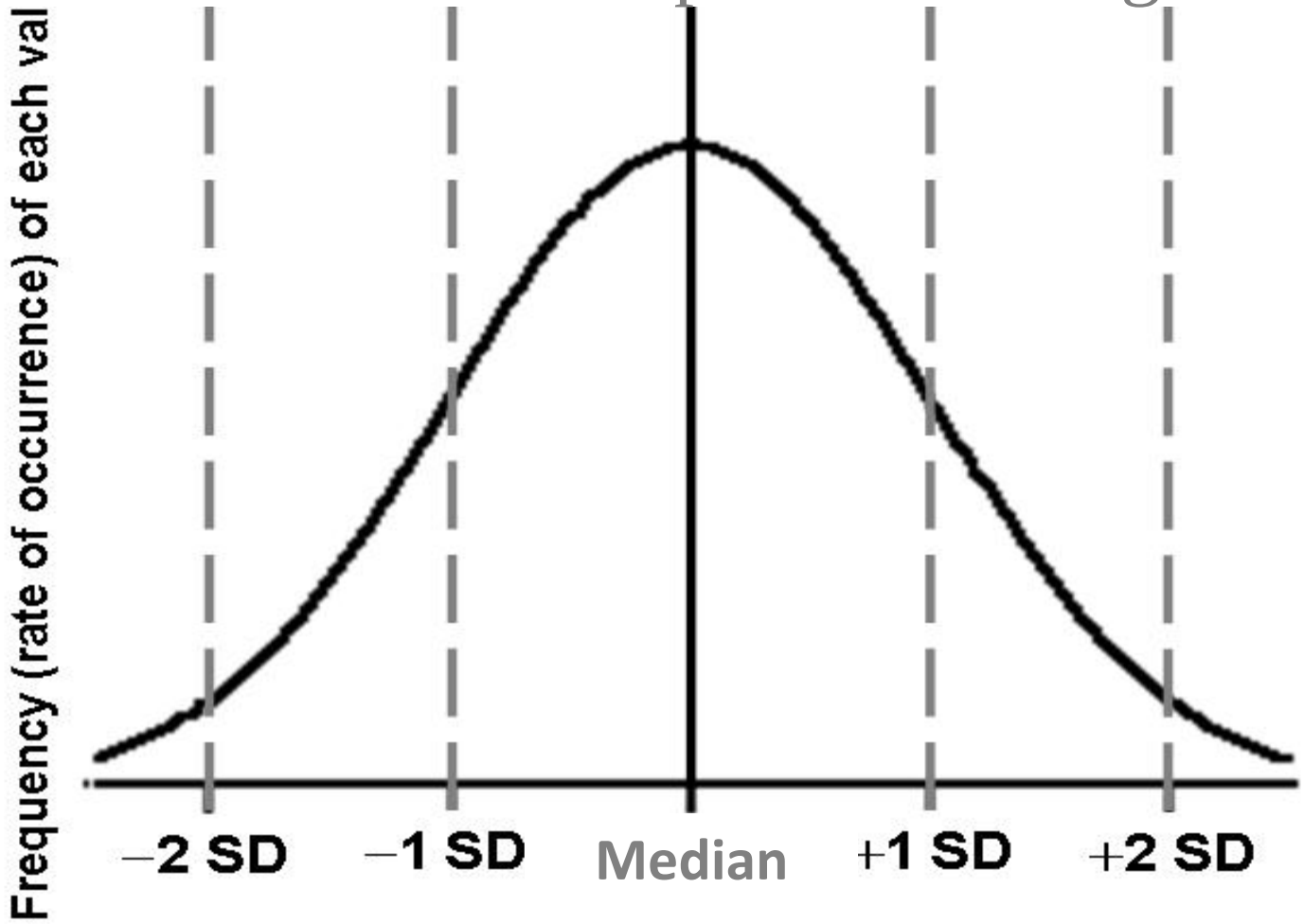
Duliousst et al, CROI 2009

Heaton et al, Neurology 2010 ***312 citations***

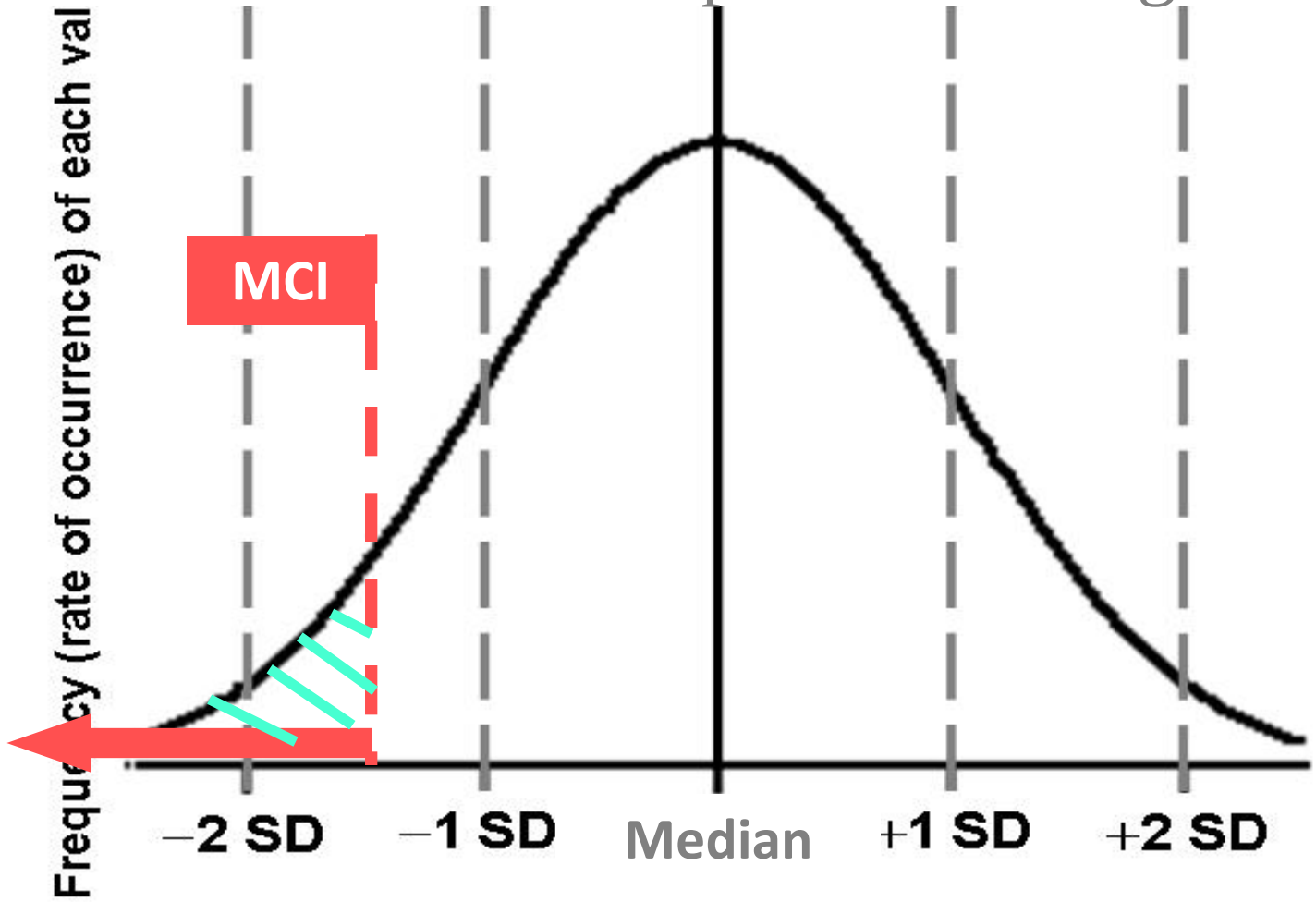
Bonnet et al, AIDS 2012

Simioni et al, AIDS 2010

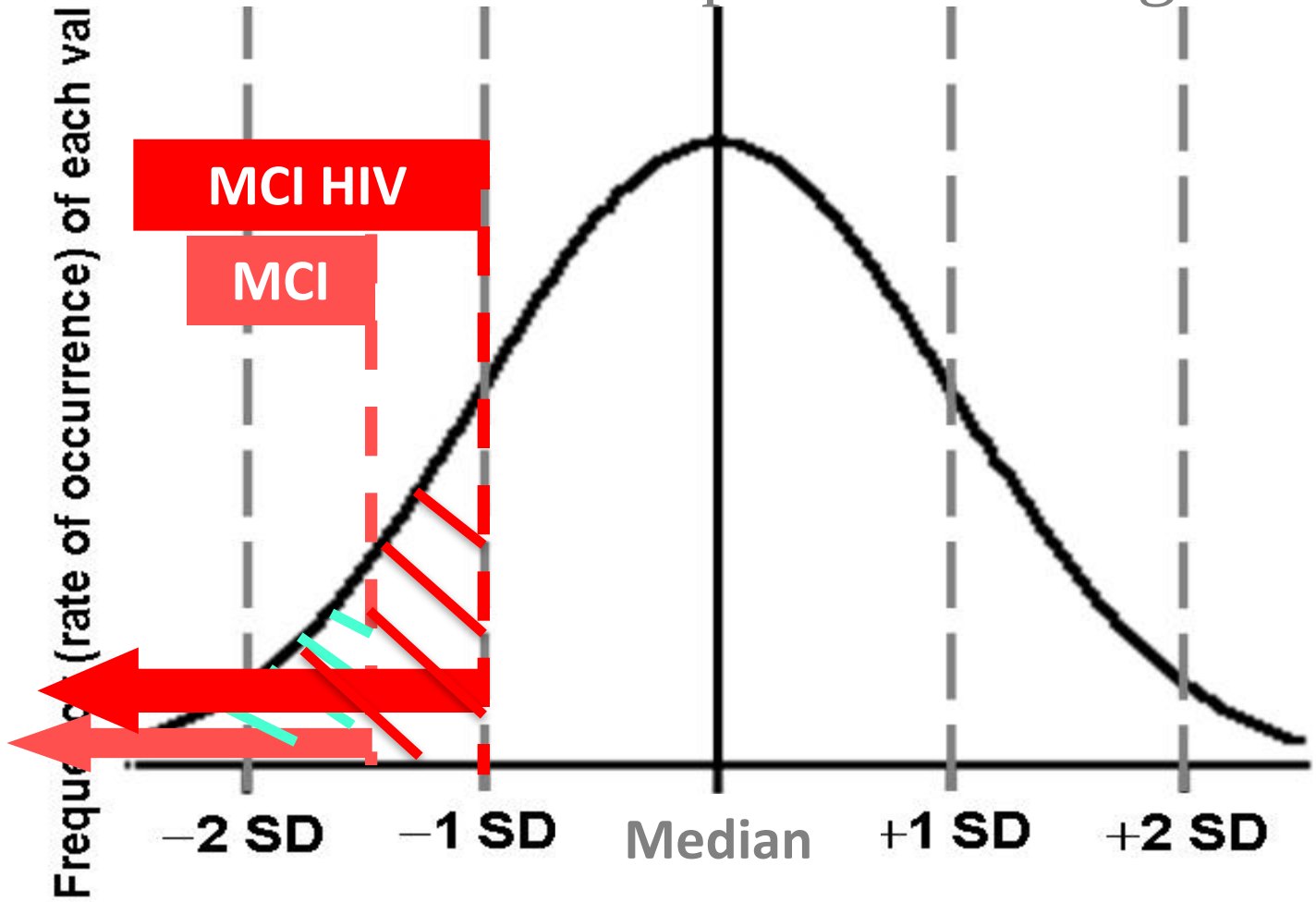
The quality of measurement or the issue of a prodromic stage



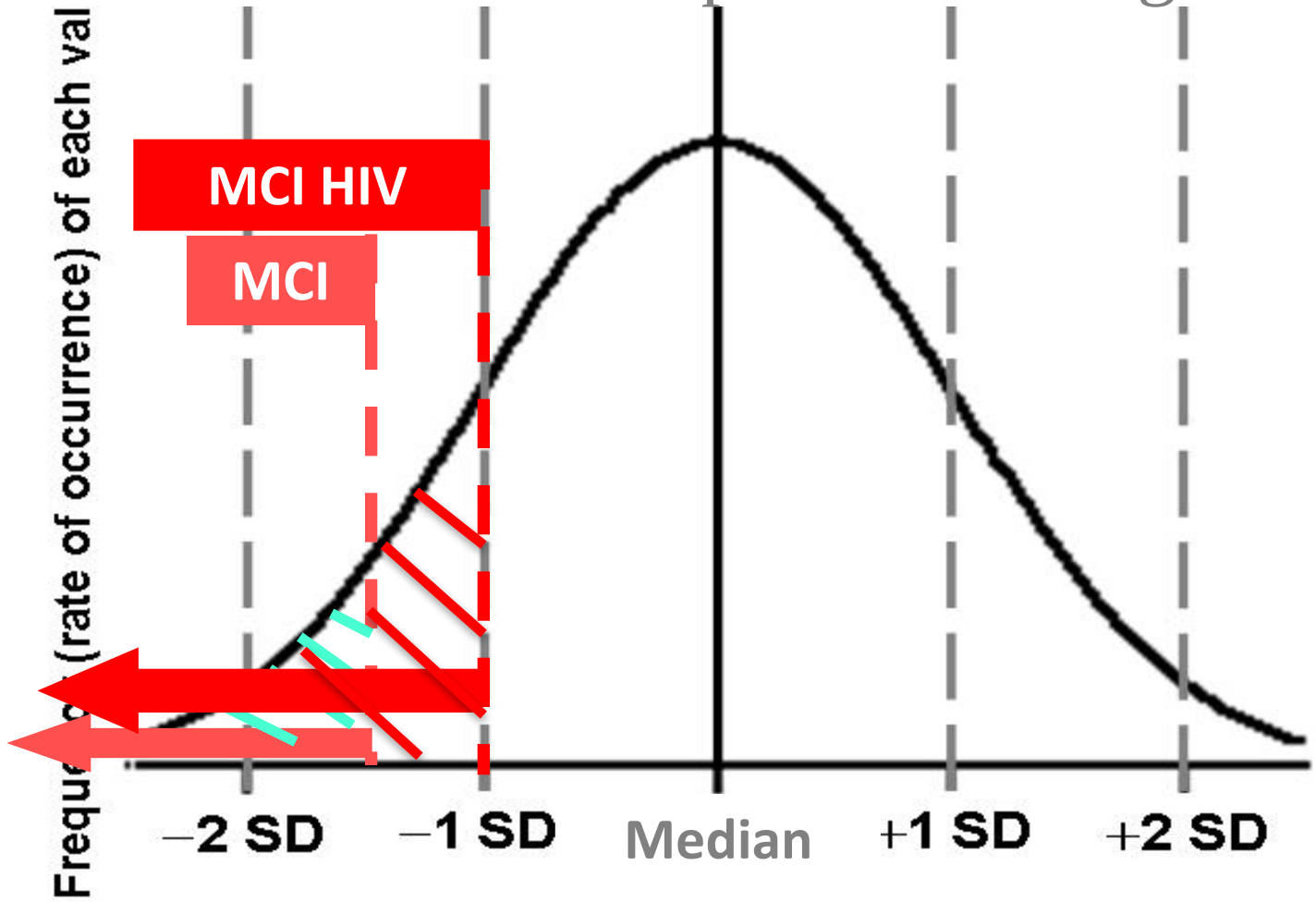
The quality of measurement or the issue of a prodromic stage



The quality of measurement or the issue of a prodromic stage



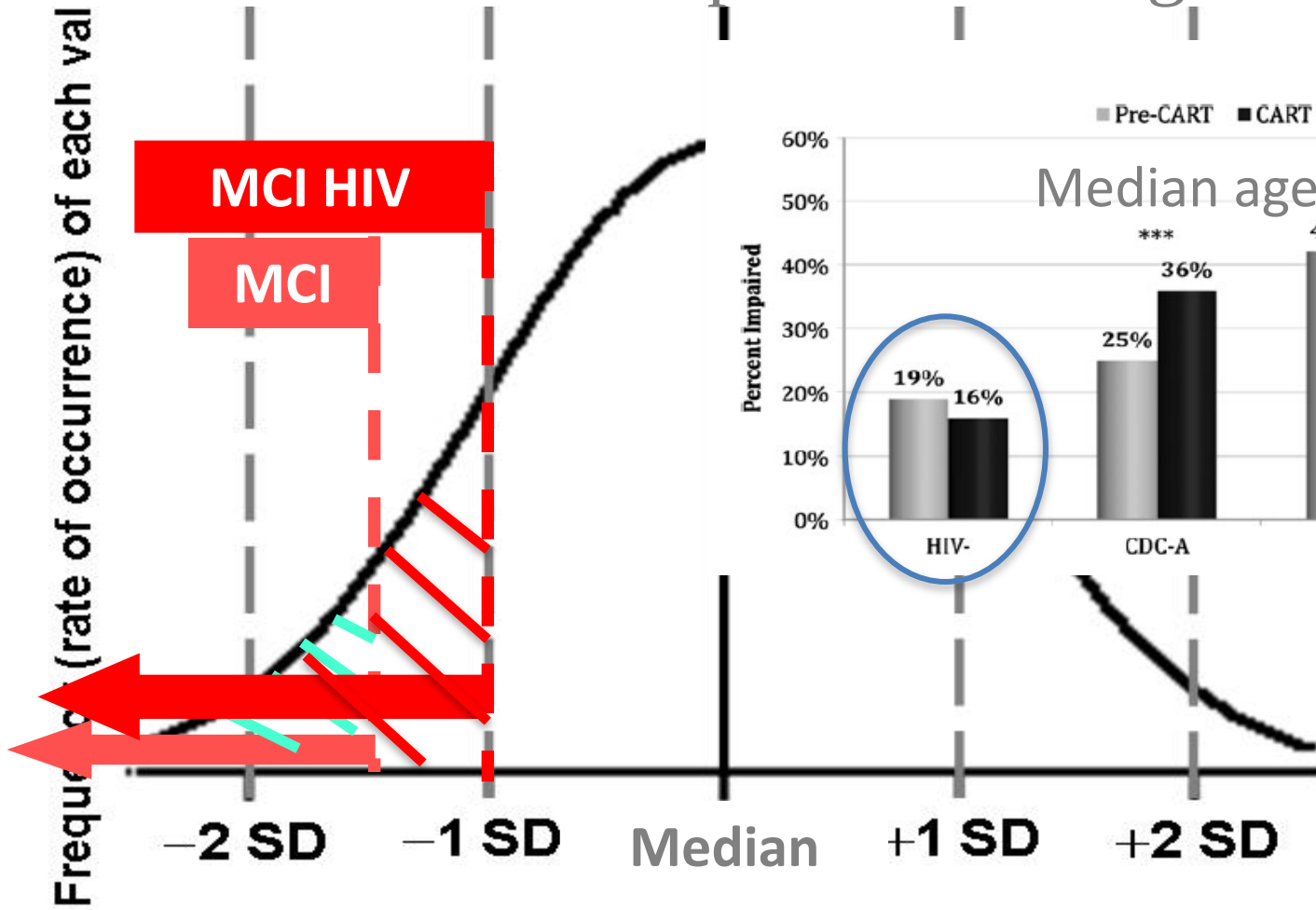
The quality of measurement or the issue of a prodromic stage

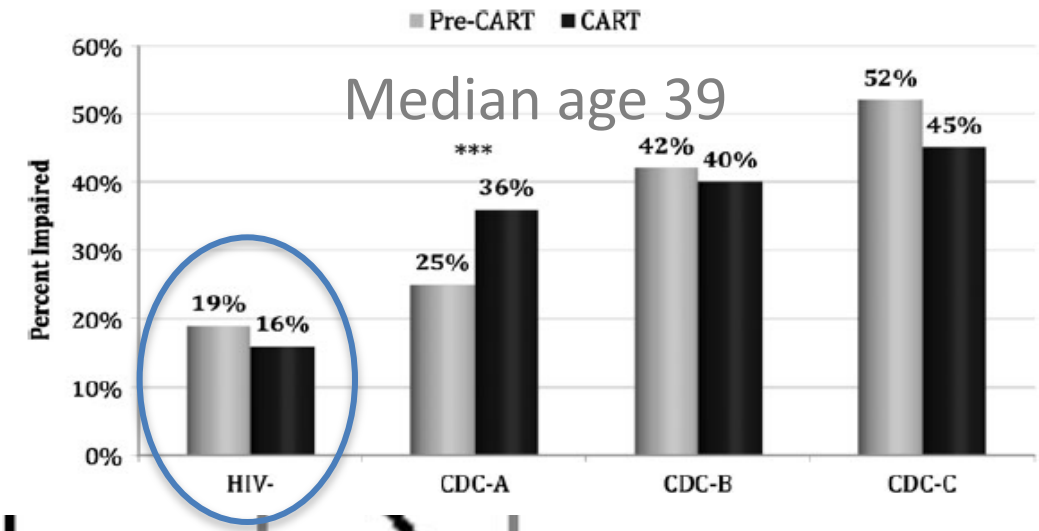


+ ANI / HIV

The quality of measurement or the issue of a prodromic stage

- Diag
  - AA
  - HI
- Rea
  - Va
  - Ins
  - Pr
  - Cc
- Reli
  - -1





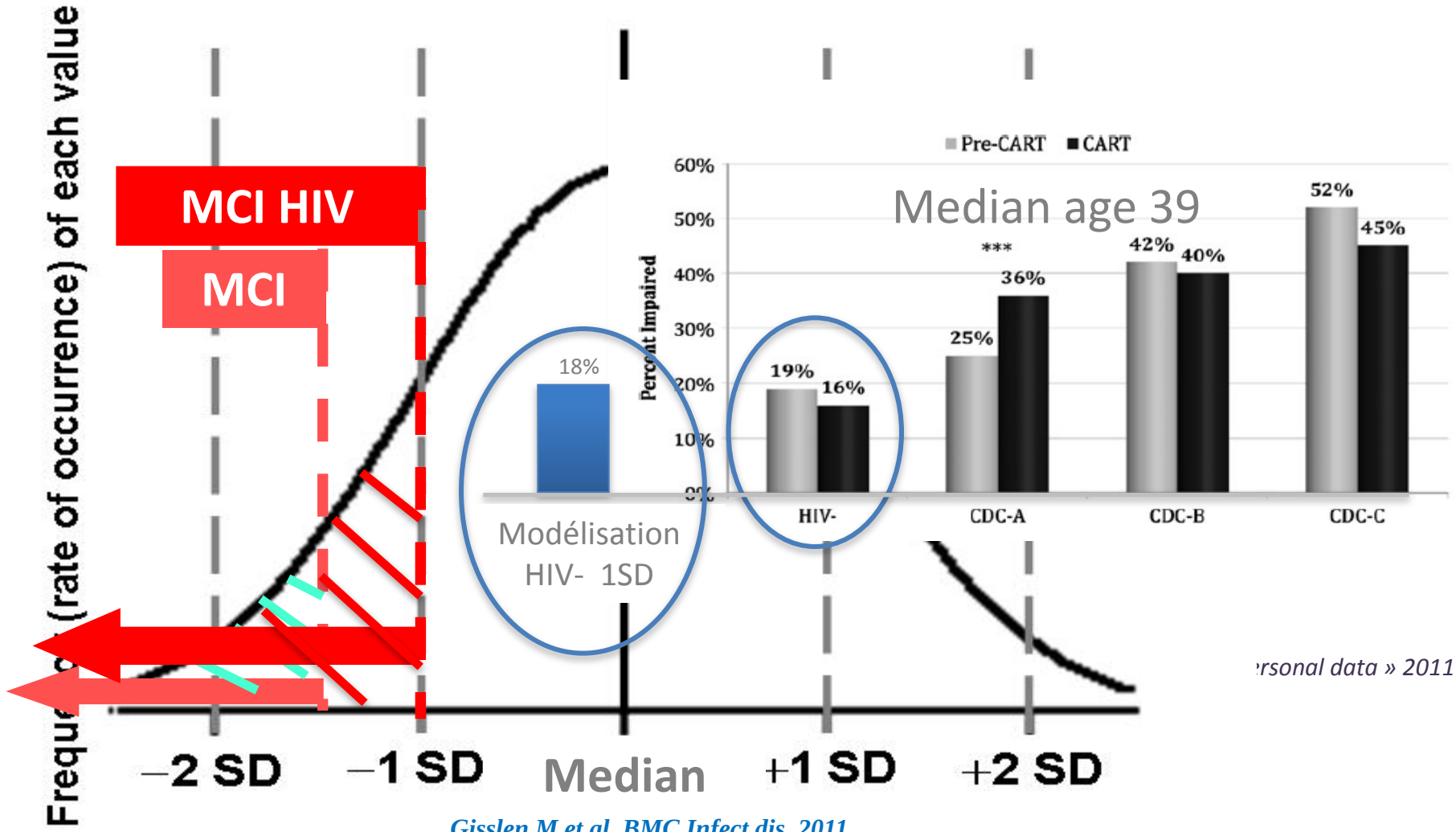
ersonal data » 2011

Heaton et al. J Neurovirol. 2011

+ ANI / HIV

The burden of comorbidities

- Diag
  - AA
  - HI
- Rea
  - Va
  - Ins
  - Pr
  - Co
- Reli
  - -1



Gisslen M et al. BMC Infect dis. 2011

ersonal data » 2011

Heaton et al. J Neurovirol. 2011

+ ANI / HIV

The quality of measurement or the issue of a prodromic stage

Asymptomatic neurocognitive impairment

A priori data

PPV 88 % → 95 %

NPV 45 % → 55 %

Diagnosis	HIVE present, n (%)	HIVE absent, n (%)	n
HAD	4 (100)	0	4
MCMD	10 (100)	0	10
NPI	4 (80)	1 (20)	5
Normal	9 (45)	11 (55)	20
Total no.	27	12	39

Cherner et al, Neurology 2002

AAN	*HNRC*	*HIVE*	*Number of cases*
HAD	HAD	HIVE+	4
HAD	MND	HIVE+	9
MCMD	*Normal*	*HIVE+*	1
MCMD	Normal	No HIVE	2
Normal	MND	HIVE+	2
Normal	ANI	HIVE+	3
Normal	*ANI*	*No HIVE*	1
Normal	Normal	HIVE+	8
Normal	Normal	No HIVE	9

Cherner et al, J Neurovirol 2007

«There does appear to be **empirical support** to adding this third category of HIV-related neurocognitive disorder, because it appears to have **a priori prognostic value** »

«We **recognize that further work needs** to be conducted on the **real-life impact of ANI**,» … «we **strongly recommend** that revised criteria be field tested and further refined through **research**.»

Antinori et al, Neurology 2007

Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy

Hispanics and men who have sex with men. Only 22% of the brains examined were neuropathologically normal. Opportunistic infections occurred in 1% to 5% of the cohort. Parenchymal HIV brain pathology was observed in 17.5% of the cohort and was associated with nadir CD4 and plasma viral load. Brains without parenchymal HIV brain pathology often had other noninfectious findings or minimal nondiagnostic abnormalities that were associated with HIV-associated neurocognitive disorder. Clinically, 60% of the cohort reported a lifetime episode of major depressive disorder and 88% had a HIV-associated neurocognitive disorder. No pathological finding correlated with major depressive disorder. Both antiretroviral treatment regimen and elevated

Table 2 NNTC cohort demographics with and without HIV brain pathology

	Overall ($N=589$)	Parenchymal HIV brain pathology ($N=103$)	No parenchymal HIV brain pathology ($N=486$)	P- value
Neurocognitive impairment ($N=336$)				.71 (FET)
NP–normal	41 (12%)	5 (8%)	36 (13%)	
Asymptomatic NPI	18 (5%)	4 (6%)	14 (5%)	
Minor NCD	71 (21%)	16 (24%)	55 (20%)	
HAD	75 (22%)	16 (24%)	59 (22%)	
NPI–other	131 (39%)	25 (38%)	106 (39%)	

I Everall et al. NNTC, J neurovirol 2009

AVC/AIT/MPAC

FdR Vasculaire

Conventionnels

Âge

Sexe masculin

HTA

tabagisme

Hyperlipidémie

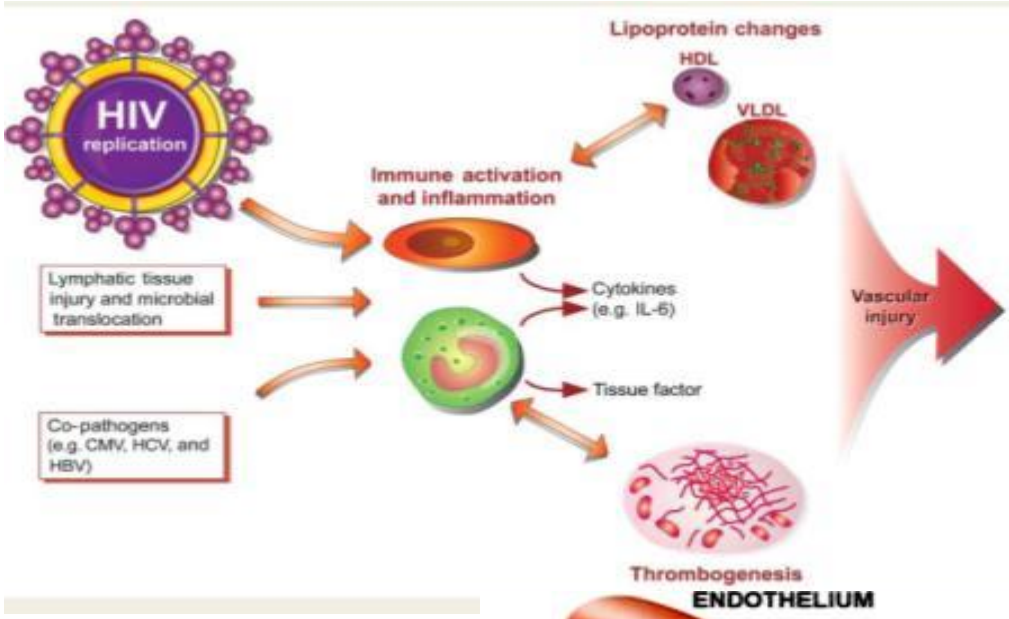
Diabète

Alcoolisme chronique

Maladies cardiaques

(*les contraceptifs oraux*)

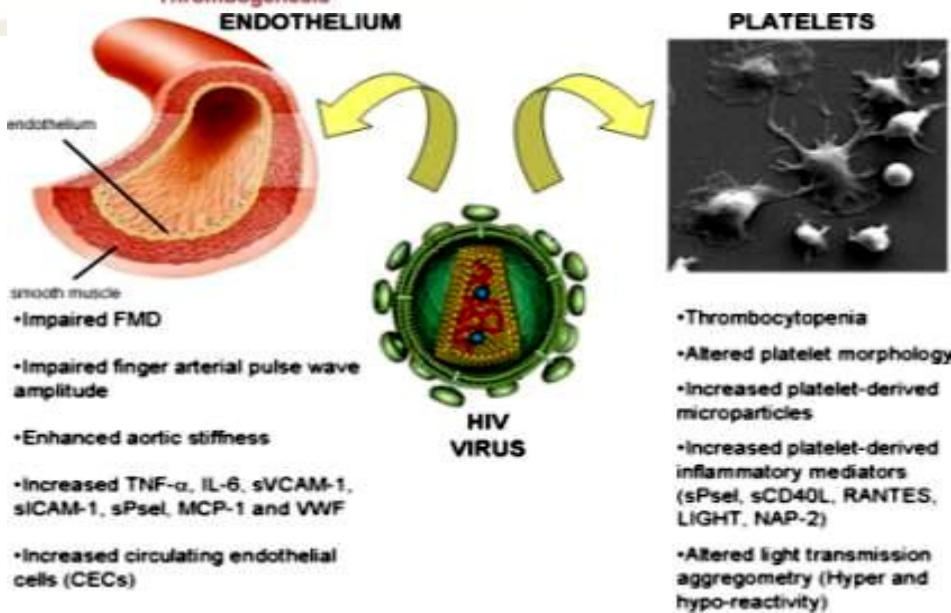
Non conventionnels



Syndrome métabolique

Inflammation artérielle

Hypercoaguabilité



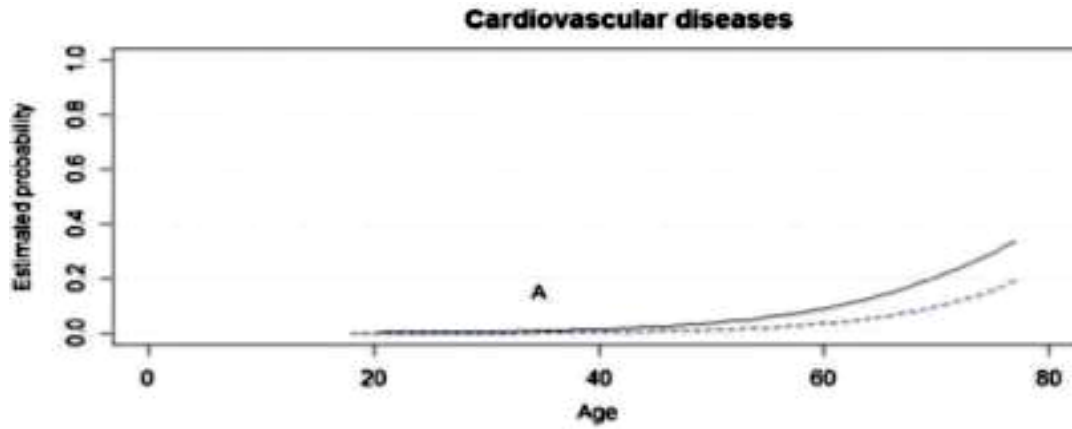
Précocité des co-morbidités/VIH

Étude rétrospective cas-témoins (n = 2854)

Âge moyen 46 +/- 8 ans

71,3% patients contrôlés

Classification CIM9



Prévalence (CV, DNID, HTA, IR, os) > pop. générale

Anticipation 10 ans (41-50 ans)

Guaraldi G et al. CID 2011

Étude Hermès

Âge vasculaire : + 7,6 ans /âge réel

DeSocio GVL et al. International Journal of STD & AIDS 2010

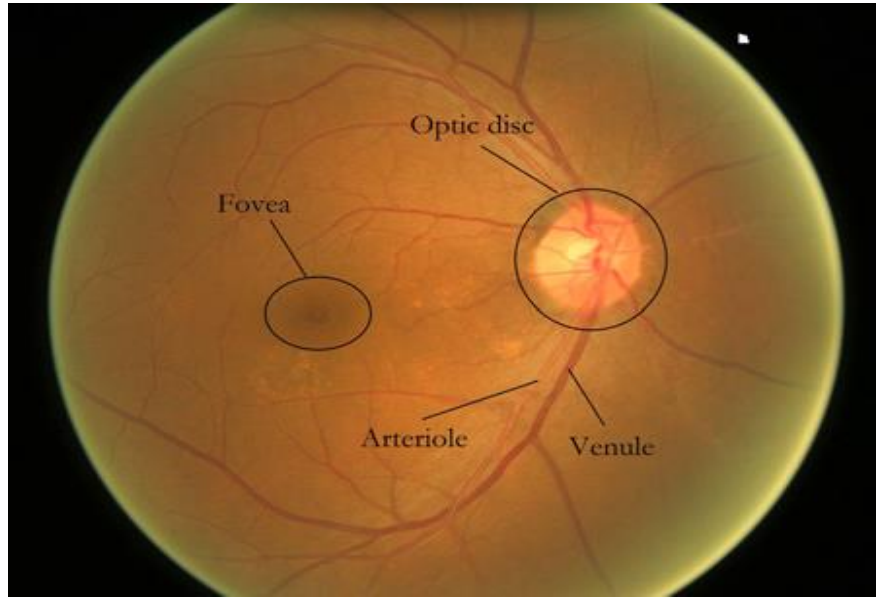
Rétinophotos

Étude longitudinale (1250 patients)

- ✓ suivi 6,1 ans, 43 ans, HTA : 19,9%; DNID 8,1%
- ✓ 85% HAART; CV pl : 2,6-3,5 log; CD4 médian : 192/mm^3
- ✓ Association âge/AA/sexe/tabac
- ✓ **Distribution des calibres des vx ≈ témoins WESDR (âge 55 ans)**

Association indépendante ARV

- ✓ **Mortalité globale**
- ✓ **Mortalité CV**



(Gangaputra 2012; Klein 2006)

Comorbidity and ageing with HIV

A prospective comparative cohort study

ageHIV cohort study

XIX International AIDS Conference
July 26th 2012, Washington DC

Judith Schouten

on behalf of the AGE$_h$IV study

aighd

amc

GGD Amsterdam

HIV Monitoring

Background & Rationale

agehiv cohort study

- Combination antiretroviral therapy (cART): decline in AIDS-associated morbidity and mortality

- Life-expectancy: still shorter than expected, particularly when cART started late[1]

- Large proportion of HIV-patients: broad range of comorbidities[2]

Are age-related comorbidities more prevalent and/or occurring at a younger age in HIV-infected individuals as compared to in HIV-uninfected individuals?

[1] Bhaskaran K, Hamouda O, Sannes M, et al. JAMA 2008 Jul 2;300(1):51-9.

[2] Hasse B, Ledergerber B, Furrer H, et al. Clin Infect Dis 2011 Dec;53(11):1130-9.

Demographic and HIV characteristics

agehiv cohort study

	HIV neg (n=452)	HIV pos (n=489)	p
Age (years)	51.5 (47.5-57.6)	52.9 (48.1-59.8)	0.009
Male gender	83.8%	89.4%	0.013
Dutch	82.1%	75.1%	0.037
MSM	63.5%	68.5%	0.105
Years of known HIV-1 seropositivity (years)		12.2 (6.5-17.3)	
Mean CD4 count in year prior to enrollment (cells/mm^3)		**573** (436-748)	
Nadir CD4 count (cells/mm^3)		210 (130-310)	
Undetectable during year prior to enrollment		**85.0%**	
Prior AIDS		30.1%	
On cART		**91.2%** • 74% started R_x-naive • 26% started ART-exp.	
Years since start of first ART (years)		11.2 (5.5-14.9)	

Comorbidity risk factors

	HIV neg (n=452)	HIV pos (n=489)	P
Smoking (packyears)	3.0 (0.0-18.5)	**7.6** (0.0-31.0)	<0.001
Currently **smoking**	23.9%	**31.9%**	0.006
Heavy daily drinking	**6.9%**	3.5%	0.019
Daily to monthly use of cannabis and/or XTC and/or cocaine	17.5%	17.6%	0.965
BMI (kg/m^2)	24.5 (22.9-27.0)	24.1 (22.3-26.7)	0.021
Blood pressure systolic (mmHg)	133 (125-143)	**135** (126-147)	0.028
Blood pressure diastolic (mmHg)	79 (72-85)	**82** (75-89)	<0.001

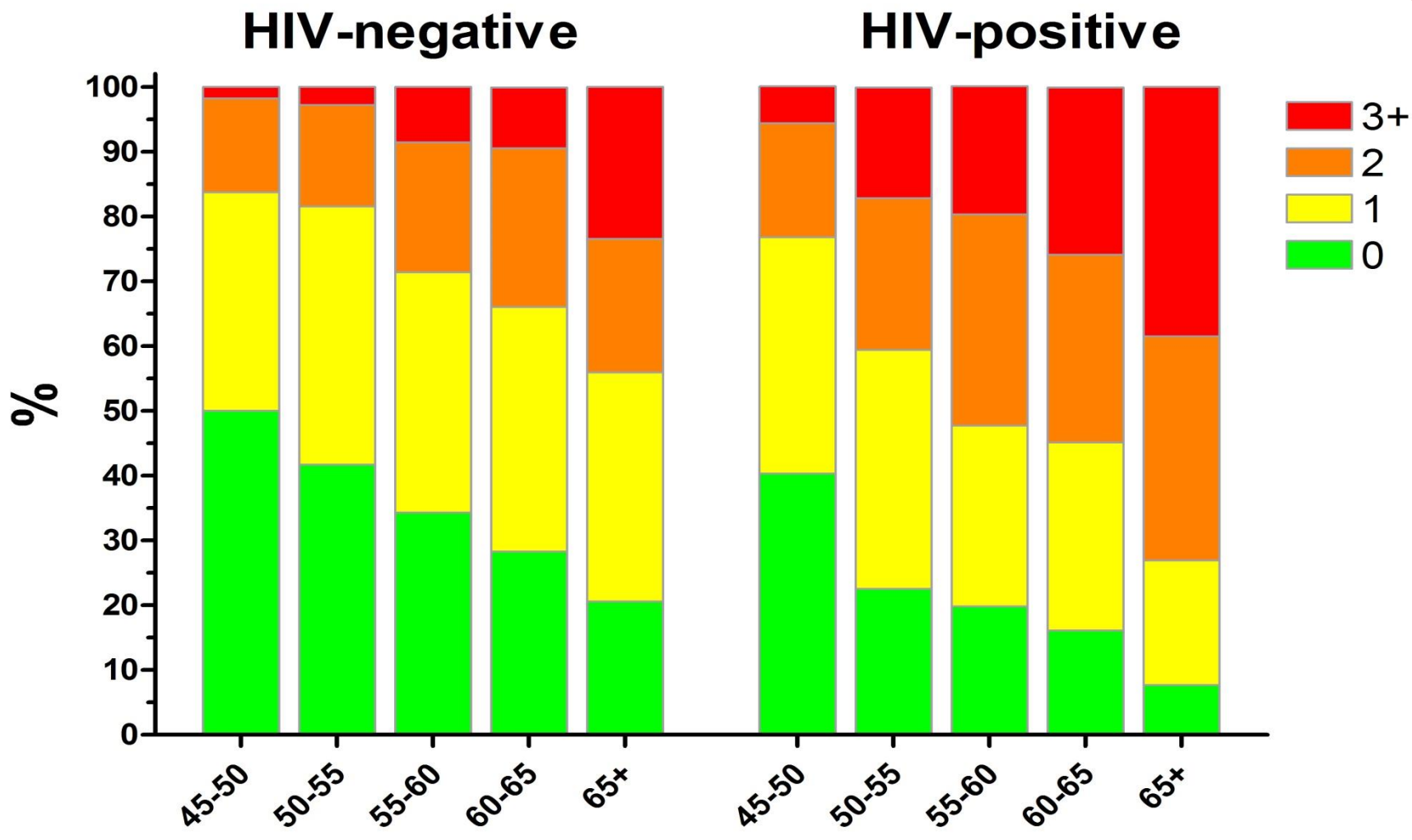
Data presented as median (IQR) or percentage as appropriate

Comorbidity prevalence

	HIV neg (n=452)	HIV pos (n=489)	P
≥1 AANCC (%)	60.4%	74.4%	<0.001
Number of AANCC (mean (SD))	0.9 (0.95)	1.4 (1.27)	<0.001

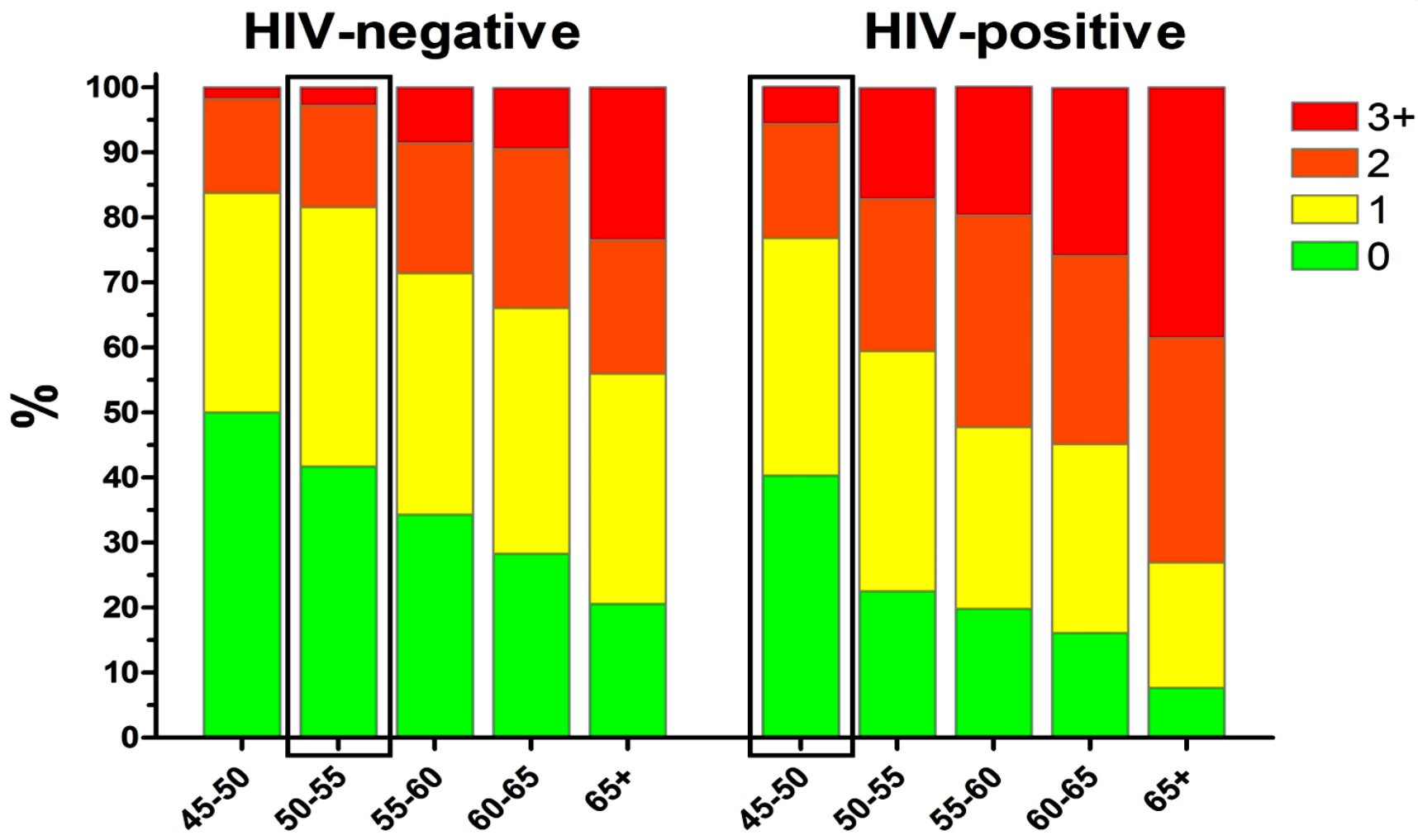
age-associated non-communicable comorbidities (AANCC)

Comorbidity in relation to age



Mean number of AANCC										
0.68	0.80	1.03	1.15	1.47		0.89	1.35	1.52	1.65	2.04
Number of participants										
166	108	70	53	34		159	111	86	62	52

Comorbidity in relation to age



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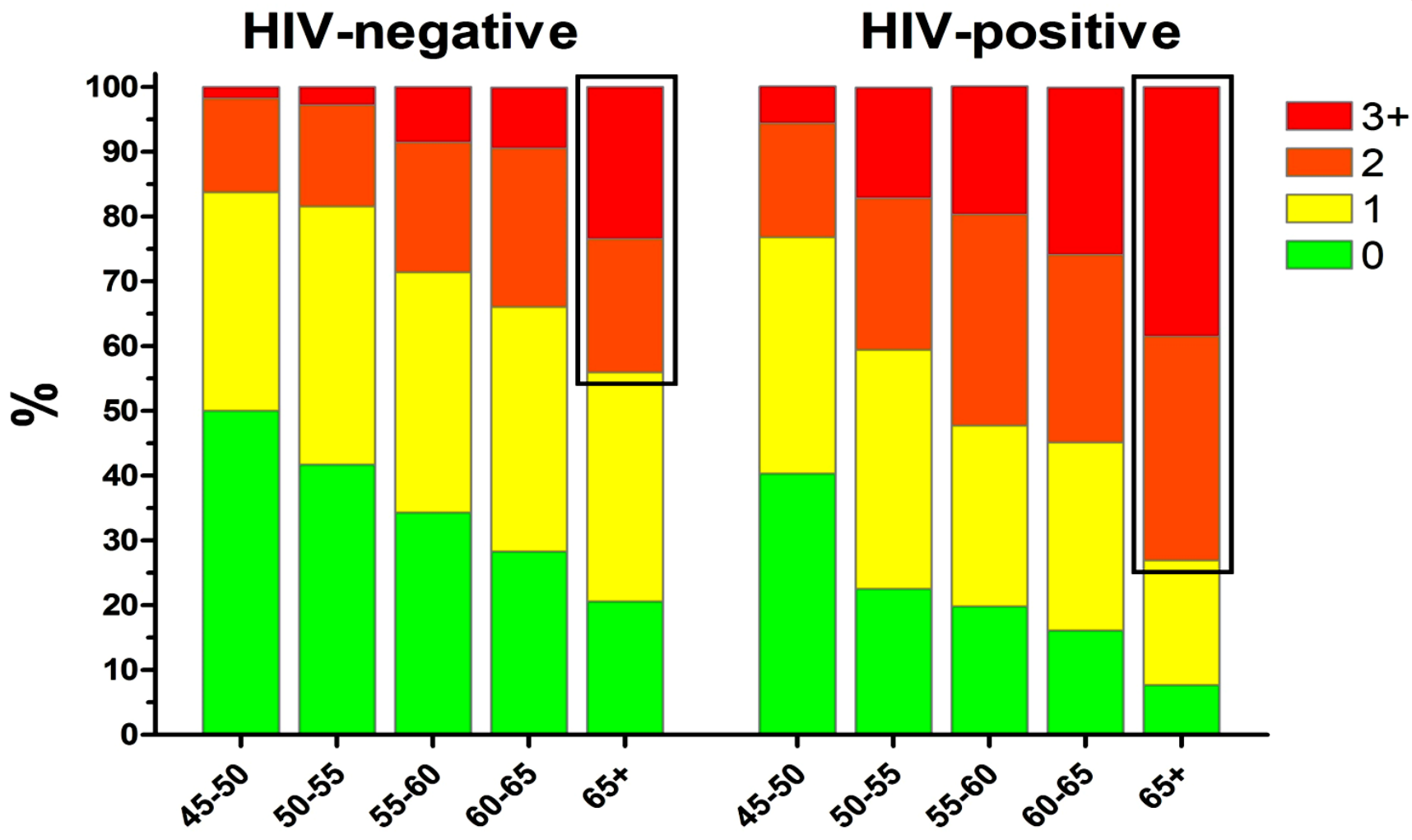

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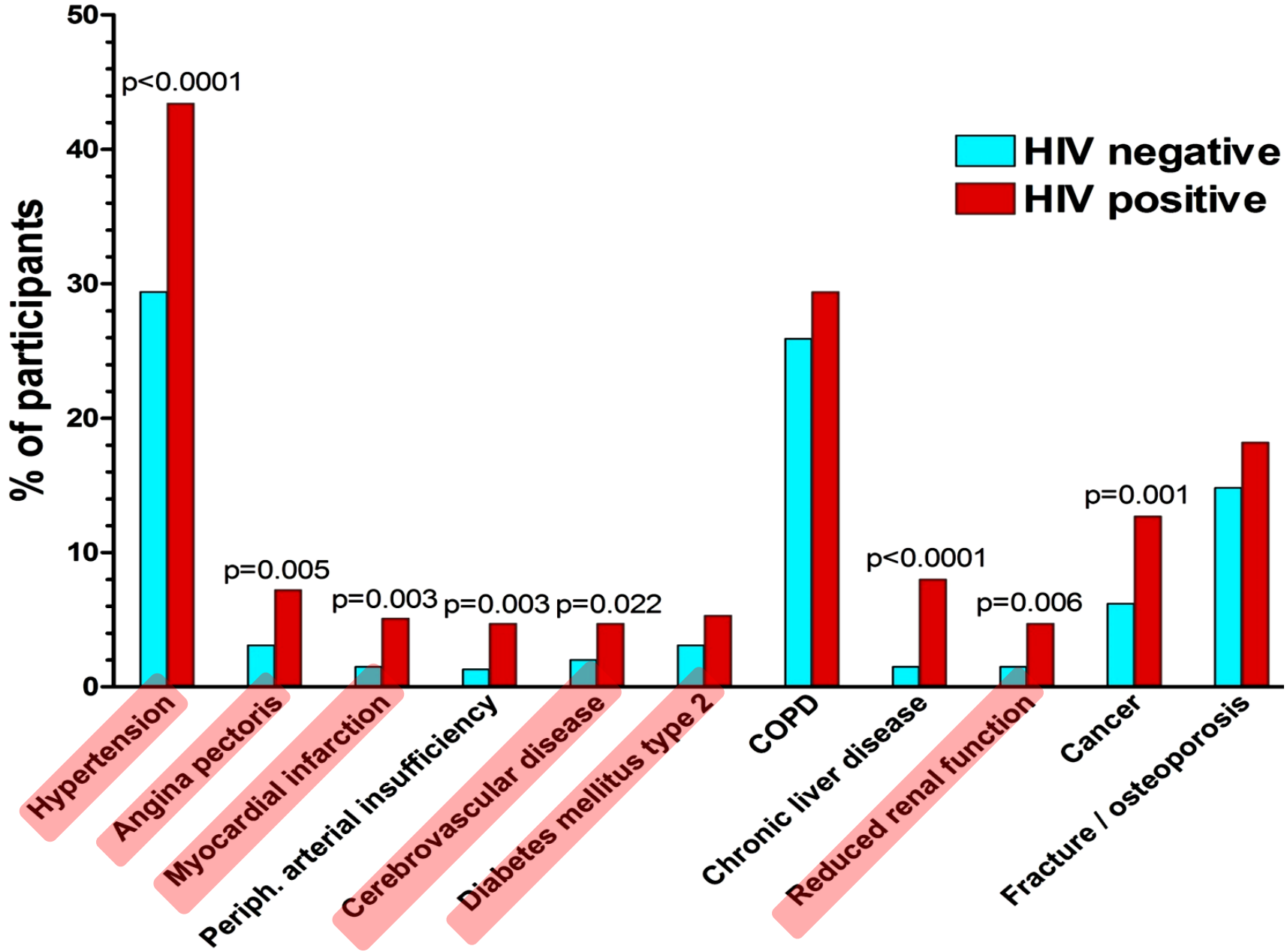
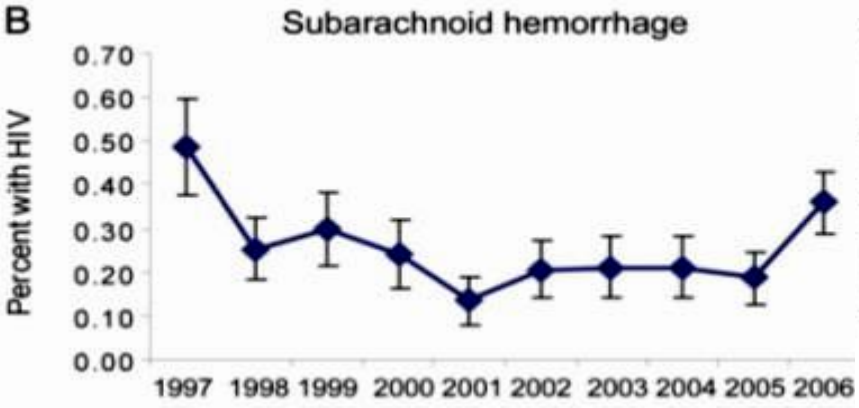
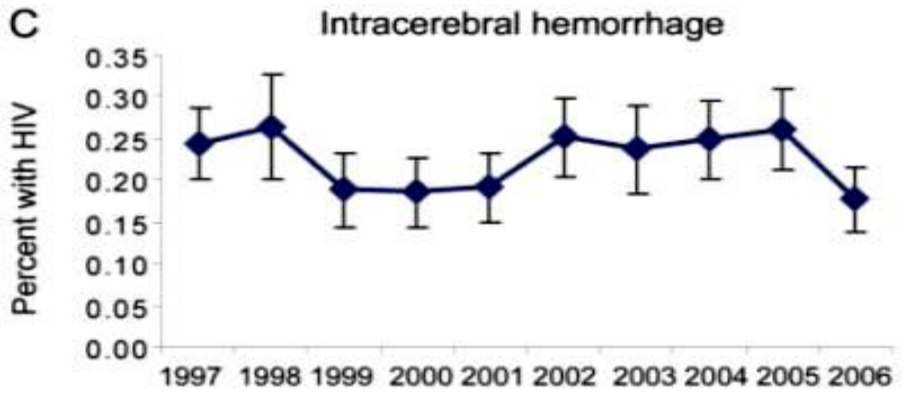
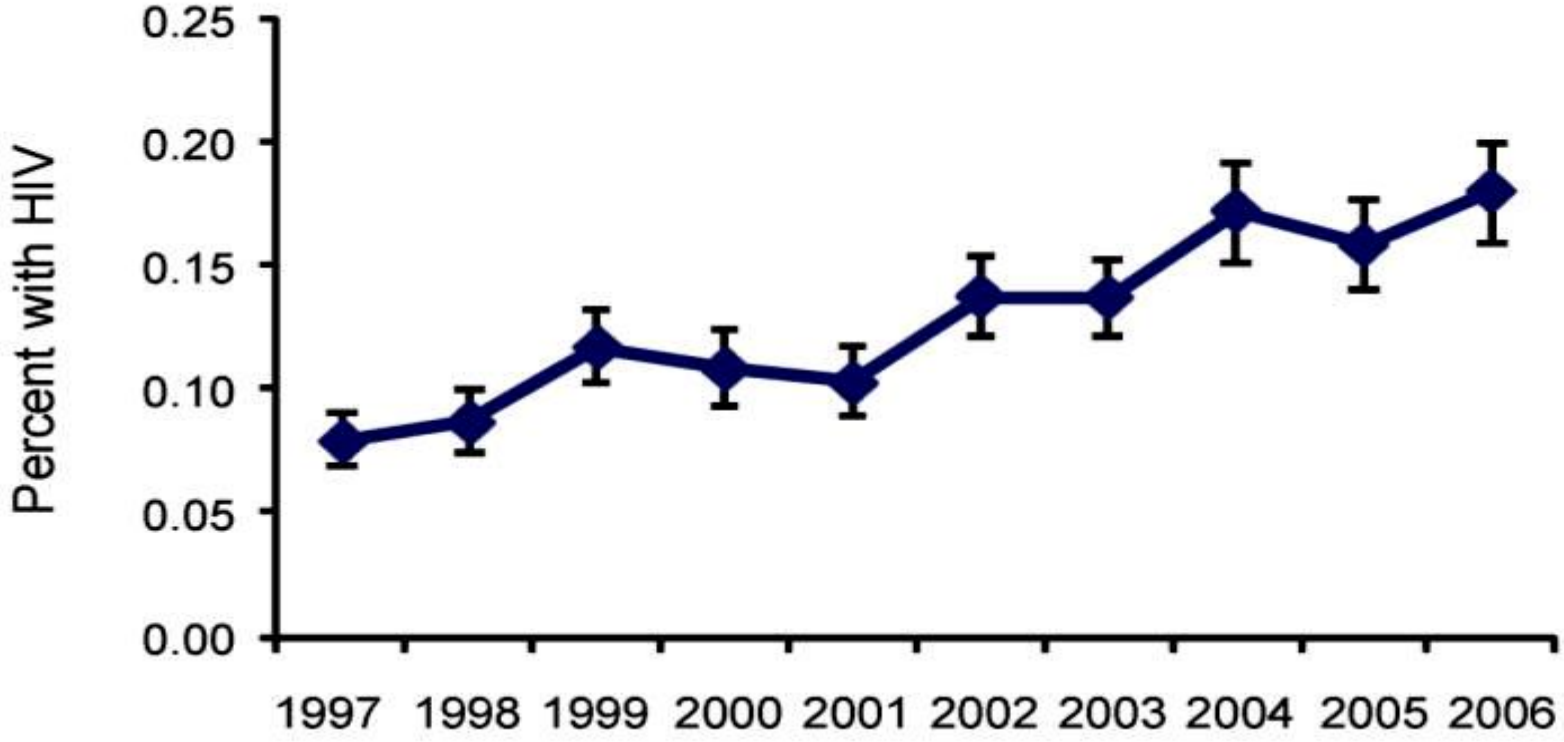
Comorbidity distribution



AIC ont doublé entre 1996 et 2007 (p < 0,0001)







(Ovbiagele, 2011)

Risque relatif des AVC/AIT dans la cohorte danoise

	VIH non IVDU vs témoins		VIH IVDU vs témoins	
	non ajusté	ajusté	non ajusté	ajusté
AVC totaux	1,60 (1,32-1,94)	1,60 (1,30-1,95)	3,70 (2,10-6,52)	3,94 (2,16-7,16)
HSA	1,85 (0,90–3,81)	1,72 (0,80–3,69)	4,41 (0,81-24,09)	4,41 (0,81-24,09)
HIC	1,43 (0,68–3,03)	1,47 (0,67-3,20)	22,13 (4,29-114,11)	35,62(4,04-314,17)
AIC	1,76 (1,22-2,53)	1,63 (1,10-2,41)	2,11 (0,60-7,48)	1,90 (0,50-7,19)
AVC non spécifié	1,48 (1,06-2,07)	1,54 (1,08-2,18)	4,02 (1,53-10,58)	4,62 (0,15-9,67)
AIT	1,58 (1,08-2,33)	1,64 (1,10-2,44)	0,99 (0,13-7,80)	1,19 (0,15-9,67)
AVC avec FdR +	1,54 (1,19-1,99)	1,55 (1,19-2,03)	-	-
AVC sans FdR	1,68 (1,25-2,25)	1,65 (1,21-2,26)	-	-
Hommes	1,63 (1,33-2,00)	1,59 (1,29-1,97)	3,61 (1,89-6,90)	3,83 (1,89-7,77)
Femmes	1,37 (0,76-2,46)	1,69 (0,89-3,23)	4,00 (1,23-12,99)	3,82 (1,18-12,41)
préARV CD4 ≤ 200 *vs CD4 > 200*	2,28 (1,09-4,76)	1,26 (1,05-4,86)		

(Rasmussen, 2011)

cohorte Suisse (n = 8444)	VIH (IRR/1000 p-a)	Analyse univariée	Analyse multivariée
	p < 0,001 (p*)	HR	HR
Âge (médian)	45 ans (68% < 50 ans)		
CD4 (médian)	528/mm^3		
ART CV </> 50 copies	69,1%/16%		
Suivi moyen	36 mois		
AIC	1,73 (1,26-2,37; p*)		
☞ < 50 ans	0,78 (0,445-1,38)		
☞ 50-64 ans	2,81 (1,75–4,52; p*)	3,59 (1,72–7,52; p*)	3,96 (1,86–8,42; p*)
☞ ≥ 65 ans	8,53 (4,59-15,9; p*)	10,9 (4,70–25,2; p*)	17,7 (7,06-44,5; p*)
DC cause CV	12,4%		

(Hasse, 2011)

AVC et VIH (MONICA)

Registration of stroke events

- **2.1 Data Collection**
  - **2.1.1 Data to be collected**

  The diagnosis of stroke is based **on clinical signs** which should last **more than 24 hours** except in cases of sudden death or if the development of symptoms is interrupted by a surgical intervention.

  Therefore, it is important to pay **great attention to both symptoms and duration**.

  Data on subcategories of stroke will also be collected to give more information about different types of stroke. The classification into subcategories of stroke should **strictly follow the criteria given under** Subsection 2.2.4.

AVC et VIH (MONICA)

Brain infarction due to occlusion of precerebral arteries

(ICD 9 433 ICD 8 432)

Symptoms:

May vary

Findings :

the occlusion must be confirmed by angiography or ultrasound or necropsy

Brain infarction due to cerebral thrombosis

(ICD 9 434 ICD 8 433)

Symptoms:

No severe headache, if at all.
Onset acute, sometimes during sleep.
Often **gradual progression** of focal neurologic deficits.
Usually, no, or only slight, disturbance of consciousness.
TIA can often be detected in history.
Often other symptoms of atherosclerosis
or underlying diseases (hypertension, diabetes).

Findings:

Brain infarction in the necropsy or in the CT-examination and no evidence for an embolic origin.

OR

CT scan of satisfactory quality shows no recent brain lesion although clinical criteria of stroke are fulfilled

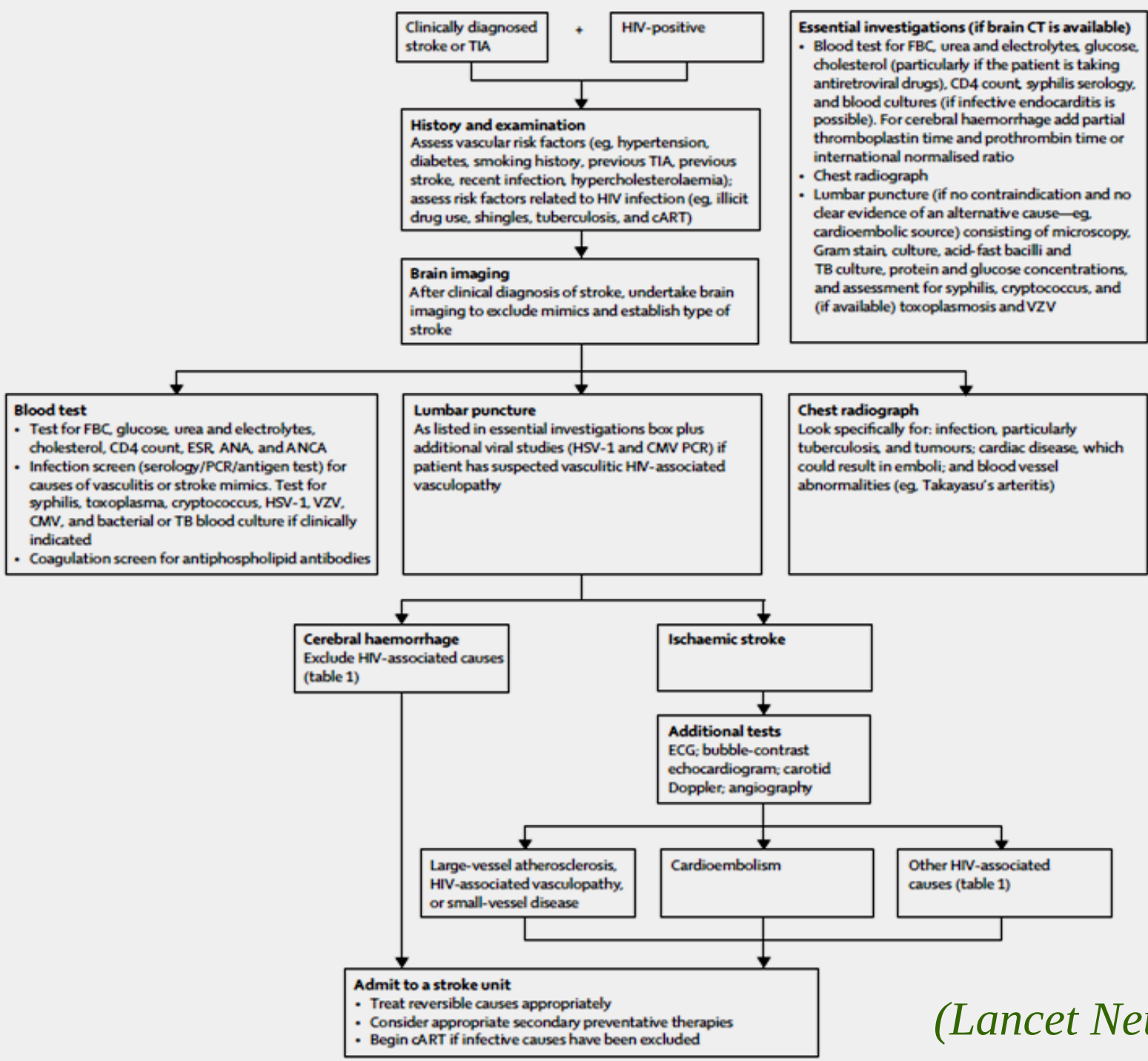
HIV infection and stroke: current perspectives and future directions

Laura A Benjamin, Alan Bryer, Hedley C A Emsley, Saye Khoo, Tom Solomon, Myles D Connor

Lancet Neurol 2012; 11: 878–90 HIV infection can result in stroke via several mechanisms, including opportunistic infection

Conclusions and future directions

Good community-based epidemiology to assess the burden and nature of HIV-related stroke is rare. Epidemiological studies with good clinical assessment of stroke patients, early imaging, clearly documented stroke types, subtypes, risk factors and causes, and importantly autopsy confirmation or exclusion of stroke and identification of the underlying cause of stroke, are needed in both high-income and low-income regions (panel 2). Improved knowledge about the mechanisms and causes of stroke should lead to improved investigation and treatment of patients. Further study is needed to assess the benefit and safety of acute stroke therapy and secondary stroke prevention in patients with HIV. Finally, the long-term effect of cART on stroke incidence is also unknown, and it might take years to establish this risk.



(Lancet Neurol 2012)

Clinically diagnosed stroke or TIA + HIV-positive

History and examination
Assess vascular risk factors (eg, hypertension, diabetes, smoking history, previous TIA, previous stroke, recent infection, hypercholesterolaemia); assess risk factors related to HIV infection (eg, illicit drug use, shingles, tuberculosis, and cART)

Brain imaging
After clinical diagnosis of stroke, undertake brain imaging to exclude mimics and establish type of stroke

Essential investigations (if brain CT is available)
- Blood test for FBC, urea and electrolytes, glucose, cholesterol (particularly if the patient is taking antiretroviral drugs), CD4 count, syphilis serology, and blood cultures (if infective endocarditis is possible). For cerebral haemorrhage add partial thromboplastin time and prothrombin time or international normalised ratio
- Chest radiograph
- Lumbar puncture (if no contraindication and no clear evidence of an alternative cause—eg, cardioembolic source) consisting of microscopy, Gram stain, culture, acid-fast bacilli and TB culture, protein and glucose concentrations, and assessment for syphilis, cryptococcus, and (if available) toxoplasmosis and VZV

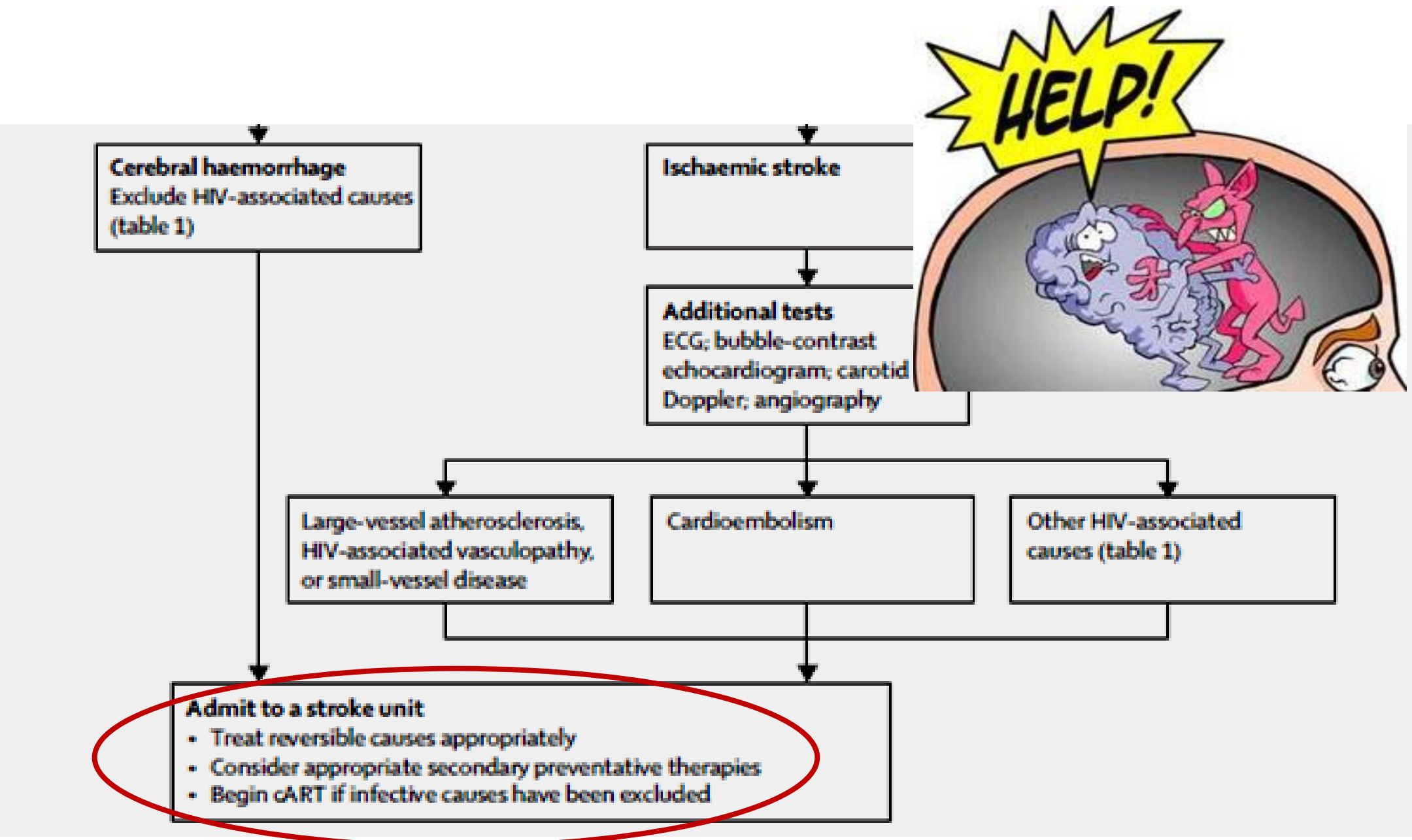
Blood test
- Test for FBC, glucose, urea and electrolytes, cholesterol, CD4 count, ESR, ANA, and ANCA
- Infection screen (serology/PCR/antigen test) for causes of vasculitis or stroke mimics. Test for syphilis, toxoplasma, cryptococcus, HSV-1, VZV, CMV, and bacterial or TB blood culture if clinically indicated
- Coagulation screen for antiphospholipid antibodies

Lumbar puncture
As listed in essential investigations box plus additional viral studies (HSV-1 and CMV PCR) if patient has suspected vasculitic HIV-associated vasculopathy

Chest radiograph
Look specifically for: infection, particularly tuberculosis, and tumours; cardiac disease, which could result in emboli; and blood vessel abnormalities (eg, Takayasu's arteritis)

Cerebral haemorrhage
Exclude HIV-associated causes (table 1)

Ischaemic stroke



UNV impliquées en dernier recours !