Comparison of HIV-1 Viral Load and Drug Resistance Mutations between CSF and Plasma of Individuals with HIV and Cryptococcal Meningitis Co-infection in Botswana

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Financial disclosure

- No financial disclosure.

Background & Rationale

- Highly active antiretroviral therapy (HAART) has successfully reduced HIV-1 morbidity, mortality and co-infections.

- However, HIV-1 can persists in different anatomical sites becoming a major barrier to ending the HIV epidemic.

(Solomon *et al*., 2018; Siedner *et al*., 2015)

Background & Rationale

- Central Nervous System (CNS) has been found to harbor replication competent HIV virus leading to reseeding of HIV infection.

- This is often associated with development of HIV associated neurocognitive disorders (HAND).

(Wong & Yukl, 2016)

Objectives

- We assessed the differences in HIV-1 viral load levels and drug resistance mutation (DRMs) between the CSF and plasma in patients enrolled in a Cryptococcal meningitis (CM) study in Botswana.

- **Hypothesis:** In a setting of CM, a high prevalence of CSF viral escape will be observed.

Methods

Study Design

- Retrospective cross-sectional study

Study population

- *Ambition study*: clinical trial evaluating the early fungicidal activity of 3 short-course, high-dose liposomal amphotericin B regimens for CM between 2014-2016.
- 45/60 plasma and CSF paired samples were available for testing.

Methods

Measuring VL

- HIV VL: measured in 38/45 (84%) paired samples.

Genotypic DR testing

- 45 pairs were available for HIV-1 protease (PR) and reverse transcriptase (RT) sequencing using Sanger based population sequencing.

Results

Table 1: Study participants characteristics

Patient characteristics	
Median age, years (Q1, Q3)	38 (32, 44)
Gender	
Male (%)	28 (62)
Female (%)	17 (38)
Median CD4 count, cells/ µL (Q1, Q3)	28 (10-46)
On ART, n (%)	
Yes	12 (27)
No	33 (73)
Duration on ART, months (Q1, Q3)	5 (1-45)
ART regimen, n=12, (%)	
TDF/3TC+EFV	6 (50)
TDF/3TC/NVP	2 (16.7)
ABC/3TC/RAL	1 (8.3)
ABC/3TC/EFV	1 (8.3)
AZT/3TC/EFV	1 (8.3)
TDF/3TC/DTG	1 (8.3)

Results

Relationship between CSF & Plasma viral load

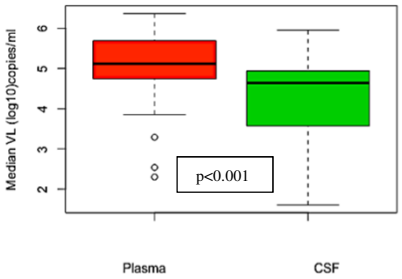

Figure 1: Median VL in CSF and plasma

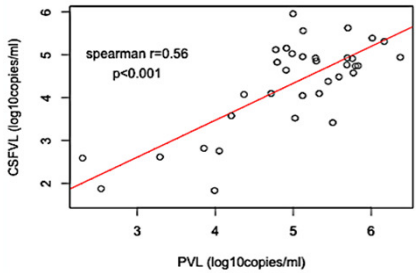

Figure 2: Relationship between CSF and plasma VL

- Plasma VL=5.1 (IQR:4.7-5.7) $\log_{10}$copies/ml
- CSF VL=4.6 (IQR:3.7-4.9) $\log_{10}$copies/ml

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Results

CSF viral load and viral escape

- CSF viral escape (HIV-1 VL $\geq$0.5 $\log_{10}$ higher in CSF than in plasma) was found in 1/34 participants (2.9%).

- No correlation between CSF VL and CD4 count, fungal burden, CSF white cell count, CSF protein level.

Results

Phylogenetic tree

- All samples successfully paired with high bootstrap values.
- All samples were subtype C.

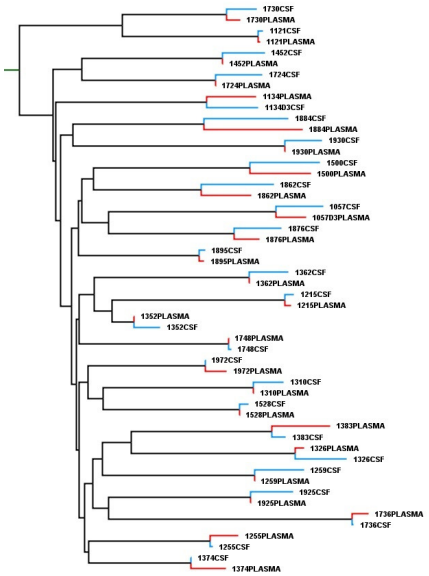

Figure 3: Phylogenetic tree for the 26 paired CSF/Plasma samples

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Results

Table 2: Characteristics of participants with HIV & DRM discordance

ID	Age (yrs)	ART regimen	Months on ART	CD4 count (cells/uL)	normal mental status	Mortality	Plasma VL log_{10} (cps/ml)	CSF VL log_{10} (cps/ml)	Plasma DRM			CSF DRM		
									NRTI	NNRTI	PI	NRTI	NNRTI	PI
1	27	naïve	N/A	40	Yes	No	6.37	4.94	None	None	None	None	None	**I84T**
2	62	naïve	N/A	16	No	Yes	4.79	4.82	None	None	None	None	None	**M46I**
3	37	ABC/3TC/EFV	3	222	Yes	No	4.05	2.76	None	**K101E**	None	None	**V106M**	None
4	61	TDF/3TC/NVP	87	158	No	Yes	5.28	4.92	M184I	None	None	M184I	None	None
5	42	TDF/3TC/EFV	110	2	Yes	No	5.8	4.74	D67N K70G M184V K129E	K101E K103N E138A G190A	None	D67N K70G M184V K129E	K101E K103N E138A G190A	None

Conclusion

- To our knowledge, this is the first study done in Botswana reporting on CSF/ Plasma HIV compartmentalization.

- PI-associated mutations observed in CSF compartment & not in plasma in 2 ART naïve participants.

- These mutations are very rare in ART naïve and this could be a case of undisclosed ART status and PIs are associated with poor CNS penetration effectiveness.

Conclusion

- Genotyping in plasma only could miss some DRMs in the CSF.

- Low cases of CSF HIV viral escape were observed, however, studies with larger sample size and a HIV mono-infected group are warranted.

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Questions?

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