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Update on CNS complications of HIV – implications for management.

Red Cross War Memorial Children's Hospital, Cape Town

Table Mountain National Park

University of Cape Town

Conflict of interest

- None

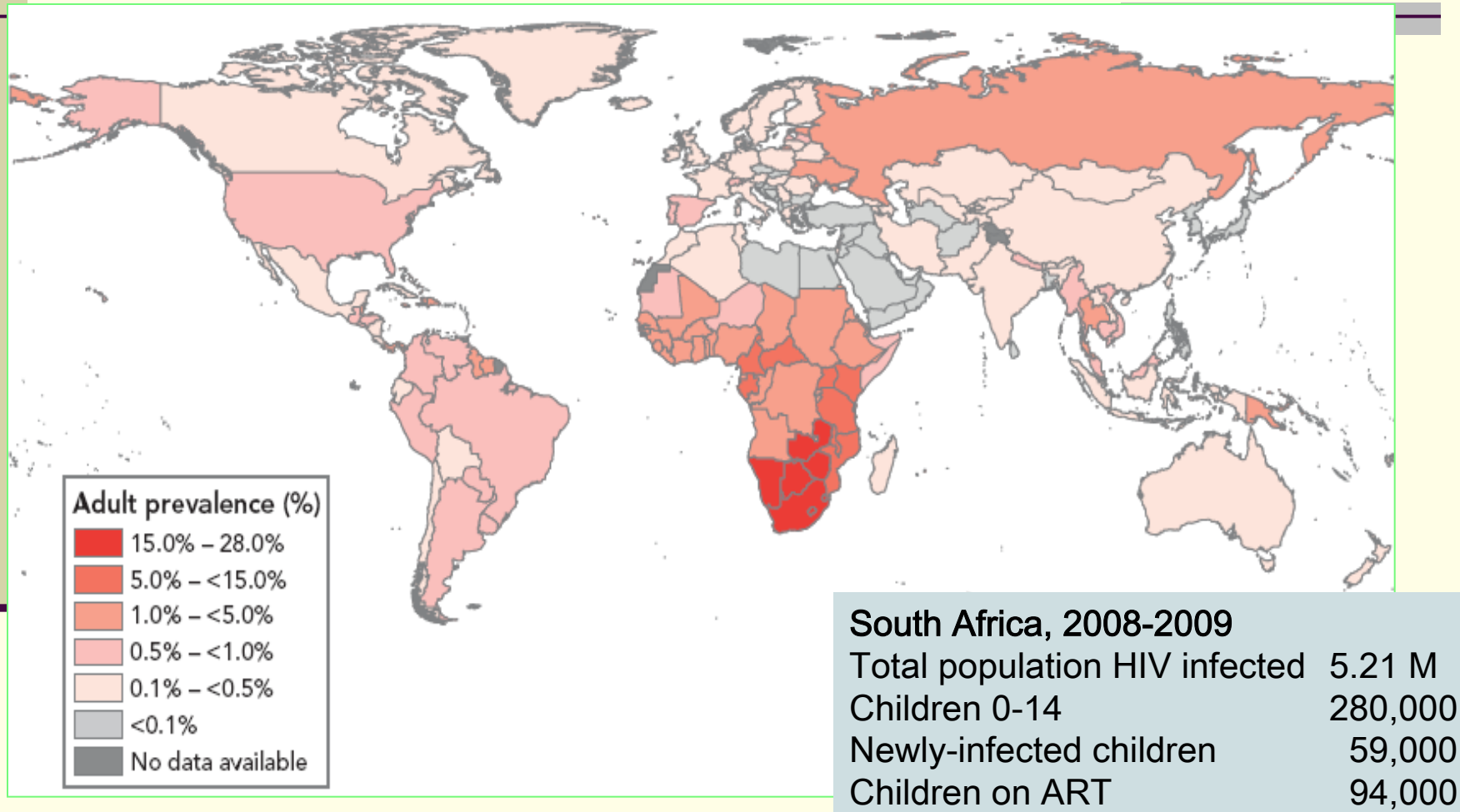
Learning objectives and Key points

- Why the brain is so vulnerable to HIV
- Could better treatments make a difference
- Neurological complications of HIV
- Common and troublesome complications
- Simple approaches
- Issues for the future

Curr Opin HIV AIDS 2014, 9:533–538

A global view of HIV infection

33.4 million people [31.1–35.8 million] living with HIV, 2008
Including 2.1 million children [1.2-2.9 million]



South Africa, 2008-2009	
Total population HIV infected	5.21 M
Children 0-14	280,000
Newly-infected children	59,000
Children on ART	94,000
Estimated ART coverage	61%

UNAIDS, http://www.who.int/lib/publications/global_report/2009/pdf/full_report.pdf
UNICEF, http://www.uniteforchildren.org/files/CA_FSR_LoRes_PDF_EN_USLetter_11062009.pdf
Statistics South Africa, http://www.statssa.gov.za/publications/P0302/P03022009.pdf

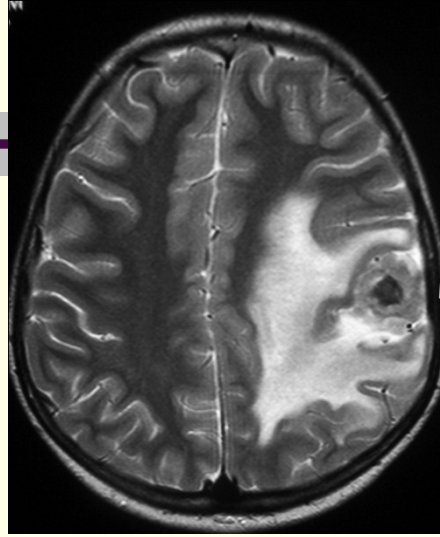
Effective policies

Brazil *(Luiza et al Ped Inf Dis J 2009)*

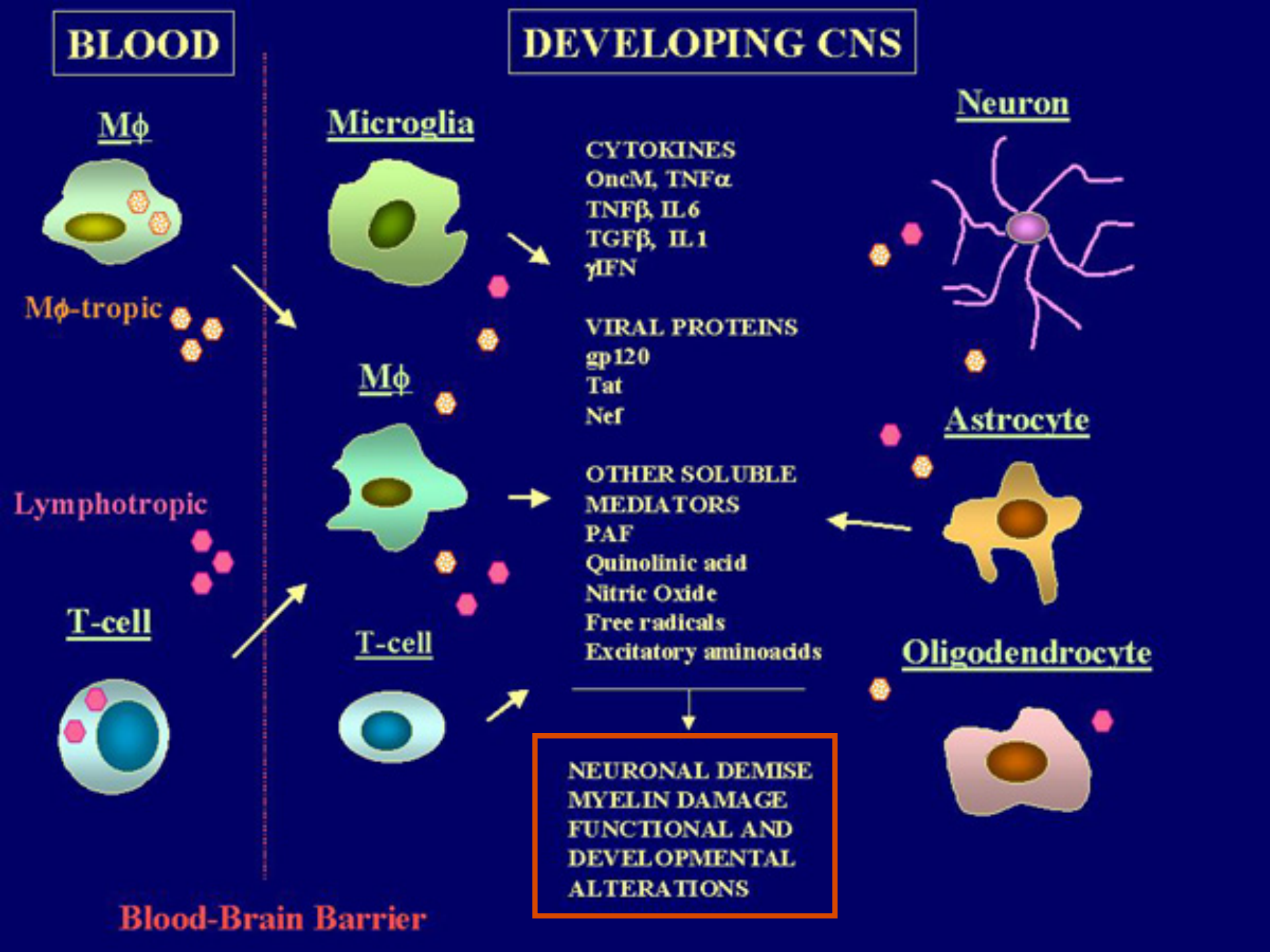
- Similar demographics / poverty challenges to RSA
- Aggressive approach to HIV
  - Free universal access to ART
  - Early diagnosis of HIV and associated infections in HIV infected pregnant women and their offspring
- Mother to child transmission prevention programs – highly effective
- Children <13 years
  - AIDS incidence 0.65 per 100 000 – rate still falling

USA

- A ten-fold decline in incidence of HIVE from 1996 after the introduction of ART, followed by stable incidence after 2002. *(Patel et al AIDS 2009)*

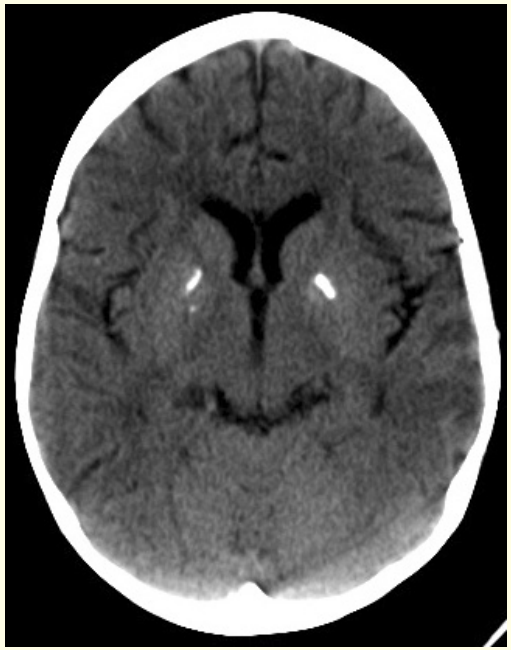


Neuropathology

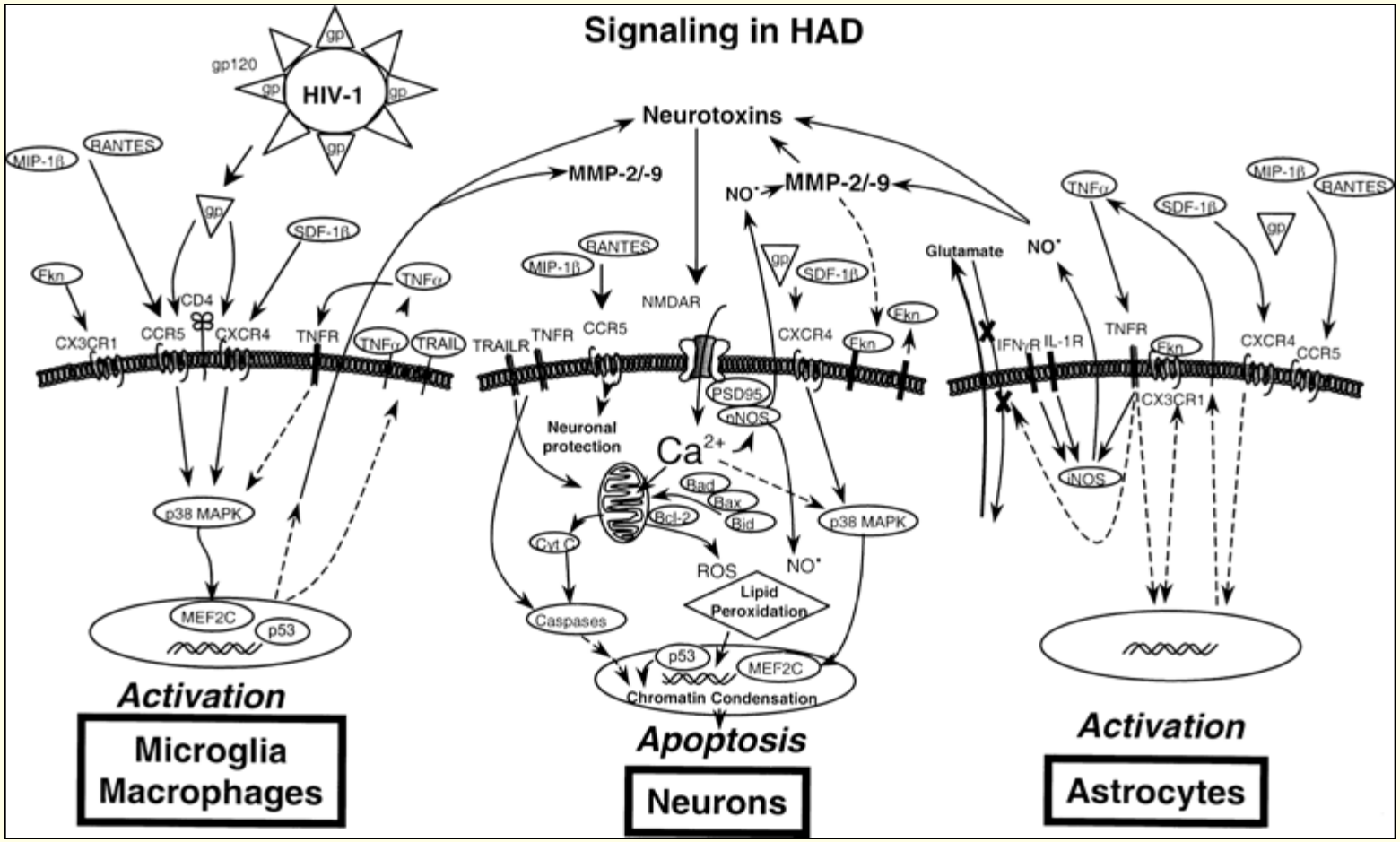

BLOOD
DEVELOPING CNS
Mϕ
Microglia
Neuron
CYTOKINES
OncM, TNFα
TNFβ, IL6
TGFβ, IL1
γIFN
Mϕ-tropic
VIRAL PROTEINS
gp120
Tat
Nef
Mϕ
Astrocyte
Lymphotropic
OTHER SOLUBLE
MEDIATORS
PAF
Quinolinic acid
Nitric Oxide
Free radicals
Excitatory aminoacids
T-cell
T-cell
Oligodendrocyte
NEURONAL DEMISE
MYELIN DAMAGE
FUNCTIONAL AND
DEVELOPMENTAL
ALTERATIONS
Blood-Brain Barrier

Summary of Mechanisms

- Direct HIV cytopathic effect
- HIV protein toxicity/gene products: GP120, nef, tat
- Immune-mediated inflammatory response
- Chemokine receptors: CXCR4, CCR5
- Vessel inflammation- vasculopathy



Pathways of neuronal injury / death



Kaul M, et al. *Cell Death Differentiation* 2005;12:878

New understandings.

Ancuta et al 2008;Dunfee et al 2007;Kaul et al 2007;Schwartz et al 2007, Venkatsan A, et al. 2007, Pkamato S, et al. 2007, Brenchley JM, et al. 2006, Lawrence D. et al 2004

- **Entry into the CNS - Elevated lipopolysaccharides**
  - induce monocyte activation
  - facilitates trafficking into the brain
  - Forms part of the pathogenesis of HIV-associated dementia (HAD)
- **Entry into the cells**
  - Related to specific macrophage-tropic HIV-1 Env variants
- **Mechanisms of toxicity leading to neuronal attrition**
  - Role SDF-1
- **The role of progenitor cells**
  - Recent research supports the concept that HIV-1 is amplified in the maturing / developing brain
  - Emerging evidence - altered hippocampal neurogenesis may contribute to the pathogenesis of NeuroAIDS

Summary of HIV neuropathology

- CNS invasion early during primary infection
- Compartmentalization of infection

- Target cells: macrophages, microglia, astrocytes
- Neuronal loss
- Effects on neurogenesis
- Role of gene expression profiles & metabolomics in dissecting the pathogenesis

- **Morphological features**: impaired brain growth / cortical and cerebral atrophy / ventricular enlargement
- **Pathological features**: reactive gliosis, microglial nodular formation / myelin pallor, calcification of basal ganglia / cerebral vascular abnormalities
- **Neurological disease**: **very common** and may be 1st AIDS-defining illness

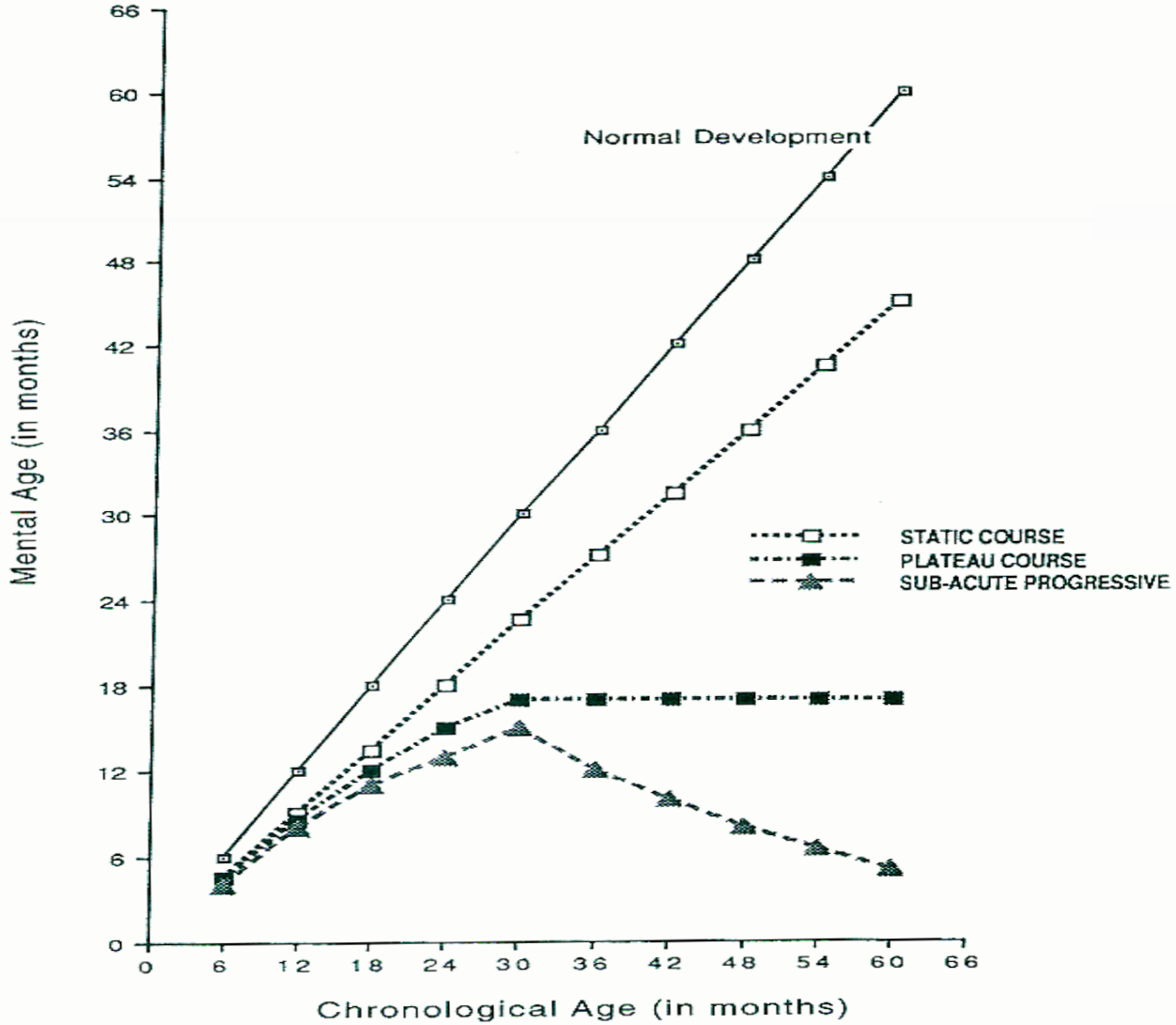


Figure 18.1. Schematic representation of the different encephalopathic courses.

Philip A Pizzo et al, Paediatric Aids, 3rd Edition

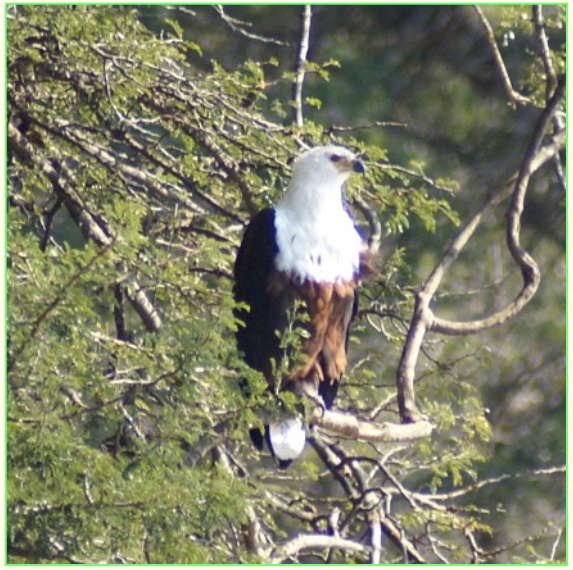
Background

- 50% of HIV1 infected children show neurological symptoms and signs during the course of the disease.

- There is paucity of data on the prevalence of **specific neurological complications** in children with HIV1

Civitello et al

European Collaborative Study



Neurological profile: RCWMCH

Govender R et al, JCN 2011

- **Convenience sample:** 78/600 children evaluated
- **Mean age:** 5.4 years (range: 0.25 – 12)
- **Neurological deficits:**
  - Normal examination: 32 (41%)
  - Global pyramidal deficit: 31 (38%)
  - Hemiplegia: 6 (8%)
  - Distal muscle weakness: 5 (6%)
  - Proximal muscle weakness: 3 (4%)
  - Cranial nerve deficits: 3 (4%)
  - Visual impairment: 13 (17%)
  - Hearing impairment: 18 (23%)

Past Medical History – "*the layering effect*"

Condition	**No. of patients**
Chronic Lung Disease	29
CMV infection	5
CNS OI	**12**
Epilepsy	**11**
Behaviour Problems	**39 (Ritalin:3)**
Other	15 FAS:2,PTB:9

Neurological profile: RCWMCH

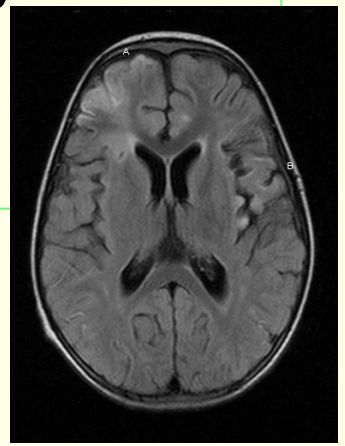
Govender R et al, JCN 2011

- **Developmental delay**
  - Gross motor: 37 (47%)
  - Fine motor: 33 (42%)
  - Language: 32 (41%), including 7 with hearing deficits
  - Social: 25 (32%)
  - Cognitive: 38/64 (59%)
- **Behaviour rating**
  - Mild problems: hyperactivity (17%), stereotypies (3%), irritability (5%), lethargy (9%)
- **Specific problems**
  - HIV encephalopathy 31(40%) fulfilled CDC criteria
  - Recurrent seizures: 11(14%)
    - idiopathic (7), symptomatic (3=infarcts, 1=CMV)
    - GTCS (8), Focal (3)
  - Stroke: 6 (8%)
  - Peripheral neuropathy: 5 (6%)
- **Overall, 45/78 (57.7%) had at least one CNS deficit**

Specific Neurological complications of HIV

- Encephalopathy
- Behaviour
- Opportunistic infections
- CNS lymphoma
- Cerebrovascular disease
- Vacuolar myelopathy
- Peripheral neuropathy

- Myopathies
- Mitochondrial toxicity
- Dyslipidaemia and lipodystrophy syndrome
- Immune reconstitution inflammatory syndrome
- Epilepsy



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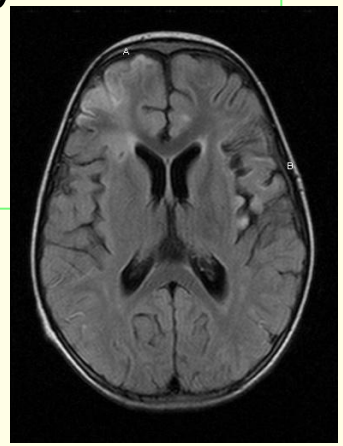
- **Epilepsy**

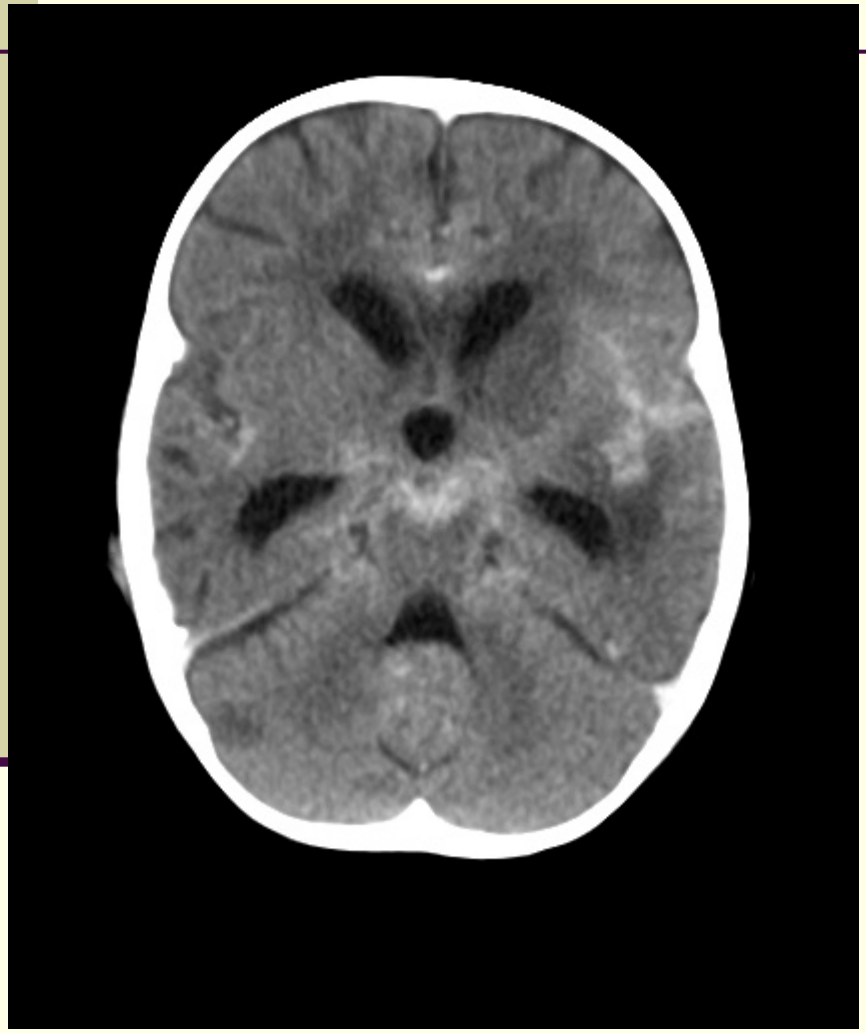


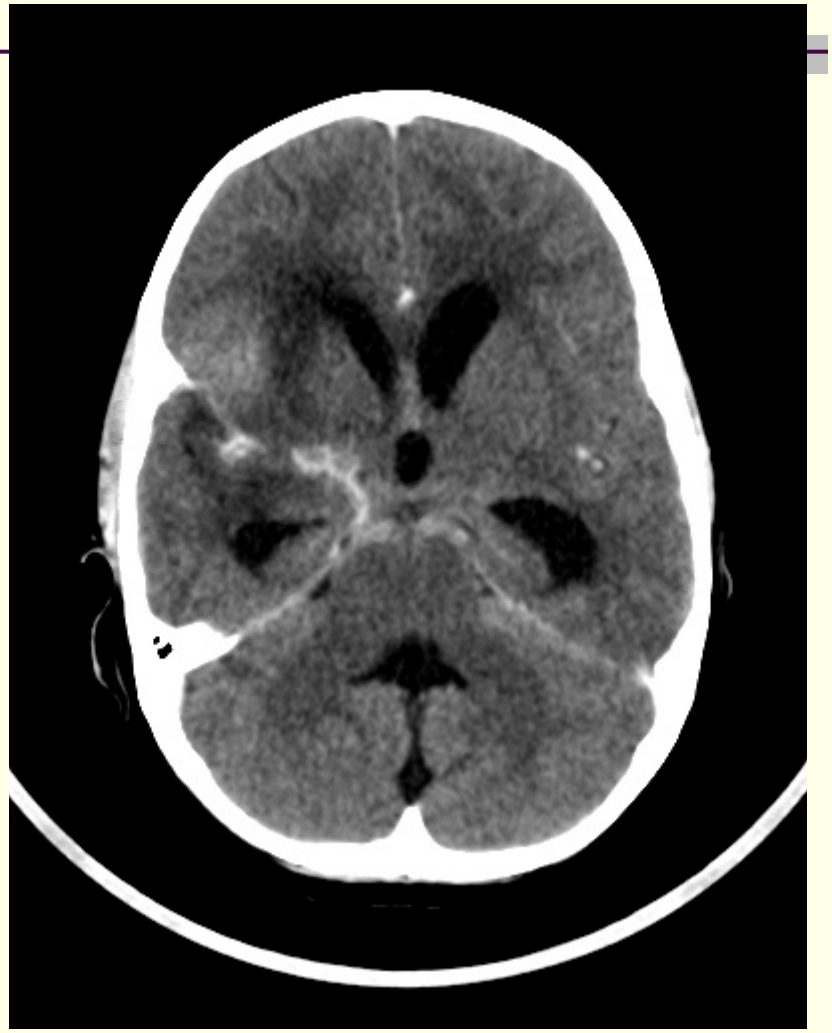
OPPORTUNISTIC CNS INFECTIONS

N=12/78 (15%)

RCWMCH

Features of TB meningitis





Courtesy of Dr N Weiselthaler, Red Cross War Memorial Children's Hospital

CT scan findings

Disease	HIV-infected	HIV-uninfected	OR (CI)
Infarct	50.0%	40.5%	1.47 (0.54-4.04)
Basal infarcts	**72.7%**	91.7%	0.24 (0.02-2.78)
Cortical infarcts	18.2%	8.3%	2.44 (0.19-31.53)
B + C infarct	9.1%	0.0	3.57 (0.13-97.23)
Granuloma	0%	15.0%	0.11 (0.01-2.01)
Hydrocephalus	**72.0%**	97.9%	0.06 (0.01-0.49)
Communicating	100.0%	80.0%	5.49 (0.29-103.46)
Non-communicating	0%	20.0%	-
Basal exudate	**37.5%**	71.4%	0.24 (0.08-0.70)

van der Weert EM et al. *Pediatr Infect Dis J 2006*;25:65-69

TBM therapy

- WHO recommends 12 months therapy
- Prospective observational study
  - 6/12 HIV uninfected and 9/12 HIV infected
- Intensified regimen - isoniazid, rifampicin, pyrazinamide and ethionamide
  - 5% drug-induced hepatotoxicity
  - 80% of the children good outcome
  - 7 (3.8%) died.
- No significant difference between groups
- Not known how relates to recommended WHO Mx

Van Toorn *et al* Pediatr Inf Dis 2014

Measles virus

- 2009-2010 South Africa epidemic measles outbreak
  - >18 000 lab confirmed cases
  - 1/3 < 1 year of age
- Cluster of patients with **Measles inclusion body encephalitis** (subacute measles encephalitis) (youngest 14 yrs of age)

Hardie *et al* Virol J 2013;

Albertyn *et al* SAMJ 2011;

Macquaid *et al* Acta Neuropathol 1998

ISSUES IN PUBLIC HEALTH

Silent casualties from the measles outbreak in South Africa

Christine Albertyn, Helen van der Plas, Diana Hardie, Sally Candy, Tamiwe Tomoka, Edward B LeePan, Jeannine M Heckmann

May 2011, Vol. 101, No. 5 SAMJ

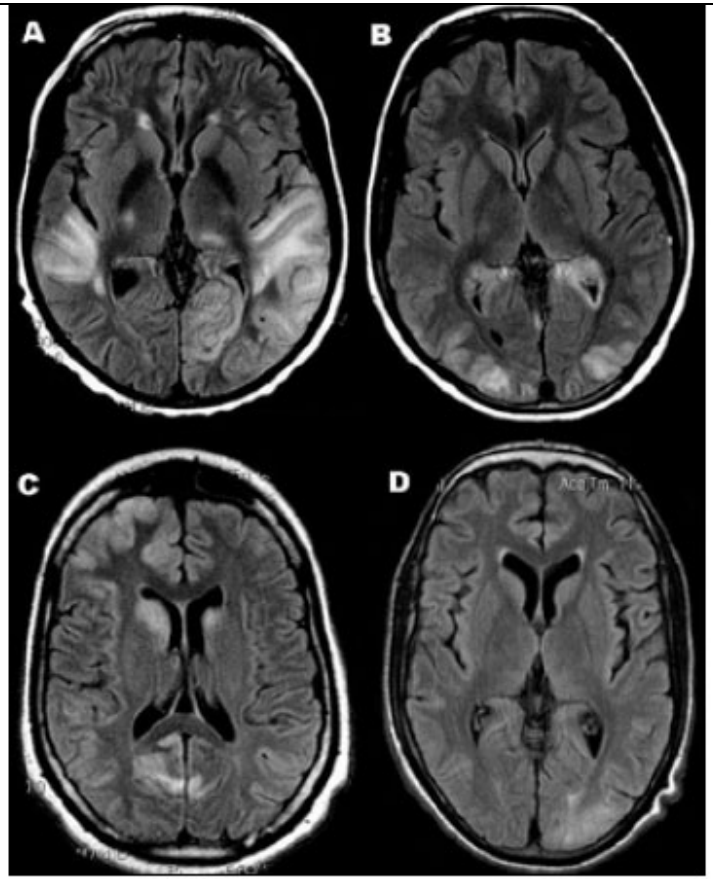


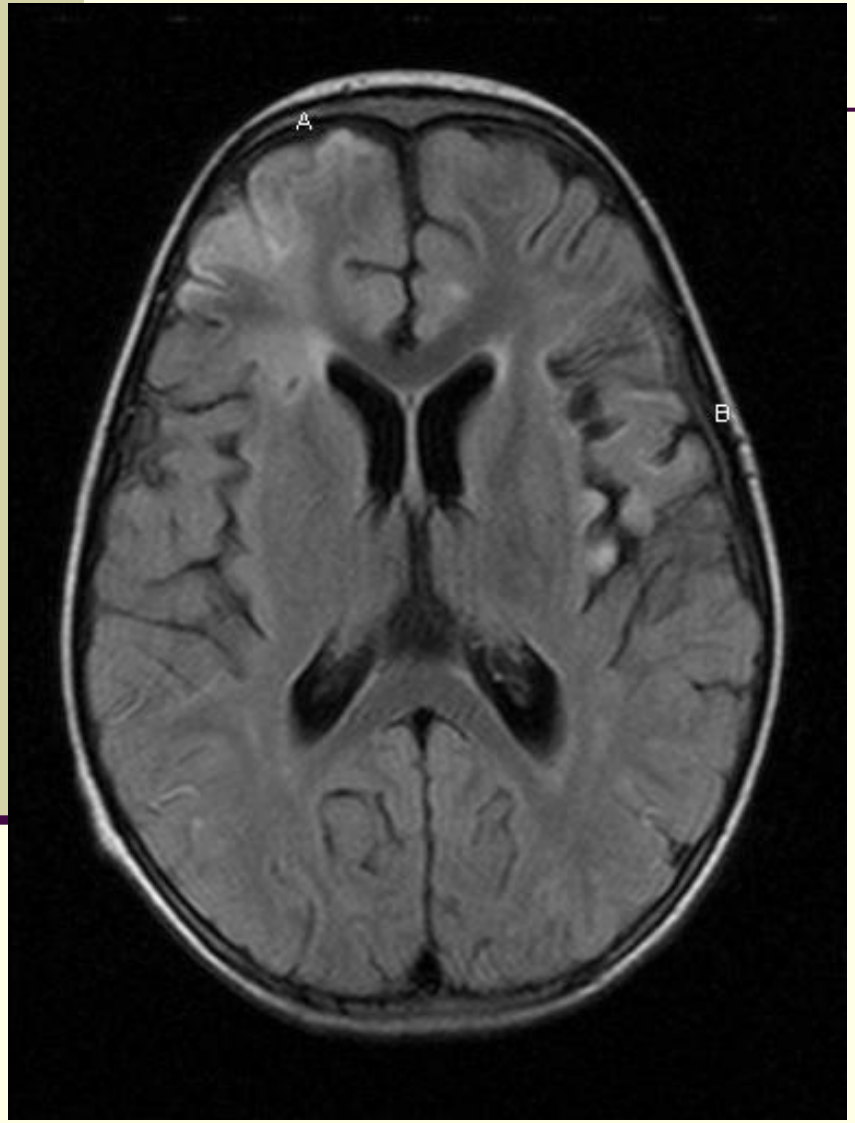
Fig. 2. Axial T2 FLAIR images demonstrating: A (Patient 6) – bilateral temporal-parietal cortical hyperintensities; B (Patient 2) – parieto-occipital cortical hyperintensities; C (Patient 3) – superficial cortical (left frontal and bilateral occipital) and deep grey matter (bilateral head of caudate) hyperintense signal abnormalities; and D (Patient 8) – hyperintense signal changes in the right occipital cortex.

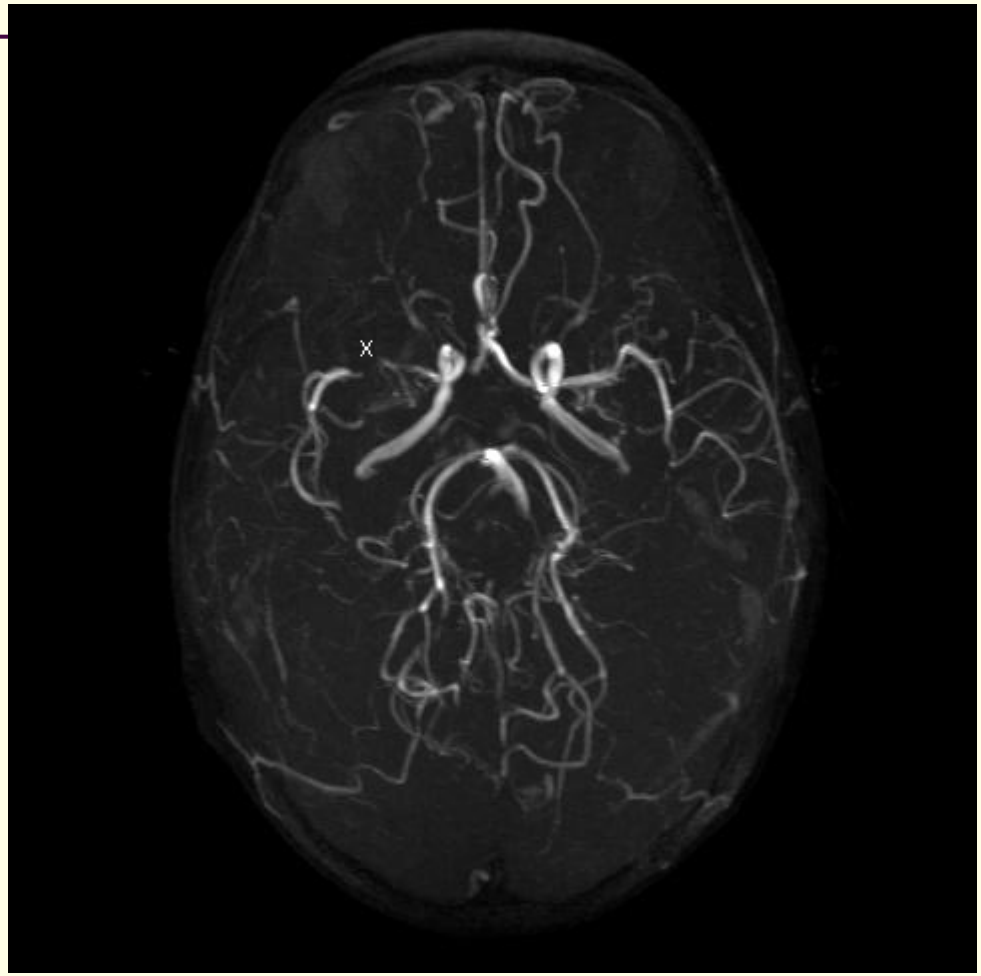
- Epilepsia partialis continuans
- Resistant to AEDs
- Evolving encephalopathy
- Poor outcome – death in most

Cerebrovascular disease

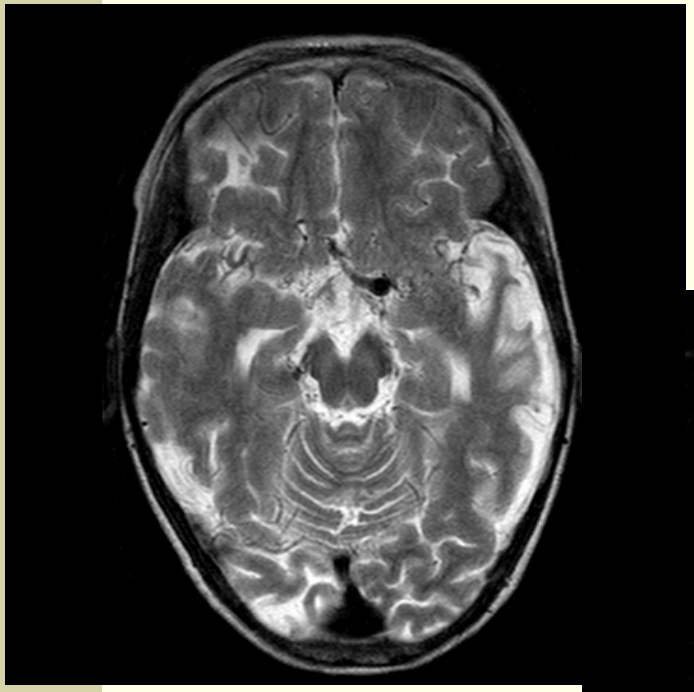
RX study 6/78 (8%)

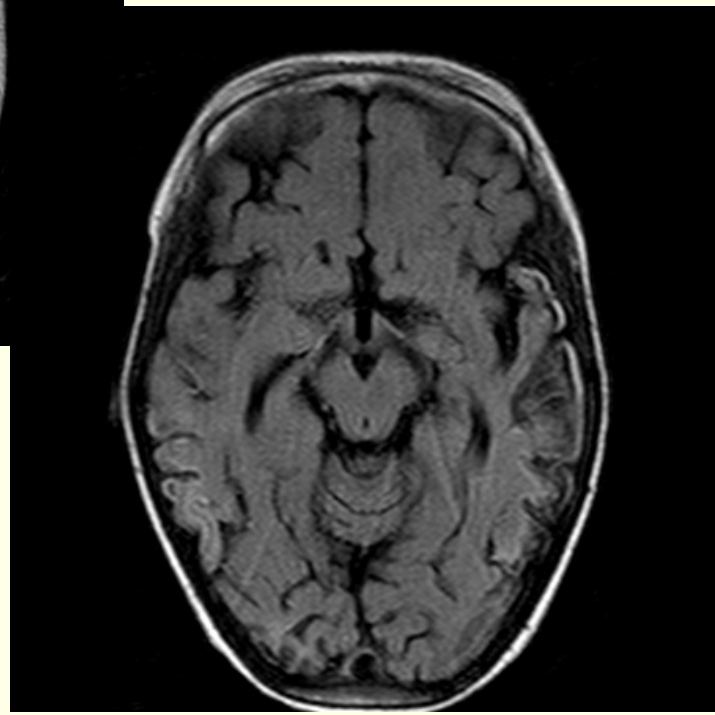
Stroke / arteriopathy





Moyamoya-like vasculopathy





Courtesy of Dr T Kilborn, Red Cross War Memorial Children's Hospital

Silent progression in disease

- Cohort perinatally HIV infected infants
  - Followed up for 14 years
  - 8 patients infarcts
- Progression in 7/8 – without further clinical manifestation
- Recommended low threshold for serial imaging
- Felt progression to Moya Moya illustrated treatment failure.

Izbudak *et al* J Neurorad 2013

Epilepsy

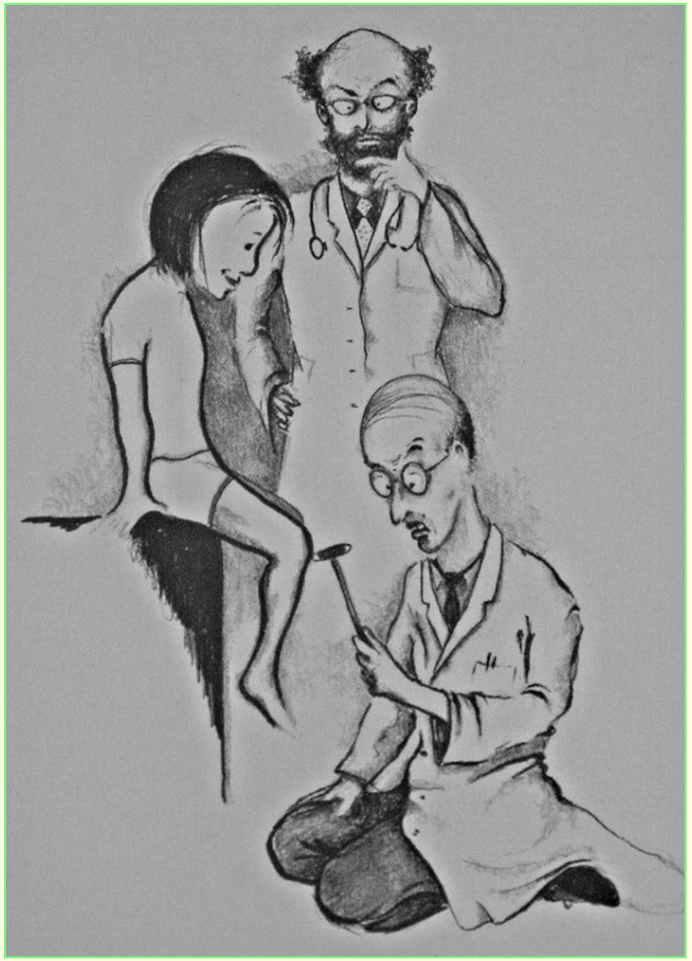
RX group 11/78 14%

Epilepsy in HIV (14% RX group)

- Several variables

1. Common disorder – co-incidence
2. Directly part of the condition
3. Secondary to acquired pathology

Layering effect…….



Prevalence of seizures

- Unknown
- Based on RX / GSH cohort 11/78 (14%)
- Extended study 27/354 (7.6%)
- Literature 3-11% (adult data)
- Impact / concern – represents 1/3 referrals to neuroHIV service

Acta Neurol Scand Suppl 2005
Seizure 2008
Samia et al JCN 2013

Specific medications

- Phenytoin, Phenobarbitone, Carbamazepine
  - increase metabolic activity of the cytochrome p450 complex
- Concurrent use with protease inhibitors
  - may result in sub-therapeutic ARV levels
  - treatment failure
  - potential resistance to the PI class of drugs
- PI
  - may in turn cause toxic levels of anticonvulsants by inhibiting cytochrome p450 system.

American Academy of Neurol 2000
Neurol 2006

Sodium Valproate

- Currently recommended first line intervention for patients on ART with epilepsy
- Metabolised by glucuronidation
- Limited effects on the cytochrome p450 system

BUT

- Possible interactions between Ritonovir, lopinavir and efavirenz – related glucuronidation and protein displacement
- Decreased valproate levels occurred in combination therapy – breakthrough seizures

Annals of Pharmacotherapy 1989, 2007
Antimicrobial agents and Chemotherapy 2004
Bipolar disorders 2007

Bone mineral density and AEDs and HIV

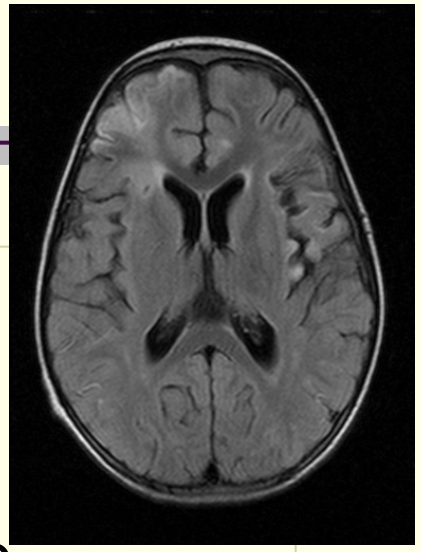
- Combined use of ART and AEDs associated with risk of low bone mineral density
- Recognized in adult populations
  - thought to be exacerbated by low CD4 counts
- Supplementation with vitamin D encouraged

Yong MK *et al* J Acquir Immune Defic Syndr 2011

Yin M, Stein E. Clin Infect Dis 2011

Dao CN *et al*. Clin Infect Dis 2011

Therapeutic challenges for HIV-1 infected children with neurological disease



- **CNS penetration of ARVs**
  - Poor
  - Agents have their own complications (lipodystrophy, cardiovascular disease, peripheral neuropathy)
- **Global management**
  - Social,
  - behavioural,
  - multisystem

Conclusion

- Children and adolescents infected with HIV in infancy suffer a different disease course compared to a decade ago

- This is compounded by the **layering effect of HIV**
  - Direct disease effects
  - Side effects from ARTs (efavirenz)
  - Socioeconomic challenges
  - Trauma of disclosure
  - Co-morbidities (previous infections, cerebrovascular events)

Acknowledgements

IDC
- Brain Eley
- Paul Roux
- Team

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- Reneva Petersen
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- Kirsty Donald
- Wendy Mathiassen
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