Jo Wilmshurst
Department of Paediatric Neurology
Red Cross Children's Hospital
University of Cape Town
South Africa
Jo.wilmshurst@uct.ac.za

Update on CNS complications of HIV – implications for management.

Conflict of interest

- None

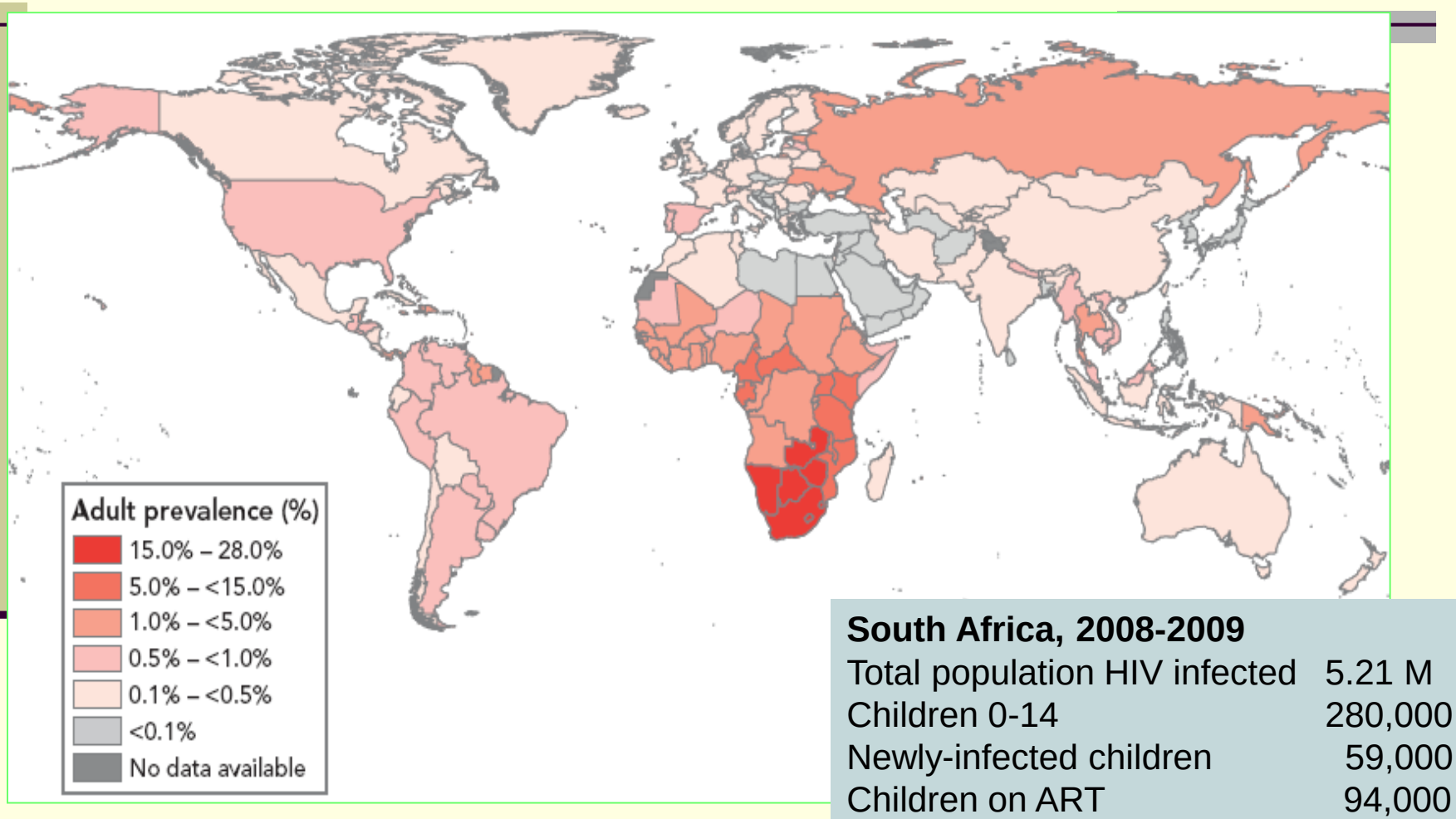
Learning objectives and Key points

- 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

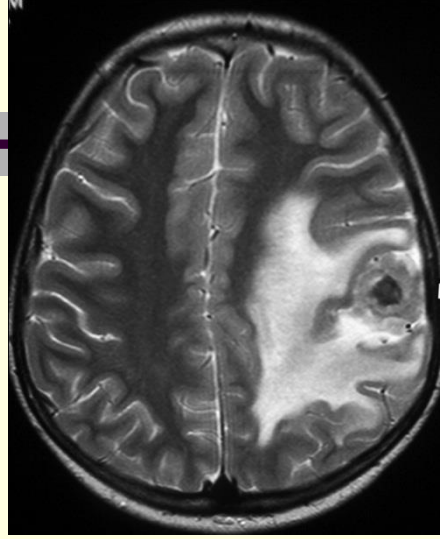
Effective policies

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

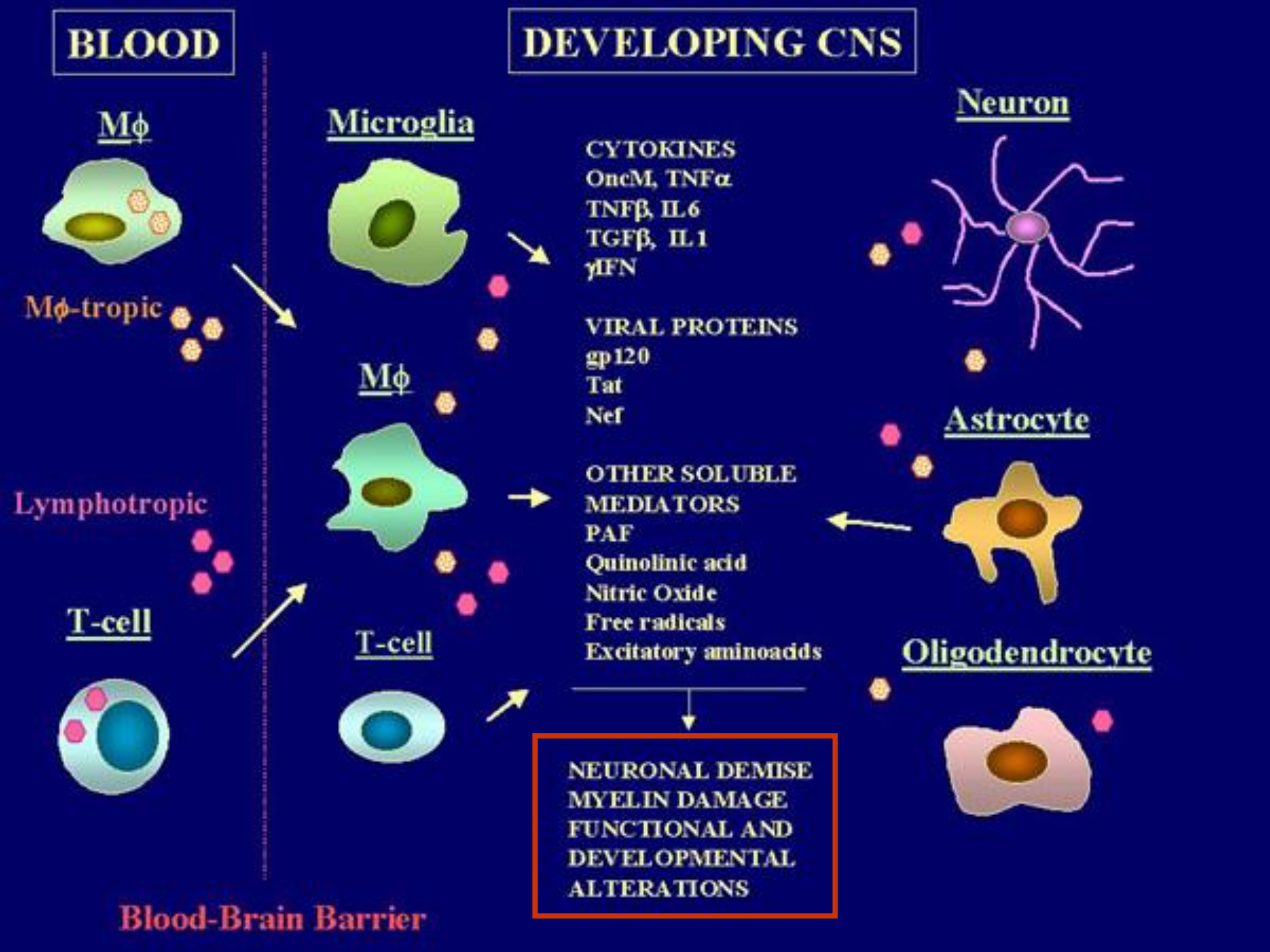
- Similar demographics / poverty challenges to RSA
- Aggressive approach to HIV
  - Free universal access to ART
  - Early diagnosis of HIV and associated infections in HIV infected pregnant women and their offspring
- Mother to child transmission prevention programs – highly effective
- Children <13 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)*



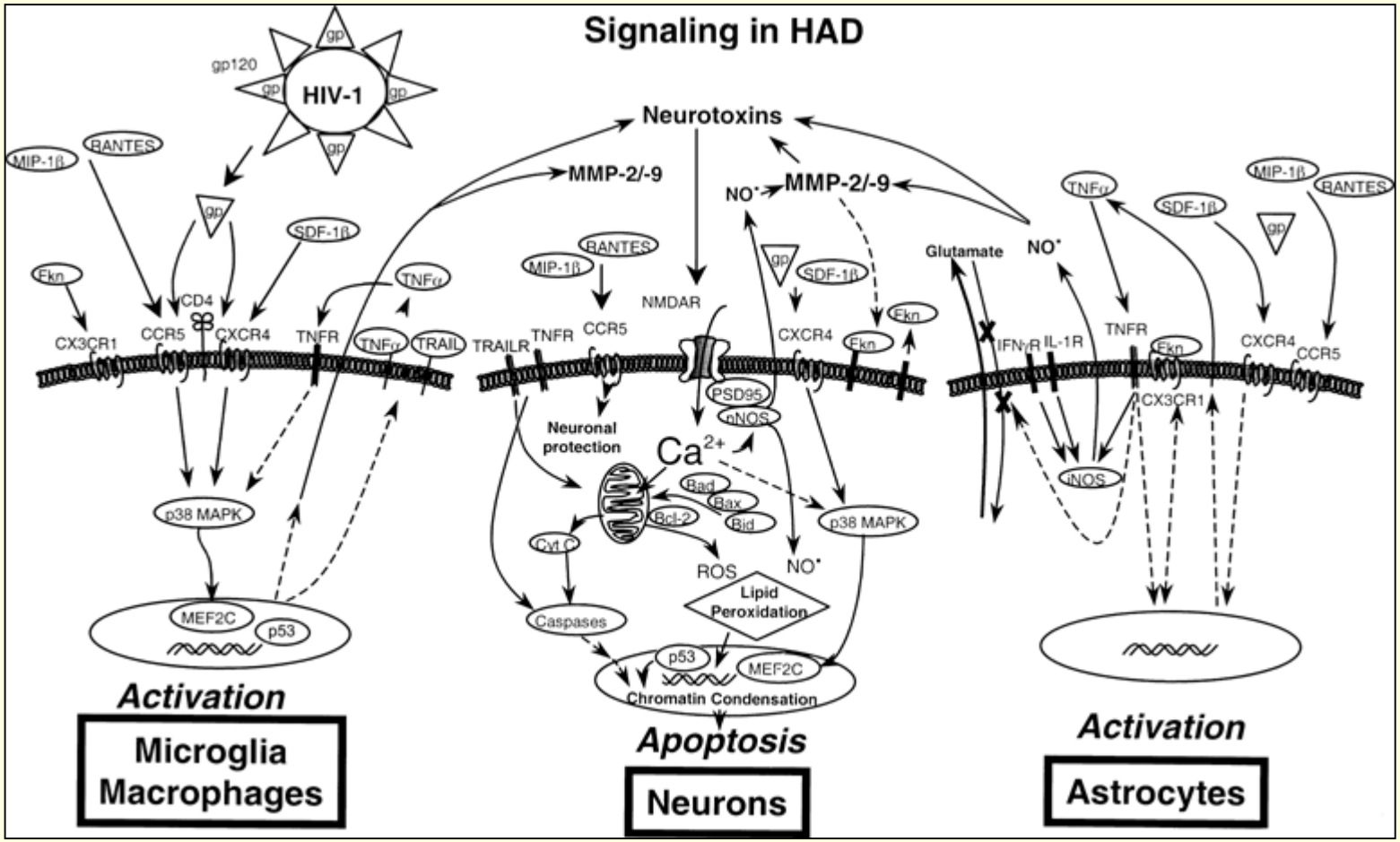
Neuropathology


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

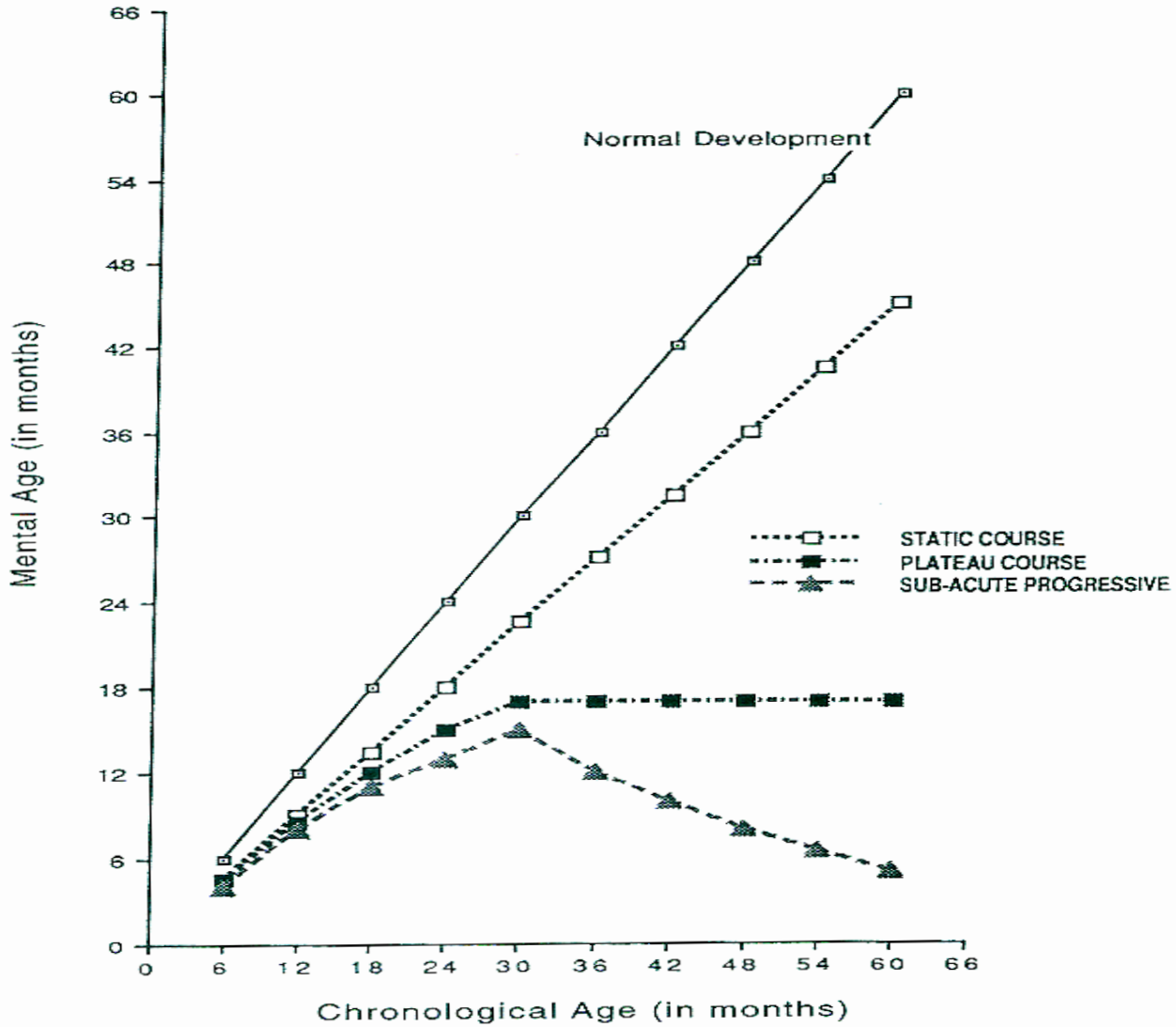


Figure 18.1. Schematic representation of the different encephalopathic courses.

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

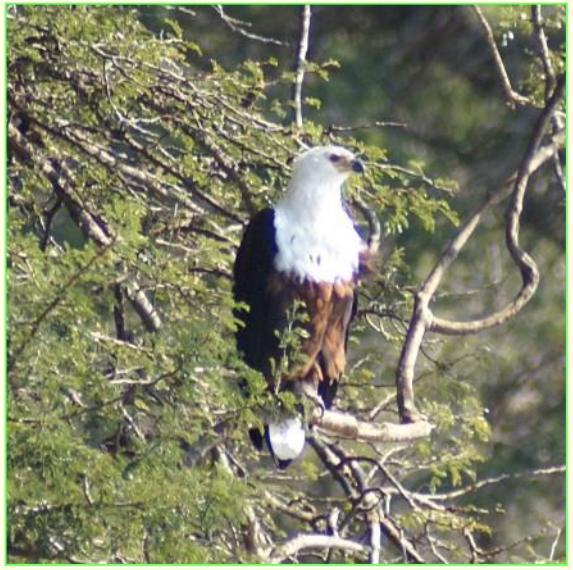
Background

- 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

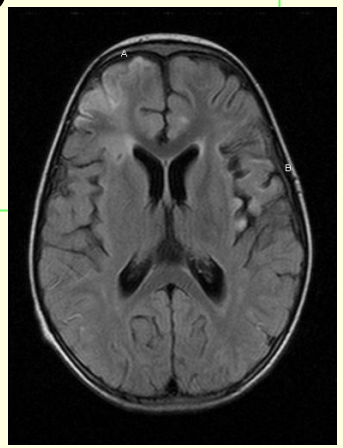
Govender R et al, JCN 2011

- **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



Specific Neurological complications of HIV

- **Encephalopathy**
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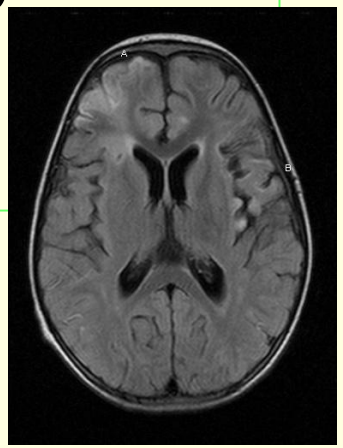
- **Epilepsy**

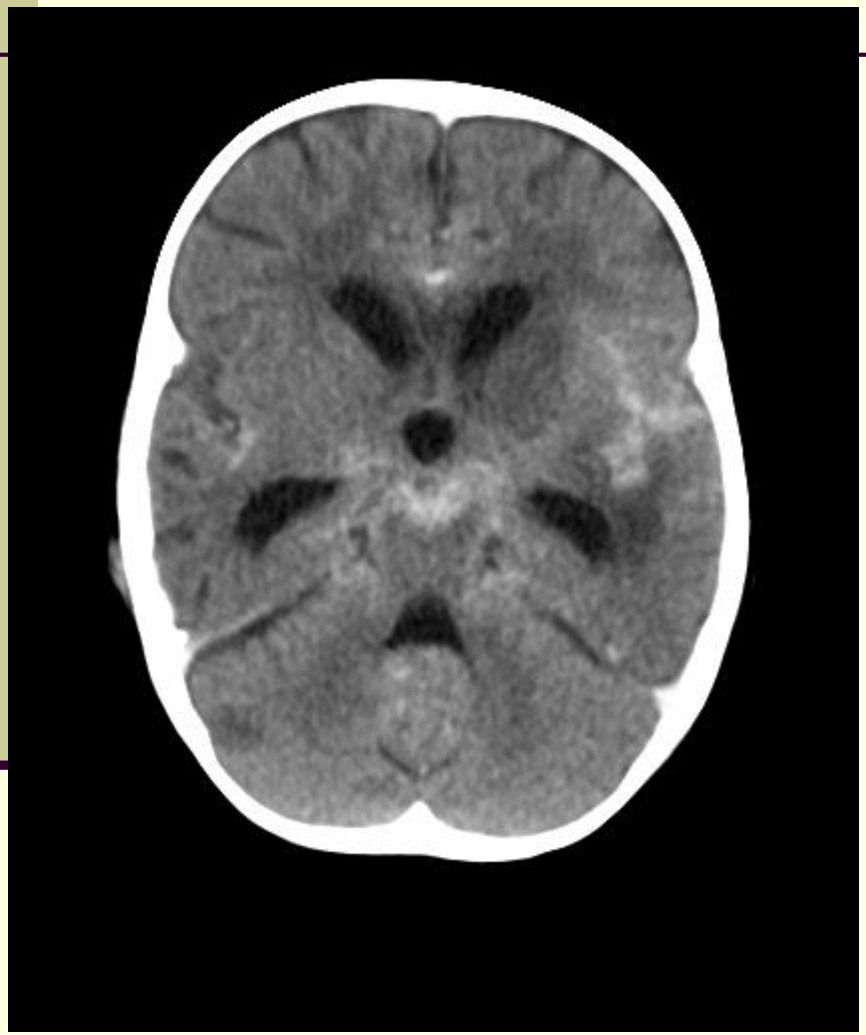


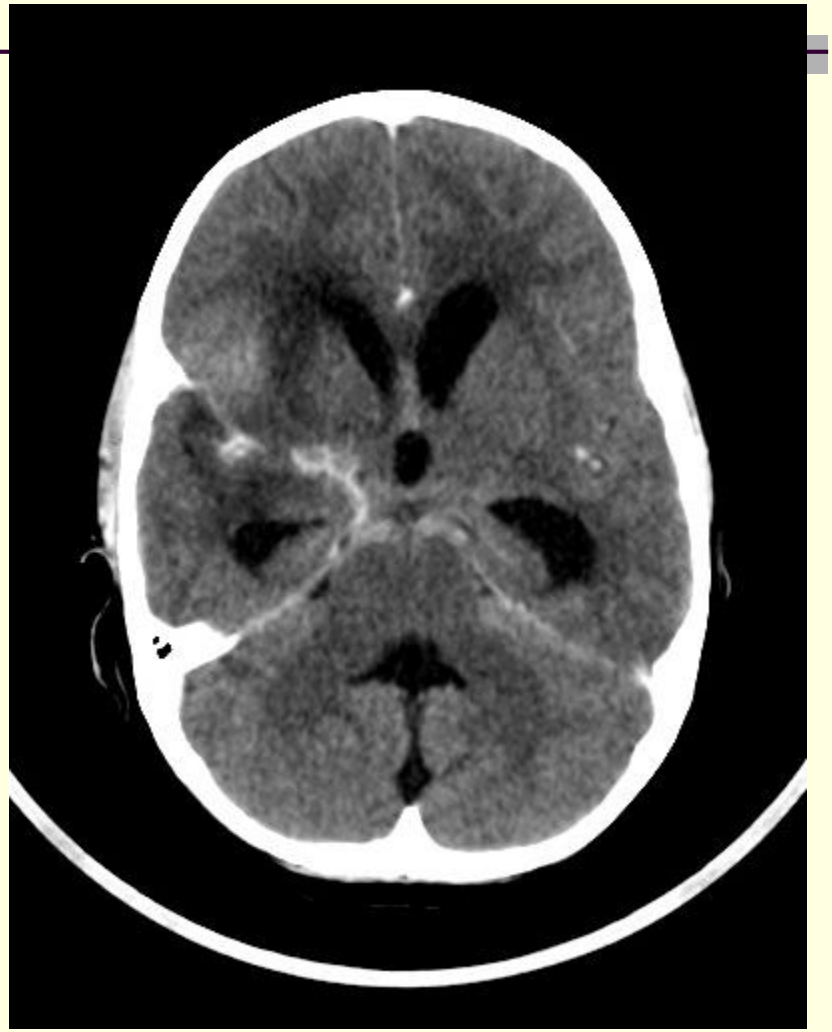
OPPORTUNISTIC CNS INFECTIONS

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**

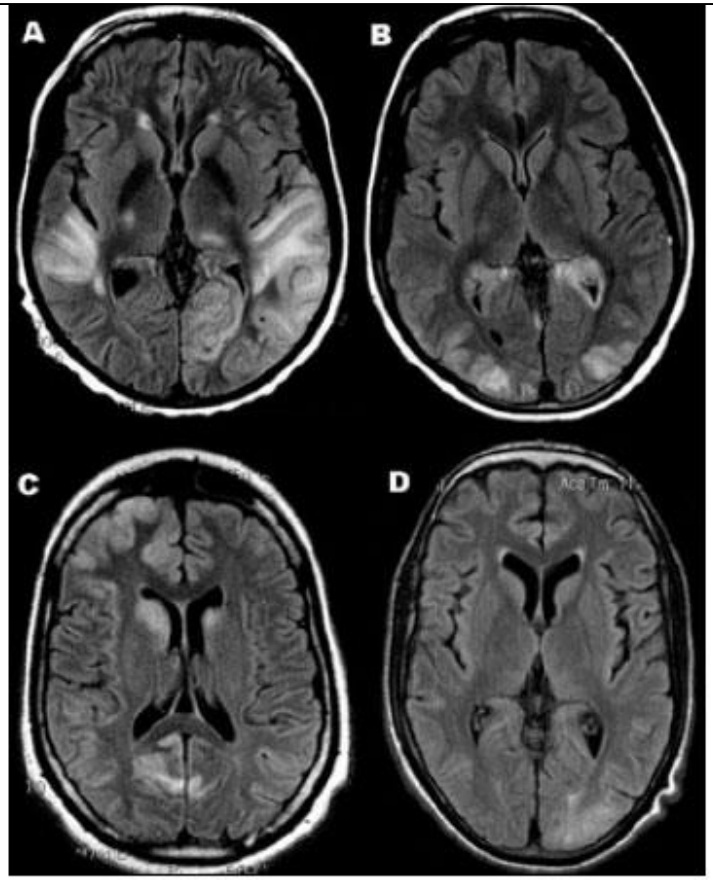


Fig. 2. Axial T2 FLAIR images demonstrating: A (Patient 6) – bilateral temporal-parietal cortical hyperintensities; B (Patient 2) – parieto-occipital cortical hyperintensities; C (Patient 3) – superficial cortical (left frontal and bilateral occipital) and deep grey matter (bilateral head of caudate) 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

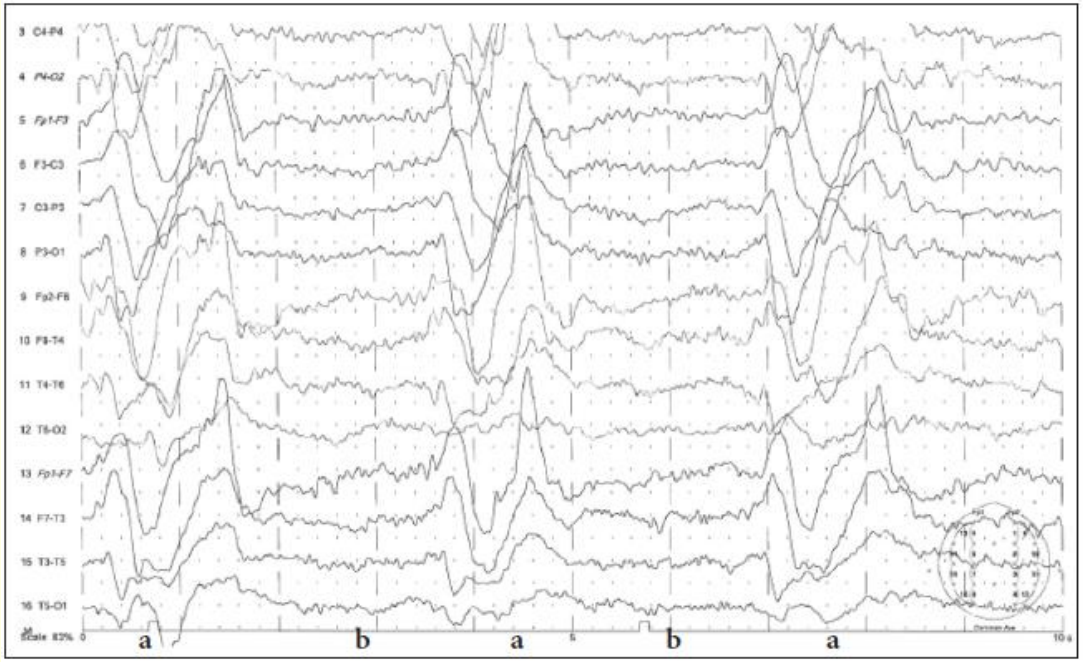
5 children (2 HIV infected, 2 died, median age presented 4½)

S Afr Med J 2015;105(9):xxxx. DOI:10.7196/SAMJnew.7788

CLINICAL ALERT

Subacute sclerosing panencephalitis in South African children following the measles outbreak between 2009 and 2011

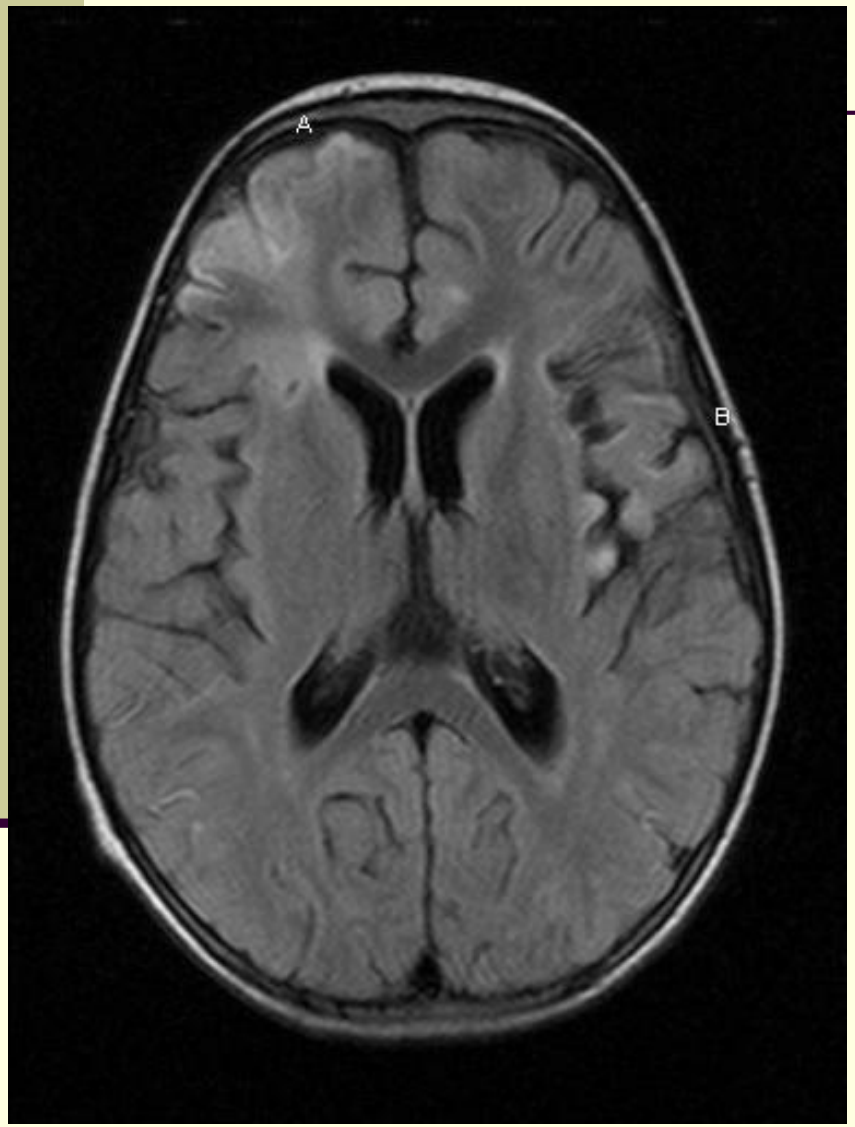
E Kija, A Ndondo, G Spittal, D R Hardie, B Eley, J M Wilmshurst

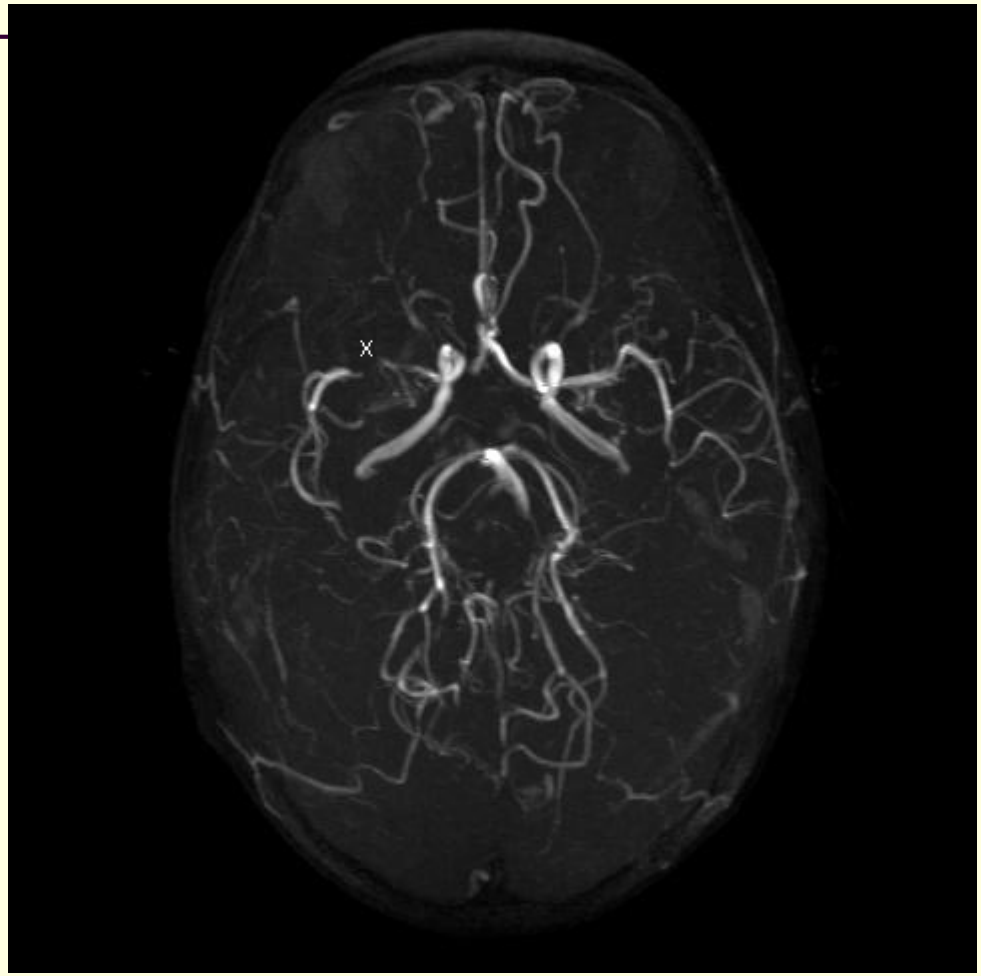


Cerebrovascular disease

RX study 6/78 (8%)

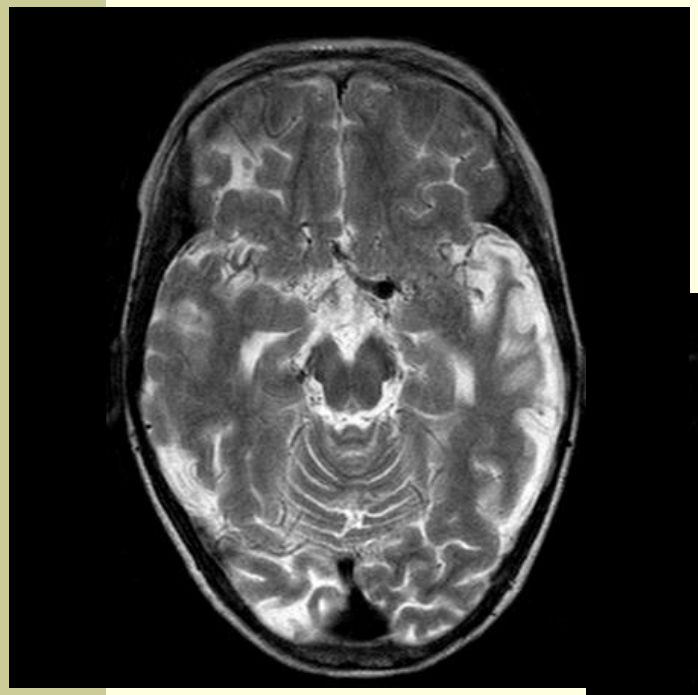
Stroke / arteriopathy

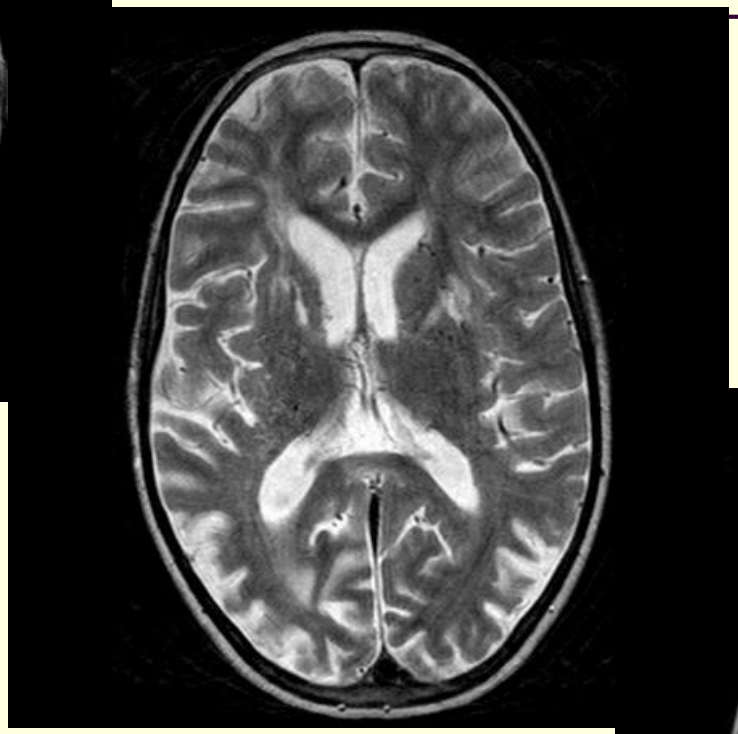


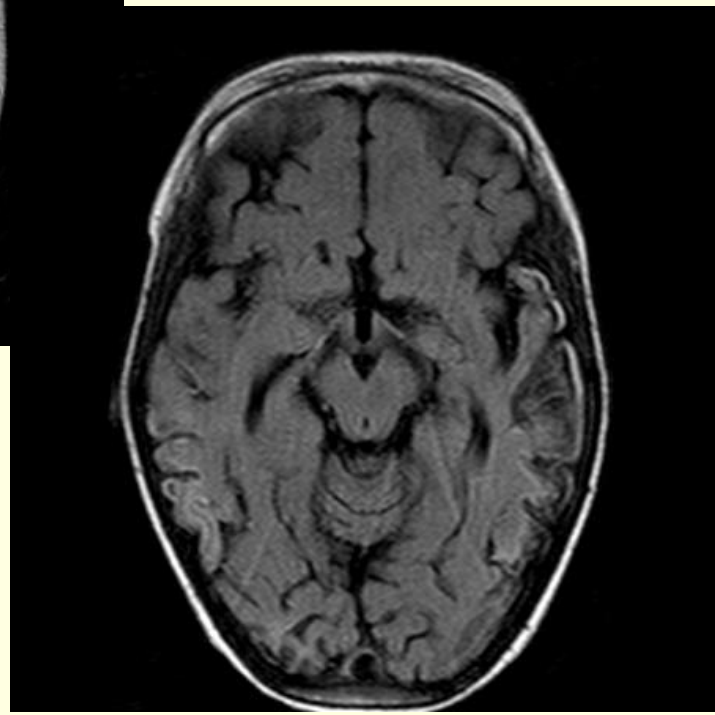


Hammond et al DMCN 2016

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

HIV and moyamoya syndrome

National SA survey

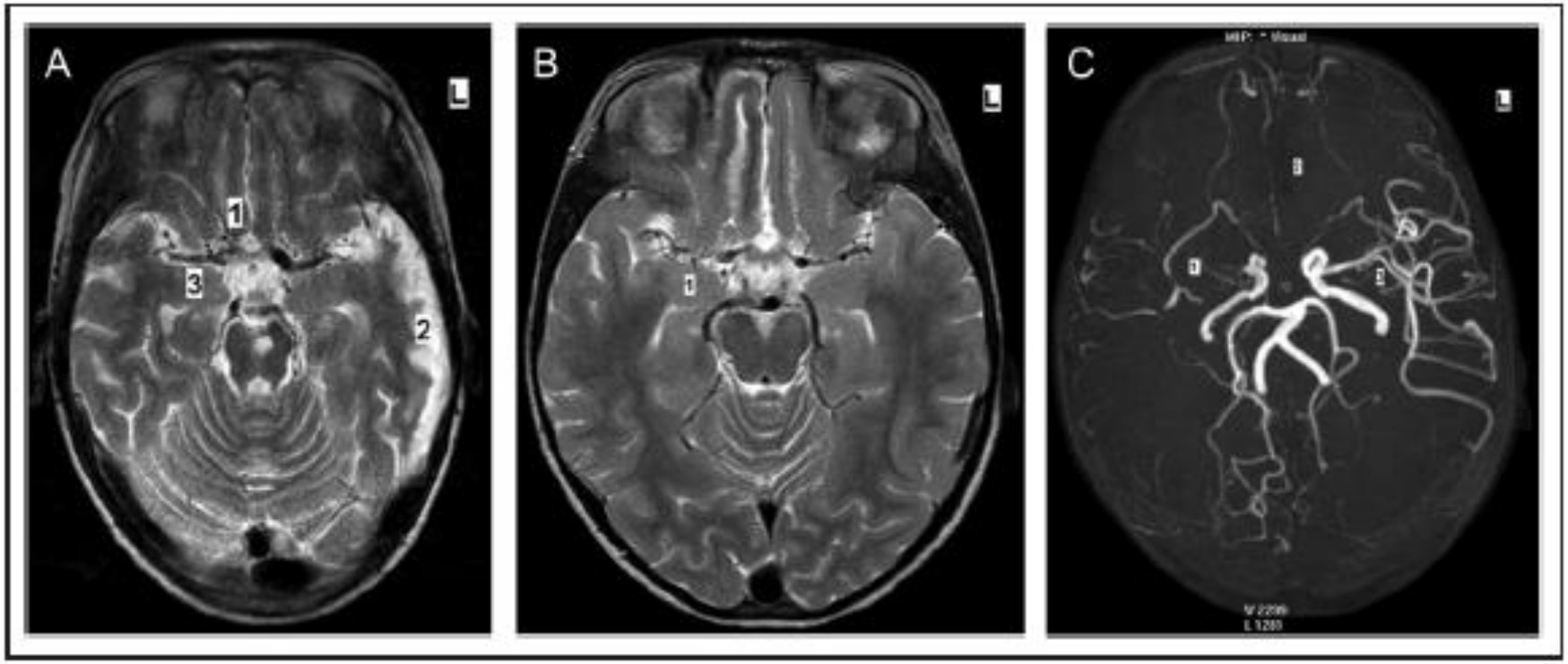
- 17 children HIV vasculopathy
- 5/17 moyamoya syndrome
- median age 5.8 yrs

Hammond et al JCN 2016

Common themes

- Hx of poor viral suppression
- Subtle presentations – evidence of silent progression
- Confused with HIVE
- Missed without MRA / MRI

South African patients with HIV moyamoya. *Hammond et al JCN 2016*



Epilepsy

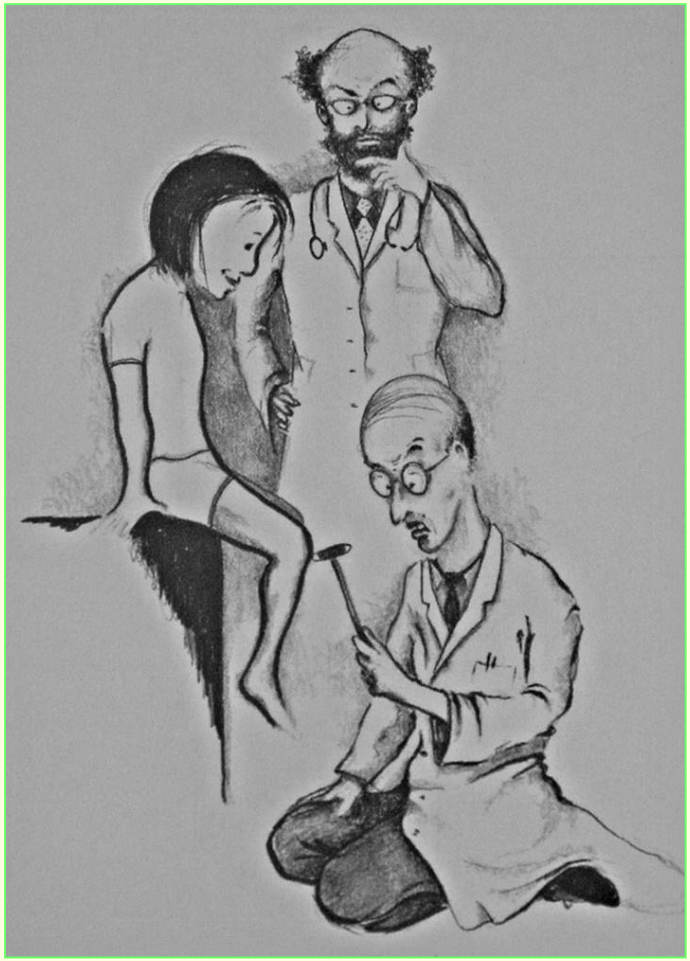
RX group 11/78 14%

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

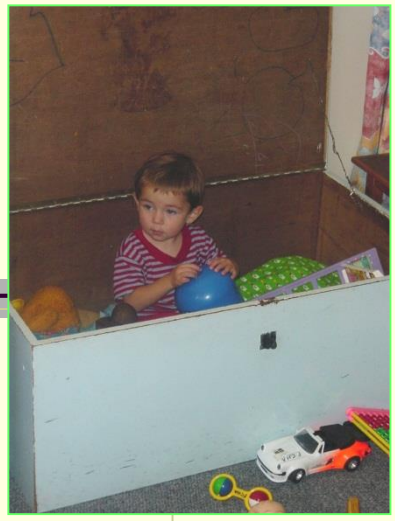
Acta Neurol Scand Suppl 2005
Seizure 2008
Samia et al JCN 2013

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

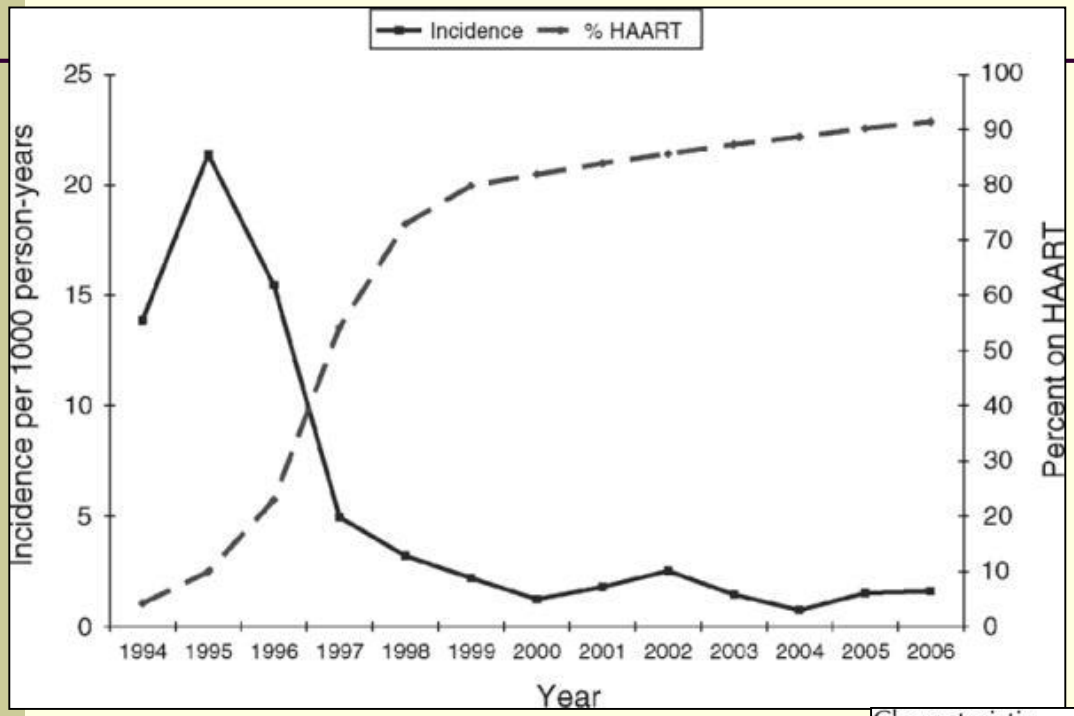
Yong MK *et al* J Acquir Immune Defic Syndr 2011

Yin M, Stein E. Clin Infect Dis 2011

Dao CN *et al*. Clin Infect Dis 2011

HIV ENCEPHALOPATHY

Incidence of HIV encephalopathy and percentage of children on ART, 1994-2006.



Characteristic	Hazard ratio[a] (95% CI)	*P*
Antiretroviral therapy		
HAART	0.50 (0.29, 0.86)	0.01
Non-HAART	Referent	
CNS-penetrating regimens		
Low	Referent	
Medium	0.86 (0.46, 1.62)	0.64
High	0.59 (0.31, 1.10)	0.10

CI, confidence interval; CNS, central nervous system.
[a]Multivariate hazard ratios adjusted for age, sex, race, birth weight, and CD4 cell percentage at baseline.

Patel K, et al AIDS 2009;23:1893-1901

The challenges of neurodevelopmental delay in children with HIV infection

- Studies support the need for early intervention
  - The greater the delay in intervention the less the reversibility seen and the poorer the cognitive outcome
- Further compounded by “the layering effect”
  - Global causes associated with delay include
    - Iron deficiency anaemia
    - Iodine deficiency
    - Malnutrition and stunting
    - Inadequate stimulation

Lowick et al Psychol, Health & Medicine 2012
Puthanakit et al Pediatr Infect Dis J 2013
Ferguson & Jelsma. Int J Rehab Res 2009

Adolescents and Executive functioning

Adolescents – executive functioning

(Koekkoek et al EJPN 2008)

- Apparently good CD4 levels
- But disturbing manifestations
- Failure of executive functions
  - Couldn't cope with Activities of Daily Living
  - Affected attentional control and working memory
  - Slowed information processing (22% down)
  - One child IQ 105 at Red Cross Children's Hospital – still needed special care facility support

"Slow progressors"

- Correlation with poor performance in
  - Executive function
    - Related to lowered corpus callosum fractional anisotrophy (FA)
    - Lowered FA in the superior longitudinal fasiculus
  - Attention
    - Related to lowered corpus callosum fractional anisotrophy (FA)
- Suggested that demyelination reflected by radial diffusivity may be prominent disease definer in paediatric HIV infection.

Hoare et al J Neurovirol 2012

Relationship between apolipoprotein E4 genotype and white matter in HIV-positive young adults in South Africa

- Investigated the Apoprotein E (ApoE) genotype to neuropsychological functioning and white matter integrity of the corpus callosum
- In HIV-positive - clade C HIV patients
- Found that **Ɛ4 allele variant of ApoE** was associated with memory impairment and white matter damage of the corpus callosum.

Hoare et al Eur Arch Psychiatr Clin Neurosci 2013

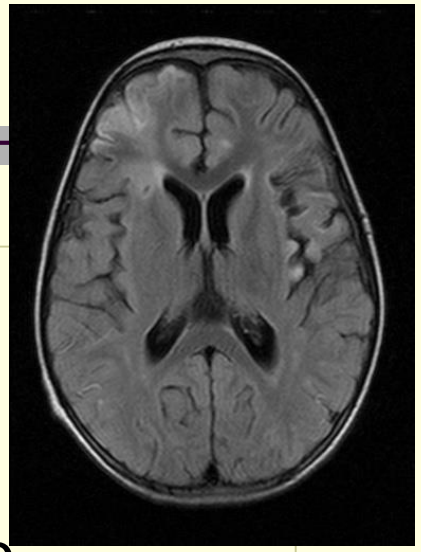
Pathogenesis: The ART of HIV therapies: dopaminergic deficits and future treatments for HIV paediatric encephalopathy *Webb et al 2009*

- Neurotoxic HIV protein Tat on cells of fetal rat midbrain impacts on **dopamine function**
- Adult based studies marked decrease on the expression of tyrosine hydroxylase in the **substantia nigra** of pts with HAD.
- **HIV impacts on dopaminergic regions** of the brain (basal ganglia and cortical motor and cognitive areas).

Pathogenesis: The ART of HIV therapies: dopaminergic deficits and future treatments for HIV paediatric encephalopathy Webb *et al* 2009

- HIV-related neuropathology (i.e. calcification and neuronal apoptosis)
  - Affects function of the basal ganglia
  - Impacts on the dopaminergic valence of cortical and subcortical brain regions which are connected by the frontostriatal circuits
- *Resulting in impairment to the cognitive and behavioural abilities they modulate*

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

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- Brain Eley
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- Team

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- Reneva Petersen
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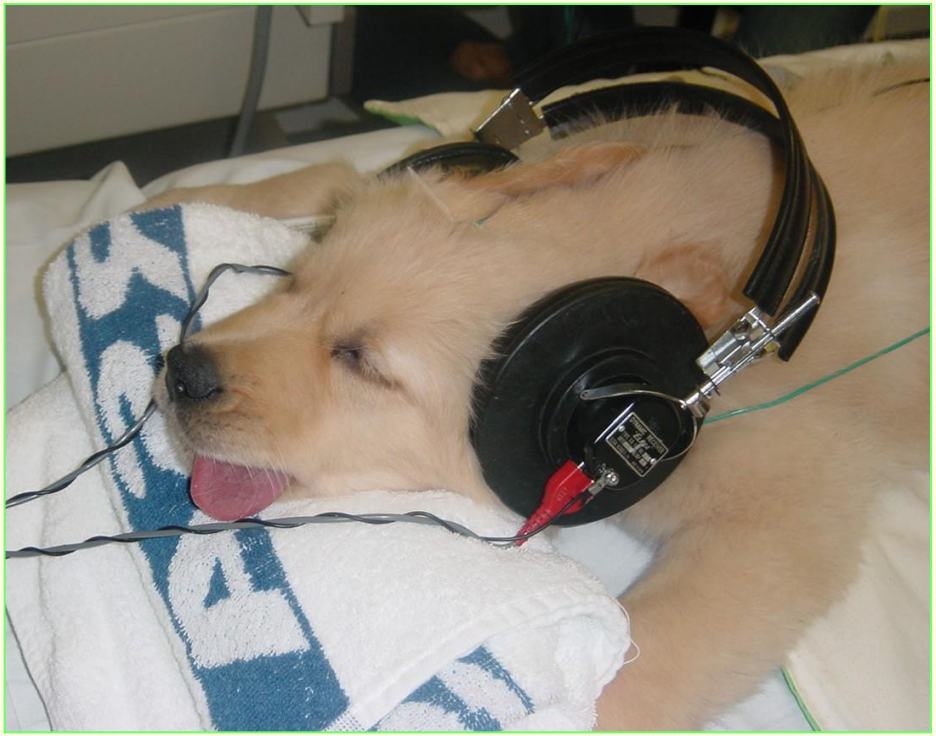
- Rajeshree Govender
- Gill Riordan
- Alvin Ndondo



Red Cross War Memorial Children's Hospital, Cape Town

Table Mountain National Park

University of Cape Town