HIV-1 DIVERSITY IN CSF AND PLASMA OF INDIVIDUALS WITH HIV AND CRYPTOCOCCAL MENINGITIS

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BACKGROUND

- Human Immunodeficiency virus. (HIV) can persist in different anatomical sites and this has become a major barrier to ending the HIV epidemic.
- The Central Nervous System (CNS) can harbor replication competent HIV virus leading to reseeding of HIV infection.
- This is often associated with development of HIV associated neurocognitive disorders (HAND).
- We assessed the differences in HIV-1 viral load levels, drug resistance mutation (DRMs) and co-receptor usage between the CSF and plasma in patients enrolled in a Cryptococcal meningitis (CM) study in Botswana.

METHODS

- This was a cross-sectional study utilizing 60 CSF and plasma paired samples from participants enrolled in a clinical trial evaluating the early fungicidal activity of 3 short-course, high-dose liposomal amphotericin B regimens for CM between 2014-2016.
- Out of 45 CSF/plasma paired samples available, HIV-1 VL was measured in 39 pairs (87%). Viral escape was defined as HIV-1 RNA ≥0.5 $\log_{10}$ in CSF than plasma and discordance as any CSF HIV-1 VL greater than plasma VL.
- HIV-1 protease (PR), reverse transcriptase (RT) and envelope were sanger sequenced using big dye sequencing chemistry. PR and RT sequences were analyzed for DRMs using Stanford HIV drug resistance database and co-receptor usage in env using Geno2pheno.

RESULTS

- A total of 34/39 participants (87%) had detectable VL in plasma and CSF with medians 5.1 (IQR:4.7-5.7) and 4.6 (IQR:3.7-4.9) $\log_{10}$copies/ml, respectively (p≤0.001), figure 1.
- There was a positive linear relationship between plasma and CSF VL (spearman r=0.49, p=0.003), figure 2.
- CSF viral escape was found in 1/34 participants (2.9%) and HIV-1 VL discordance in 6/34 (18%).
- No correlation was found between CSF HIV-1 VL discordance and CD4 count, fungal burden, CSF white cell count, CSF protein level.

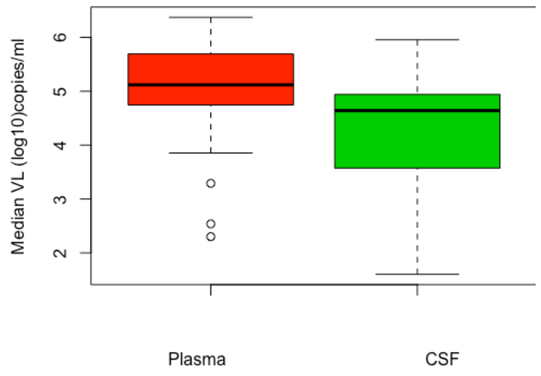

Figure 1: Median VL in CSF and plasma

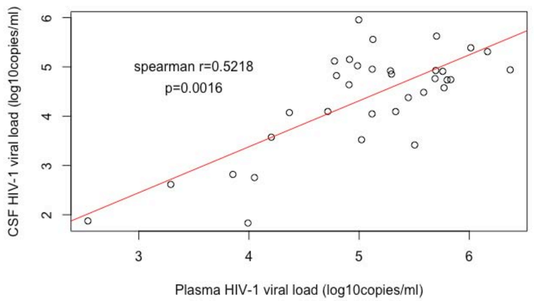

Figure 2: Relationship between CSF and plasma HIV-1 viral load

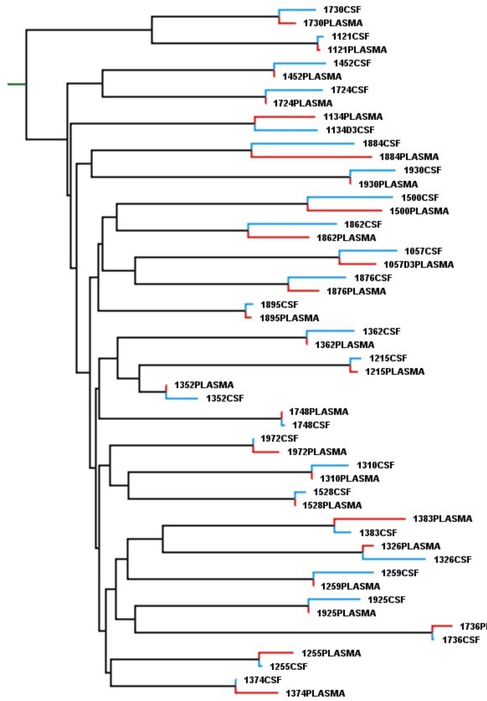

Figure 3: Phylogenetic tree for the 26 paired CSF/Plasma samples. The pairs had bootstrap values of 100

- A total of 26/45 (58%) pairs were successfully sequenced, of these, 5 pairs had major DRM in CSF and/or plasma.
- HIV-1 DRM discordance was observed in 3/26 (12%) paired samples.
- Two participants had PI associated mutations in the CSF and none in the plasma and the third had discordant NNRTI mutation in CSF and plasma.

Table 1:Characteristics of participants with HIV-1 DRMs

ID	Age (years)	ART regimen	Duration on ART (months)	CD4 count (cells/uL)	Mortality	Mental status	Plasma VL $\log_{10}$ (copies/ml)	CSF VL $\log_{10}$ (copies/ml)	Plasma DRM			CSF DRM		
									NRTI	NNRTI	PI	NRTI	NNRTI	PI
1930	27	ART naïve	N/A	40	No	N	6.37	4.94	None	None	**None**	None	None	**I84IT**
1736	42	TDF/FTC/EFV	110	2	No	N	5.80	4.74	D67N, K70G, M184V, K129E	K101E, K103N, E138A, G190A	None	D67N, K70G, M184V, K129E	K101E, K103N, E138A, G190A	None
1134	37	ABC/FTC/EFV	3	222	No	N	4.05	2.76	None	**K101E**	None	None	**V106M**	None
1895	62	ART naïve	N/A	16	Yes	A	4.79	4.82	None	None	**None**	None	None	**M46MI**
1528	61	TDF/FTC/NVP	87	158	Yes	A	5.28	4.92	M184MI	None	None	M184MI	None	None

- HIV-1 env V3 loop was sequenced from 18/45 (40%) pairs.
- 17/18 (94%) and 15/18 (83%) were CCR5-using strains in the CSF and plasma, respectively (p=0.8).
- 2/18 pairs had discordant co-receptors; Plasma samples were CXCR4 using strains while CSF had CCR5 using strains.

LIMITATIONS

- The relatively low number of participants in our study limited the power of some statistical analysis.
- A lack of a control group, i.e. HIV infected individuals without CM hence could not determine whether discordance or escape was due to CM or due to HIV compartmentalization.

CONCLUSION

- To our knowledge, this was the first study in Botswana to report on CSF/ Plasma HIV-1 compartmentalization.
- We observed lower rates of CSF HIV viral escape in participants with HIV-associated CM in Botswana. Discordant DRMs were found in CSF and plasma. There was no significant difference in co-receptor usage between CSF and plasma.
- Our findings suggest that compartmentalization may occur at lower rates in participants with advanced HIV-disease and CM.

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