Neuro-Symptomatic Cerebrospinal Fluid (CSF)/Plasma HIV RNA Levels Discordance With Asynchronous And Discordant Emergence Of Drug Resistant HIV Variants

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Conclusions

Progressive neurologic dysfunction in the context of HIV CSF viral escape (CVE) is a rare but emerging trend. The phenomenon occurred in a patient with intermittent and suboptimal virological control. The emergence of drug resistant strains to NRTIs, NNRTIs and PIs first demonstrated in the CSF ensued.

Resistance associated mutations (RAMs) to NRTIs and NNRTIs and levels of resistance were concordant in the CSF and the plasma while discordant for PIs. Additional V82A/V-HIV variants in the plasma led to PIs resistance that were one or two levels relatively higher for all PIs that were not susceptible in the CSF.

The identification of drug resistant HIV variants harboring significant RAMs in the CSF and/or plasma, in neuro-symptomatic patients, constitutes an indication for ART regimen optimization and adherence support that may be followed by viral suppression in both compartments and neurological improvement.

1. Background

Neuro-symptomatic HIV CVE associated with compartmentalized or systemic drug resistance emergence, and antiretroviral therapy (ART) failure have been recognized in some patients with complete or incomplete HIV viremia suppression.[1-4]

However, this clinical phenomenon remains either undiagnosed or under reported in Southern Africa. Neither case report nor series from this subcontinent can be found in the 2016 Global HIV-1 CVE Consortium Meeting report.[1]

Management of patients with neuro-symptomatic CVE comprises clinical suspicion, comprehensive investigations, rational ART modifications and adherence optimization. The arrest and reversal of neurological deficits are not uncommon.[1-4]

2. Objective

To characterize resistance associated mutations (RAMs) and **drug resistance levels** in **both the CSF and the plasma** after the confirmation of a **neuro-symptomatic CVE** in a 55-year-old **South African adult male HIV positive** from **rural KwaZulu Natal** on **ART for more than 6 years** but only **about 1 year of ritonavir boosted protease inhibitors**

3. Methods

Viral suppression was suboptimal and labile, and adherence was intermittent

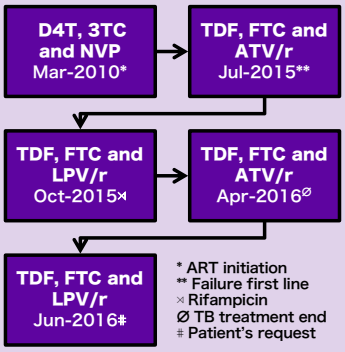

Figure 1. Antiretroviral Therapy History

The neurological dysfunction noted in Oct-2015 progressed despite improvement in viremia control in Jul-2016 **prompting HIV CVE investigations.**

4. Results

Table 1. HIV CSF Viral Escape

Plasma/CSF HIV RNA Reversed Ratio	10622* (4.0)/472* (2.7) 25374* (4.4)/2780* (3.4)
CSF RNA ≥1 log higher than plasma RNA *copies/mL (Log)	
Meningeal inflammation	Pleocytosis: 10 cells/µL: 100% Lymphocytes Elevated Protein: 1.27g/dL [0.15-0.45]
HIV CNS encephalitis	Brain MRI: Diffuse white matter hyperintensity on the T2/T2 FLAIR sequences

Absence Of Alternative Neuro-Pathology Diagnosis:
CSF: PCR: CMV, HSV1-2, VZV, JCV; GXP MTB/Rif & CrAg: Negative
Serum RPR: Non-Reactive
Serum Vitamin B12 Levels: Normal

Table 2. Drug Resistant Variants & Drugs Resistance Levels

Mutations		Drugs	Mutation Scoring		Resistance Levels***	
CSF*	Plasma**		CSF	Plasma	CSF	Plasma
D67N, K70R, M184V, T215F	D67N, K70R, M184V, T215F	ABC	40	40	Intermediate	Intermediate
		AZT	80	80	High	High
		D4T	65	65	High	High
		FTC	60	60	High	High
		3TC	60	60	High	High
		TDF	15	15	Low	Low
K103N, K238T	K103N, K238T	EFV	90	90	High	High
		ETR	0	0	Susceptible	Susceptible
		NVP	90	90	High	High
		RPV	0	0	Susceptible	Susceptible
M46I, L10F	M46I, V82A/V L10F	ATV/r	10	35	Potential Low	Intermediate
		DRV/r	5	5	Susceptible	Susceptible
		FPV/r	25	50	Low	Intermediate
		IDV/r	20	60	Low	High
		LPV/r	15	55	Low	Intermediate
		NFV	45	85	Intermediate	High
		SQV/r	10	35	Potential Low	Intermediate
		TPV/r	5	5	Susceptible	Susceptible

*HPP/DDMRI/HPRL in-house HIV-1 resistance assay: Nov 1, 2016 | **NHLS Capetown: Dec 7, 2016 | ***Standford HIV-1 Drug Resistance Database (Version 6.0.5 last updated on 10/16/09)
MRI: Magnetic Resonance Imaging PCR: PolymeraseChain Reaction CMV: Cytomegalovirus HSV: Herpes Simplex Virus VZV: Varicella Zoster Virus JCV: John Cunningham virus GXP MTB/Rif: GeneXpert M. tuberculosis Rifampicin CrAg: Cryptococcal Antigen RPR: Rapid Plasma Reagin

5. References

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