Guy's and St Thomas' NHS Foundation Trust

Neurocognitive disorders in young people with HIV

Dr Daniella Chilton

What we will cover today

Guy's and St Thomas' NHS Foundation Trust

- **Background**
- **Prevalence**
- **Normal changes during adolescence**
- **HIV and the brain**
- **The domains and tests and what they translate into**
- **Contemporary studies**
- **Psychosocial factors**
- **Overview and intervention possibilities**

Background

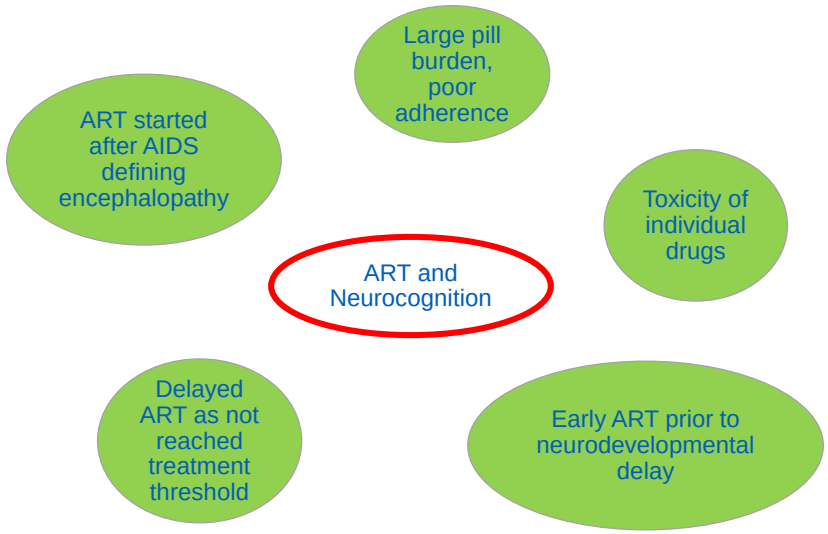
- **2.1 million children <15 living with HIV**
- **Most perinatally acquired (PHIV)**
- **Expected to survive into adulthood**
- **Little is known about neurocognitive function in this group**
- **Ageing from adolescence into young adulthood**

- **European setting is different in terms of volume of patients, and resources**
- **Plan services which will meet the future needs of these pt as they age**

Robbins R et al, AIDS CARE 2019
https://doi.org/10.1080/09540121.2019.1626343

Rationalising the literature

- **Huge changes in how we treat children living with HIV**
- **Pre-1995, 50% died before the age of 2**
- **Pre-1997, in Europe and USA, toxic treatments, suboptimal control**
- **High pill burden, poor adherence**
- **Geographical and economic variations**
- **Great variability in exposure to ART and severity of disease**
- **Variability in how we define neurocognitive impairment (NCI)**
  - Functional
  - Objective measurement using standardised tools



showing we care

NHS Guy's and St Thomas' NHS Foundation Trust

Prevalence data

- **South Africa - 45% HIV infected youth affected by NCI[1]**
- **9.4x more likely if history of HIVE[1]**
- **35% Romanian young adults (transfusion in infancy) mild NCI[5]**

- **22-84% prevalence in adults[2]**
- **Incidence of HAD falling due to ART**
- **Incidence of milder NCI increasing as cohort ages and lives longer**
- **33% of pt without comorbidities had ANI in CHARTER study[3]**
- **Applying the current definition of ANI to the HIV positive population, 16-21% would be classified as abnormal – is the definition too broad?[4]**

1.Hoare J et al, Neurology 2016: 87(1):86-93
2.Barber T et al, AIDS Care 2014: 26(2):160-168
3.Jernigan, T et al, J Neurovirol 2011;17(3):248-257
4.Gisslén et al. BMC Infectious Diseases 2011, 11:356
5. Temereanca A, AIDS Res Hum Retroviruses 2019: doi: 10.1089/AID.2019.0132

showing we care

NHS Guy's and St Thomas' NHS Foundation Trust

Development in adolescence

- **Developing an identity**
- **Become more independent**
- **Consider the future**
- **Adapt to more complex social interactions**
- **Academic pressures**
- **Increasing responsibilities**

NEUROCOGNITIVE CHALLENGE

Executive function processes

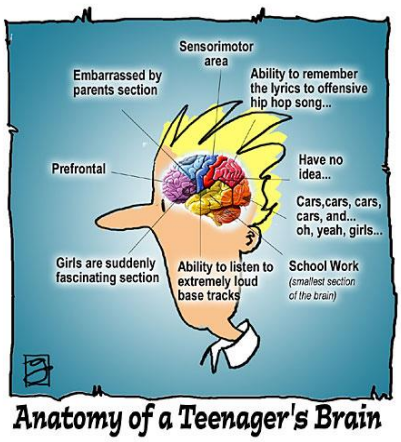
- **Goal setting**
- **Cognitive flexibility**
- **Organising**
- **Prioritising**

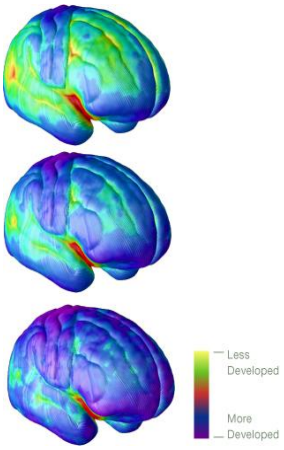
ADHERENCE

showing we care

NHS Guy's and St Thomas' NHS Foundation Trust

Prefrontal cortex maturation - 3rd decade
impulse control, planning, emotional regulation

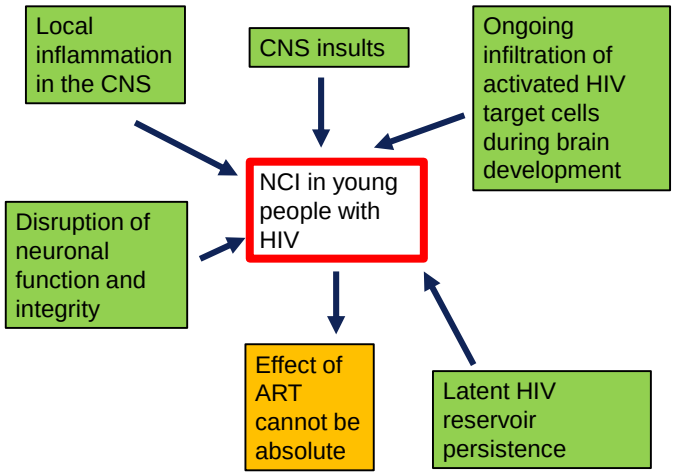




showing we care

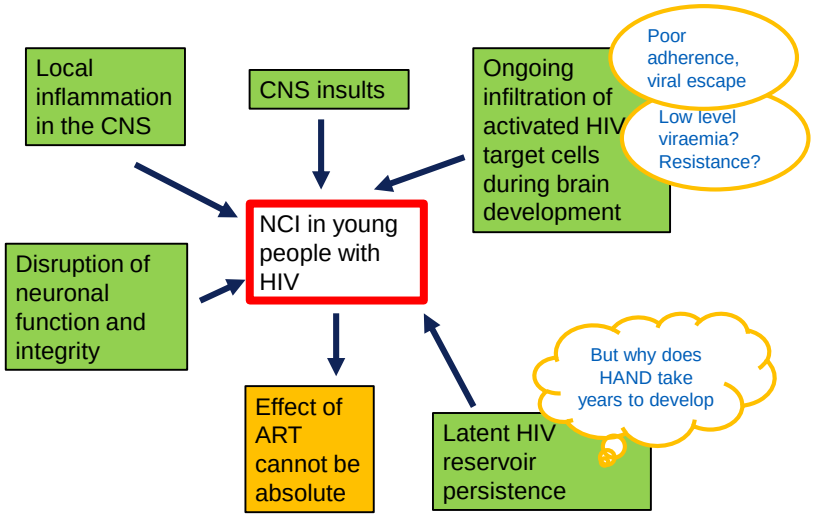
NHS Guy's and St Thomas' NHS Foundation Trust

The science bit



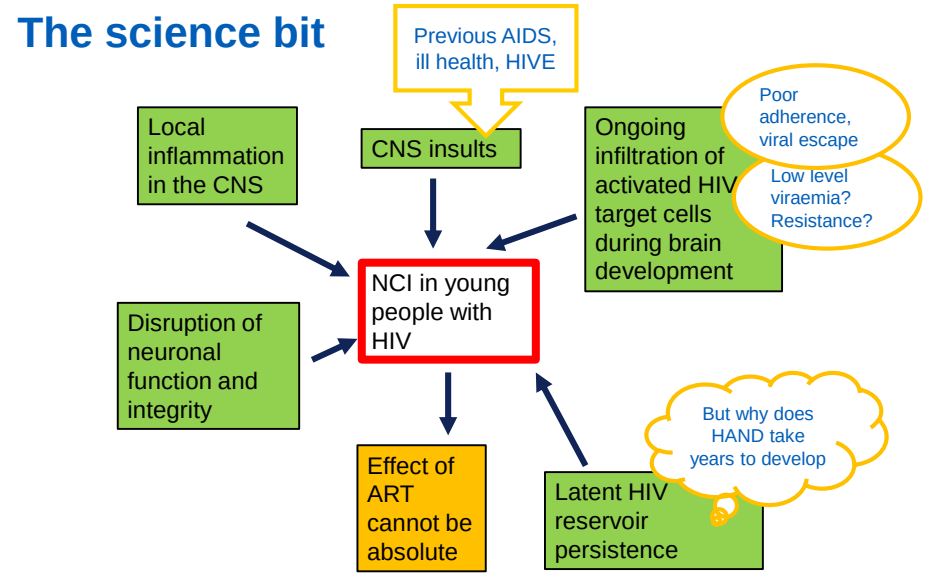
Eggers C, J Neurology 2017: 264: 1715-1727
Benki-Nugent S, Curr Top Behav Neurosci. 2019: doi: 10.1007/7854_2019_102

The science bit



Eggers C, J Neurology 2017: 264: 1715-1727
Benki-Nugent S, Curr Top Behav Neurosci. 2019: doi: 10.1007/7854_2019_102

The science bit

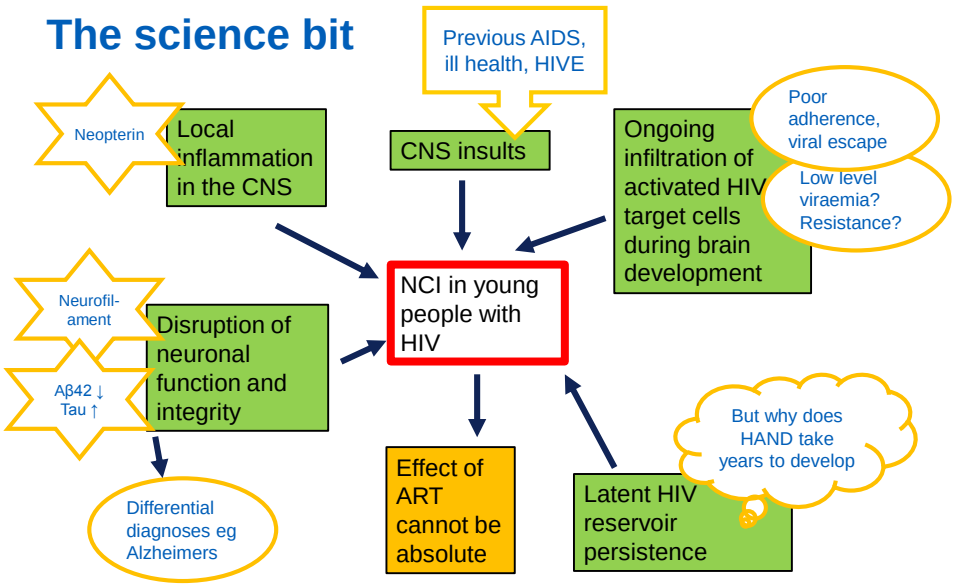


showing we care

Eggers C, J Neurology 2017: 264: 1715-1727
Benki-Nugent S, Curr Top Behav Neurosci. 2019: doi: 10.1007/7854_2019_102

NHS Guy's and St Thomas' NHS Foundation Trust

The science bit

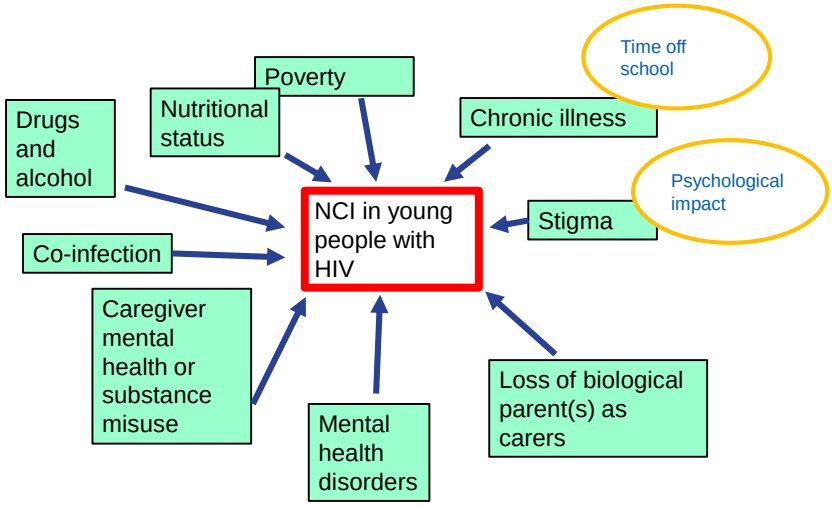


showing we care

Eggers C, J Neurology 2017: 264: 1715-1727
Benki-Nugent S, Curr Top Behav Neurosci. 2019: doi: 10.1007/7854_2019_102

NHS Guy's and St Thomas' NHS Foundation Trust

Confounding factors



showing we care

Laughton B et al. Journal of the International AIDS Society 2013, 16:18603

NHS Guy's and St Thomas' NHS Foundation Trust

Patient M

NHS Guy's and St Thomas' NHS Foundation Trust

- **24-year-old black female**
- **Born in UK**
- **Perinatally acq HIV diagnosed 1995, aged 1**

- **Mother from Ivory Coast**
- **Came to UK 1989**
- **HIV diagnosed late in pregnancy**

Nadir CD4	3	
Lifetime CD4	3 -125	
Current CD4	8	Sep-19
VL	120	Sep-19

Medical History

NHS
Guy's and St Thomas'
NHS Foundation Trust

In childhood

- CMV pneumonitis (1995 at diagnosis)
- Lymphocytic interstitial pneumonia

In adulthood

- Multiple admissions – at least yearly
- Oesophageal candidiasis
- Contact of TB treated with 6 months INH (2008)
- Swine flu (2009)
- Recurrent bacterial pneumonia
- Bronchiectasis
- This year- pharyngeal abcess, perianal abcess, adenovirus requiring admissions

Social history

Childhood

- Paediatric team often noted appearance unkempt
- Social worker and key worker involved
- Police frequently called by neighbours
- Mum went prison for GBH (2009)
- Registered as 'child-in-need'
- Mum kicked her out several times
- Emergency foster care in 2011

Currently

- Smoker 10/day
- Sometimes marijuana
- Lives with and cares for her mum
- Previous male partner - physically violent towards each other. Police involved
- Baby boy born in January 2017 – lives with father's parents
- Male partner (HIV negative) – sex without condoms – would not disclose to him

showing we care

NHS
Guy's and St Thomas'
NHS Foundation Trust

Year	Combination	Reason for Change
1996	Zidovudine	
1996-1999	Zidovudine, lamivudine	Virological failure
1999-2000	Didadosisne, stavudine, nelfinavir	Virological failure
2000- 2006	Abacavir, lamivudine, efavirenz	Poor adherence
2006- 2008	Truvada, kaletra	Poor adherence
2008- 2014	Truvada/Ataz/r	Clinical decision
2014-2016	Truvada/Dar/r	Poor adherence
Feb 2016-June 2016	Dar/r (liquid)	Pregnancy
June 2016-Jan 2017	Truvada/Dar/r	Intensification- pregnancy
August 2016 – Jan 2017	Truvada/Dar/r/Dolutegravir	Intensification- pregnancy
Jan 2017- March 2017	Truvada/Dar/r	Post-natal – deintensification
March 2017- Sept 2017	Truvada/Rezolsta	Rezolsta “too big”
Sept 2017 – Nov 2018	Truvada/Dar/r	1 pill option / adherence
Nov 2018 – current	Symtuza (TAF/FTC/Dar/Cobi)	

Year	Combination	Reason for Change
1996	Zidovudine	
1996-1999	Zidovudine, lamivudine	Virological failure
1999-2000	Didadosisne, stavudine, nelfinavir	Virological failure
2000- 2006	Abacavir,lamivudine, efavirenz	P
2006- 2008	Truvada, kaletra	P
2008- 2014	Truvada/Ataz/r	Clinical decision
2014-2016	Truvada/Dar/r	Po
Feb 2016-June 2016	Dar/r (liquid)	Pre
June 2016-Jan 2017	Truvada/Dar/r	Int
August 2016 – Jan 2017	Truvada/Dar/r/Dolutegravir	Int
Jan 2017- March 2017	Truvada/Dar/r	Post-natal – deintensification
March 2017- Sept 2017	Truvada/Rezolsta	Rezol
Sept 2017 – Nov 2018	Truvada/Dar/r	1 pill option / adherence
Nov 2018 – current	Symtuza (TAF/FTC/Dar/Cobi)	

Resistance mutations: M41L, T215F, E138G, M184V, T215CDGY

Functional swallowing difficulties ‘Conversion disorder’: dysphagia and dysphonia

Pill fatigue

Neurodevelopmental history

- Learning difficulties (2008)
- Dyslexia
- Neuropsychometry 2015:
- Verbal reasoning index <1st %ile)
  Perceptual reasoning index (< 1st %ile)
  Full Scale IQ 56
- ADHD – no formal diagnosis

Psychiatric history

- Aged 15 assessed by adolescent psychiatric team - attended police station "rather kill myself than go home"
- Low mood and suicidal ideation (2015)

Education

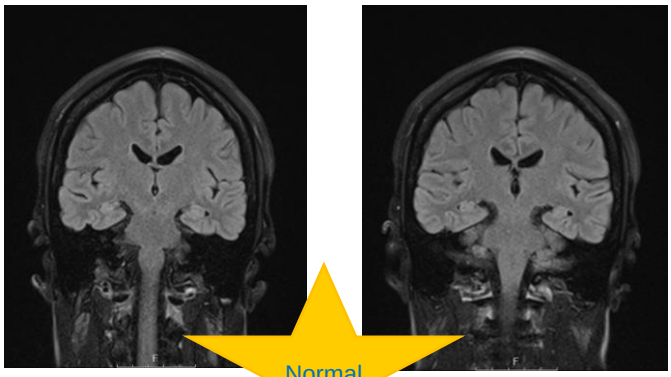
- School for additional learning needs
- Expelled from school aged 14
- Episodes of aggression

showing we care

NHS Guy's and St Thomas' NHS Foundation Trust

MRI BRAIN

NHS Guy's and St Thomas' NHS Foundation Trust



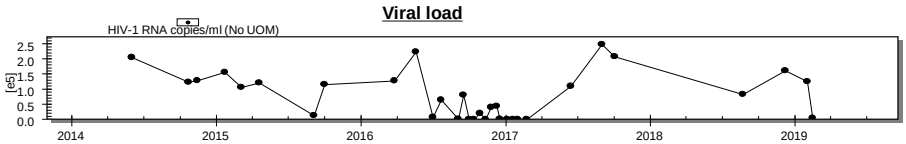
Normal

2014 2018

Adherence

Guy's and St Thomas' NHS Foundation Trust

- **Non adherent to ART except during pregnancy and brief periods in childhood**
- **Previous child protection plan for adherence**
- **HIV Neurorehab centre admission for DOT, but rebound afterwards**
- **Swallow investigated (normal)**
- **Now on one pill/day, Symtuza**
- **Resistance precludes use of cabotegravir / rilpivirine (injectable)**
- **Resistance mutations M41L, T215F, E138G, M184V, T215CDGY**



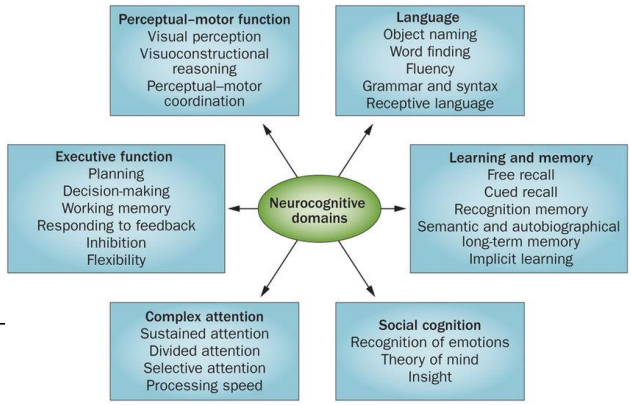
Patient M – learning points

- **Multiple confounding factors contributing to NCI**
- **Establishing ability to consent to sex and understanding of possibility of transmission**
- **M has capacity to make decisions**
- **Cannot resolve NCI without ART**
- **NCI may contribute to poor adherence**
- **Solution not in sight –**
  - How can we help M adhere and maintain VL<20?
  - Community CNS
  - Daily texts / phonecall
  - Psychology support

showing we care

Diagnosis of HAND

- **Requires testing in at least 5 domains**
- **Test performance at least 1 SD <mean in at least 2 of these domains**
- **MUST exclude organic causes**
- **MUST exclude mood disorders using validated scales**
  - GAD-7 for anxiety
  - PHQ-9 for depression



showing we care

Definitions in HAND

Table 1 Criteria for HIV-associated neurocognitive disorders [8]

HAND	HIV-associated neurocognitive disorders
ANI	**HIV-associated asymptomatic neurocognitive impairment**
	Cognitive impairment involving at least two cognitive domains (performance of at least 1 SD below the mean for norms on neuropsychological tests)
	The cognitive impairment does not interfere with everyday functioning.
MND	**HIV-1-associated mild neurocognitive disorder**
	Cognitive impairment involving at least two cognitive domains (performance of at least 1 SD below the mean for norms on neuropsychological tests)
	The cognitive impairment produces at least mild interference in daily functioning
HAD	**HIV-1-associated dementia (HAD)**
	Marked cognitive impairment involving at least two cognitive domains (performance of at least 2 SD below the mean for norms on neuropsychological tests)
	The cognitive impairment produces marked interference with day-to-day functioning

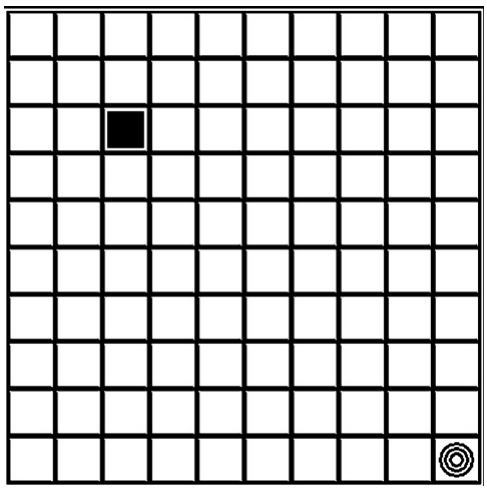
Neurocognitive testing

- **Neurocognitive testing takes many forms**
- **6 Domains**
- **Systematic review of 23 articles in SSA**
  - Most using color trails test 1 and 2
  - WAIS Digit symbol test
  - Translated into local languages and adapted to be culturally appropriate
  - Lack of normative data

Domain	Test
Executive function	Groton Maze
	Color Trails 2 (normative data for age 18-29 years, with 7-9 years of education)
Speed of info. Processing	Detection task (age adjusted)
	Color Trails 1 (normative data for age 18-29 years, with 7-9 years of education)
Attention/working memory	Identification Task (age adjusted)
	Coding (raw no. correct) (normative data not available so omitted from NPZ-6)
Learning	One card learning (age adjusted)
	International shopping list
Memory	International shopping list delayed
	One back task
Fine motor skills	Pegboard dominant hand (age/sex adjusted)
	Pegboard non-dominant hand (age/sex adjusted)

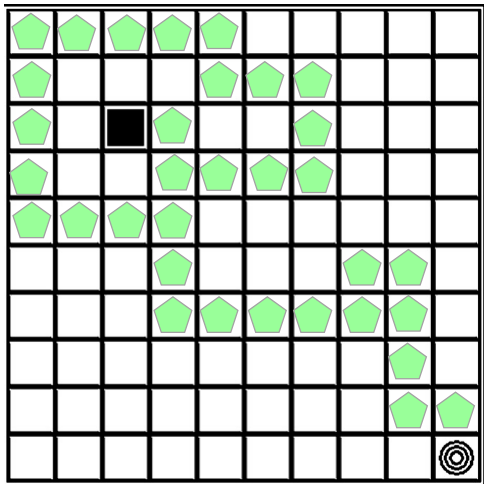
Nyamayaro P, The Clinical Neuropsychologist 2019: doi: 10.1080/13854046.2019.1606284
Judd A, CID 2016: 63;1380-1387

Groton Maze – Executive function

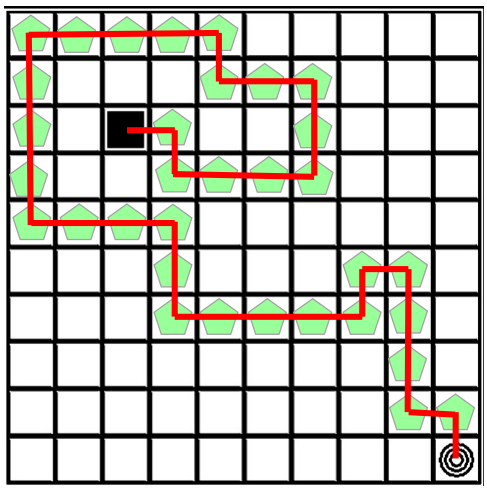


showing we care
NHS Guy's and St Thomas' NHS Foundation Trust

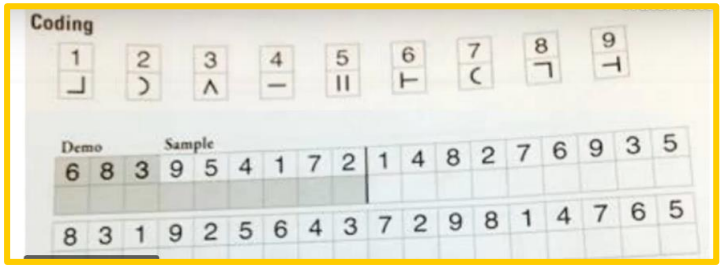
Groton Maze – Executive function



Groton Maze – Executive function



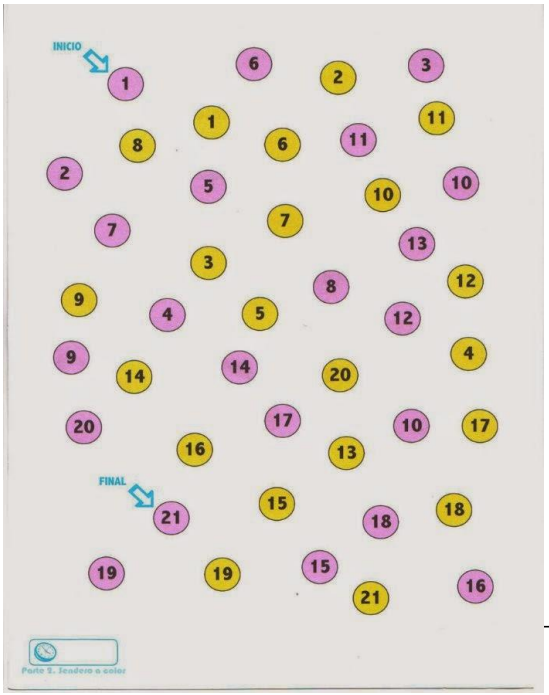
WAIS coding test



Assesses working memory, processing speed

showing we care

NHS Guy's and St Thomas' NHS Foundation Trust



Color Trails

Test executive function and processing speed

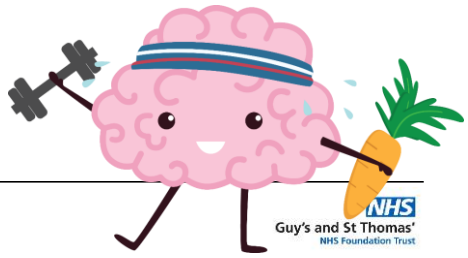
NHS Guy's and St Thomas' NHS Foundation Trust

Activity time

Your task is to complete a color trail B assessment

This test will examine your executive functioning and processing speed

On this page are some numbers and letters. Begin at 1 and draw a line from 1 to A, A to 2, 2 to B, and so forth until you reach the end. Remember first you have a number, then a letter, then a number, and so on. Draw the lines as fast as you can.



showing we care

Guy's and St Thomas' NHS Foundation Trust

Results

How did you do??

Time Taken	Cognitive Age
<50 sec	20
50-54	30
55-60	40
61-65	50
66-80	60
>81	70

showing we care

Guy's and St Thomas' NHS Foundation Trust

What does it all mean? Functional manifestations

- **Poor executive function means:**
  - Difficulty thinking flexibly, prioritising, working towards goals, paying attention, staying focused
  - Academic achievements compromised
  - Adherence
- **Poor processing speed means:**
  - Takes longer to take in information
  - Multi step tasks pose a problem
  - More time in exams?
  - Difficulty in applying for jobs and benefits

There may be no effect on functional ability – what is the significance?

AALPHI

MRC Medical Research Council

- **'Adolescents and Adults living with perinatal HIV infection'**
- **UK study comparing young adults PAHIV with HIV – but exposed adolescents**
- **Age range: 13-21 PAHIV, 13-23 HIV-**
- **300 PAHIV**
- **100 HIV – but 'exposed':**
  - 50% mother has HIV
  - 44% sibling has HIV (many in study)
  - 6% close friend has HIV
- **Impact of lifelong HIV and long term ART on cognitive function, psychosocial issues, sexual and reproductive health, medical outcomes.**

Clinical Infectious Diseases 2016;63(10):1380-1387

AALPHI

- **Factors considered included:**
  - HIV status
  - CDC stage
  - Sex, Age, Ethnicity, Birth outside the UK
  - Psychosocial
  - Environmental

- **HIV factors:**
  - Year first presented for treatment
  - Age at HIV diagnosis
  - Age at ART start
  - Current ART status
  - Current Efavirenz use
  - Nadir and most recent CD4 counts
  - Median cumulative years with VL<400
  - CDC stage
  - History of any encephalopathy diagnosis

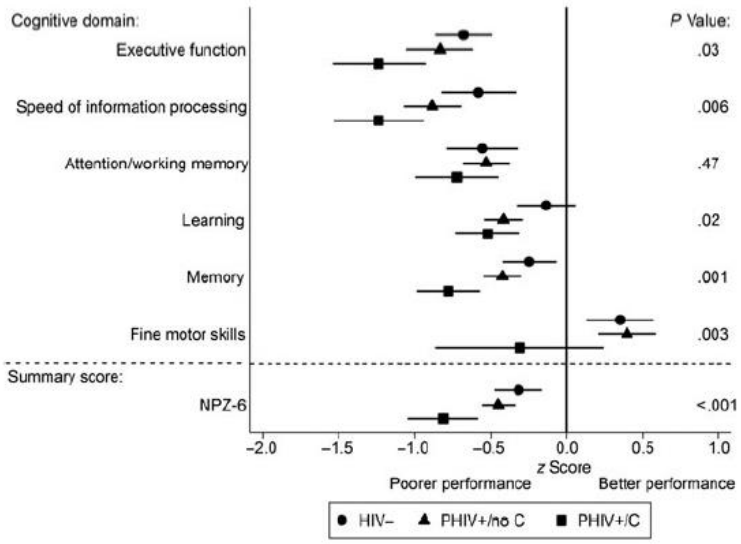
AALPHI

- 296 PAHIV, 97 HIV-
- Sociodemographics were similar
- Median age 16 across both groups
- Mostly black African and born outside the UK
- Most attending school and living with parents
- 24% HIV- had experienced parental death vs 36% PAHIV
- 27% PAHIV had CDC stage C diagnoses in the past – these pt presented at a younger age, and started ART earlier in life

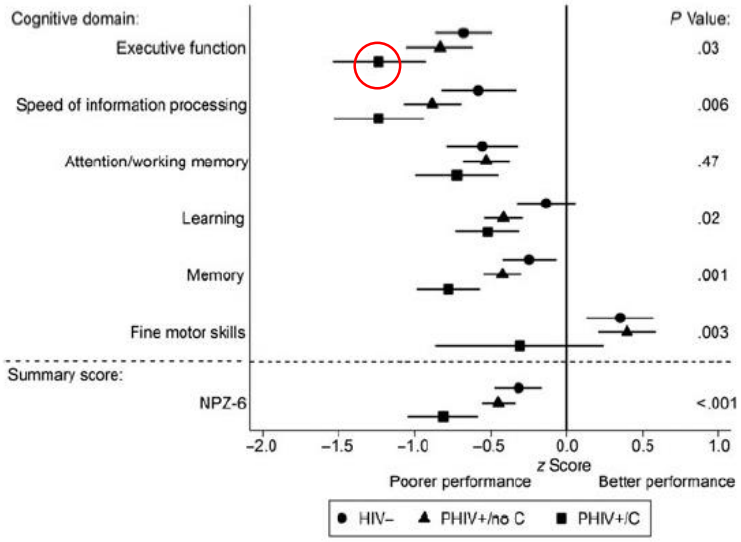
Cognitive impairment in:
61% PAHIV + CDC stage C
46% PAHIV no CDC stage C
40% HIV-

showing we care
Guy's and St Thomas' NHS Foundation Trust

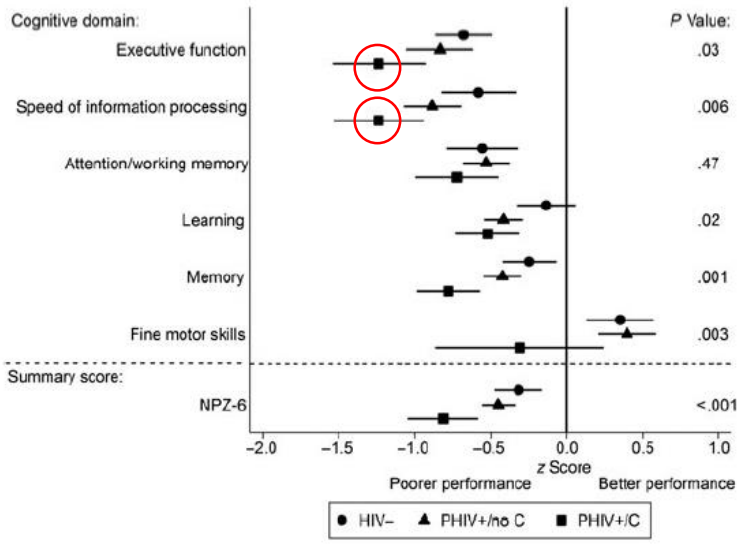
AALPHI



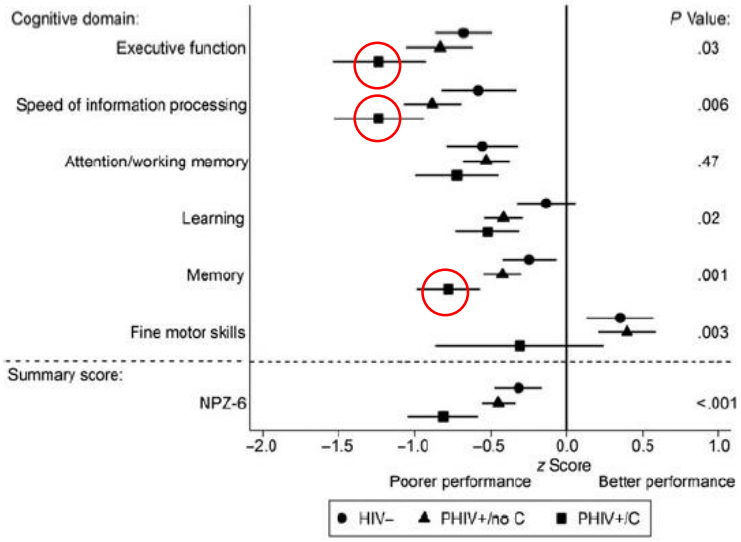
AALPHI



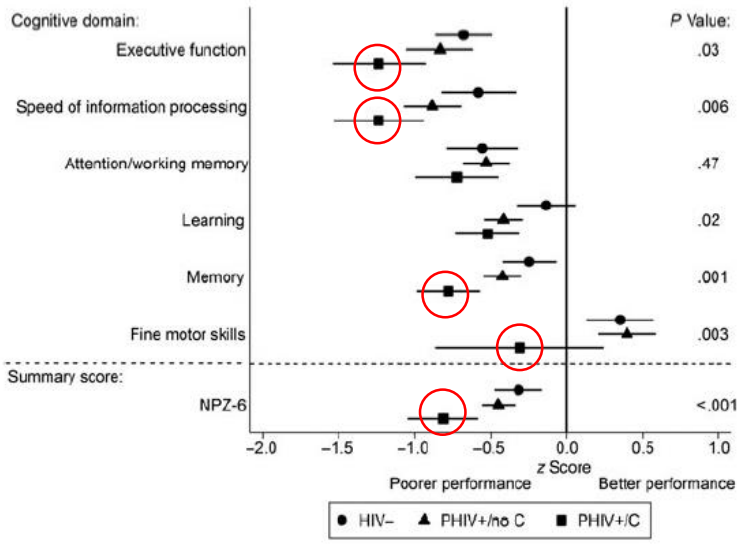
AALPHI



AALPHI



AALPHI



AALPHI

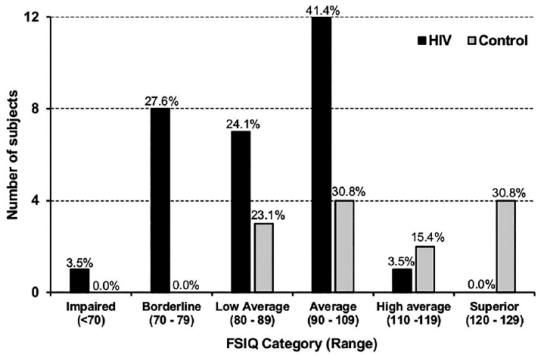
- NPZ-6 scores:
  - Improved with age – maturation and develop compensatory skills
  - Were lower in Black Ethnicity
  - Were lower in worse depression scores

- No difference in cognitive scores between PHIV with no hx AIDS and HIV- cohort, but both performed less well than normative data.
- Those with a hx of AIDS at higher risk of neurocognitive issues
- Parental death, more adult carers, and ever having used drugs or alcohol were associated with lower NPZ-6 scores in univariate analysis (but not in multivariate analysis – confounding factors)

Other small cohort studies concur

- Well matched cohorts (HIV exposed but uninfected)
- Similar results
- Longitudinal data shows improvement over time in most domains during progression through adolescence

Robbins R, AIDS Care 2019: https://doi.org/10.1080/09540121.2019.1626343



Willen E, AIDS Care 2017; 29(3): 387-393

showing we care

NHS Guy's and St Thomas' NHS Foundation Trust

Management of HAND

- **Look for CNS viral escape**
- **Optimise ART**
- **Treat concurrent mental health disorders (may be a feature of HAND)**
- **Evidence for computerized cognitive rehabilitation training.**
  - Preliminary positive results in Uganda
- **Caregiver training on practical strategies to encourage developmental milestones**
- **Address other risk factors (BP, chol, smoking, co-infection)**
- **Remove toxicities – Efav? Alcohol, Drugs**

showing we care

Boivin MJ, Neuropsychology. 2010;24(5): 66773.

NHS Guy's and St Thomas' NHS Foundation Trust

CPE score

	4	3	2	1
NRTI's	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir
NNRTI's	Nevirapine	Efavirenz Etravirine	Rilpivirine	
PI's	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase inhibitors	Dolutegravir	Raltegravir	Elvitegravir	

A value of 1, 2, 3, or 4 is assigned to the different antiviral substances (first line). The CPE values of a patient's cART components are summed up to arrive at the CPE score. A high score stands for better penetration into the CNS

Evidence is scanty, but worth considering?

Letendre S, Clin Infect Dis. 2018;67(8):1182-1190

Ethics of screening

- **Repeated testing – practice effect**
- **Diagnosis of ANI may cause anxiety with no practical benefits**
- **But diagnosis may make functional intervention possible**
  - School help, extra time in exams
  - Applying for benefits and housing, adjustments in the workplace
- **NCI may affect adherence – targeted support ?delayed transition**
- **CHIVA recommend screening at key educational milestones, and before transition**
- **EACS recommend screening but don't specify frequency**
- **Screening for mental health issues incl PTSD**

showing we care

NHS Guy's and St Thomas' NHS Foundation Trust

Overview

- **Evidence that there is NCI in young adults with PHIV, particularly in the context of AIDS and HIVE**
- **Multiple biological mechanisms and psychosocial mechanisms**
- **Executive function and processing speed particularly affected**
- **Impact on academic achievement and ability to work, QOL**
- **It's not all bad news – some of our pt similar to well matched HIV-controls, and improvement over time has been shown**
- **Optimising HIV control in plasma and CNS, treating mental health issues**
- **Screening suggested in this population as targeted intervention may improve QOL and achievement**
- **Planning services to look after pt with NCI as this cohort age**

Thank you to Dr Naomi Fitzgerald who contributed case study slides

?

showing we care
NHS Guy's and St Thomas' NHS Foundation Trust