# PML-IRIS ensuing CNS and subsequent peripheral viral escape of ARV-resistant variants


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## Background

**Inflammation and immune cells recruitment can affect the dynamics of HIV-1 viral replication. Herein, we present a patient whom, as a consequence of a robust inflammatory response in the setting of unmasking PML-IRIS, developed HIV-1 viral escape with selection of drug resistant mutations (DRM) in CSF first and peripheral blood after.**

## Methods

**PBMCs and CSF mononuclear cells were used for immunophenotyping along with a flow cytometric T cells responses assay to JC virus (JCV), BK and CMV. Plasma and CSF ARV concentrations were measured by tandem mass spectrometry. CSF and plasma HIV phylogenetic analysis was performed.**

## Results

**A man with HIV/AIDS [CD4: 6 cells/μL (1%), HIV-1 plasma viral load (pVL): 716,531 cp/mL, CSF VL: 1200 cp/mL, no DRM] achieved prompt clinical improvement after cEVG/TAF/FTC initiation. 10 weeks after starting ARV, while HIV-1 VL remained below the limit of detection (bLOD) in plasma and CSF, he developed new ataxia and confusion with multiple parenchymal enhancing lesions. JCV DNA was detectable in CSF and unmasking PML-IRIS was diagnosed. Addition of steroids resulted in clinical and radiological resolution but on week 54, after steroids tapering, he developed a second PML-IRIS flare with new hand tremor: CNS pleiocytosis was found, CSF VL increased to 15,441 cp/mL and pVL to 185 cp/mL. Steroids were restarted with clinical improvement and prompt suppression of plasma and CSF HIV-1 VL bLOD. HIV clinical genotype in CSF revealed a novel E94G in Integrase (INT) and M184V/I in RT but ARV regimen was not changed given suppression of VL bLOD in both CSF and plasma along with complete clinical and radiological resolution.**

**On week 96, pVL progressively increased to 509 cp/mL with new appearance of E94G INT and M184I RT. ARV regimen was changed to cDRV+FTC/TAF with consequent suppression of pVL bLOD. Retrospective analysis of ARV concentrations documented poor CNS penetration. Specific CD4 T cells responses to JCV were documented in CNS and peripheral blood.**

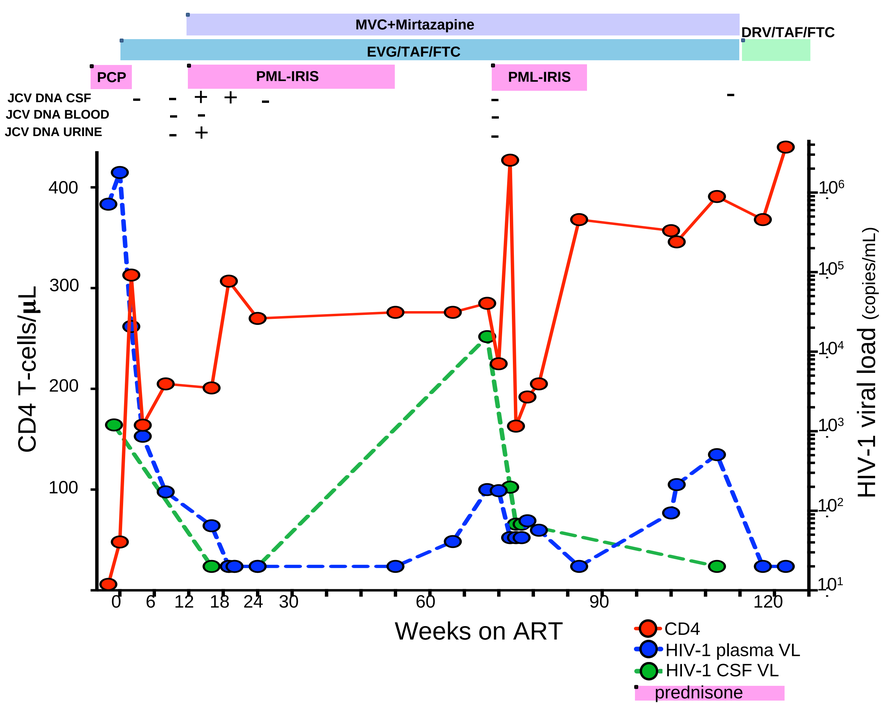



**Figure 1**. Clinical, immunological and virological course

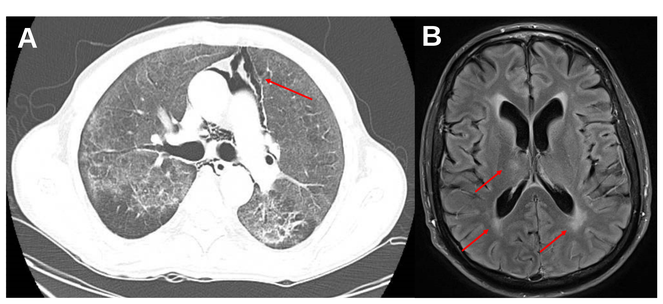



**Figure 2**. Initial presentation with PCP Pneumonia complicated by pneumomediastinum (**A**) and elevated CMV plasma viral load (6 log) with histological evidence of CMV colitis. MRI Brain prior ART: linear ventricular and thalamic FLAIR hyperintensities (**B**). Lumbar puncture: negative DNA PCR for JC, CMV, EBV, HSV.

## Results

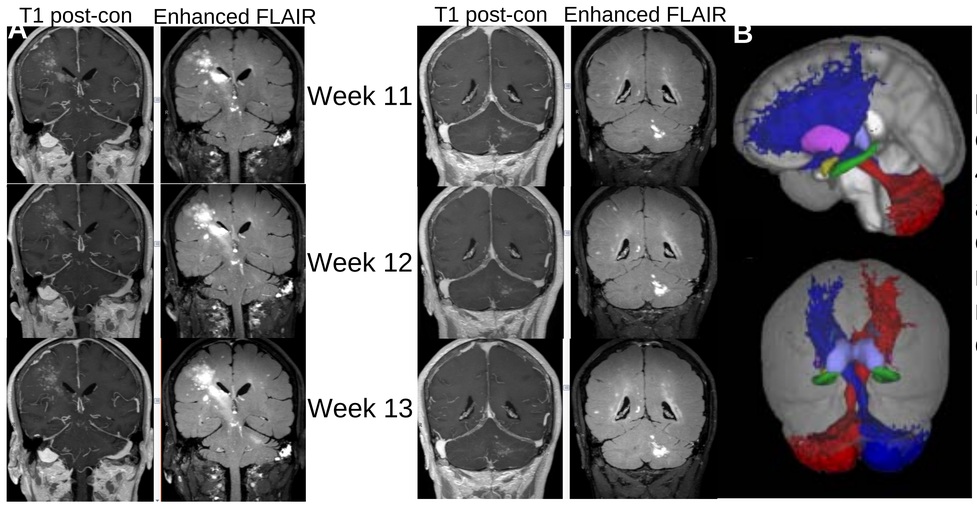



**Figure 3**. On week 10 after ARV initiation, developed confusion and ataxia (CD4 205/8%, pVL 65, CSF VL < 40 cp/mL, JC CSF: 67 cp/mL). MRI reveals punctuate areas of contrast enhancement (**A**) tracking along the cortical-thalamic-cerebellar pathways (**B**) and consistent with PML-IRIS. A course of steroids, maraviroc and mirtazapine was started with prompt resolution of all clinical symptoms

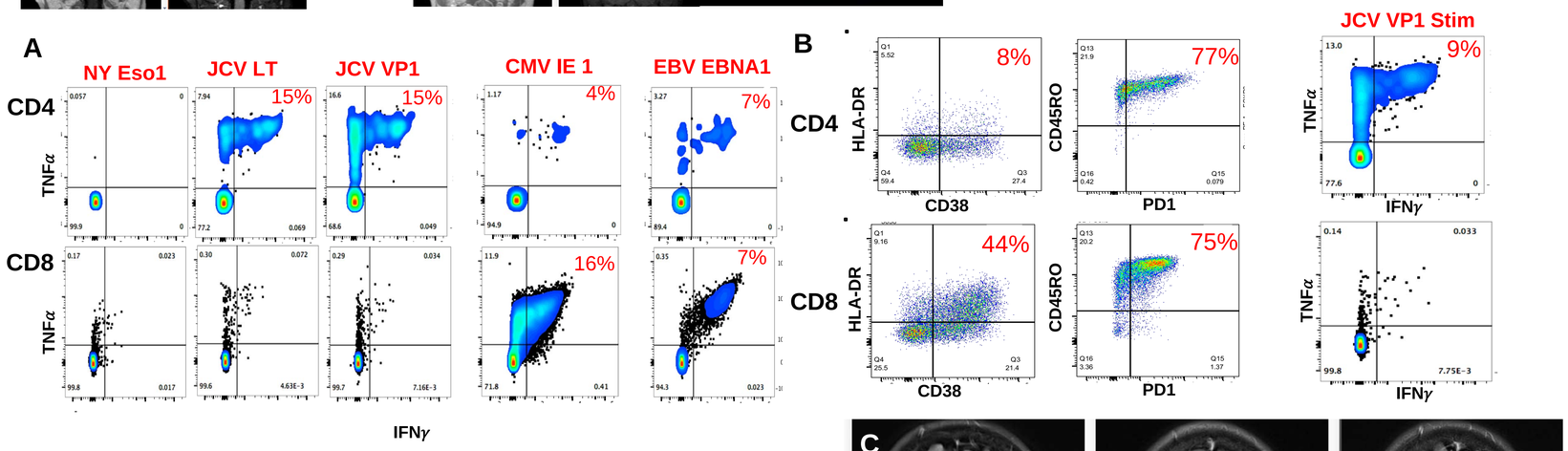
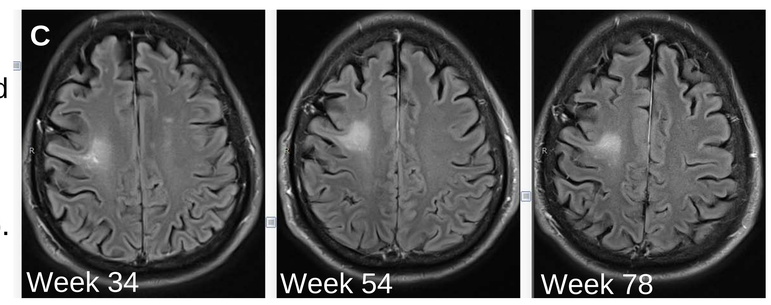
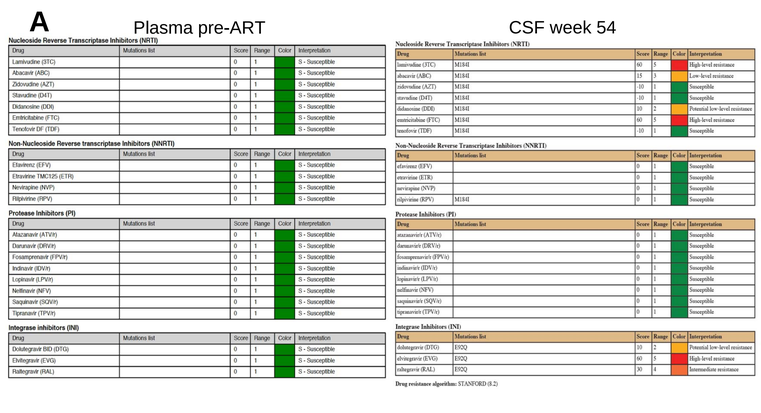



**Figure 4**. Prednisone was slowly tapered but on week 54 developed left hand hemichorea. CSF HIV-1 RNA 15,441 cp/mL (26 WBC). Stimulation of peripheral blood (**A**) and CSF (**B**) T cells with viral peptides revealed high proportion of JC-specific CD4 T cells. MRI: persistent FLAIR hyperintensities without contrast enhancement **(C)**. The recurrent neurological symptoms were attributed to a new flare of PML-IRIS



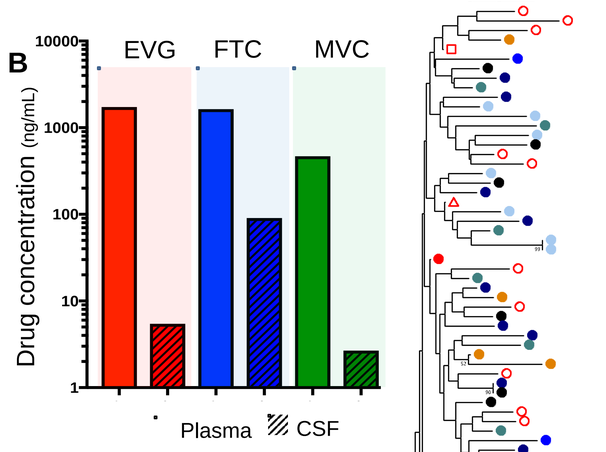




**Figure 5.** Clinical genotypic analysis at time of CNS escape on week 54 documented the presence of M184I and E92Q in CSF (**A**). CSF had lower concentration of ARV compared to plasma at time of CNS escape.

**Single Genome Sequences**

| Taxa | Weeks ART | Sample | Total Sequences p6pol | Total Sequences Integrase | %M184I (N) | %E92QA (N) |
|---|---|---|---|---|---|---|
| ○ | 0 | Plasma RNA | 16 | 16 | 0% (0) | 0% (0) |
| ● | 11 | PBMC DNA | 9 | 14 | 0% (0) | 0% (0) |
| ● | 46 | PBMC DNA | 21 | 24 | 0% (0) | 0% (0) |
| ● | 58 | PBMC DNA | 9 | 23 | 0% (0) | 9% (2) |
| ● | 104 | PBMC DNA | 23 | 15 | 4% (1) | 7% (1) |
| ● | 117 | LN Core1 | 20 | 25 | 0% (0) | 0% (0) |
| ● | 117 | LN Core2 | 9 | 24 | 1 (1%) | 8% (2) |

**Bulk Sequences**

| Taxa | Weeks ART | Sample | %M184I | %E92Q |
|---|---|---|---|---|
| △ | -2 | Plasma RNA | 0% | 0% |
| □ | 0 | Plasma RNA | 0% | 0% |
| ● | 2 | Plasma RNA | 0% | 0% |
| ◆ | 54 | CSF RNA | >20% | >20% |

- Neighbor-Joining Trees
- 1000 reconstructions,
- Rooted on HXB2
- Bootstrap values >50 shown

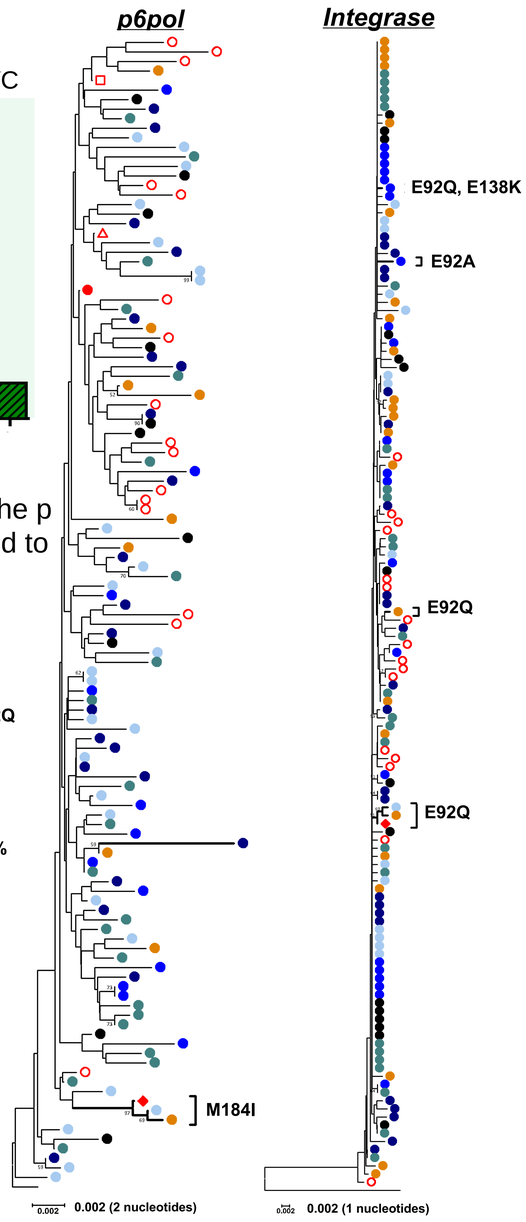



**Figure 6**. Phylogenetic analysis of bulk and single genome sequences documented the absence of M184I and E92Q at time of ART initiation and its appearance in PBMC and a cervical lymph node core biopsy DNA after the CNS escape..

## Conclusions and Future directions

**The emergence of the same DRMs in PBMC and lymphoid tissue several weeks after the resolution of PML-IRIS underline the role of incidental CNS inflammatory processes and trafficking of immune cells in shaping HIV-1 viral quasispecies in CNS and in distant compartments. Incidental inflammatory processes and CNS penetration of ARVs can alter the dynamics of HIV-1 viral replication, the selection of DRMs and the size of the viral reservoir.**