Neurocognitive impairment in HIV

Dr Dami Collier
Introduction

• Prevalence of HIV associated neurocognitive disorder (HAND)
• Pathogenesis of HIV CNS infection
• CNS as a reservoir for HIV in mature infection
• Clinical case
• Gaps in knowledge and research priorities
• HERB study
Clinical syndromes

- HIV encephalitis
- HIV associated dementia- Pre-HAART
- HIV Associated Neurocognitive Disorder (HAND)- Post-ART
- Cerebral small vessel disease

- PI/ABC/d4T- associated diabetes and dyslipidaemia
- EFV-Neurotoxicity
Definitions

- **HAND**

<table>
<thead>
<tr>
<th>Asymptomatic Neurocognitive Impairment (ANI)</th>
<th>Mild neurocognitive Disorder (MND)</th>
<th>HIV- associated Dementia (HAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No interference with ADLs</td>
<td>At least mild interference with ADLs</td>
<td>Marked interference with ADLs</td>
</tr>
<tr>
<td>At least 1.0 SD below mean of normative population in at least two cognitive domains</td>
<td>At least 1.0 SD below mean of normative population in at least two cognitive domains</td>
<td>At least 2.0 SD below mean of normative population in at least two cognitive domains</td>
</tr>
</tbody>
</table>

- **CSF escape**: The occurrence of detectable HIV RNA in CSF when undetectable in plasma

- **CSF discordance**: CSF VL greater than 0.5 or $1 \log_{10}$ of the plasma VL
HAND Prevalence

• Pre-ART up to 50% of those with Advanced AIDS presented with HAD before they died\(^1\)

• Up to 50% of PLHIV in Europe and the USA might have some cognitive impairment\(^2,3\)

• In Africa- some limitations to estimates

• Screening tools- IHDS 4.8-80% \(^4\)

• NP testing- 60-76% (51-67% ANI/MND) \(^5,6,7\)

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6 Hakkers et al. The Montreal Cognitive Assessment-Basic (MoCA-B) is not a reliable screening tool for cognitive decline in HIV patients receiving combination antiretroviral therapy in rural South Africa. Int J Infect Dis. 2018;67:36-40.

HIV entry into the CNS occurs early in infection. How does the virus gain entry into the CNS?

A) Direct entry of free HIV particles transcellularly through the BBB and BCSFB
B) Through tight junctions in the BBB and BCSFB
C) Hitch-hiking in CD4+ T cells
D) Hitch-hiking in activated monocytes
E) All of the above

BBB- Blood brain barrier; BCSFB-Blood CSF Barrier
HIV entry into the CNS occurs early in infection. How does virus gain entry across the BBB or BCSFB into the CNS?

A. Direct entry of free HIV particles transcellularly through the BBB and BCSFB
B. Through tight junctions in the BBB and BCSFB
C. Hitch-hiking in CD4+ T cells
D. Hitch-hiking in activated monocytes
E. All of the above
Pathogenesis of HAND

- CNS is a sanctuary site
- Loss of the BBB/BCSFB integrity
- Permitting viral entry in primary infection => latent reservoir
- Progressive HIV infection and persistent immune activation => chronic neuronal injury
- HIV is neurotoxic
- Legacy effect of early CNS damage
- Poor drug penetration
- ARV neurotoxicity
- Comorbidities
- Drug and Alcohol
CNS compartmentalisation

**CNS latent reservoir**

- Non-replicating
- Latently infects CD4 memory T cells (other long-lived cells)
- Occurs in primary infection
- Integrated provirus
- Clonal expansion
- Can be activated and cause ongoing infection
- Source of rebound on treatment discontinuation

**Viral escape- (low level replication)**

- Replicating
- Anatomical sites where drugs are excluded
- Cell-to-cell spread
- Active replication in the CNS evidenced by high VL in the CSF in the presence of suppressed plasma VL
- Up to of 10% of suppressed PLHIV
- Risk factors- low nadir CD4, long duration of ART, hx of poorly controlled HIV, CPE score, DRMs, PI-based ART

CNS compartmentalisation

Sturdevant Plos pathogens 2015
What proportion of HAND is attributable to CSF escape/discordance?

A) 5-10%

B) 10-40%

C) CSF escape is not a cause of HAND

D) Unknown
Clinical case

- 35 yo female

- Diagnosed in 2006

- Nadir CD4 8, peak VL 43 789

- Initiated ART in 2008 with D4T, 3TC, NVP

- 2010 =>TDF, 3TC, LPV/r due to VF

- 3TC=>FFC due to programmatic switch

- PC: “Wanted to quit her job”

- 2013 chronic headaches and not able to concentrate and perform expected tasks

- No focal neurological deficit

- IHDS: 6/12

- CSF: prot $0.51g/L$, glu 3.4 (blood glu 5.0), cell count 36 - 2 PMN, **14 lymphocytes**, 20 RBC, CRAG neg

- CSF VL: 30 180, Plasma VL: 3831
Plasma genotypic resistance testing - could not be amplified

CSF genotypic resistance testing -
- NRTI - None
- NNRTI - G190A
- PI - None

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>FTC</th>
<th>EFV</th>
<th>Lopinavir</th>
<th>Ritonavir</th>
<th>3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
</tr>
<tr>
<td>CSF</td>
<td>&lt; 0</td>
<td>1.01</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
<td>&lt; 0</td>
</tr>
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</table>
Prevalence of CSF escape/discordance

• Eden JID 2010. 69 asymptomatic patients on suppressive ART. 10% with CSF discordance.

• Rawson. J Infect. 2012. 140 patients. CNS escape in 21% subjects overall and in 9/69 (13%) of those on ART with undetectable plasma HIV RNA. Associated with the CPE score

• Kugathasan & Collier CID 2017. 146 patients. 16% with CSF discordance and 6% with CSF escape.

• Mukherji CID 2018. Meta-analysis of 3 large cohorts; CHARTER, NNTC, HNRC. 1063, 7% with CSF escape.
CSF escape and resistance

- Canestri CID 2010. 11 patient with acute and subacute neurological dysfunction
  - Suppressive ART
  - Viral escape
  - 7/8 with genotypic resistance

  - 6 of 7 CSF HIV-RNA strains had genotypic resistance
  - Associated with more frequent treatment interruption and elevated neopterin levels

- Beguelin JIAIDs Soc 2014- 1 case with CSF resistant virus

- Nightingale J Neuro 2016. PARTITION study. 143 patients. 18% of patient with LLV had CSF discordance, 6/7 with discordance had resistant mutations

- Mukherji CID 2018. Meta-analysis of 3 large cohorts; CHARTER, NNTC, HNRC. 1063, 7% with CSF escape. M184V mutation to RTI was found more frequently in the plasma and CSF samples of those with CSF escape compared to those without escape
Drug-dependent fitness landscape

At low drug concentration, the advantage of being drug-resistant does not overcome the cost of resistance.

At intermediate drug concentration, drug-resistant virus outcompetes drug-sensitive virus and continuously replicates.

At high drug concentration, not even drug-resistant virus can grow.

Cost of resistance; in the absence of drug, drug-resistant virus is less fit than drug-sensitive virus.

## Clinical spectrum of CSF escape/discordance

<table>
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<th>Table 1</th>
<th>Classification of CSF escape</th>
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<tbody>
<tr>
<td><strong>Biology</strong></td>
<td><strong>Neurological presentation</strong></td>
</tr>
<tr>
<td>Asymptomatic CSF escape</td>
<td>Equivalent to plasma blips? Stable or asymptomatic; incidental finding in cohort or other study</td>
</tr>
<tr>
<td>Neuro-symptomatic CSF escape</td>
<td>Virological failure in CNS compartment New or progressive CNS symptoms and signs</td>
</tr>
<tr>
<td>Secondary CSF escape</td>
<td>CNS viral replication related to another infection with inflammation Reflects provoking infection</td>
</tr>
</tbody>
</table>

*Occasionally higher

CSF escape and HAND

• Mukherji CID 2018. Meta-analysis of 3 large cohorts; CHARTER, NNTC, HNRC. 1063, 7% with CSF escape. Neurocognitive deficits were more frequent in participants with CSF escape (35% vs 20%)

• Anderson Antiretroviral Therapy 2017. LLV at any level was associated with worse neurocognitive performance and the presence of CSF escape at first or second visit was associated with a decline in neurocognitive performance compare to those without CSF escape
What proportion of HAND is attributable to CSF escape/discordance?

A) 5-10%

B) 10-40%

C) CSF escape is not a cause of HAND

D) Unknown
Clinical biomarkers

- CSF VL - untreated HIV, VL is 1 log lower in CSF than in blood
- Neurofilament light chain (NFL) – neuronal injury, elevated in PHI
- Neopterin - macrophage activation, elevated asymptomatic CSF escape
- Plasma and CSF NFL highly correlated
- Immune response in neurosymtomatic CSF escape is compartmentalised
- MRI imaging

Management

• cART has improved neuropsychological functioning and reduced neurological abnormality

• No evidence-base to guide interventions

• Exclude OIs and consider comorbidities

• An assessment for CSF HIV resistance should be undertaken and ART optimised to the resistance profile

• Optimise ART to improve brain penetration – AZT, DTG

British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015

Research Gaps

1. What is the prevalence of HIV Associated Neurocognitive Disorder in this population?
2. What is the contribution of CSF escape to NCI in this SA cohort?
3. Is there independent replication in the CNS?
4. Does suboptimal drug penetration into the CNS lead to acquisition of drug resistance in these CSF escape viruses?
5. Is independent replication associated with emergence of peripheral drug resistant strains in ART experienced individuals?
6. What are the clinical correlates of CNS HIV-1 escape?
Study Aim

• To investigate the occurrence of replication of HIV in the brains of South African patients with NCI

• To investigate if the viruses in the brain ≠ viruses in the blood

• To study the evolution of drug resistance in CNS compartmentalised virus and whether compartment shifts occur from the CNS to the peripheral blood in HIV-1 subtype C

• To discover the clinical markers of replicating HIV-1 in the brain?
Study description

• *Design*: Longitudinal cohort study

• *Setting*: RK Khan ARV clinic, Durban

• *Inclusion*: NCI OR headaches OR fever who require a lumbar puncture (LP) for clinical reasons, >18 years, on ART for ≥ 1 year

• *Exclusion*: coma, seizure, neurological deficit indicating a space occupying lesion in CNS, overt CNS diseases of infectious aetiology (such as TB, cryptococcal or bacterial meningitis) or CNS malignancy, platelet <100, INR >1.3

• Sample size: 200
542 screened

39 symptomatic

510 asymptomatic

4 excluded
- 3 uncontrolled epilepsy
- 1 brain tumour

14 recruited

4 Without CSF results
- 3 unsuccessful LP attempts
- 1 incidental focal weakness

2 with HIV in CSF

8 Without HIV in CSF
Thank you for your attention