RELAPSE OF SYMPTOMATIC CSF HIV ESCAPE UPON PREVIOUSLY OPTIMIZED C-ART REGIMEN CHANGES

Francesca Ferretti[1*], Valentina De Zan[1], **Filippo Turrini**[1], Enzo Boeri[1], Simonetta Gerevini[1], Nicola Gianotti[1], Hamid Hasson[1], Adriano Lazzarin[1], Paola Cinque[1]

[1] IRCCS San Raffaele Scientific Institute Milan, Italy; *Current address: Chelsea and Westminster Hospital NHS Trust, London, UK

Background

In HIV-infected patients receiving effective combination antiretroviral treatment (cART), discordant HIV replication in cerebrospinal (CSF) can be associated with neurological symptoms and magnetic resonance imaging (MRI) evidence of white matter changes, the so-called 'neuro-symptomatic CSF viral escape'. Symptomatic escape seems to originate from low-grade HIV replication in the brain and although the clinical presentation may be severe, the outcome is usually good upon cART optimization.

Aim of our research was to identify and characterize possible cases of relapse in the long-term follow- up.

Population and Methods

21 cases of symptomatic CSF escape followed between 2003 and 2017. Median CSF HIV-RNA 1056 c/mL (IQR 63-75,000); plasma (PL) HIV-RNA detectable in 10 of 21 patients, median 1055 c/mL (IQR 92-8194); cognitive impairment observed in 12 patients and cerebellar symptoms in 11. MRI: diffuse bilateral white matter hyperintensities on T2- weighted sequences in 15 of 20 patients.

Escape: onset of new neurological symptoms and/or signs in cART-treated patients with HIV-RNA detectable in CSF, but not in plasma, or CSF HIV-RNA higher than plasma level.
Relapse: re-occurrence of symptomatic CSF escape following clinical and, when follow-up CSF sample of first episode was available, virological regression of first episode.

HIV-RNA: COBAS Amplicor HIV-1 Monitor, Roche, Basel, Switzerland, 4 patients (detection limit 50 copies/mL); Abbott Real Time HIV-1 m2000, Abbott Molecular Inc., Des Plaines, IL, USA, 17 patients (lower limit of quantification, LLQ 40 c/mL; lower limit of detection, LLD 1 c/mL).

Conclusions

Symptomatic CSF escape may relapse months to years after recovery, if cART efficacy in the CNS is weakened by simplification or loss of adherence.

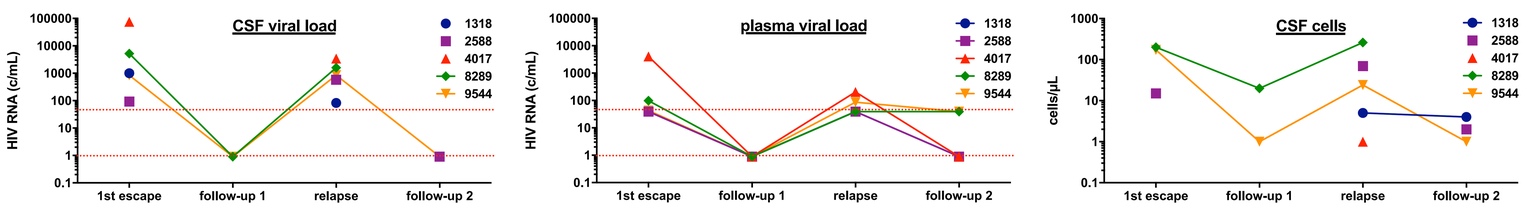
Symptomatic CSF escape may require long-term administration of an optimized cART regimen to prevent relapse. AZT withdrawal was associated with relapse and its reintroduction with relapse resolution. However, subsequent substitution of AZT with dolutegravir has not been so far associated with relapse.

More in general, the evidence of relapse in patients with previous CSF escape further supports the hypothesis that the CNS is a reservoir for HIV, and a potential obstacle to eradication.

Results

Patient				CSF escape, 1st episode							CSF escape, 1st episode, follow-up						CSF escape relapse								CSF escape relapse, follow-up						Last follow-up *(e)*		
Pt ID	gender, age	Nadir CD4/µL	Previous HIV-E	Ongoing ART (duration, months)	CD4+ cells/µL	PL VL (c/mL)	CSF VL (c/mL)	CSF cells/µL	Neurological symptoms/signs	MRI *(a)*	Optimized ART (duration, weeks)	PL VL (c/mL)	CSF VL (c/mL)	CSF cells/µL	Clinical outcome	MRI *(a)*	Optimized ART (duration, months)	New ongoing ART (duration, months)	CD4+ cells/µL	PL VL (c/mL)	CSF VL (c/mL)	CSF cells/µL	Neurological symptoms/signs	MRI *(a)*	Re-optimized ART (duration, weeks)	PL VL (c/mL)	CSF VL (c/mL)	CSF cells/µL	Clinical outcome	MRI *(a)*	Total FU since 1st episode (months)	Total FU since relapse (months)	Current ART (duration, months)
1318	F, 45	176	Yes	TDF, FTC, DRV/r bid (9)	300	<40	1000	n.a.	Cerebellar, cognitive impairment	Severe diffuse WM hyperintensities (PV, cerebellum, CC, CS), edema, venular stasis	AZT, 3TC, TDF, DRV/r bid, RAL (12)	<1	n.a.	n.a.	Recovery	n.a.	38	AZT, 3TC, TDF, DRV/r bid, RAL (unchanged) *(b)*	412	<40	83	5	Cerebellar, cognitive impairment, headache	Severe diffuse WM hyperintensities (PV, cerebellum, CC, CS), edema, venular stasis	AZT, 3TC, DRV/r bid, MVC, DTG (14)	<1	<1	4	Recovery	Improved	81	44	Unchanged (40)
2588	M, 45	222	No	ABV, 3TC FPV/r (42)	617	<40	93	15	Brain focal and cerebellar, cognitive impairment	Moderate diffuse WM hyperintensities (PV, cerebellum, CC, CS), edema, venular stasis	AZT, ABV, 3TC, FPV/r (12)	<1	n.a.	n.a.	Recovery	n.a.	11	ABV, 3TC FPV/r (6)	726	<40	578	70	Cerebellar	Mild diffuse WM hyperintensities (PV, cerebellum, CC, CS), edema, venular stasis	AZT, ABV, 3TC, FPV/r (20)	<1	<1	2	Recovery	Improved	92	74	FTC, TDF, DTG (7)
4017	F, 50	110	Yes	TDF, FTC FPV/r (25)	146	4067	75000	0	Brain focal and cerebellar	Mild edema (PV, CS)	ABC, 3TC, LPV/r (12)	<1	n.a.	n.a.	Recovery	n.a.	43	TDF, FTC, NVP (33) *(c)*	387	205	3439*(c)*	1	Brain focal and cerebellar	Mild edema (PV, CS)	AZT, 3TC, DRV/r bid (12)	<1	n.a.	n.a.	Recovery	n.a.	121	44	3TC, ABV, DTG (2)
8289	M, 28	9	No	TDF, FTC, ATV (7)	290	98	5200	200	Brain focal and cerebellar	Mild diffuse WM hyperintensities (PV, cerebellum, CC, CS), edema, venular stasis	AZT, 3TC, DRV/r bid (6)	<1	<1	20	Recovery	Improved	41	ABV, 3TC DRV/r OD (3)	722	<40	1596	260	Headache, cerebellar	Normal	AZT, 3TC, DRV/r bid, RAL (12)	<40	n.a.	n.a.	Recovery	n.a.	89	45	AZT, 3TC, DRV/r bid (39)
9544	M, 39	n.a.	No	TDF, FTC, DRV/r OD (143)	522	43	837 *(c)*	173	Brain focal and cerebellar, cognitive impairment, headache	Severe diffuse WM hyperintensities (PV, cerebellum, CC, CS), edema, venular stasis *(Figure)*	AZT, 3TC, DRV/r bid, MVC (10)	<1	<1	1	Recovery	Improved *(Figure)*	22 (MVC changed to RAL after 8 weeks)	ABV, 3TC, DRV/r bid (2)	733	86	853 *(c)*	24	Brain focal and cerebellar, cognitive impairment	Severe diffuse WM hyperintensities (PV, cerebellum, CC, CS), edema, venular stasis, atrophy *(Figure)*	AZT, 3TC, DRV/r bid (8) *(d)*	<1	181	1	Improved	Improved	66	41	Unchanged (41)
																									AZT, 3TC, DRV/r bid (21), plus DTG (2) *(d)*	<40	<1	1	Recovery	Improved *(Figure)*			

- **CSF escape relapsed in 5 of 21 cases (24%)** during a median follow-up of 66 months (range 12-121) after cART optimization. Relapse was in one case (patient 1318) the likely consequence of poor adherence of the previously optimized therapy, whereas it occurred in four (patients 2588, 4017, 8289 and 9544) 4-20 weeks after simplification of the previously optimized cART.
- **CSF resistance mutations** against 2 or 3 drugs included in the simplified cART were identified in 2 cases (4017, 9544).
- **Clinical resolution and HIV-RNA clearance** occurred in all cases after cART re-optimization according to resistance profile and/or predicted neuropenetration (including AZT in 3 patients).
- **No new escape episodes up to the last follow-up** despite 3 patients had underwent cART simplification, either maintaining AZT (n=1), or switching to a new dolutegravir-containing regimen without AZT (n=2).



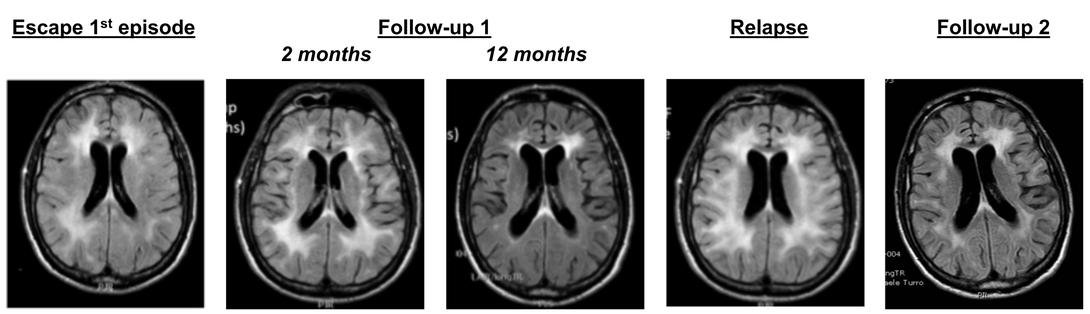


Figure. Upper panels: CSF and plasma viral load and CSF cell count of the five patients with CSF relapse. Red dotted lines represent the LLQ and LLD of the assay (40 and 1 c/mL). **Lower panels:** Sequential MRI axial FLAIR sequence images of patient 9544 (see Table for description).

Table notes

***HIV-E**, HIV encephalitis; **WM**, white matter; **PV**, periventricular; **CC**, corpus callosum; **CS**, corticospinal tract*

***(a)** As by T1 sequences following gadolinium enhancement and T2 and Fluid-attenuated Inversion Recovery (FLAIR) sequences.*

***(b)** ART was taken irregularly over the last months*

***(c)** Patient 4017, CSF resistance mutations at CSF escape relapse: M184I; NNRTI: V106A/V, E138A, G190A (nucleoside reverse transcritase inhibitors, NRTIs); patient 9544, CSF resistance mutations at 1st CSF escape: M41L, D67N, M184I, L210W, T215Y, K219E (NRTIs). Y181C (non nucleoside RTIs, NNRTIs); patient 9544, CSF resistance mutations at relapse: M41L, D67N, K70R, M184V, L210W, T215Y, K219E (NRTIs); L100LI, Y181C (NNRTIs); PI: M46I, L76V (protease inhibitors)*

***(d)** Clinical improvement and CSF viral load decline from 853 to 181 c/mL was observed 8 weeks after AZT reintroduction, and eventually to <1 copy/mL 23 weeks later, following intensification with dolutegravir for 14 days prior to the lumbar puncture.*

***(e)** Last follow-up: December, 31, 2018*