PLASMA RAMS IN REVERSE TRANSCRIPTASE GENE ASSOCIATE WITH CSF HIV-1 ESCAPE

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BACKGROUND

- Several risk factors for cerebrospinal fluid HIV-1 escape (CSFE) have been reported: length of HIV infection, cART interruptions and poor adherende, low CD4 nadir, low CPE score, persistent low-level viremia and the use of certain ARVs);
- CSF-plasma discordance and CSFE have been reported more frequent among patients on PIs (especially ATV)-based cART in Indian and US cohorts[1-2] and two cases recently from Uganda[3]
- PIs (ATV) containing-regimens are recommended as second-line cART in many of the above countries after failure to NNRTI containing regimens. Yet in certain countries (including Italy) PIs have been used in first-line or early switches thus possibly having patients on PIs without previous failures/resistance associated mutations (RAMs)

OBJECTIVE

We sought to assess whether the presence of plasma RAMs may be a determinant of CSFE beyond the drug class composing the antiretroviral treatment

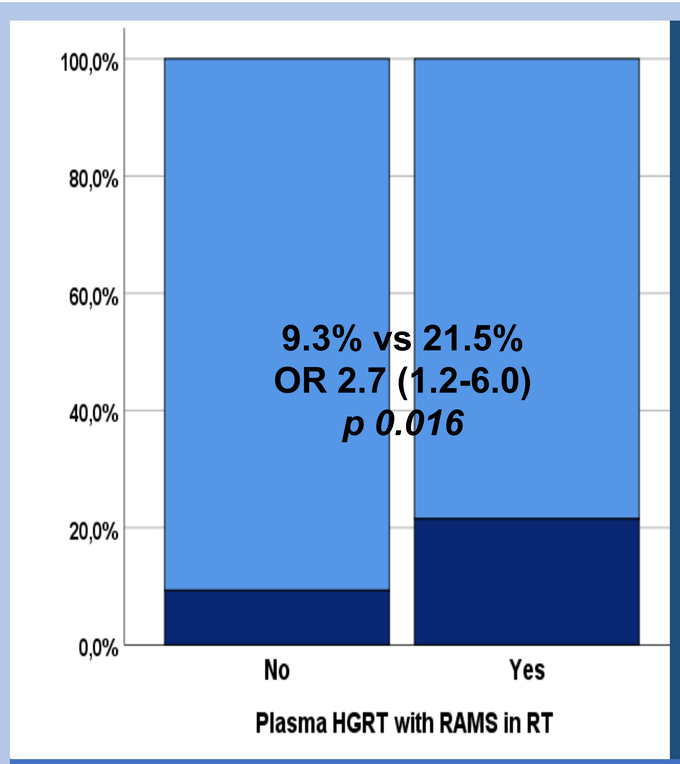
METHODS

- Retrospective cross-sectional multicentric study on PLWH on cART undergoing lumbar puncture (LP) for any reason
- Time: 2007-July 2019
- Place: 4 Italian hospitals (Brescia, Torino, Roma, Milano)
- Inclusion criteria:
  - Age≥ 18 years
  - Being on cART since at least 6 months
  - Available coupled plasma and CSF HIV-RNA measurements
  - Available historical cumulative plasma genotypic resistance testing (HGRT) for reverse transcriptase (RT) and protease (Pr) genes
- Exclusion criteria: secondary CSFE
- CSFE was defined as any measurable CSF HIV-RNA coupled with a plasma HIV-RNA <50 copies/mL and any difference ≥0.5 Log10 between CSF and plasma HIV-RNA when the latter was detectable

RESULTS

- **197 patients** were enrolled (middle table)

- The main reasons for LP were diagnostic assessment in diseases without eventually CNS involvement (25.4%), HIV-associated neurocognitive disorders (28.4%), CNS infections (19.8%) and research purposes (16.2%)



Main Results

1. **CSFE was not associated with PI use** in the whole cohort (16.6% vs 8.6%, p.14)
2. **Having a cumulative plasma HGRT positive for RAMs in RT associated with a higher risk of CSFE** (figure on the left); no such an association was observed for RAMs in PI (17.4% vs 13.8%)

Parameters	CSFE (n 28)	No CSFE (n 169)	p
Gender, male	17 (60.7%)	114 (67.5%)	*NS*
Age, years	48 (41-52)	50 (43-54)	*NS*
Plasma HIV-RNA, Log10 cp/mL	1.7 (1.7-1.9)	1.7 (1.7-2.6)	*NS*
HIV-RNA<50 cp/ml, n	20 (71.4%)	106 (62.7%)	*NS*
CSF HIV-RNA, Log10 cp/mL	**2.1 (1.8-3.6)**	**1.7 (1.7-1.7)**	**<.01**
CD4+ nadir, cells/mmc	81 (17-184)	87 (24-209)	*NS*
CD4+ nadir <200 cells/mmc, n	20/25 (80.0%)	117/158 (74.0%)	*NS*
Current CD4+ count, cells/mmc	341 (181-676)	299 (100-557)	*NS*
Time on cART, month	26 (10-86)	67 (17-175)	*NS*
Time on current cART, month	24 (9-48)	19 (5-36)	*NS*
Continuous virologic suppression, month	17 (7-35)	25 (9-61)	*NS*
CPE score	7 (6-8)	7 (6-8)	*NS*
Type of cART, n			*NS*
Mono/Dual	3 (10.7%)	21 (12.4%)	
2 NRTI + 1 PI	14 (50.0%)	75 (44.4%)	
2 NRTI + 1 nNRTI	2 (7.1%)	16 (9.5%)	
2 NRTI + 1 INI	3 (10.7%)	29 (15.2%)	
3 different class drugs	4 (14.3%)	8 (4.7%)	
≥ 4 drugs	2 (7.1%)	20 (11.8%)	
Plasma HGRT, n	**19 (67.8%)**	**64 (37.9%)**	**<.01**
RT RAMs	**17 (60.7%)**	**62 (36.7%)**	**.016**
Pr RAMs	4 (14.3%)	19 (11.2%)	*NS*

- **CSFE was not associated with PIs use in any subgroup identified by cART type** (3 different-classes-, 3 drugs-NRTIs- and ≥4 drugs-based cART) too.
- **PIs use was more common in patients with a positive HGRT for RAMs in RT** (44.9% vs 29.3%, OR 2.0 [1.1-3.8], p.04)
- **At the CSFE** diagnosis **patients showed higher proportion of positive CSF RAMs in RT compared to patients without CSFE** with available CSF GRT (55.6% vs 19.0%, p.04)
- At multivariable analysis, **only RAMS in RT and CD4 nadir were independent predictors of CSFE** (table below)

Parameter	aOR (95CI)	p
Age, years	*NS*	*NS*
Nadir ≤ 200 CD4+ cells/mmc	**6.6 (1.1-43.0)**	**.047**
Plasma HIV-RNA < 50 cp/mL	*NS*	*NS*
Time on cART, months	0.98 (0.97-1.0)	.056
cART including PIs	*NS*	*NS*
Presence of plasma RAMs in RT	**13.1 (2.4-70.4)**	**<.01**
Presence of plasma RAMs in Pr	*NS*	*NS*
CPE score	*NS*	*NS*

CONCLUSIONS

- In our multicentric cohort, we did not find any association between CSFE and cART-related characteristics or parameters, including PIs use
- Salvage therapy based on drugs with intermediate CSF penetration (such as PIs) and archived RAMs in RT may lead to functional dual/monotherapy
- **PIs use *per se* may not be a risk factor for CSFE** in a setting where boosted PI-based cART is among the first-line recommended regimens and boosted DRV is the most commonly used PI
- Besides low CD4 nadir, **the positivity of HGRT for plasma RAMs in the RT gene** and not the use of PIs *per sé* **was an independent predictor of CSFE**

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