Neurocognitive Issues among Aging HIV Positive Adults

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Edwina Wright
FRACP PhD

The Alfred Hospital, Burnet Institute, Monash University,
Peter Doherty Institute, Melbourne, Australia
Conflicts of Interest

- Gilead Sciences donated study drug for VicPrEP
- Receipt of unrestricted research funds
  - Gilead
  - Abbott
  - Janssen Cilag
  - Boehringer Ingelheim
- Funding for consultancy work, lectures and developing educational resources that has been used for research purposes only
  - ViiV, Merck, Gilead, and Abbott
Overview

AIM

Review neurocognitive issues in ageing HIV+ adults

• Acute HIV infection
• START Neurology Substudy
• Factors that influence neurocognitive performance (NCP) in virologically suppressed populations, diagnosis and management

The effect of age highlighted where possible
**HIV-1 Associated Neurocognitive Disorders: HAND**

**Asymptomatic Neurocognitive Impairment (ANI)**
Asymptomatic
Impairment ≥ 2 domains, ≥ 1SD below the mean for matched controls

**Mild Neurocognitive Disorder (MND)**
Mild symptoms but still working and active
Impairment: same as ANI

**HIV-Associated Dementia (HAD)**
Significant impairment ADLs
Impairment ≥ two domains, ≥2SD below the mean for matched controls

*Caveats: no delirium, no confounding conditions*

HAD: Synopsis

Clinical

Screening
In practice, done for patients with cognitive complaints

Pathogenesis

Caudate, Globus pallidus, Putamen

Diagnosis of Exclusion

Treatment
Combination Antiretroviral Therapy

HAD: Synopsis

Clinical/Host/Viral Factors

- Nadir and current CD4 cell count
- **Older age** at time of seroconversion
- **Diabetes**: OR 5.34 (1.66-17.7, p<0.01)
- Host genotype
  - \( MCP-1-2578G \) RH 4.5 (1.36-16.28, p 0.0015)
  - \( CCL3L1^{low}-CCR5^{det} \) RH 3.1(1.33-7.6, p 0.009)
  - \( DARC-46 C/C \): \( \downarrow \) time to HAD
  - ApoE e4/e4: variable findings
  - TNF\( \alpha \)308 A allele: OR 5.5 (1.8-17.0)
- Injecting drug use, female gender
- HAD subtype D> subtype A

HAD: Synopsis

**Treatment of HAND with cART:** >50% patients improve ≥ 18/12

**Theory:** Regimens with high CNS penetration => lower CSF viral load => improved neurocognition

**Metric:** CNS penetration effectiveness (CPE) score

**Evidence:**

Meta-analysis 16 observational studies
- 6/6 => ↑ CPE regimens => ↑ cognition or ↓ CSF viral load
- 2/6 studies were adequately powered

One RCT: No difference in NCP at week 16 between patients receiving high vs low CPE regimens. Ceased- futility

**HIV Causal Collaboration:**
- 62,938 HIV+ patients USA & Europe followed 37 months
- High CPE scores increased risk of HAD by 70% in those initiating ART, but not CNS OIs
- ? Toxicity, poor adherence, channeling bias
Antiretroviral Treatment Coverage

- 36.7 million people are HIV+
  - 40% of PLWH do not know their HIV status
  - 62% of PLWH are not virally suppressed

In 2015 WHO recommended that all HIV+ people should be offered ART

ART in Early HIV infection

Massive depletion CD4+ T cells gut

CNS: ↑ levels CSF NFL & altered ratios CNS metabolites brain MRI scan²

SEARCH: Acute HIV infection³
- 53% mild neurological findings
- Age ≠ neurological findings

SEARCH: Acute HIV infection⁴
- cART vs cART+ raltegravir & maraviroc
  - No difference NCP
  - Mean age: 27 years SD ± 7

HIV reservoirs => HIV cure⁵

START Neurocognitive Substudy

HIV-infected, ARV naïve, CD4+ cell counts > 500 cells/mm\(^3\)
Co-enrolled in START Study
N=600

Early ART Group
N=300
Immediately initiate ART

Deferred ART Group
N=300
Defer ART until CD4+ <350 cells/mm\(^3\) or symptoms develop

Funding: NIMH, NINDS and NHMRC
**Change in QNPZ-8 from baseline, 95% CIs**

Difference in QNPZ-8 change
Immediate versus Deferred arms
-0.017 (95% CI -0.061 – 0.028)
P-value = 0.46
Findings START Neurology Substudy

1. ART deferral to <350 CD4+ cells is not associated with poorer NCP over 3 years of follow-up in START

2. Immediate ART at > 500 CD4+ cells is not associated with a cost in terms of poorer NCP (i.e. CNS toxicity)

3. No preferential benefit of either strategy for the NCP of older people

1. Use of ART regimens with high CPE scores neither benefitted, nor disadvantaged either treatment group
HAND in HIV virologically suppressed populations

*NEAD Cohort: 21% n=203

#CHARTER Cohort: 30%, n=1,555

^ACTG longitudinal linked randomised trial (ALLRT) study, 26% baseline, n=1,160 patients

#Sydney 18%, n=116

#BK 37%, n=64

#Geneva 72%, n=200

*Prospective cohort study; #Cross-sectional study; ^ RCT

What proportion of your patients who are fully virologically suppressed may have HAND?

≈30%

ANI > MND >> HAD
Why is HAND so prevalent in virologically suppressed populations?

HAND
• Legacy effect?
• Poor CNS HIV control?
• Ongoing CNS parenchymal infection +/or inflammation?

HAND plus or HAND x
• Cardiovascular risk factors?
• Ageing?
• cART toxicity?
• Neurodegeneration?

Mothobi and Brew, Curr Opin ID 2012
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Causes of HAND in virologically suppressed populations: the evidence

• Legacy effect?
  – Can only determine by monitoring change over time

• Poor CNS HIV control?
  – Uncommon: ≈ 10% of patients on cART detectable CSF VL

• Ongoing CNS infection +/- inflammation?
  – Progression of HAND despite full CSF suppression
  – Recent pilot studies ARV intensification with maraviroc or paroxetine and fluconazole showed improved NCP

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Causes of HAND in virologically suppressed populations

• Several CV risk factors associated with ↓NCP
  – Diabetes, low eGFR, carotid intima media thickness, prior CVD, BMI, high total cholesterol and hypertension\(^1,2,3,4\) => brain injury and inflammation\(^5\)
  – No evidence reversal of CV risk factor improves NCP, yet

• Ageing
  – Variable findings re accelerated ageing in CNS\(^6\)
  – >3,000 participant cohort study: odds NCI \(\uparrow\) 20% for each decade after age 50 years\(^7\)
    • Effect of underlying CV risk factors?
    • cART toxicity?

Causes of HAND in virologically suppressed populations

• cART toxicity
  – Observed cell culture & animal models\(^1,\,2\)
  – cART disrupts microglial phagocytosis of amyloid in brain and increase amyloid \(\beta\) generation by neurons\(^3\)
  – One RCT: ↑ CPE regimens may be CNS toxic\(^4\)
  – Efavirenz\(^5\), raltegravir\(^6\) and dolutegravir\(^7\) - CNS AEs/toxicity
  – ARV duration: may play role\(^1\), but not seen in recent work\(^8,9\)

\(^1\) Underwood, Robertson & Winston, AIDS 2016
\(^2\) Vivithanaporn et al, AIDS 2017
\(^3\) Guinta et al, Mol Brain 2011
\(^4\) Marra et al, Neurology 2009
\(^5\) Ma et al, J Neurol 2016
\(^6\) Maddedu et al, AIDS 2012
\(^7\) Hoffman et al, HIV Medicine 2017
\(^8\) Gott et al, PLoS One, 2017
\(^9\) Coban et al, AIDS 2017
Causes of HAND in virologically suppressed populations

• Neurodegeneration?
  – Clinical, CSF, histopathological data suggesting that AD and PD may be more prevalent
  – *No evidence from neuropsychological testing that older HIV+ people* perform more like HIV-people with Alzheimer’s disease
  – Mostly cross-sectional studies

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Management of HAND in virologically suppressed populations

HAND

• Legacy effect
  – Symptoms stable => observe & annual review

• Poor CNS HIV control with CSF escape
  – Switch to higher CPE cART regimen or to active cART regimen if resistance present

• Ongoing CNS parenchymal infection+/or inflammation
  1. Observe and review
  2. Intensify cART regimen: ?maraviroc
  3. Switch to higher CPE score regimen?
Management of HAND in virologically suppressed populations

**HAND plus or HAND x**

- **Cardiovascular risk factors?**
  - Optimise management of cardiovascular risk factors

- **Ageing?**
  - Console your patients!
  - Optimise exercise, diet, sleep, decrease alcohol use

- **cART toxicity?**
  - ? temporal relationship to new cART regimen? Chronic cART use?

- **Neurodegeneration?**
  - Believe your eyes despite patients’ youth and investigate accordingly

Monroe et al. HIV Med 2017
Summary

Older age at time of HIV infection is a risk factor for developing HIV-associated dementia.

Age is not associated with greater/lesser likelihood of neurological findings during acute HIV infection.
Summary

- **Patients > 500 CD4 cells, no evidence that immediate or deferred treatment preferentially benefits NCP**
- **No benefit/disadvantage high CPE score in either treatment strategy**
- **No benefit/disadvantage in older populations of either strategy**

Recent evidence from a large cohort study showing older age is associated with greater risk of developing NCI
Summary

**ART CNS Toxicity**
- Suggested in US Causal Study, not observed in START Neurology Substudy
- Some populations may be more vulnerable—older/those with CVD
- Duration and type of ART may be important

More studies
- Impact of modifying CV risk factors
- Intensifying cART regimens
- ART toxicity
- The impact of age

Upon neurocognitive performance of our ageing patients
Acknowledgments

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Thank you!!!
END