

HIVE & neurocognitive impairment in a paediatric population

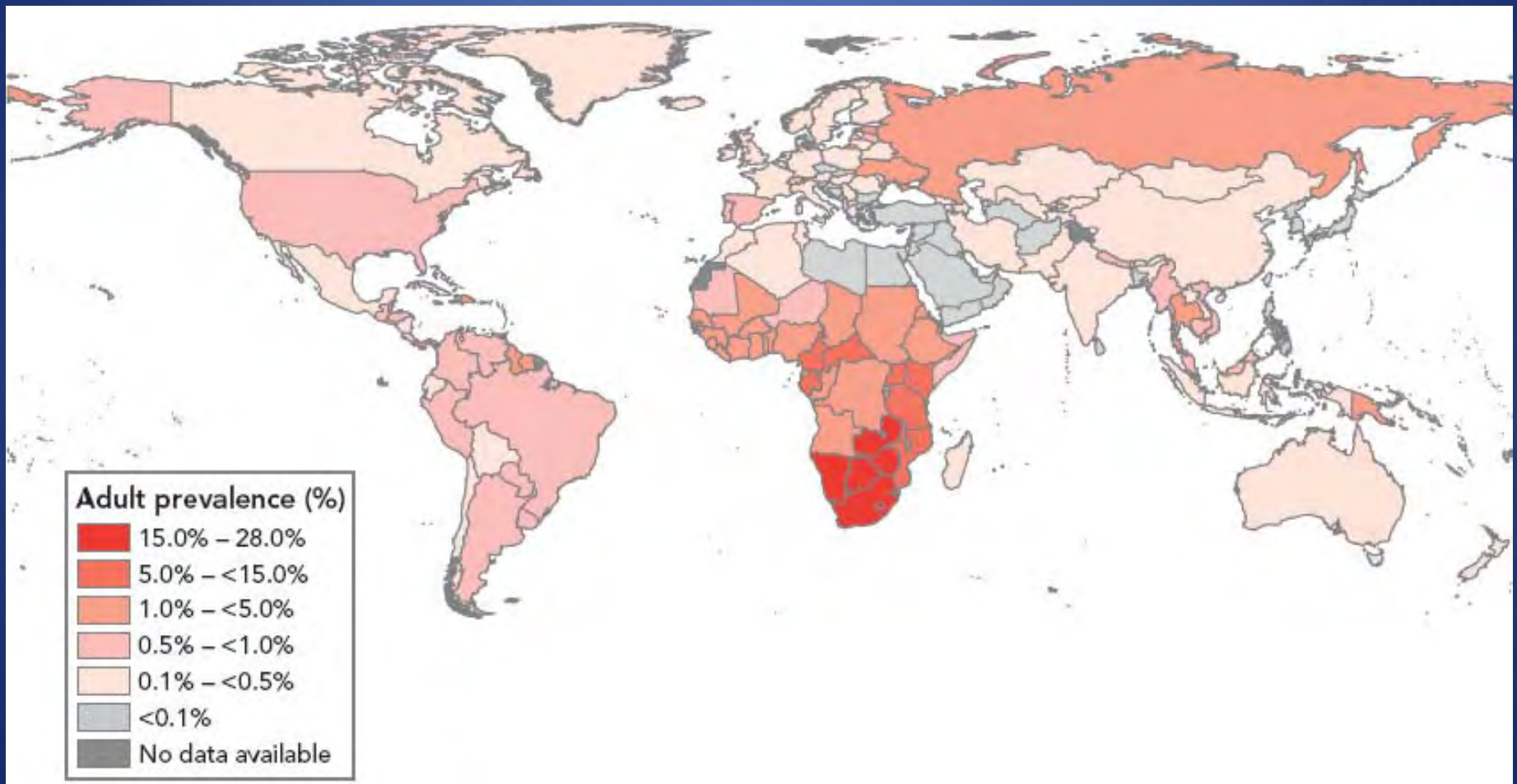
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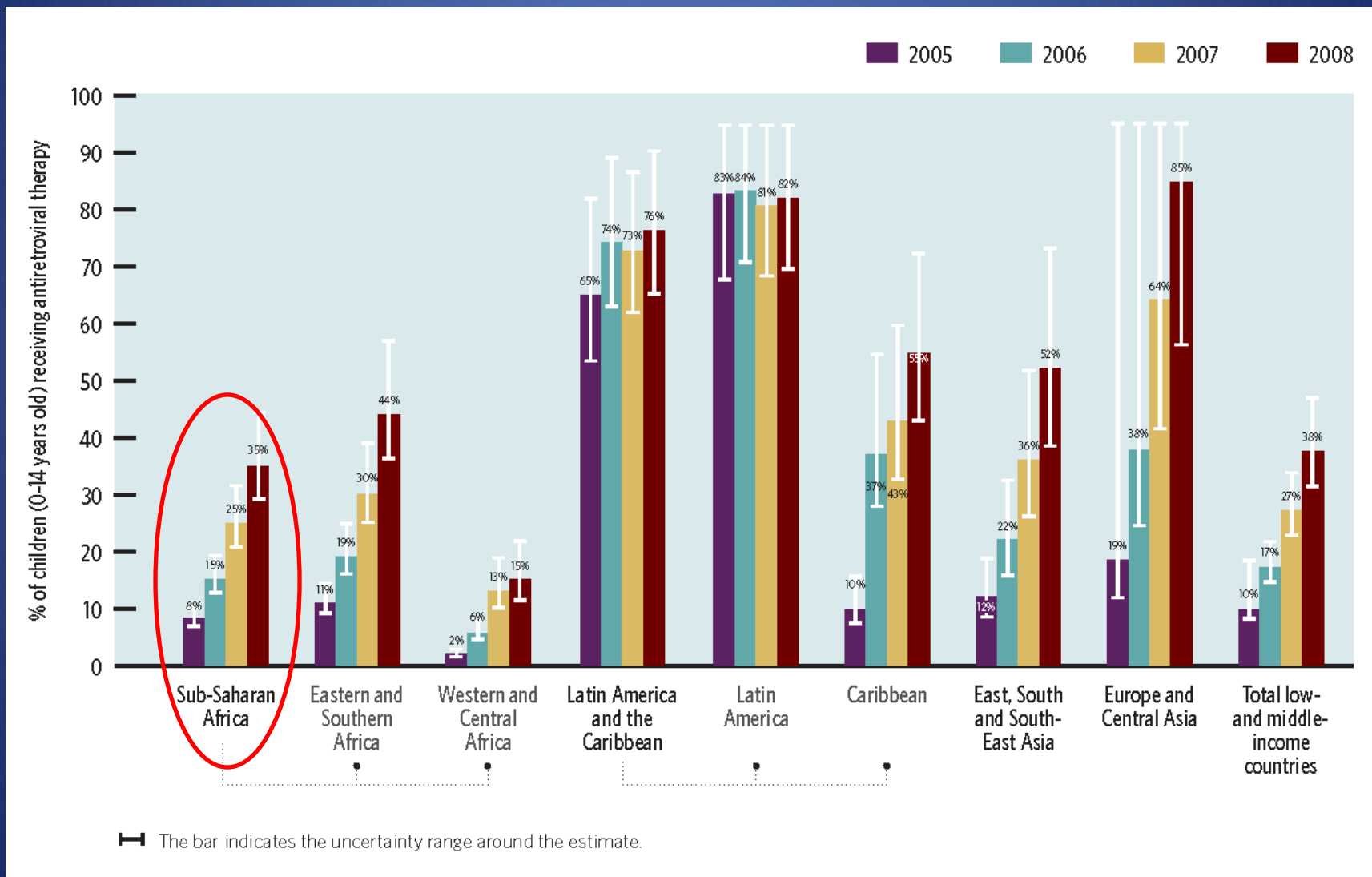
A global view of HIV infection



UNAIDS, http://www.who.int/lib/publications/global_report/2009/pdf/full_report.pdf

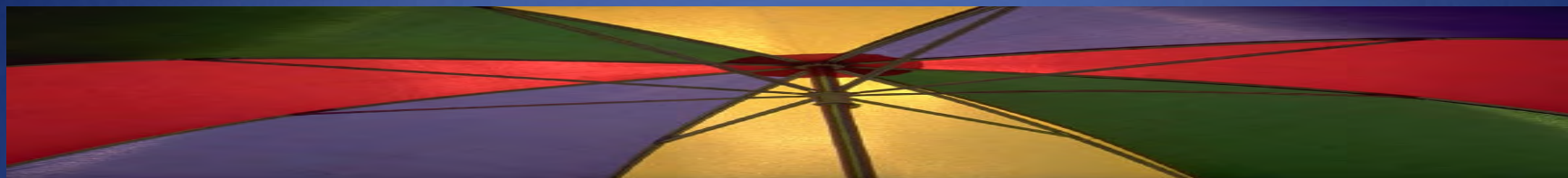
UNICEF, UNAIDS, WHO, http://www.uniteforchildren.org/files/CA_FSR_LoRes_PDF_EN_USLetter_11062009.pdf

Percentage of children receiving antiretroviral therapy in low- and middle-income countries, 2005–2008



- Access to ART (National)
- 2002 : 2.1% of newly diagnosed children
- 2007/2008: 36.9% in the that year.
- The Western Cape: newly diagnosed children commenced on ART being 96.1% in the 2007/2008 year.
- www.ci.org.za (*children's institute*)

Definitions



- HIV refers to the disease, damage or malfunction of the brain caused by HIV-1.
 - Static HIV is an unchanging, less threatening type of encephalopathy, whereas,
 - progressive HIV gradually becomes more destructive over time.
- Currently, HIV is classified as a stage 4 AIDS-defining illness (WHO) reflecting the severity of the disease.

Case definition: HIV encephalopathy

CDC (1994) ¹	Newton et. al. (2006) ²
<p>At least one of the following progressive features present for ≥ 2 months:</p> <ul style="list-style-type: none">a. Failure to attain or loss of developmental milestones or loss of intellectual ability verified by standard developmental scale or neuropsychological testsb. Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy on CT scan or MRI (serial scanning is required for children < 2 years)c. Acquired symmetric motor deficit manifested by 2 or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance	<p>A simplified case definition of HIV encephalopathy consists of:</p> <p>Any child who is HIV positive,</p> <ol style="list-style-type: none">1. Lack of growth in head circumference assessed by serial measurements at least 3 months apart,2. Altered neurodevelopmental milestones such as loss of skills (particularly motor) and lack of acquisition of skills,3. Diffuse symmetrical hyperreflexia, and4. Lumbar puncture to exclude CNS infections

¹ MMWR 1994;43:RR-12

² J Neurovirol 2008;14:89-101

Clinical manifestations

STATIC COURSE

- Fixed deficits
- No loss of skills
- Skills acquired at a stable but slow rate
- Deficient but stable IQ
- Motor dysfunction (non-progressive)
- Static course

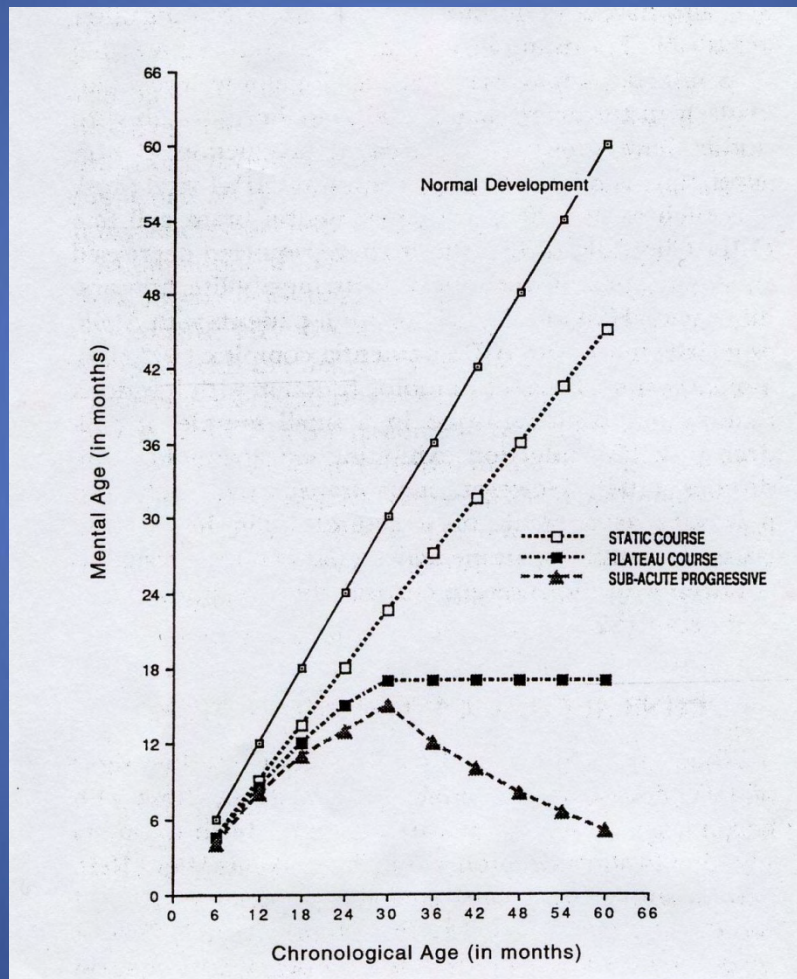
PLATEAU COURSE

- No loss of skills
- No or slower acquisition skills
- Decline in rate of cognitive development
- Motor dysfunction (non-progressive)
- Acquired microcephaly
- More indolent course

SUBACUTE PROGRESSIVE COURSE

- Loss of milestones
- Progressive motor dysfunction
- Oromotor dysfunction
- Acquired microcephaly
- Cognitive deterioration
- Apathy
- Progressive long track signs
- Movement disorders (uncommon)
- Cerebellar signs (uncommon)
- Seizures (uncommon)
- More rapid course (weeks to months)

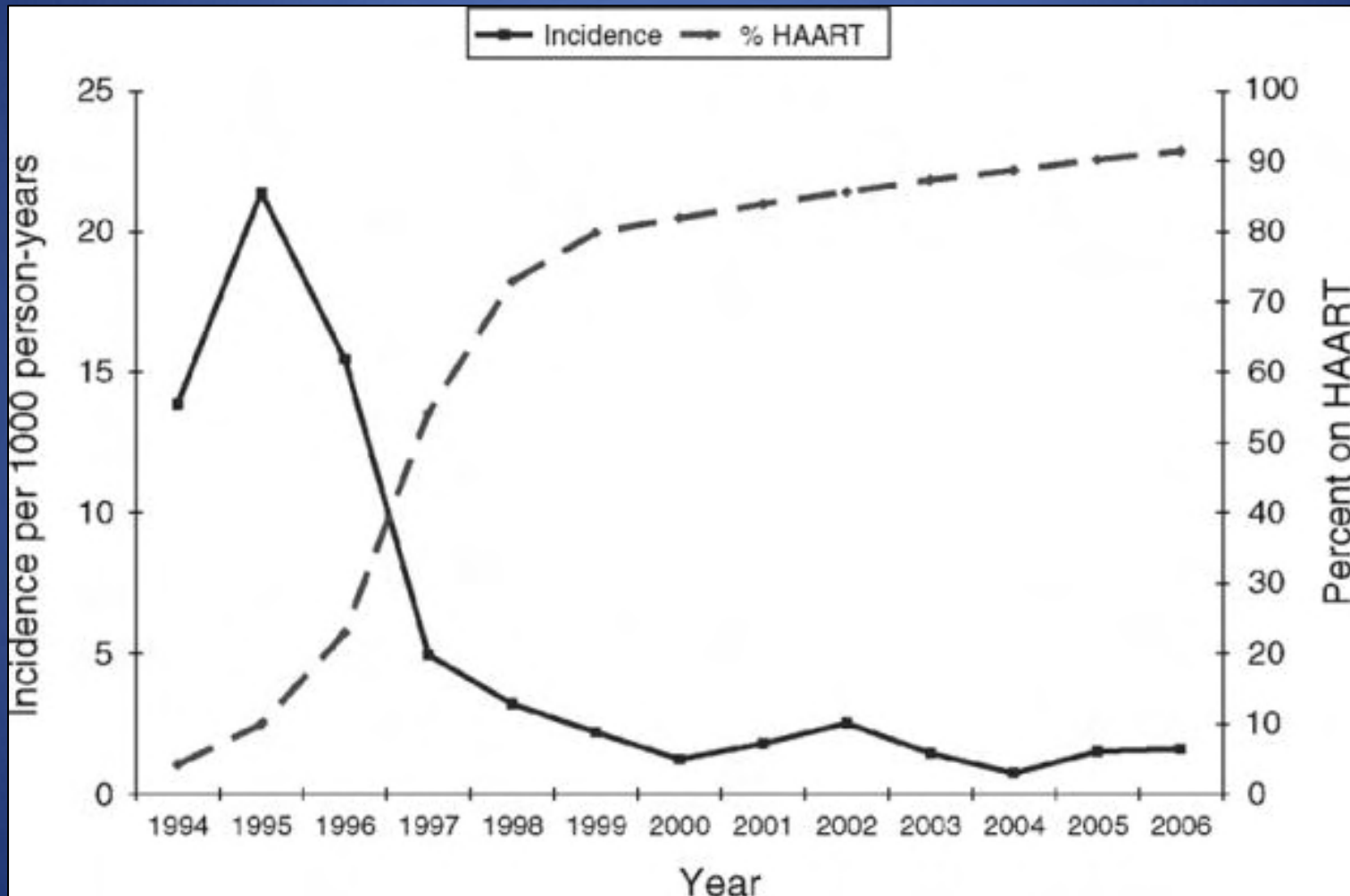
Clinical course of HIV encephalopathy



Positive impact of HAART

- Antiretroviral treatment has been proven to prolong survival rates of children suffering from HIV/AIDS by promoting normal growth and development *(Smith et al 2006)*.
- ART has dramatically decreased the rate of HIV in the United States from 35-50% to less than 2% *(Van Rie et al 2008)*.

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



Effects of HIV-1 on cognition and behaviour

- General clinical effects well described
- Effects on cognition and behaviour less well described
- Recent systematic review *Abubakhar et 2004*
 - *Studies in sub-Saharan Africa*
 - *Development, cognition, behaviour; as primary outcome*
 - *Paucity of data*
 - *All but 1 study focused on pre-school age groups*



HIV Neuro clinic

- Started 2008
- Dr Walker and Dr Donald
- Referral form
- Aim of seeing, diagnosing, essential investigations, management plan and then referral back to general clinic
- Establish guidelines from data collected



HIV-Neuro clinic database

- Data is collected prospectively on children attending a multidisciplinary Paediatric Neurology clinic from 2008-2011.
- Data is anonymised and collated.
- University ethical approval has been obtained.

Results

- 89 new children were seen and details documented between July 2008 to May 2011. (Oct. 2011, 120)
- Fifty-two children (58.4%) were diagnosed with HIV.
 - CDC criteria (small heads, Long Tract signs)
 - Ages ranged from 10 months-13 years (mean 55.8 months).
 - 18 were 6 years or older

clinically

- 31/52 (59.6%) microcephaly
- 38/52 (73%) long tract signs (mostly spastic diplegia)

History

- 40/52 (77%) had delayed early motor milestones and
- 35/52 (67%) had delayed early language milestones
- 11/18 (61%) 6 years or older reported school difficulties and were referred for formal testing

Additional CNS diagnoses/issues

- 11/52 (21%) had had at least 1 seizure
- 37/52 (71%) parents/caregivers reported behavioural problems
 - 9/52 (17%) had a formal diagnosis of ADHD
- 23/52 (44%) had active ear problems
 - 7 Acute otitis
 - 16 Chronic suppurative otitis media



Treatment protocol

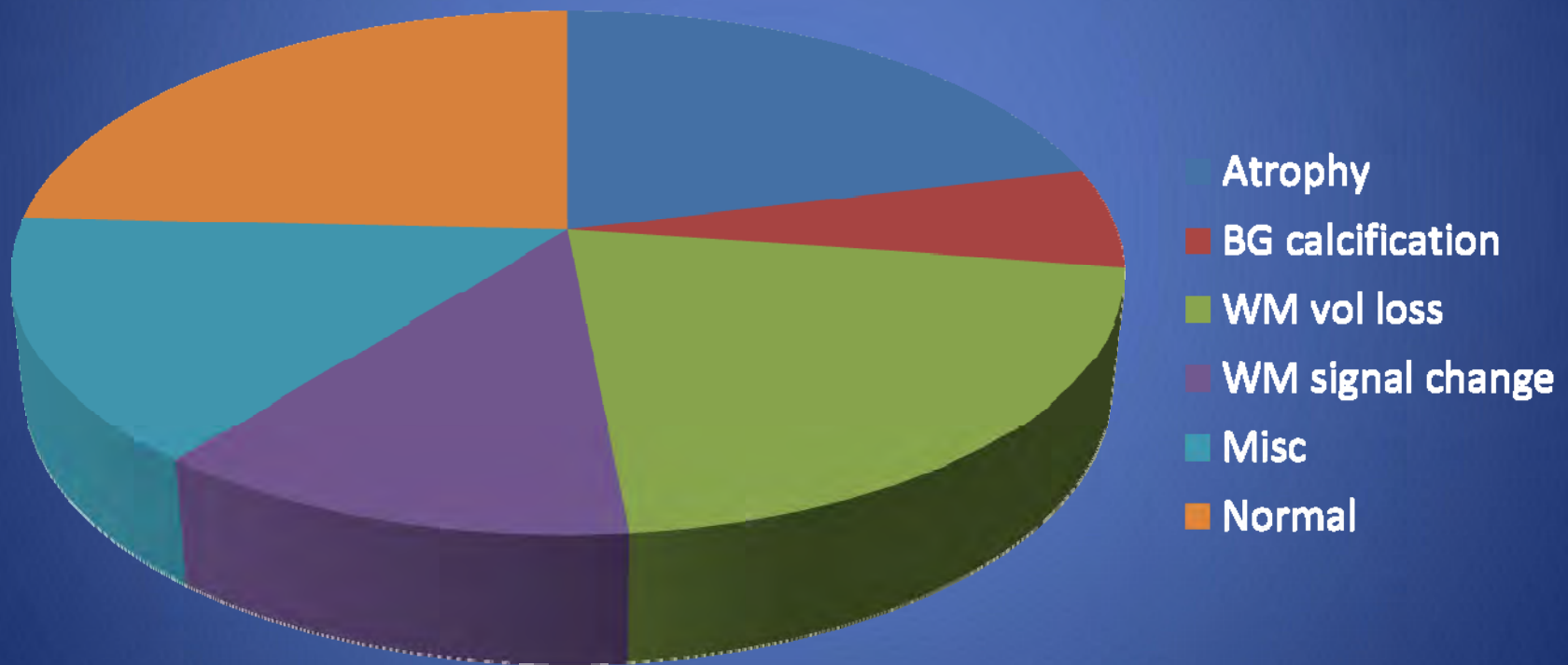
- All except one child in the group were on antiretroviral treatment (ART) at assessment

Neuro-imaging

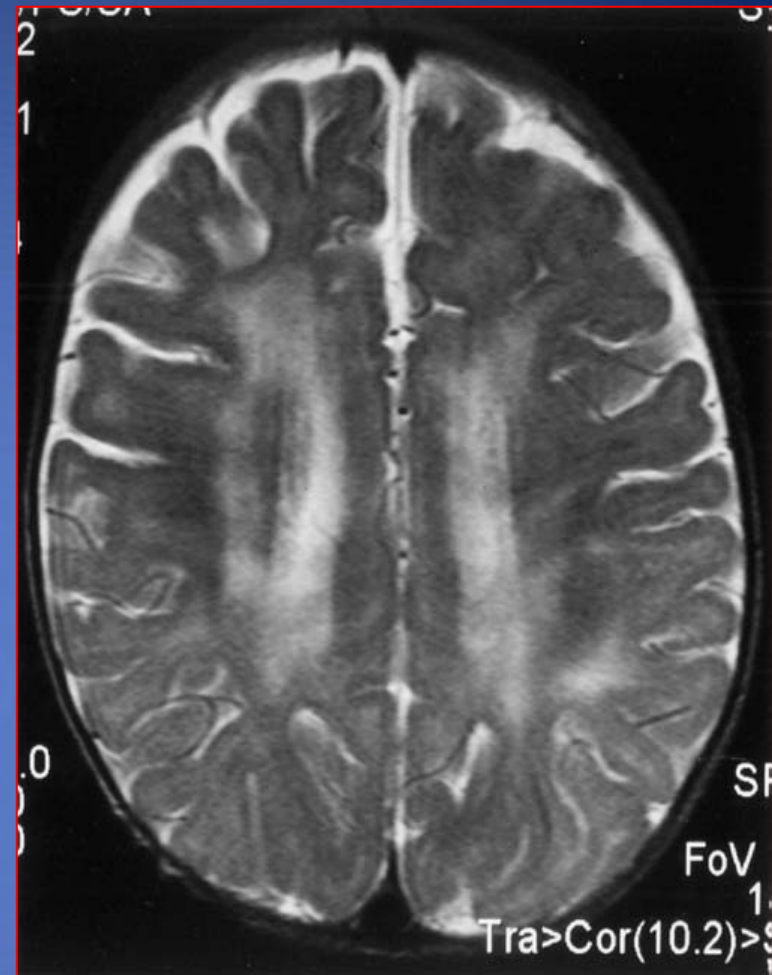
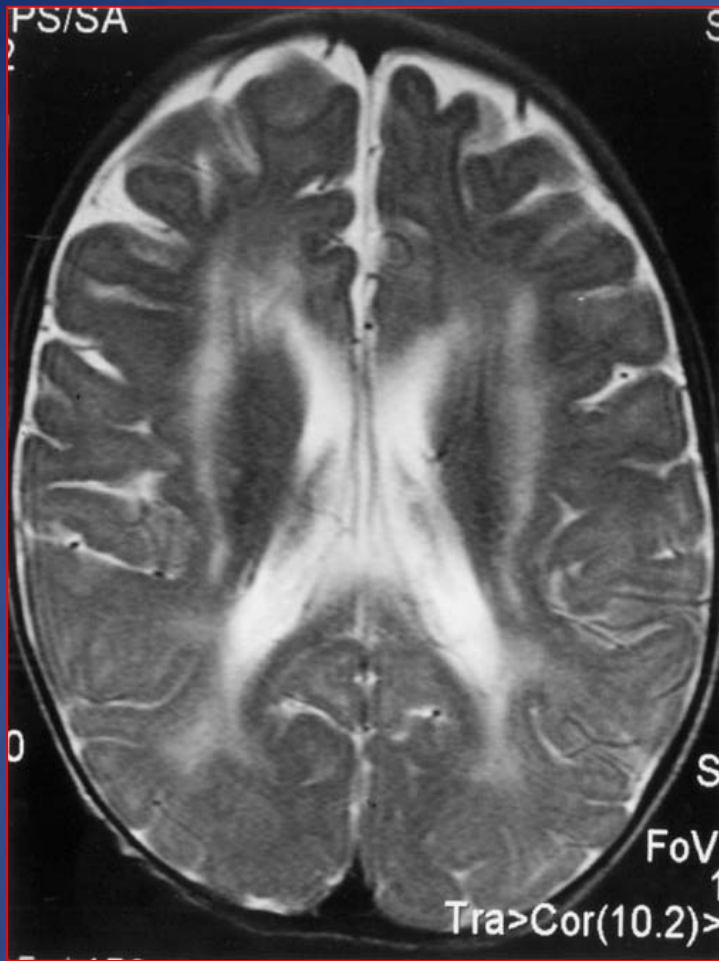
- At initial assessment 20 children had had neuro-imaging (CT or MRI)
 - A further 10 now done
 - 5 done awaiting reporting and 10 on waiting list for imaging

Imaging results

Imaging results







white matter hyperintensity related to HIV encephalopathy.

(a) Bilateral deep white matter hyperintensity, which is periventricular and symmetrical.

(b) superior extent of the leukoencephalopathy involving the centrum semi-ovale.

(Andronikou et al 2004)

Cognitive impairment in HIV positive children without HIVE

- With the anticipated decrease in childhood mortality, the impact of HIV-associated disability will become increasingly important
- How does cognitive function and behaviour affect morbidity?

Questions

- • What is the degree of motor, cognitive, language and social–emotional impairment related to paediatric HIV in sub-Saharan Africa?
- • Which domains of functioning are most affected?
- • What are the known risk factors?

? HAART and the CNS

- Sub-Saharan Africa carries the global burden of 87% of new HIV infections in children
- <15yrs primarily infected vertically
- HAART seems to improve or even reverse some of the neurological pathology seen in HIV+ children
- However some studies have remarked that even if a child is virologically suppressed on HAART, neurological improvement is not guaranteed
- as most anti-retroviral agents do not cross the blood-brain barrier readily and are postulated to allow a consequent viral reservoir in the brain

Older HIV positive children

- There are very few published studies describing the clinical profile of older (>6year) vertically infected HIV children
- and even fewer studies which have HAART naïve study participants
- The studies describing specific cognitive impairments in HIV children have highlighted certain domains most commonly affected – visual perceptual and visual motor skills, attention, executive functions, memory and language
- Studies have also reported an increase in behavioural problems in HIV infected children
- A recent article reviewing all studies in sub-Saharan Africa (SSA) highlighted the paucity of data in this field

CHER trial

- The CHER trial in South Africa informed optimal timing of HAART for infants less than 12 months old.
- CHER publication notes 8 "encephalopathy" cases in infants with deferred therapy compared to one in the immediate therapy arm
- A subsequent poster presented at the International AIDS Society (IAS) meeting in July 2009 noted detriments in general and locomotor scores on Griffiths with deferred therapy in infants less than 12 month old
- WHO guidelines now call for immediate therapy for infants less than 12 months old.
- The WHO guidelines for children older than 12 months remain unchanged

What about treating older children

- These changed guidelines therefore did not affect the vast majority of children living with HIV
- A recent NIMH/NIH scientific meeting convened in July 2009 addressed neuroAIDS issues in Africa and again noted the lack of clear data for children over 12 months of age.
- it is impossible to ignore the lack of research data for children over 12 months old, where guidelines continue to recommend deferring therapy until immunological compromise occurs.

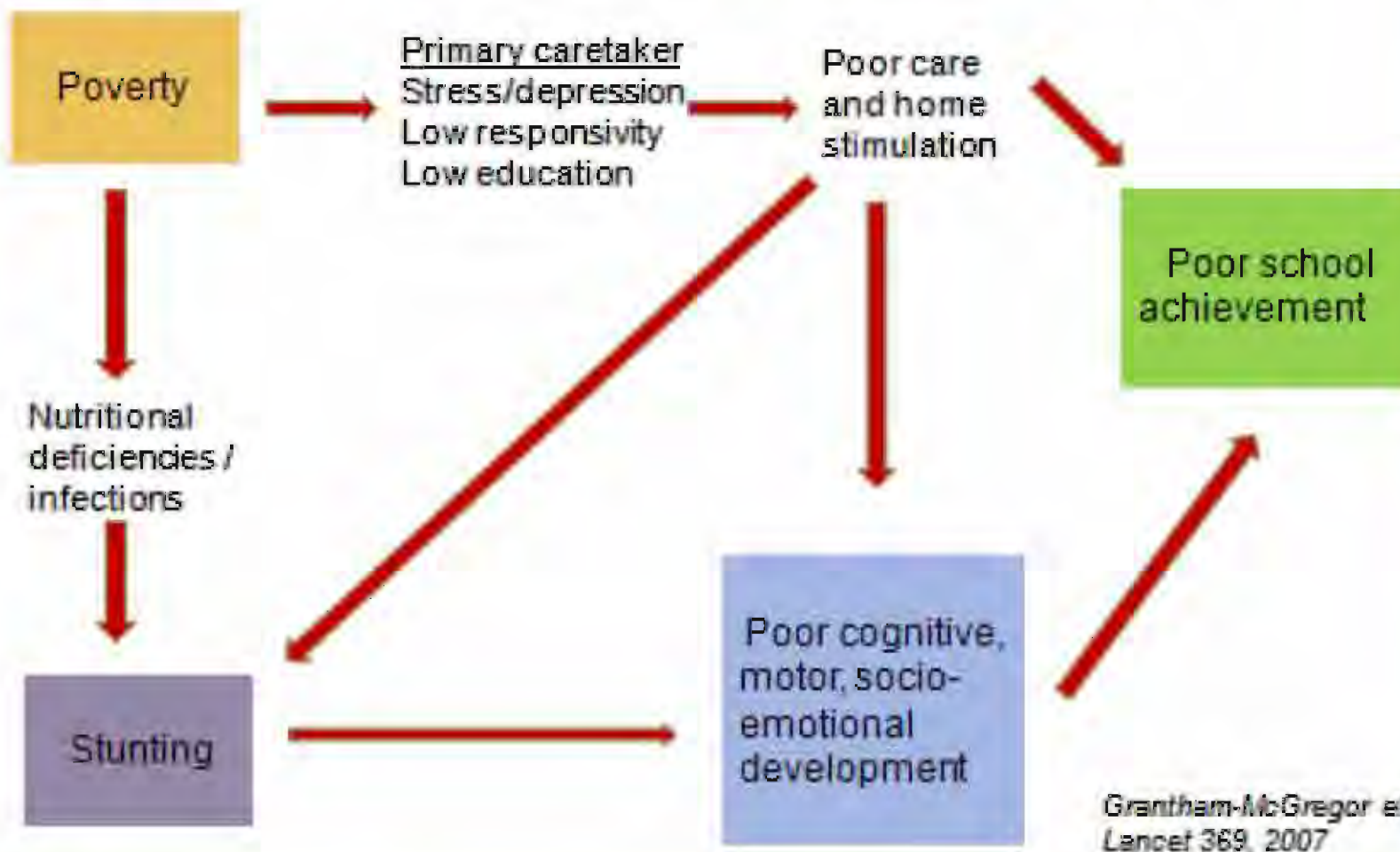
What do we need to know?

- The epidemiology and description of neurocognitive and behavioural disturbance in HIV positive children in SSA
- Define diagnostic criteria
- Develop screening tools
- The effect of HAART
- Is early HAART protective
- Study in progress

What can we do?

- Issues: early recognition
 - Need for regular OFC measurements
 - Thorough neurological examination
 - Developmental screen (including some direct questions about behaviour)
 - Asking about school and requesting reports
- “Whole-istic” management

Relations between poverty, stunting, child development and school achievement



What can we do - continued

- Issues: schooling and disclosure
 - With very few exceptions, our children with school difficulties had not disclosed HIV status to the schools
 - facilitate disclosure process



Future

- Roll-out of ART to both children and adults with HIV has improved the outlook for children in South Africa
- **BUT**
- Often unable to disclose to the school, parents are reticent to seek help for children with LD's
- Unsupported in a system which is focusing on their medical needs, not adequately recognizing their cognitive and behavioural problems.
- More and more children with HIV are now going to be reaching school-going age with the improved treatment accessibility.

Think “HAND”

- More adult spectrum of HIV related CNS compromise (HAD/HAND spectrum) needs to be actively sought
- Psychiatric disturbances likely also under-recognised and under-reported
 - Especially adolescents (*Mellins et al 2009*)
- *Donald/Hoare study hopefully will provide direction*

Take home message

- Head circumference at birth and 6 monthly thereafter
- Developmental screen/surveillance
- Ask about behaviour
- Ask for school reports



Treat the treatable

- Treat epilepsy (beware interactions)
- Manage behaviour: consider medication
- Remember side effects of ARV's (nb EFV)
- Check ears (and test hearing)...

Thank you

