AWACC

ANNUAL WORKSHOP ON ADVANCED CLINICAL CARE - AIDS

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

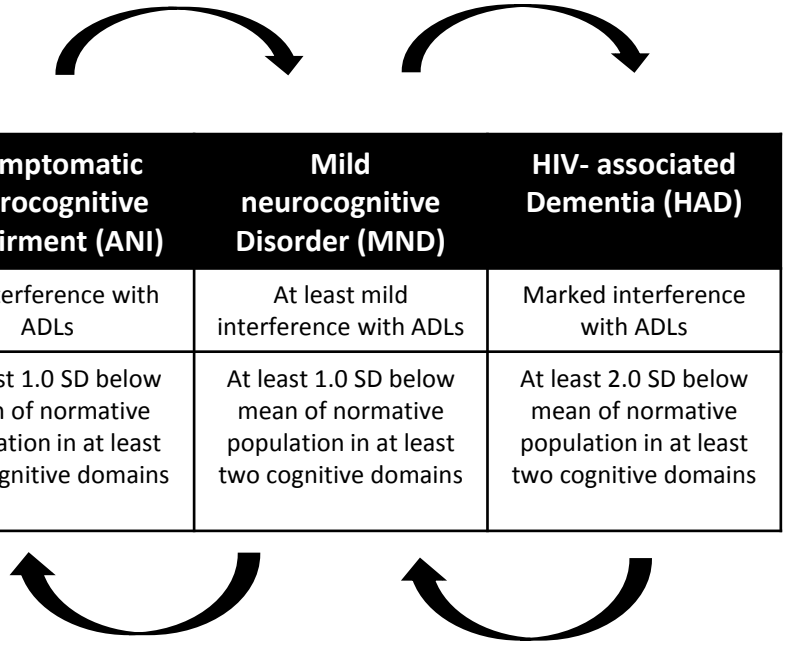
Clinical syndromes

- 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

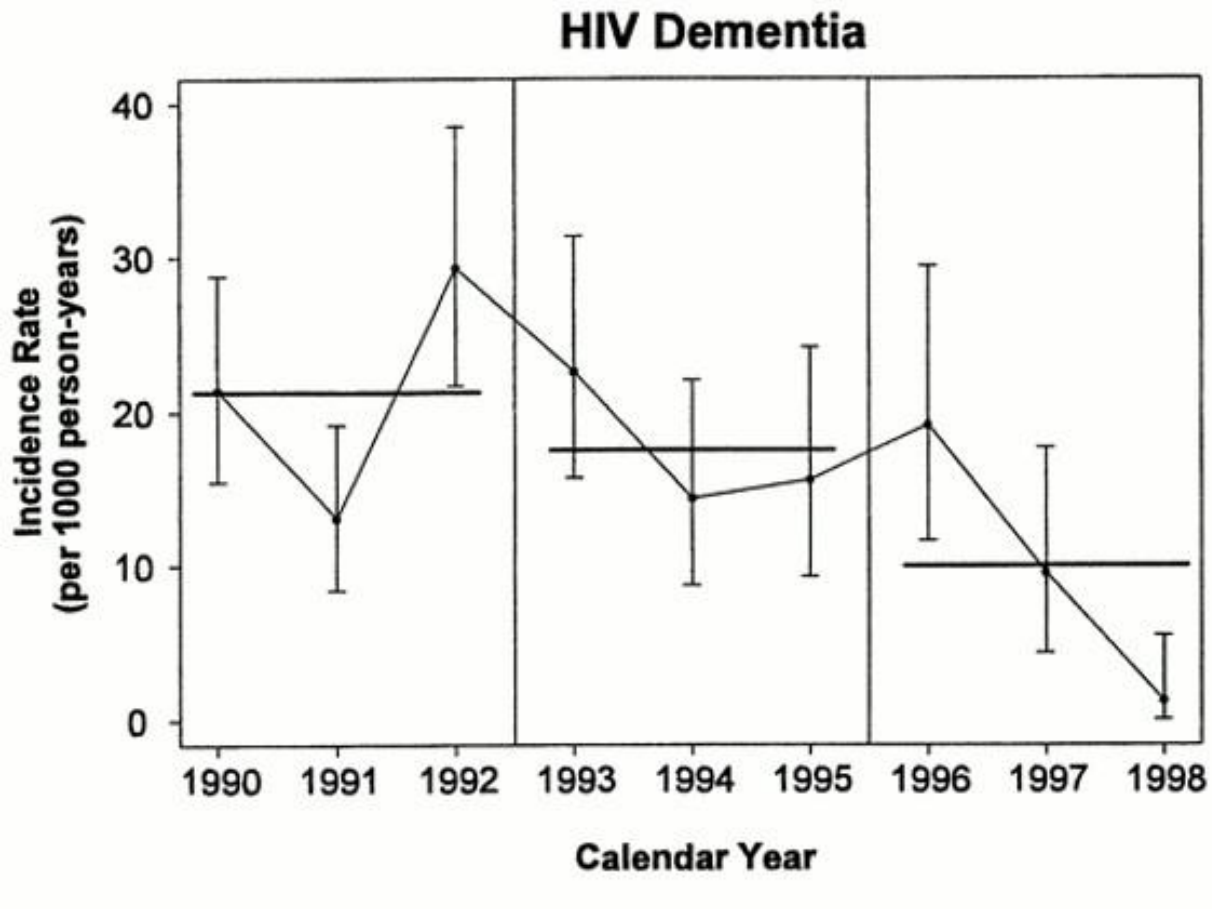
- HAND



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

- 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



Sacktor el at. Neurology 2001. HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998

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]

1 Grant et al. Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. Studies with neuropsychologic testing and magnetic resonance imaging. Ann Intern Med. 1987; 107:828–36.
2 Simioni et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS. 2010; 24:1243–50
3 Heaton et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010;75(23):2087-96
4 Habib et al. Neurocognitive impairment in HIV-1-infected adults in Sub-Saharan Africa: a systematic review and meta-analysis. Int J Infect Dis. 2013;17(10):e820-31
5 Kelly et al. HIV associated neurocognitive disorders (HAND) in Malawian adults and effect on adherence to combination anti-retroviral therapy: a cross sectional study. PloS one. 2014;9(6):e98962
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.
7 Joska et al. Characterization of HIV-Associated Neurocognitive Disorders among individuals starting antiretroviral therapy in South Africa. AIDS Behav. 2011;15(6):1197-203

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

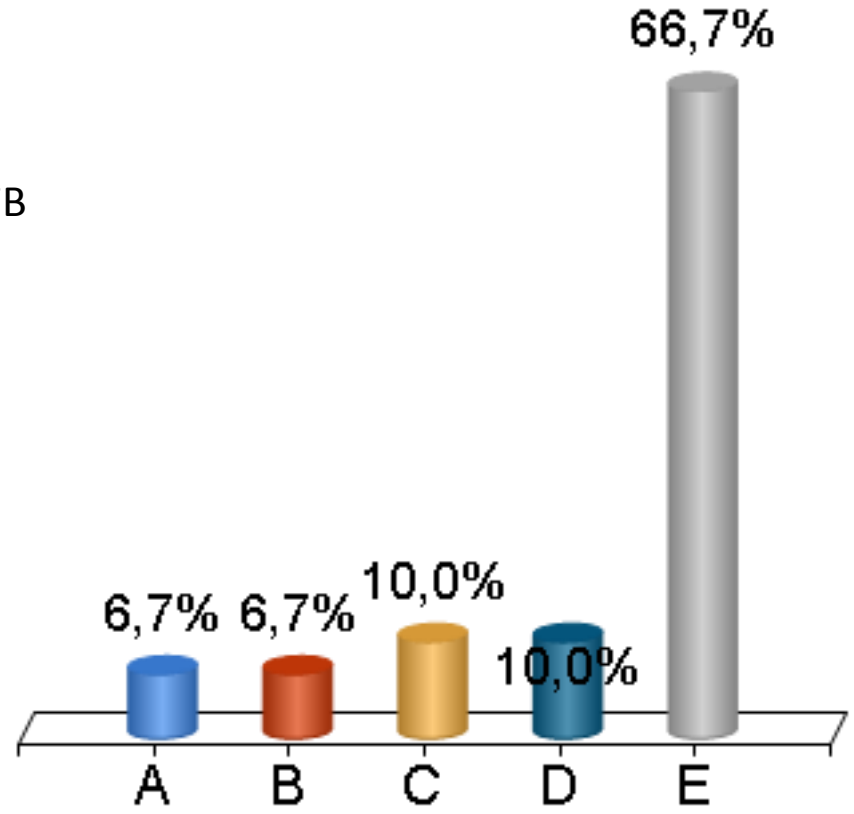
A) Direct entry of free HIV particles transcellularly through the BBB and BCSFB

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

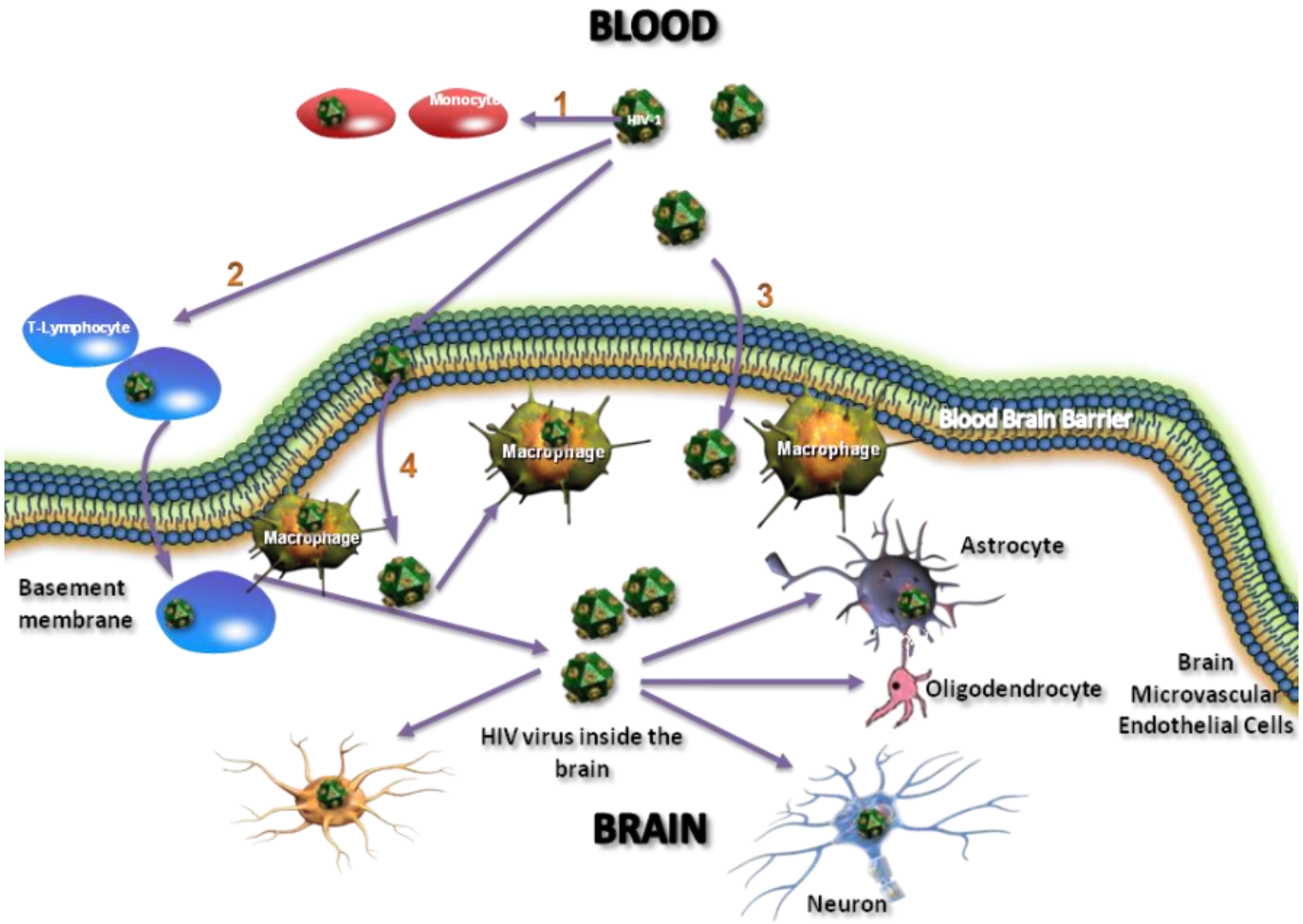
C. Hitch-hiking in CD4+ T cells

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

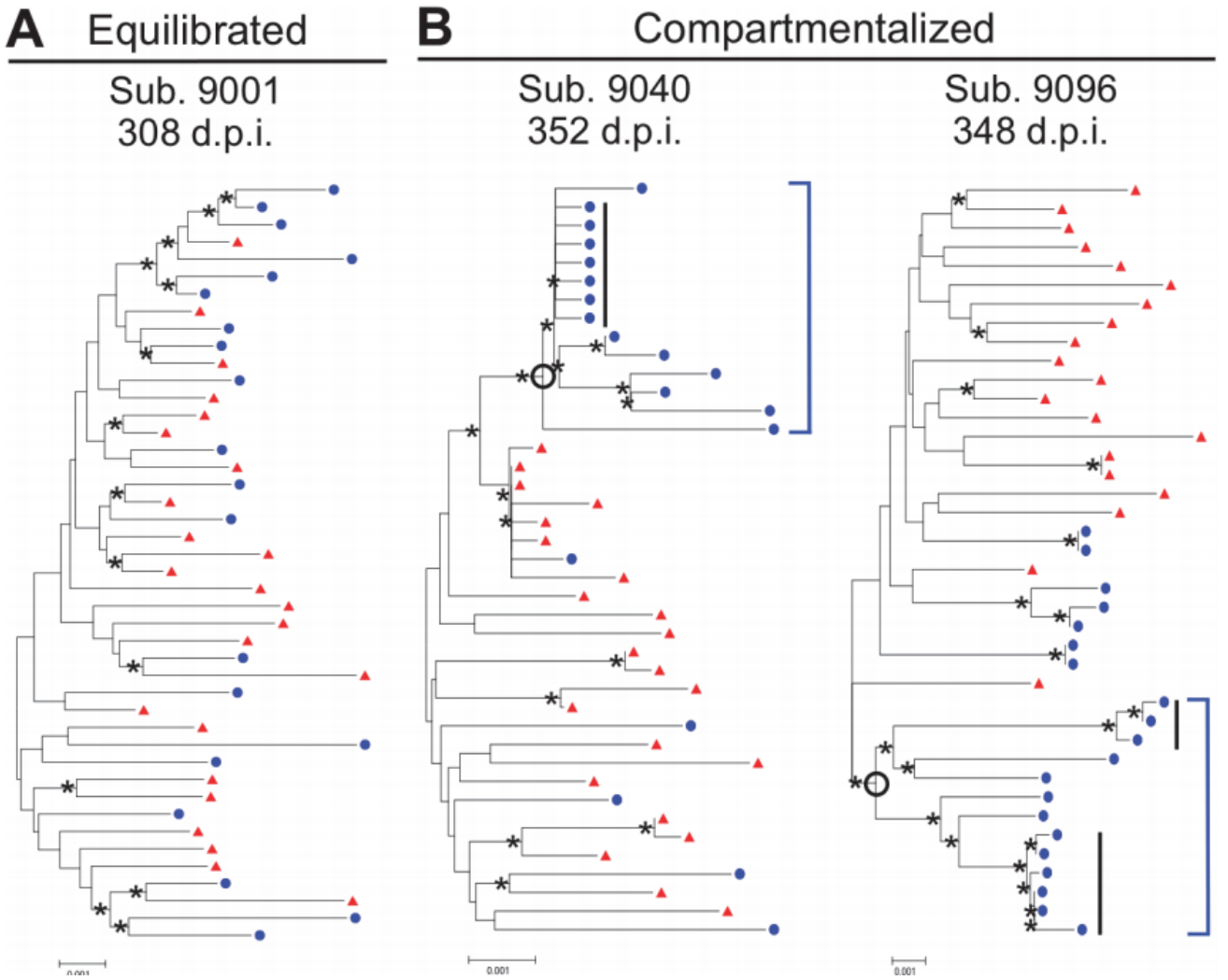
- Non-replicating
- Latently infects CD4 memory T cells (other long-lived cells)
- Occurs in primary infection
- Integrated provirus
- Clonal expansion
- Can be activated and cause on-going infection
- Source of rebound on treatment discontinuation

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

Sigal et al. Cell host & Microbe 2012, Nightingale et al. Lancet ID 2014

CNS compartmentalisation



CSF

Plasma

Sturdevant Plos pathogens 2015

What proportion of HAND is attributable to CSF escape/discordance?

A) 5-10%

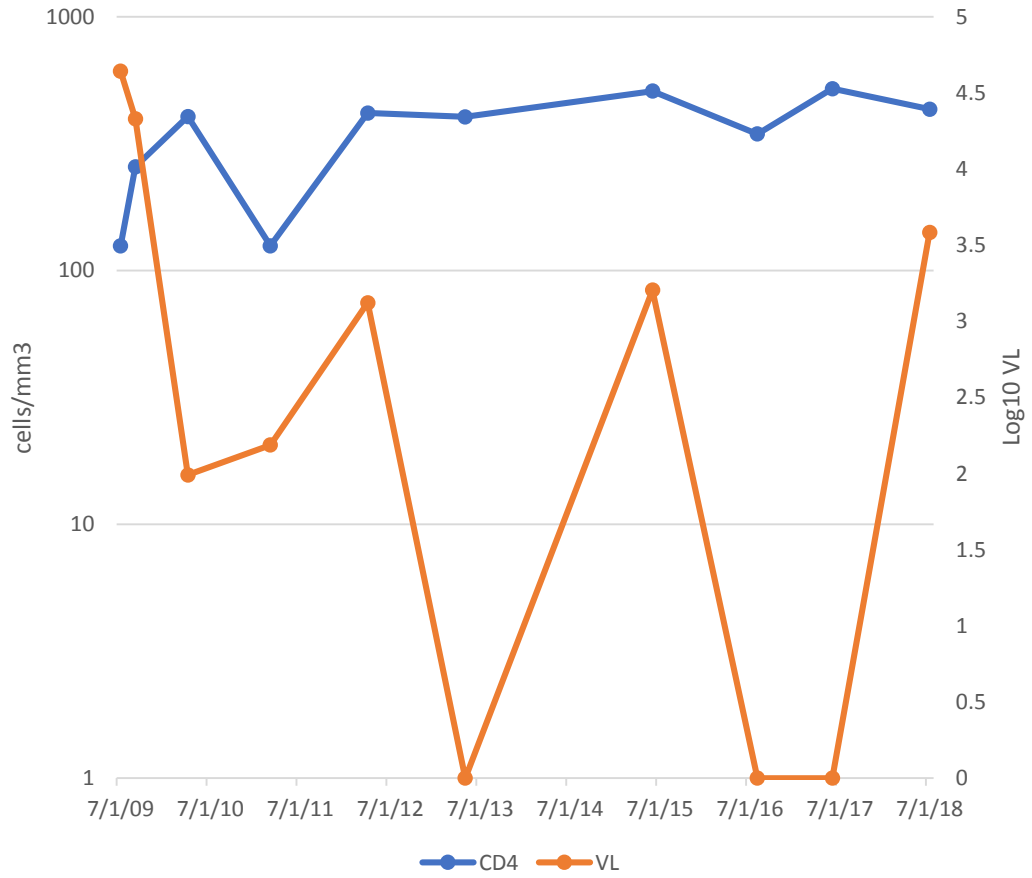
B) 10-40%

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

	Concentration (ng/ml)					
	TDF	FTC	EFV	Lopinavir	Ritonavir	3TC
Plasma	< 0	< 0	< 0	< 0	< 0	< 0
CSF	< 0	1.01	< 0	< 0	< 0	< 0

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

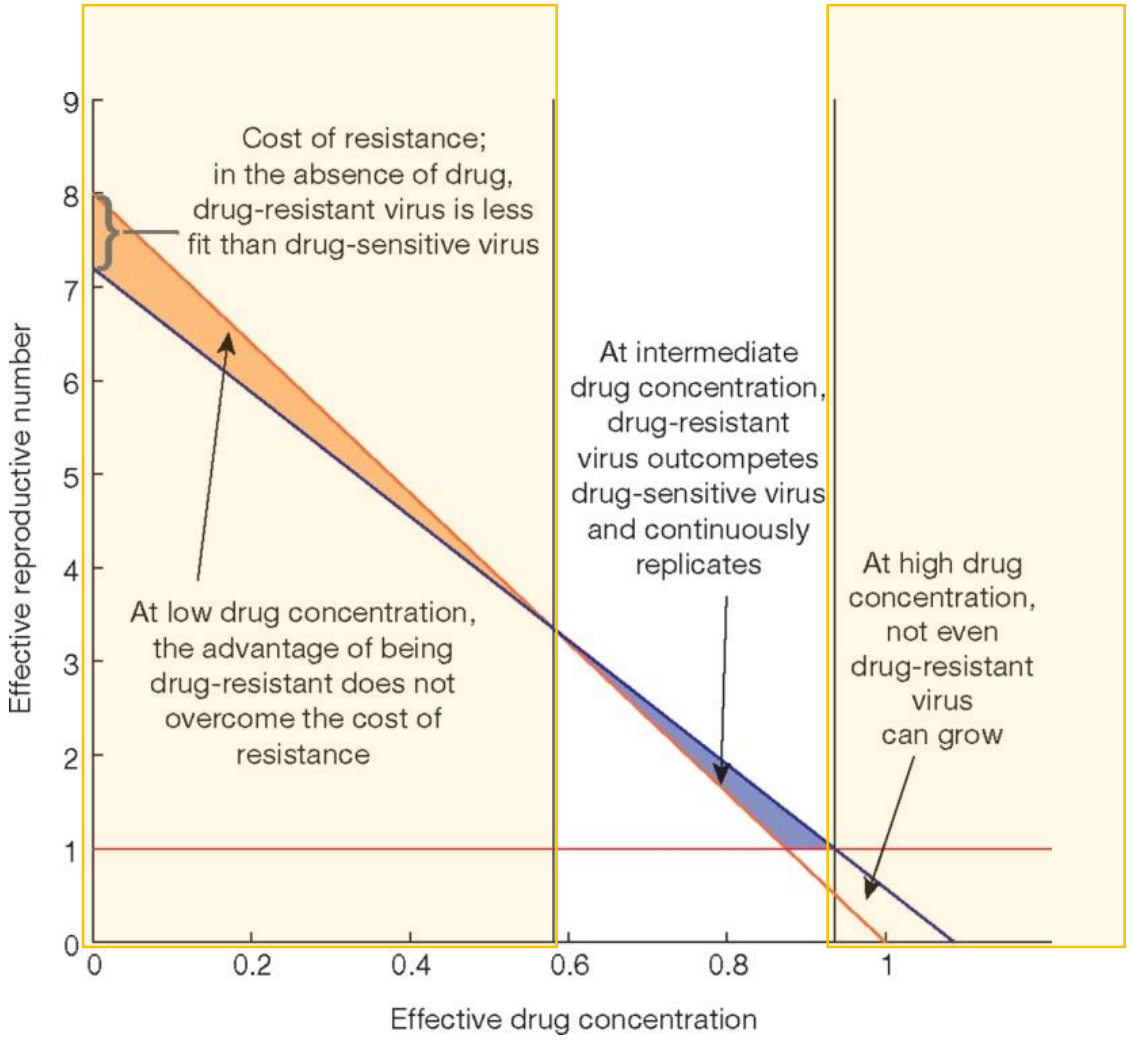
- Peluso AIDS 2012. 10 patients. Neurosymptomatic.
  - 6 of 7 CSF HIV-RNA strains had genotypic resistance
  - Associated with more frequent treatment interruption and elevated neopterin levels

- 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



R Lorenzo-Redondo *et al. Nature* 1–6 (2016) doi:10.1038/nature16933

Clinical spectrum of CSF escape/discordance

Table 1 Classification of CSF escape

	Biology	Neurological presentation	Plasma HIV RNA (copies/mL)	CSF HIV RNA	CSF WBC
Asymptomatic CSF escape	Equivalent to plasma blips?	Stable or asymptomatic; incidental finding in cohort or other study	<50	50–200*	Normal
Neuro-symptomatic CSF escape	Virological failure in CNS compartment	New or progressive CNS symptoms and signs	<50 or 50–500	>50 or >×2 plasma	Usually elevated
Secondary CSF escape	CNS viral replication related to another infection with inflammation	Reflects provoking infection	<50 or 50–500	>50 or >plasma	Elevated, as by provoking infection

*Occasionally higher

Ferretti F, Gisslen M, Cinque P, Price RW. Cerebrospinal Fluid HIV Escape from Antiretroviral Therapy. Curr HIV/AIDS Rep. 2015;12(2):280-8

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%

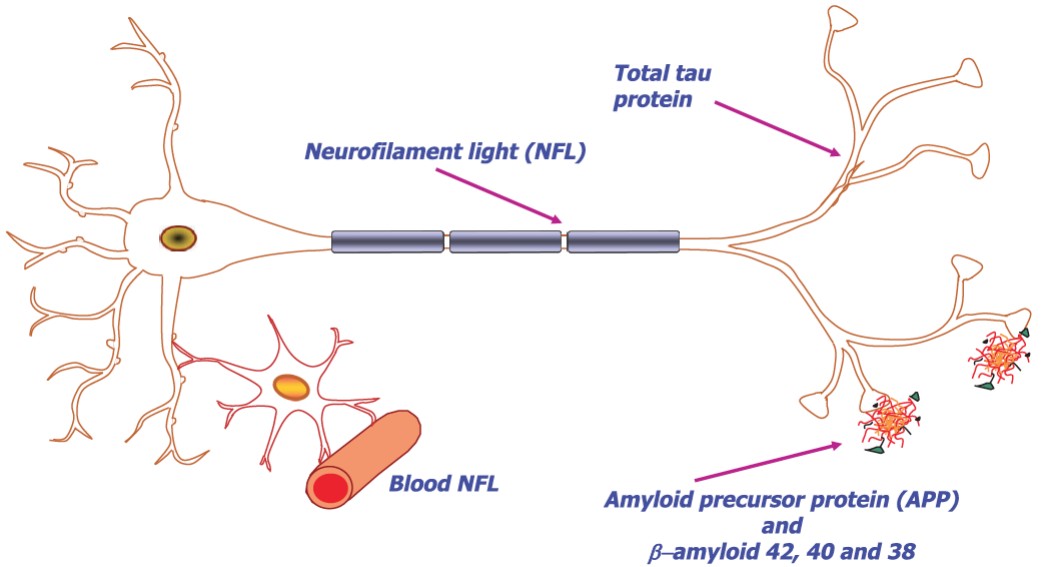
B) 10-40%

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



Yilmaz A, et al. Neurofilament light chain protein as a marker of neuronal injury: review of its use in HIV-1 infection and reference values for HIV-negative controls. Expert Rev Mol Diagn. 2017;17(8):761-70

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

Mind Exchange Working G. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. Clin Infect Dis. 2013

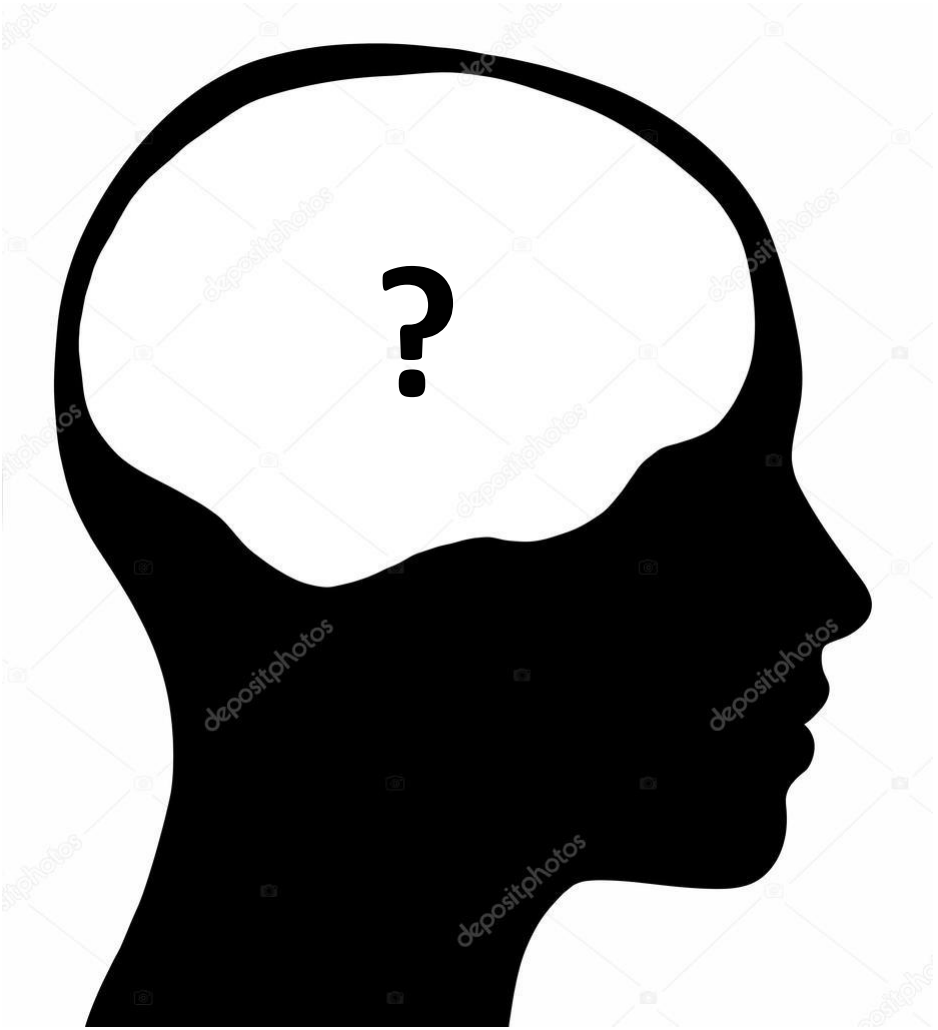
Research Gaps

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?

HIV Escape and Resistance in the Brain (HERB Study)

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?



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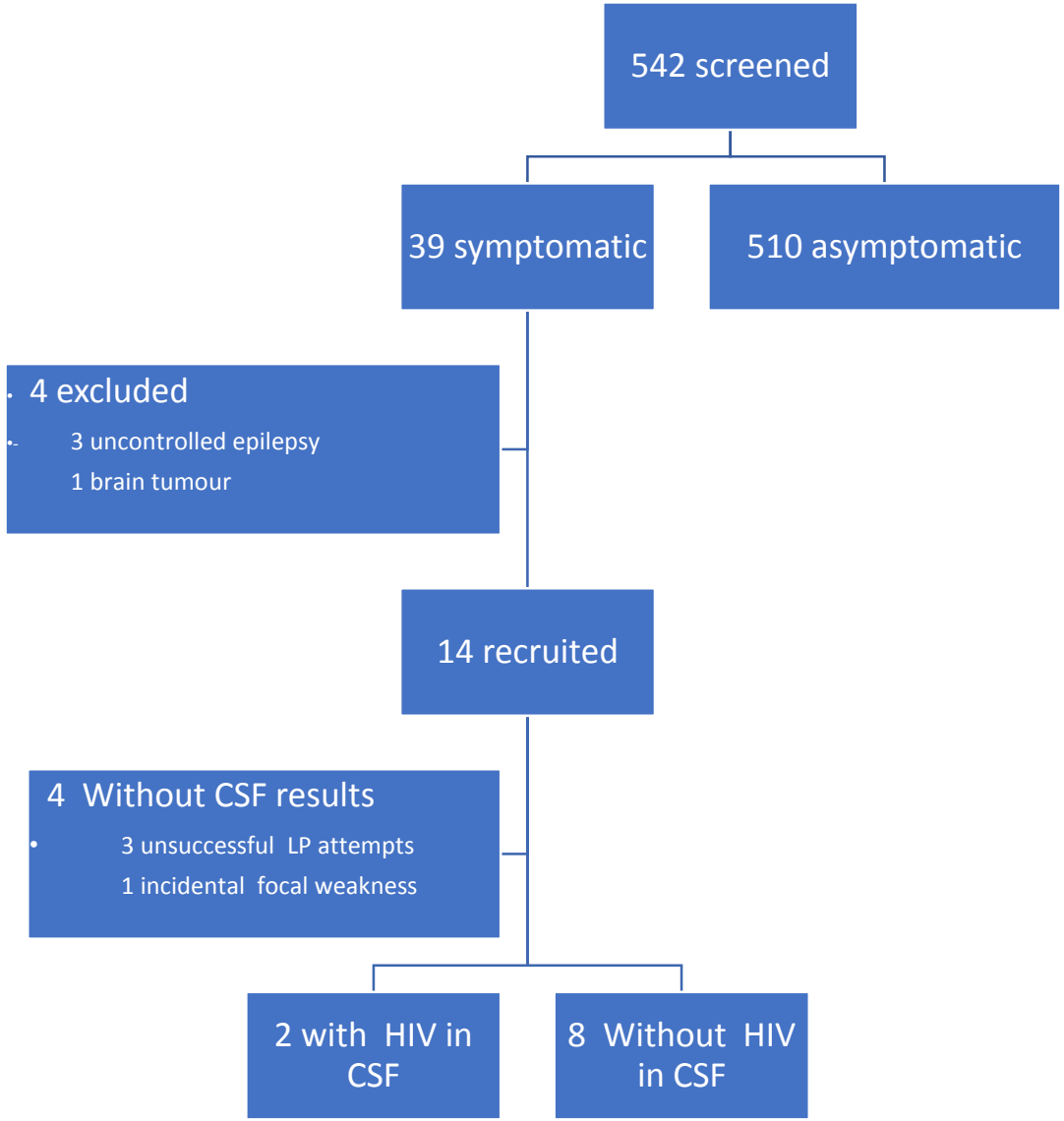
Study description

- *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