

HIV: New onset seizures & Epilepsy

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Declaration

Dr Cock has received:

- Hospitality from all major AED manufacturers
- Invited talks & honoraria for UCB Pharma, Janssen-Cilag, Sanofi-Synthelabo, GSK, Eisai, Novartis
- Unrestricted Research Grants from UCB Pharma, Johnson&Johnson & Pfizer

<http://www.whopaysthisdoctor.org/>

This presentation reflects the views of author

Overview

- Epidemiology
- New onset seizures
 - Diagnostic Approach
 - Management
- Epilepsy
 - AEDs
 - Antiretroviral Therapy

Epidemiology

Epidemiology, causes, and treatment of epilepsy in sub-Saharan Africa

THE LANCET **Neurology**

Awa Ba-Diop, Benoît Marin, Michel Druet-Cabanac, Edgard B Ngoungou, Charles R Newton, Pierre-Marie Preux

- SSA High Incidence Epilepsy
81.7 per 100 000(95%CI 28.0–239.5) vs 45.0(30.3–66.7)
- Up to 13% due to CNS infections
Neurocystercercosis>Malaria>others
- Acute symptomatic Sz
 - Worldwide incidence 29-39/100,000/yr
 - In HIV+ve up to 20% (200,100,000/yr)
 - HIV Risk factor for Convulsive SE

Hauser and Beghi, Epilepsia, 2008;
Sikazwe et al., Hiv Medicine, 2016; Kariuki et al., Neurology, 2015

New onset Seizures & HIV

			% of those with seizures			
Year	Country	N	Incidence	Status Ep	GTCS	Epilepsy
1989	USA	100		12	65	70
1990	USA	81	11	14	80	54
1997	Australia	50	10		94	
1999	Spain	17	3		71	60
2005	India	99	20	8	62	
2008	Germany	51	6		78	67
2012	South Africa	27	8 (paed)		67	78
2015	Korea	34	3	6	67	67

Holtzman et al., American Journal of Medicine, 1989; Wong et al., Archives of Neurology, 1990; Dore et al., Journal of Neuro-AIDS, 1997; Pascual-Sedano et al., Archives of Neurology, 1999; Kellinghaus et al., Seizure-European Journal of Epilepsy, 2008; Samia et al., Journal of Child Neurology, 2013; Kim et al., Journal of Korean Medical Science, 2015

Causes of Seizures in HIV

			Cause (%)						
Year	Country	N	Toxo	Crypto	PML	Viral	Lymph	NK*	Other
1989	USA	100	28	13	1	3	4	24	
1997	Australia	50	22	8	6	6	2	44	
2005	India	99	23	41	1	3	1	3	44
2008	Germany	51	14		14			21	
2009	South Africa	37	3	3	3	3		27	54
2014	Zambia	95	33	14	8	40			5+
2015	Korea	34	0	3	41	6	0	18	32

*Includes HIVEnceph

Other: Stroke, Metabolic; **TB**; Neurosyphilis; Drug toxicity

Holtzman et al., American Journal of Medicine, 1989; Dore et al., Journal of Neuro-AIDS, 1997; Sinha et al., Neurology Asia, 2005; Modi et al., Epilepsia, 2009; Kalungwana et al., American Journal of Tropical Medicine and Hygiene, 2014

Seizures in context HIV

- High likelihood neuropsychiatric & cognitive impairments (50%) in adults
- Associated with Neurological deficits (13%) and Developmental delay (50%) in children

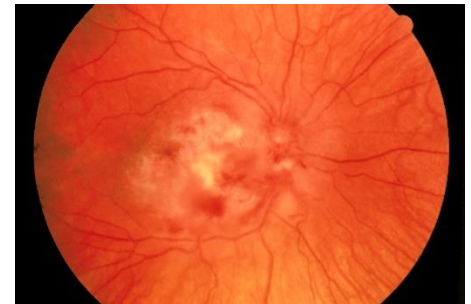
Kalungwana et al., American Journal of Tropical Medicine and Hygiene, 2014

Samia et al., Journal of Child Neurology, 2013

New onset seizures in HIV

Diagnostic approach

- Well or ill?
 - Fever; meningism; confusion/LoC; rash
- Focal Neurological signs
 - Focal weakness/sensory loss
 - Cranial neuropathies
 - Retinopathy?
- Background
 - FH, Febrile Convulsions, TBI etc..
 - Medication
 - Development/cognitive function



Initial Investigations

- Bloods
 - Ca^{++} , Mg^{++} , Na^+
 - Full blood count, CRP
- CSF
 - Recommended in all even if afebrile
 - Cell, Protein, Sugar
 - Additional if available
 - India Ink, Gram, Culture, CrypAg, Cytol,
 - PCR TB, JCV, CMV, VZV, HSV, HIV load, ToxoAb

CT before LP?

- CT prior to LP if
 - Dec Level of consciousness
 - Focal signs
 - Papilloedema
 - Preceding Seizures
 - Impaired immunity

CT First

- Diagnosis
- Safety



LP Delay

- lifethreatening

CT before LP?

- Early LP (Pre CT) may be justified Glimaker, Scand J Inf Dis 2013
- Cross sectional observational study, SA
- 100 or 132 CT requests/12m, HIV+ve, Seizures
 - 99 No comment re papilloedema
 - 55 Abnormal: Active SOL(12), Oedema(13), Brain shift (5)
 - 68 had LP (35 before CT), 24% Abn (75% Meningitis)
 - 9 deaths (5 from meningitis); none from LP

Feature	Prevalence Ratio (95%CI)	P (*sig multivar)
CD4<200 (*50)	2-7 (3.7) (2.1-6.6)	0.0017 (*0.0001)
Focal Signs	3.8 (2.2-6.7)	0.0001
Vomiting	3.3 (1.7-6.4)	0.0184
GCS<15	2.9 (1.4-5.9)	0.0020
No ICP features	0.2 (0.1-0.5)	0.0002

CSF

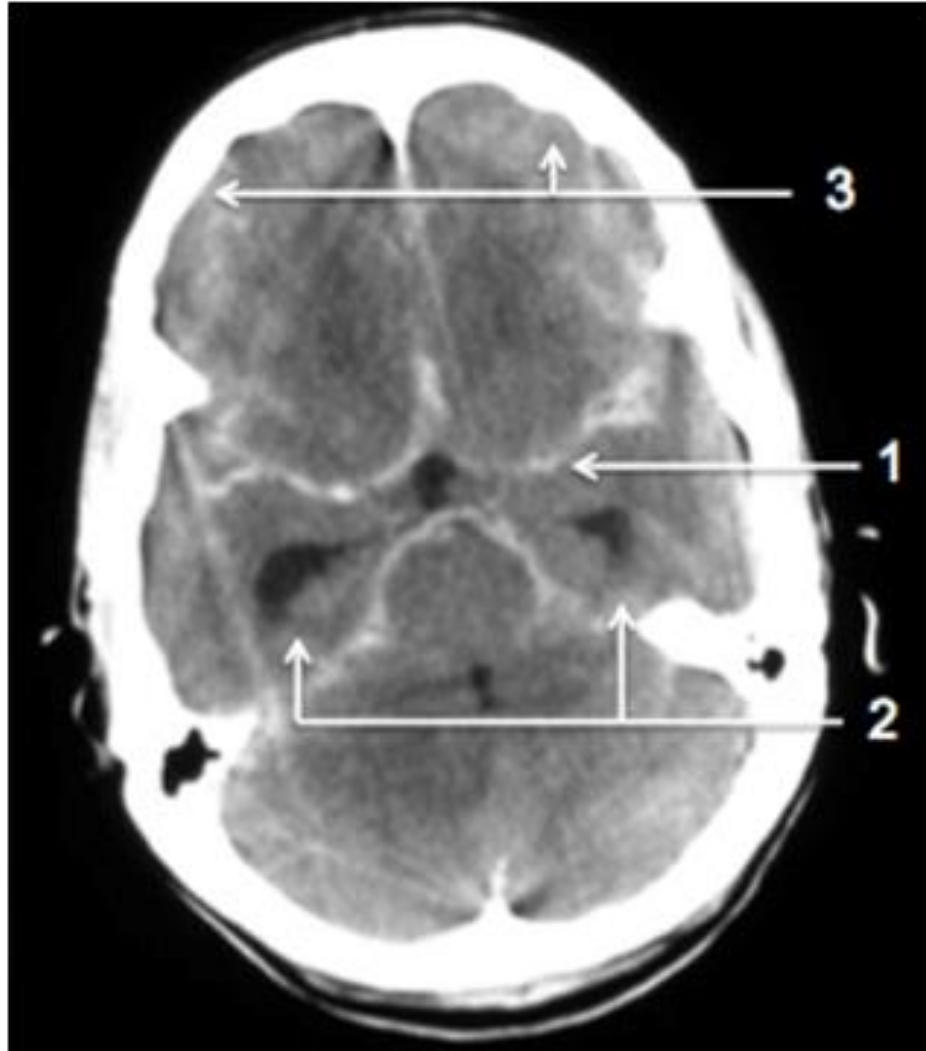
	look	Lympho- cytes	Poly- morphs	Protein	Glucose Ratio
Normal/HIV	Clear	<5/ <50	0	0.2-4g/L	~60%
Bacterial	Turbid/ purulent	↑	↑ ↑ ↑	↑ ↑	<50%
Viral	Clear /Turbid	↑ (20-300)	0	n/↑	>50%
Cryptococc	Clear /Turbid	↑ (20-200)	0	n/↑	n/ sl ↓
TBM	Turbid /Viscous	↑ ↑ (100- 500)	0 / sl↑	↑ ↑ ↑	<50%

- May identify treatable cause in ~25%
- Frequently not done/declined
- nt/cognitive function

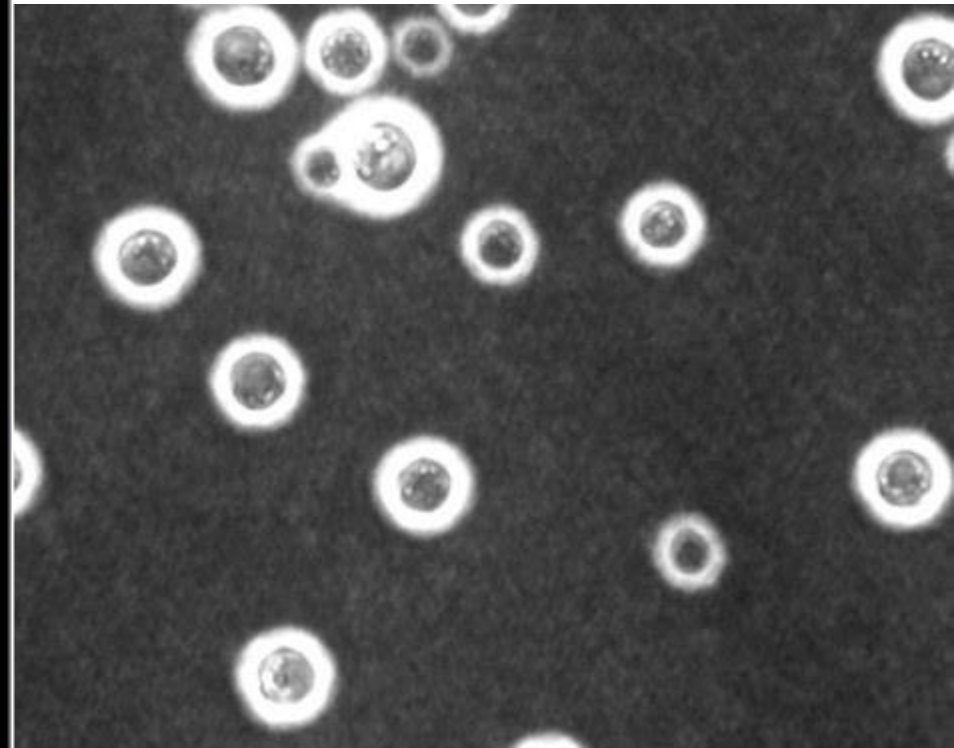
Imaging

- **C**ohort Study **H**IV-**A**ssociated **S**eizures and **E**pilepsy (**CH**ASE, Zambia)
 - N=43/95 with no other cause (inc CSF)
 - 80% Advanced disease; 44% opportunistic infection
 - 70% Abnormal imaging
 - 56% White matter (mostly Vasogenic Oedema)
 - Deep Gray (19%); Post fossa (21%); Cortical (28%)
 - 16% Atrophy
 - None predictive of seizure recurrence

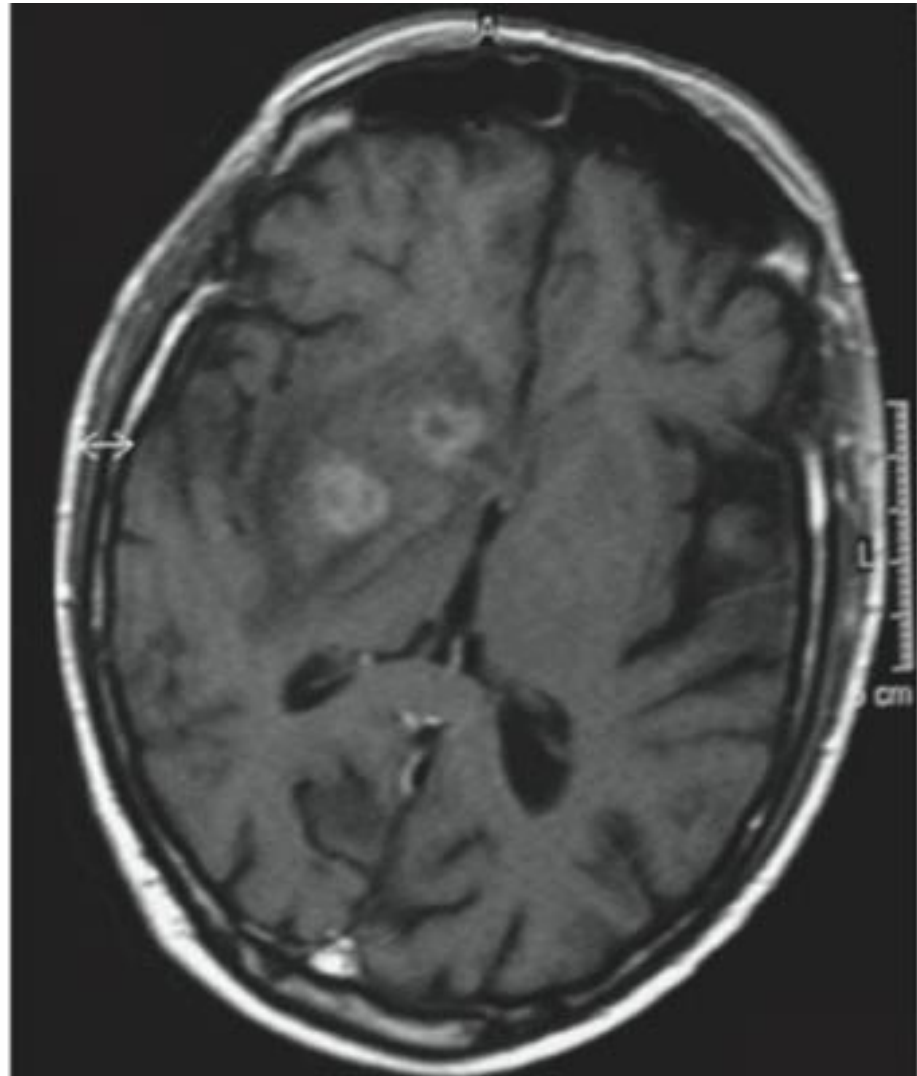
Cryptococcal Meningitis



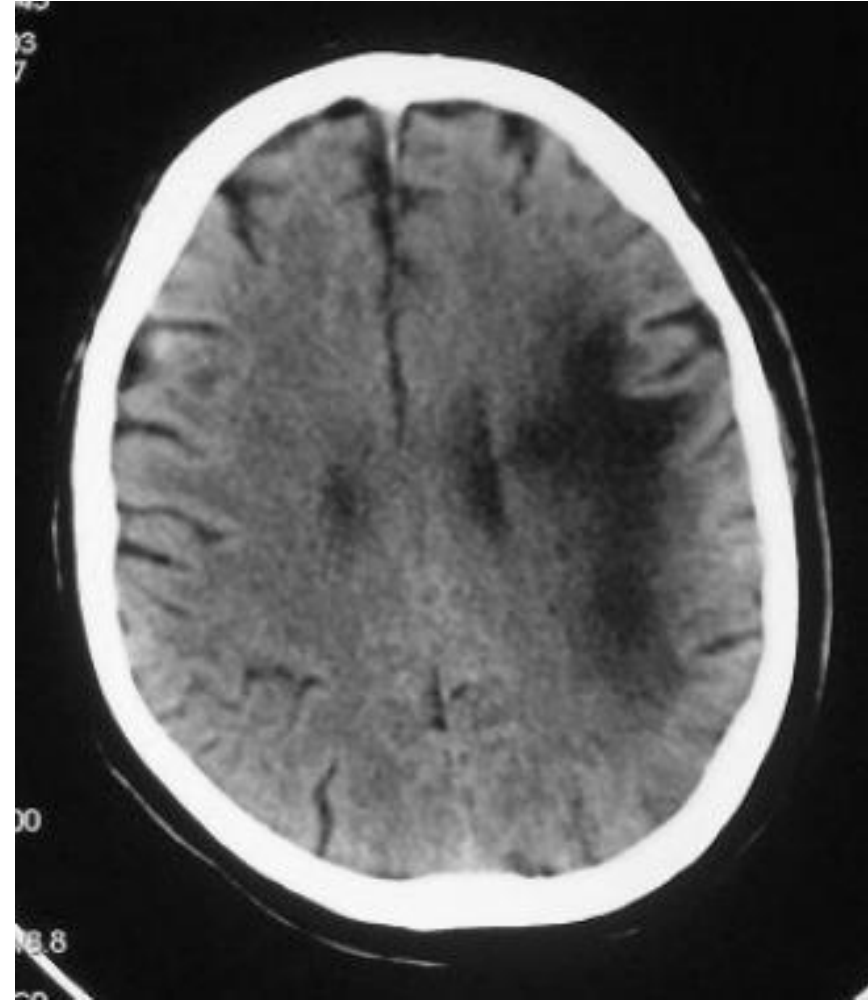
1. Basal meningeal enhancement
2. Dilated Temp Horns
3. Effaced sulci



Toxoplasmosis



CNS Lymphoma PML



Normal CT

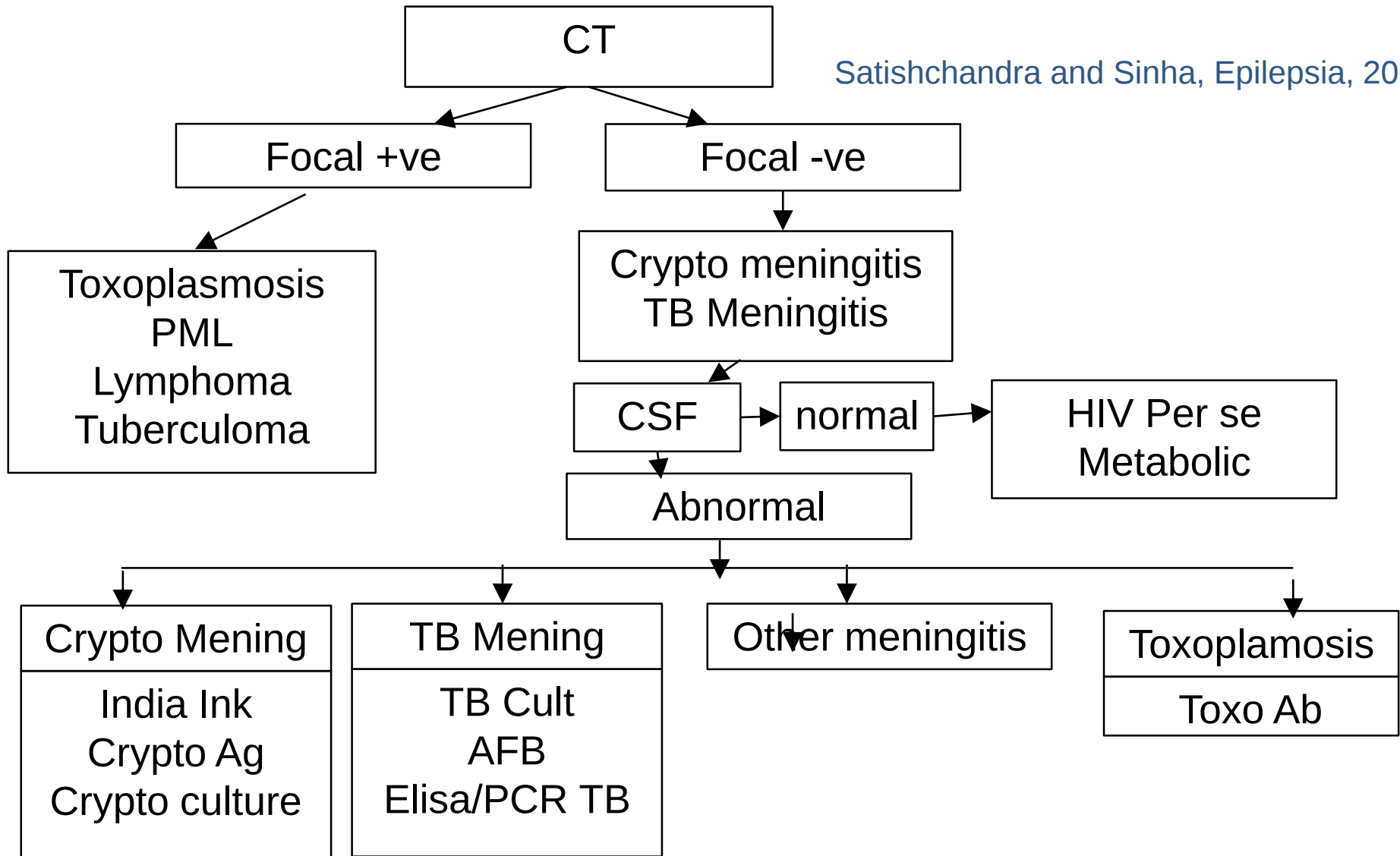
- ? Atrophy
 - HIV Encephalopathy
- ? Early disease (e.g. PML)

EEG

- Often unhelpful
- Non-specific/generalized slowing

New onset seizures in HIV

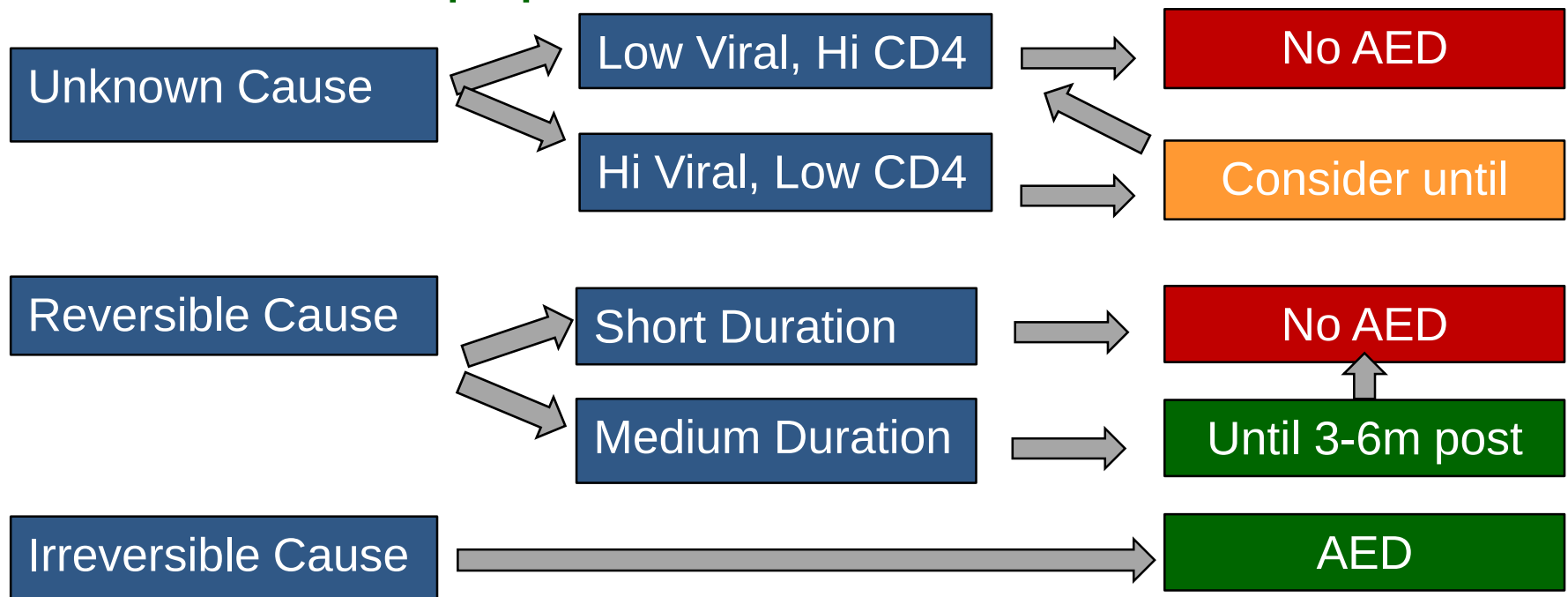
Satishchandra and Sinha, Epilepsia, 2008



Treat Op Infection; ARV (NB Interactions)

AED Treatment

- Status Epilepticus Rx takes priority over ARV
- For others, may not be needed at all or for short term (3-6m) only
- General Population recurrence data may not be valid in HIV population



AED selection in HIV: ILAE/AAN guidelines

Effect of AED on ARV			
AED/ARV	PI ARV	II ARV	N(N)RTI
PHT	Lop, Rit		Nev
CBZ			Efav, Nev
PB			?
VPA	Lop, Rit, Ataz		Efav
			Zid
LTG			
BZD			Zid

Increased

No Change

Decreased

Virologic failure

EI-AEDs 63% vs 27%

OR 4.58 (CI 1.47-14.25, p0,009)

Okulicz et al, AIDS Res Th 2011

Effect of ARV on AED						
ARV/AED	PHT	CBZ	PB	VPA	LTG	BZD
PI ARV	Lop, Rit			Lop, Rit	Lop, Rit	
II ARV					Ralt	Ralt
N(N)RTI	Zid	Efa		Efav		

Birbeck et al., Neurology, 2012

AED selection in HIV: ILAE/AAN guidelines

- Level C* evidence:

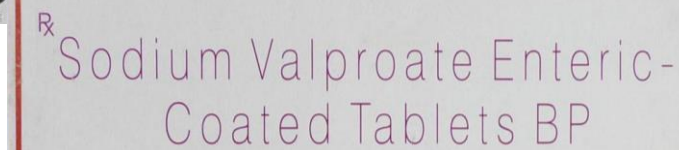
- May need to avoid EI AEDs with PI or NNRTIs, or monitor levels ARV to ensure efficacy
- PHT: May need 50% inc Lopinavir/Ritonavir
- VPA – may need lower Zidovudine dose
- VPA and Efavirenz OK
- Riton/Atazan may need inc LTG dose (Ralte/Atazan OK)

Birbeck et al., Neurology, 2012

- Level U

- Everything else!

*Expert opinion and panel consensus



Siddiqi and Birbeck, Current Treatment Options in Neurology, 2013

HIV developing in known epilepsy

- ARV and AED co-administration unavoidable
- Careful choice ARV, and/or switch to alternative AED
- Low threshold repeat Investigation (MRI, CSF) if seizure deterioration

ARV May prevent epilepsy?

- Botswana, Perinatal HIV infection, enrolled aged 0-18
- Confirmed HIV, at least 6m f/u, initiated cART
- Excluded HIV by other routes, Sz prior to cART
- Early Treatment: cART<12m, or CD4<25% to 5y, or <350m³ >5y
- 1244 Eligible, identified 29 cases and 58 matched controls.

Retrospective case-control	Case (29)	Controls (58)
Age at cART Rx (months, range)	72 (24-96)	70 (22-120)
WHO Stages 1-4 (%)	7-3-24-66	14-2-20-22
WHO no/mild-Ad-Sev IS (%)	21-21-59	31-10-29

Early Treatment	OR (95%CI)	p
1 (WHO def)	0.36 (0.14 - 0.92)	0.03
2 (CD4<500>5y)	0.37 (0.14 -1.0)	0.05
3 (early vs late)	0.32 (0.13 - 0.76)	0.01

Summary

- New onset seizures common in HIV
- Often Acute Symptomatic
 - Toxoplasma, Cryptococcus, TB, PML, encephalitis
- Remote symptomatic & HIVE also
- CT & LP ideally in all
 - clinical urgency/resource availability
- AEDs – avoid Eis/consider interactions
- ARV also important