HIV Escape and Resistance in the Brain: the HERB study pilot phase

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INTRODUCTION

- The brain is considered an anatomically privileged site and HIV-1 entry to the central nervous system (CNS) is facilitated by loss of the integrity of the blood brain barrier early in HIV infection.
- Independent replication of HIV-1 in the CNS may then be facilitated by a tropism shift from R5-T cell tropic to R5-macrophage tropic, poor brain penetration of antiretrovirals (ARVs) or drug resistance.
- HIV associated neurocognitive impairment (HAND) remains an important HIV-associated comorbidity despite ARVs and cerebrospinal fluid (CSF) escape/discordance is now recognised in the context of individuals with a reconstituted immune system with an estimated prevalence of 10%. However the contribution of CSF escape/discordance to HAND remains uncertain.
- The prevalence of CSF escape/discordance amongst HIV-positive individuals) in sub-Saharan Africa (SSA) is unknown.

METHODS

- Longitudinal cohort study of people living with HIV (PLHIV) ≥18 years on ARVs for ≥1 year who require a lumbar puncture (LP) for clinical reasons, including but not limited to neurocognitive complaints.
- Paired CSF and blood were sampled at baseline, 6, 12 and 24 months.
- Viral load testing was done with the Abbott m2000 RealTime System™.
- HIV genotyping was done by Sanger sequencing and next generation sequencing by Illumina MiSeq platform. Resistance calling was done using Stanford HIV drug resistance database.
- Random drug levels were done on plasma and CSF using mass spectrometry.
- Ethics approval was granted by UKZN Biomedical Research Ethics Committee BE604/17 and the University College Hospital Research Ethics Committee 14865/001.

OBJECTIVES

This study aimed to:

- Determine the prevalence of CSF viral escape in South African patients with mild-moderate chronic neurological symptoms.
- Determine if CNS viruses in these patients were compartmentalised.
- Determine if CNS compartmentalisation was associated with emergence of drug resistant strains in ARV experienced PLHIV.

RESULTS

	All N=22 or n/N
Male % (number)	0.5 (1)
Median age years (IQR)	38.0 (33.0-49.5)
Median time on ARTs years (IQR)	9.0 (5.3-10.6)
Symptoms	
Headache	92.3 (12/13)
Memory impairment	41.0 (5/13)
Executive functioning impairment	25.6 (3/13)
Attention deficit	15.4 (2/13)
ART regimen % (number)	
TDF+3TC/FTC+EFV	68.2 (15)
AZT+3TC or TDF+3TC+LPV/r	31.8 (7)
Detectable plasma VL % (number)	18.2 (4)
Detectable CSF VL % (number)	17.6 (3/17)
CSF Escape	0.0 (0/17)
CSF Discordance	5.9 (1/17)
CSF VL less than plasma VL	11.7 (2/17)
Median CD4 cells/mm³ (IQR)	630 (432-706) n=21/22
Nadir CD4 cells/mm³ (IQR)	168 (83-301) n=21/22
IHDS <10 % (number)	59.0 (13/22)
Karnofsky performance scale > 70% % (number)	100 (14/14)
CESD-R-10 >10 % (number)	78.6 (11/14)

Table 1. Characteristics of participants at baseline

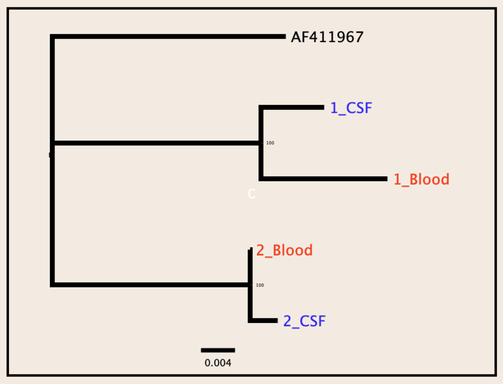

Figure 1. ML tree of RT. 897 nucleotides. 2 patients with detectable virus in blood and CSF.

Participant	Regimen		Plasma	CSF
1	TDF/FTC/LPV	VL copies/ml	4194	168
		DRMs	NRTI- M184V	NRTI- None
			NNRTI- K103N, P225H	NNRTI- None
			PI- None	PI- None
2	TDF/FTC/LPV	VL copies/ml	3831	30180
		DRMs	NRTI- None	NRTI- None
			NNRTI- G190A	NNRTI- G190A
			PI- None	PI- None

Table 2. Drug Resistance mutations. NNRTI resistance is evident in 2 patients with detectable virus in blood and CSF.

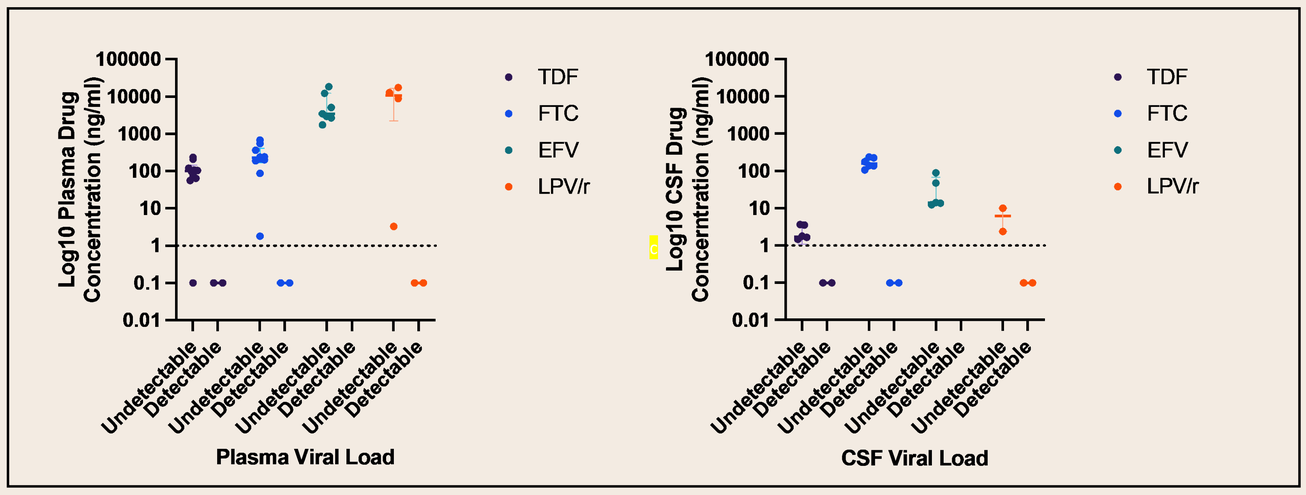

Figure 2. Drug levels. Drug levels are 2-3 $\log_{10}$ lower in CSF compared to plasma. Two participants with detectable virus in CSF and plasma had undetectable drug levels in both compartments (dotted line).

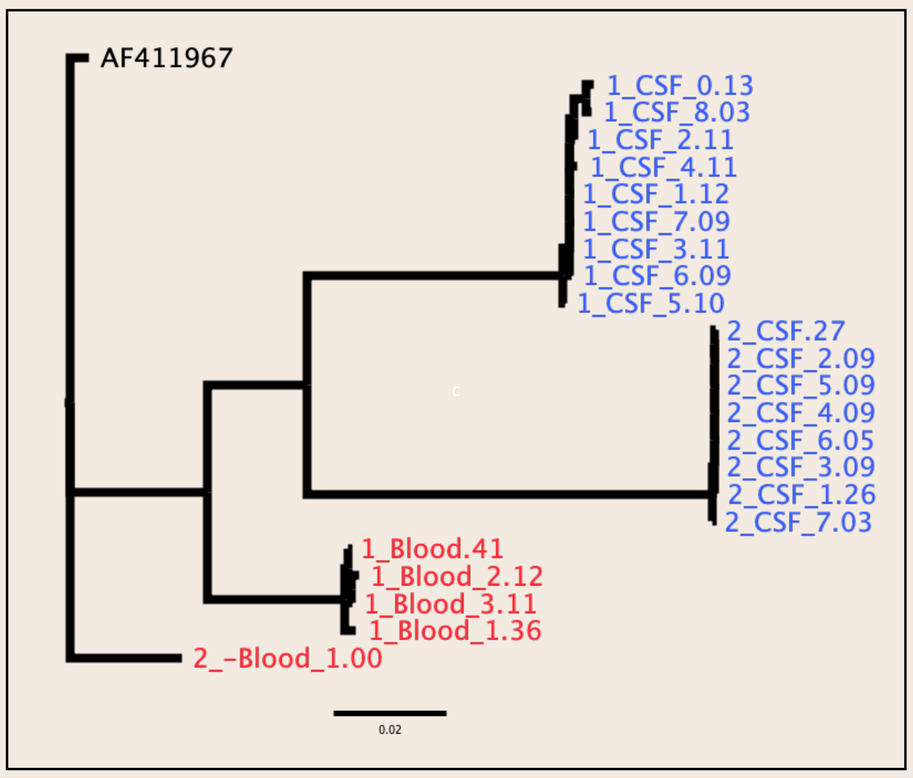

Figure 3. Maximum likelihood phylogenetic tree showing HIV RT haplotypes generated by CliqueSNV

CONCLUSIONS

- The prevalence of CSF discordance in neurosymptomatic PLHIV in this pilot phase was 6% and consistent with previously published data from resource rich settings.
- Virological failure and detectable HIV-1 in the CSF in this pilot study appears to be driven by poor ARV adherence.
- From the constructed haplotypes it is inferred that there is compartmentalisation or independent replication of HIV-1 in the CNS of some of these participants.
- Symptoms of depression were common, with 78.6% scoring a CESD-R-10 > 10.

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