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# HIV Viral Escape in Central Nervous System: A Retrospective Cohort

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## ABSTRACT

**Introduction:** Combination antiretroviral therapy (cART) effectively reduces HIV replication in plasma and cerebrospinal fluid. CSF HIV escape is defined by viral replication in CNS despite virologic suppression in plasma or by higher viral load in CSF than in plasma. The aim of this study was to characterize the patients who met criteria of CNS HIV escape during a 4-year period in a Portuguese hospital.

**Methods:** Retrospective cohort study of adult patients with chronic HIV-1 infection with detectable CSF HIV viral load meeting criteria for CNS HIV escape (n=12), from November 2014 to September 2018.

**Results:** Twelve patients were identified, who presented with long-term HIV infection and low nadir CD4+ T-cell count, and had been on cART for a mean duration of 6 years. Current regimen included in most two NRTIs (n=11) and PI (n=10). Most patients presented with recent onset neuropsychiatric symptoms.

Mean CD4+ T-cell count at the time of viral escape was 361 cells/μL and median viral load in plasma and CSF was respectively 40 copies/mL and 550 copies/mL. Nine patients (75%) had low level viremia in peripheral blood (20-500 copies/mL) in the previous 6 months. Three patients presented concomitant CNS infections (EBV (n=2) and syphilis (n=1)).

All patients who had available genotype resistance tests for CSF HIV RNA (n=4) revealed new resistance-associated mutations (M184V (n=3) or Y115F and K65R (n=1)). In 11 patients cART was modified, achieving clinical improvement.

**Conclusion:** The diagnosis of CNS HIV viral escape should be considered in patients on cART who experience neurological or psychiatric symptoms.

**Keywords:** CNS HIV viral escape, CPE score, Neuropsychiatric symptoms.



## INTRODUCTION

Human immunodeficiency virus (HIV) enters the central nervous system (CNS) early during the course of infection, establishing a unique viral reservoir in this compartment [1,2]. Combination antiretroviral therapy (cART) has changed the HIV epidemic, since it effectively reduces viral load in blood and cerebrospinal fluid (CSF) to undetectable levels by current commercially available assays [1–4].

Nonetheless, HIV may continue to replicate at low levels in CNS despite virologic suppression in peripheral blood [1,3], leading to viral CNS compartmentalization both with or without neurologic symptoms [2]. This clinical entity is termed CNS HIV escape and is defined in current guidelines either by detectable HIV viral load in CSF but undetectable in plasma or by higher HIV viral load in CSF than in plasma [5]. Although asymptomatic in most cases, CSF/plasma discordance can be neurologically symptomatic [2,3], and even cases of severe neurologic impairment have been reported[2]. Moreover, neuroimaging features that might be helpful in the recognition of neurosymptomatic escape have been described [3].

According to published literature, CNS HIV escape occurs in approximately 4-20% of cART-experienced HIV-infected adults. Some risk factors have been identified, such as low CD4+ T-cell count nadir and duration of HIV infection [4]. Recently, a prospective study of 1063 participants found that the use of cART regimens containing protease inhibitors (PI), which have been shown to have lower CNS penetration is an independent predictor of CNS escape [4].

Our aim in this retrospective cohort study was to analyse the cases of CNS HIV escape during a period of nearly 4 years within an infectious diseases department at a Portuguese hospital that has approximately 3000 HIV-infected patients on treatment.

## METHODS

### *Patients*

From a total of 42 lumbar punctures performed with CSF HIV viral load request, from November 2014 to September 2018 in Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal, we retrospectively identified patients with HIV-1 infection who

presented with detectable HIV RNA in CSF samples. We selected patients who were over 17 years old and were on cART for more than 6 months and we compiled patients who met criteria of CNS viral escape as defined below (n=12). Nineteen patients were excluded as had undetectable CSF HIV viral load and the remaining (n=11) have not met the criteria below nor were on antiretroviral therapy for at least 6 months.

### *Definition*

We defined CNS HIV escape according to European AIDS Clinical Society (EACS) current guidelines: HIV viral load detectable in CSF (>20 copies/mL) but undetectable in plasma (<20 copies/mL) or higher HIV viral load in CSF than in plasma [5-7].

### *Data analyses*

Demographic, clinical, laboratory and imaging data from patients' records were collected. We analysed demographic variables (age, sex, origin, race), clinical data (presence of symptoms, duration of HIV infection, history of AIDS-defining conditions, current and previous cART regimens, clinical evolution and time of follow-up), laboratory investigations (CD4+ T cell count, HIV viral load in plasma and CSF, CD4/CD8 ratio, CSF studies, genotypic resistance testing) and magnetic resonance imaging.

### *Laboratory methods*

HIV viral load was measured in CSF and plasma by RT-PCR, with a quantitative detection threshold of 20 copies/mL. Genotypic viral resistance tests were performed in CSF or plasma samples harbouring adequate HIV RNA levels for amplification and interpreted according to widely used genotypic resistance interpretation algorithms (ANRS, Rega and HIVdb).

### *Statistical methods*

Baseline characteristics for continuous variables were summarized using mean and standard deviation (SD) if normally distributed and using median and interquartile range (IQR) if non-normally distributed. Non-continuous variables were presented as frequency and percentages.

## RESULTS

### *Patients characteristics*

Between November 2014 and September 2018, HIV viral load in CSF was measured in 42 adult patients with chronic HIV infection at our institution. Twelve of these patients (29%) met the criteria for CNS viral escape, all of which were on cART for more than 6 months.

As summarized in **Table 1** below, the population comprised 9 men and 3 women with a mean age of 42 years (± 8). Half of the patients were from sub-Saharan Africa, while the others were of Portuguese origin. The mean duration of HIV-1 infection was 9 years (± 8) and most patients had experienced advanced immune suppression in the past (median nadir CD4+ T-cell count was 47 cells/µL (12-92) and 92% of patients had stage 3 infection according to the Centers for Disease Control and Prevention (CDC) case definition 6), with diverse AIDS defining conditions, which had occurred at a median of 2 years (2-6) before the event. Four (4) patients had chronic co-infection with hepatitis viruses (Two (2) patients with hepatitis B virus and Two (2) patients with hepatitis C virus).

Patients had been on cART for a mean duration of 6 years (± 4), and most of them had experienced previous multiple cART regimens. The current cART regimen consisted of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus a protease inhibitor (PI) boosted with ritonavir in 9 patients; two NRTIs plus an integrase inhibitor (II) in 2 patients; and NRTI plus a ritonavir-boosted PI plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) in one patient. The most common ritonavir-boosted PI was darunavir (800 mg QD) (6 patients), followed by atazanavir (2), lopinavir (1) and saquinavir (1), as depicted in **Table 2** below. Both patients whose regimen included an Integrase strand transfer inhibitor (INSTI) were on dolutegravir**.** Mean CNS penetration-effectiveness (CPE)7 score for current regimen was 7(± 1). Periods of non-adherence to cART were reported in patients' medical records in three cases and one patient had experienced treatment failure**.**

### *Clinical manifestations*

Most patients presented with recent onset of neurological or psychiatric symptoms at the time of viral escape, as shown in **Table 2** below. Reported symptoms included unusual or bizarre behaviour (3 patients), cognitive impairment (2), imbalance (2), seizures (2), psychomotor retardation (2), meningoencephalitis (2), headache (1) and memory alterations (1).

One patient (Case 10 in **Table 2**) had history of longstanding, stable depression.

### *CSF parameters*

Nine patients had elevated proteins in CSF (>50 mg/dL) and 8 patients presented pleocytosis (white blood cells count ≥ 10/µL). Median protein level was 79 mg/dL (52-155) and median CSF cell count was 12/µL (6-28). Two patients (Case 4 and 12 in **Table 2**) had concomitant detectable EBV DNA (9350 and 11700 copies/mL, with no evidence of primary CNS lymphoma), one of whom was treated with acyclovir for 14 days (Case 4 in **Table 2**). One patient (Case 8 in **Table 2**) had neurosyphilis and was treated accordingly.

### *MRI findings*

Eight patients had MRI brain imaging at the time of viral escape presentation. In 5 patients MRI showed white matter hyper intensities on T2 weighted image; two of which demonstrated a concomitant perivascular pattern of enhancement. Representative imaging examples are shown in **Figure 1** below. In one patient MRI revealed leptomeningeal enhancement, which was attributed to coexisting meningoencephalitis (Case 4 in **Table 2**)? Finally, two patients demonstrated no MRI abnormalities.

In one case (Case 1 in **Table 2**), brain MRI was repeated after cART modification, revealing imaging improvement **(Figure 2).**

### *CNS HIV viral escape*

Mean CD4+ T-cell count at the time of CSF/plasma discordance was 361 cells/µL ( ± 266), with one-third of the population presenting with CD4+ T-cell count under 200 cells/µL, and mean CD4+/CD8+ ratio was 0.58 ± 0.34. Median viral load in plasma and CSF was respectively 40 copies/mL (0-184) and 550 copies/mL (209-5149). Most patients (75%) had low level viremia measurements (HIV RNA in plasma between 20 and 500 copies/mL) in the previous 6 months.

**Table 1:** Demographic characteristics and HIV history of the sample (n=12).

| Characteristic | n=12 |
|---|---|
| **Demographic** | |
| Age (years), mean ± SD | 42 ± 8 |
| Male sex, n (%) | 9 (75) |
| **Origin n (%)** | |
| Portugal | 6 (50) |
| Guinea Bissau | 4 (33) |
| Angola | 1 (8) |
| Cape Verde | 1 (8) |
| **HIV-1 disease and co-infections** | |
| Time since HIV-1 diagnosis (years), mean ± SD | 9 ± 8 |
| CD4+ T-cell count nadir (cells/μL), median (IQR) | 47 (12-92) |
| AIDS diagnosis, n (%) | 11 (92) |
| **AIDS-defining conditions, n (%)** | |
| Toxoplasma encephalitis | 3 (25) |
| Progressive multifocal leukoencephalopathy | 2 (17) |
| Extrapulmonary tuberculosis | 2 (17) |
| Pulmonary tuberculosis | 2 (17) |
| Oesophageal candidiasis | 1 (8) |
| Disseminated cryptococcosis | 1 (8) |
| Intestinal cryptosporidiosis | 1 (8) |
| Kaposi's sarcoma | 1 (8) |
| Time since last AIDS-defining condition (years), median (IQR) | 2 (2-6) |
| HCV co-infection, n (%) | 2 (17) |
| HBV co-infection, n (%) | 2 (17) |
| **cART** | |
| Duration of all regimens (years), mean ± SD | 6 ± 4 |
| Receiving first regimen, n (%) | 1 (8) |
| **Number of previous regimens, n (%)** | |
| 1 | 7 (58) |
| 2 | 2 (17) |
| 3 | 2 (17) |
| **Current regimen, n (%)** | |
| NRTIs+PI | 9 (75) |
| NRTIs+INSTI | 2 (17) |
| NRTI+NNRTI+PI | 1 (8) |
| CPE score, mean ± SD | 7 ± 1 |
| **Previous genotypic viral test, n (%)** | |
| M184I/V | 4 (33) |
| Negative | 3 (25) |

cART: Combination Antiretroviral Therapy; CPE: Central Nervous System Penetration-Effectiveness; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; INSTI: Integrase Inhibitor; IQR: Interquartile Range; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Analogue Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; SD: Standard Deviation

### *Viral resistance*

As shown in **Table 2** above, genotype resistance tests for CSF HIV RNA were available for 4 patients (33%), all of which revealed new resistance-associated mutations. In all 4 patients, the virus present in CSF was resistant to at least one drug of the current cART regimen. Genotypic resistance test for plasma HIV RNA was possible in 2 patients, one of which showed a similar resistance profile to the CSF one.

### *Follow up*

In 11 patients, cART was modified as follows: quadruple regimen with 2 NRTIs plus PI plus INSTI in 5 patients (addition of INSTI in 4 patients and addition of PI in 1); NNRTI plus PI plus II in 3 patients and NNRTI plus PI plus NRTI in 1 patient (all 4 patients were previously on 2 NRTIs plus PI) and 2 NRTIs plus PI in 2 patients (modification of the current PI in one and substitution of

**Table 2:** HIV history and clinical and virological findings of the population (n=12).

| Case ID | Age, Sex | Signs/symptoms (Duration) | Non-adherence (NA) or treatment failure (TF) | Time since last opportunistic Infection | CD4+ T-cell count (cells/µL) | | Current cART regimen | Previous genotypic test | CSF | | Plasma | | Change in cART | Symptom improvement | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Nadir | At event | | | HIV RNA (copies/mL) | Genotypic test | HIV RNA (copies/mL) | Genotypic test | | | |
| 1 | 43, F | Seizures, cognitive impairment, psychomotor retardation (4 months) | - | <1 y | 3 | 51 | TDF<br>FTC<br>DRV/r QD | No resistance mutations | 291 | No amplification | 80 | NP | TDF<br>FTC<br>DRV/r QD<br>RAL | Partial | 3 y |
| 2 | 45, M | Hetero-aggressive behavior (1 month) | NA | 6 y | 24 | 142 | ABC<br>3TC<br>DRV/r QD | No resistance mutations | 630 | No amplification | <20 | NP | ABC<br>3TC<br>DRV/r QD<br>DTG | Partial | <1 y |
| 3 | 42, M | Unusual behavior (2 years) | TF | 2 y | 44 | 181 | TDF<br>FTC<br>ATV/r | NP | 5449 | M184V | 1013 | M184V | TDF<br>FTC<br>LPV/r<br>RAL | Total | 3 y |
| 4 | 42, F | Meningoencephalitis, cognitive impairment (3 months) | - | 1 y | 8 | 60 | TDF<br>FTC<br>DRV/r QD | NP | 71 | No amplification | <20 | NP | TDF<br>FTC<br>DRV/r QD<br>RAL | Partial | 3 y |
| 5 | 50, F | Unsteadiness in walking (2 months) | - | 4 y | 49 | 248 | ABC<br>TDF<br>LPV/r | M184I, V19E, K201, L10V | 9829 | No amplification | 196 | NP | TDF<br>ETV<br>DRV/r BID | Total | 2 y |
| 6 | 51, M | Memory alterations, psychomotor retardation (4 months) | - | 8 y | 52 | 431 | ABC<br>3TC<br>DRV/r QD | NP | 264 | M184V | <20 | NP | ETV<br>RAL<br>DRV/r BID | Total | <1 y |
| 7 | 54, M | Unsteadiness in walking (2 months) | - | 10 y | 85 | 536 | TDF<br>FTC<br>SQV/r | NP | 4250 | M184V | 111 | NP | ETV<br>RAL<br>DRV/r BID | Total | 2 y |
| 8 | 36, M | Seizures (1 year) | - | 5 y | 94 | 548 | TDF<br>ABC<br>DRV/r QD | M184I | 10895 | Y115F, K65R | 450 | NP | RPV<br>DTG<br>DRV/r QD | Total | 2 y |
| 9 | 37, M | Unusual behavior (2 months) | NA | - | 394 | 982 | TDF<br>FTC<br>ATV/r | NP | 191 | No amplification | 148 | NP | TDF<br>FTC<br>DRV/r QD | Total | <1 y |
| 10 | 45, M | Chronic depression (years) | - | 2 y | 35 | 433 | ABC<br>3TC<br>DTG | No resistance mutations | 32 | No amplification | <20 | NP | TDF<br>FTC<br>DRV/c | Partial | 2 y |
| 11 | 25, M | Chronic headache (1 year) | - | 2 y | 249 | 499 | TDF<br>FTC<br>DTG | K70E, M184V, N115H, T97A | 469 | No amplification | <20 | NP | TDF<br>FTC<br>DTG<br>DRV/c | Partial | <1 y |
| 12 | 38, M | Meningoencephalitis (2 weeks) | NA | 2 y | 5 | 223 | TDF<br>ETV<br>DRV/r QD | M184V, K103N, P225H, V90I | 2020 | No amplification | <20 | NP | | | <1 y (LFU) |

3TC: Lamivudine; ABC: Abacavir; ATV/r: Atazanavir/ritonavir; cART: Combination Antiretroviral Therapy; CSF: Cerebrospinal Fluid; DRV/c: Darunavir/cobicistat; DRV/r QD: Darunavir/ritonavir 800/100 mg once daily; DRV/r BID: Darunavir/ritonavir 600/100 mg twice daily; DTG: Dolutegravir; ETV: Etravirine, F: Female; FTC: Emtricitabine; LFU: Lost to Follow-Up; LPV/r: Lopinavir/ritonavir; M: Male; NP: Genotypic test not performed; RAL: Raltegravir; RPV: Rilpivirine; SRV/r: Saquinavir/ritonavir; TDF: Tenofovir Disoproxil Fumarate; y: Years

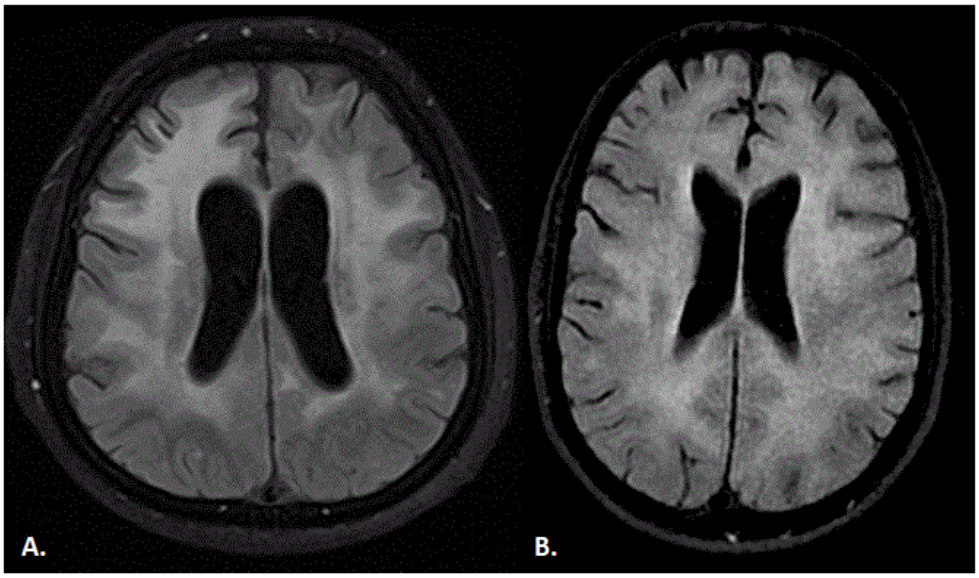


**Figure 1:** A. Case 2, B. Case 6. Brain MRI-Axial FLAIR images with deep and subcortical white matter hyper intense lesions.

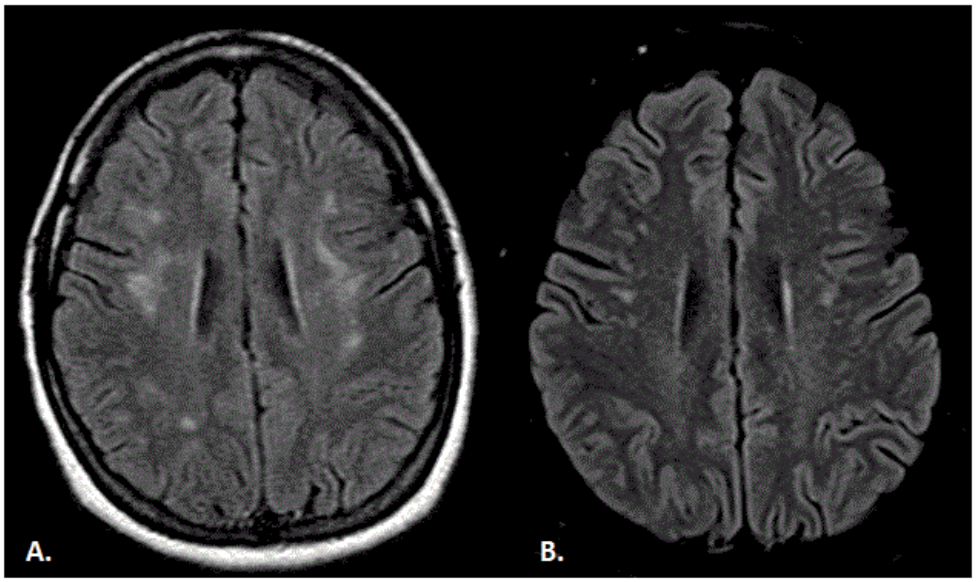


**Figure 2:** Case 1. Brain MRI-Axial FLAIR images with subcortical white matter hyper intense lesions in first MRI (A). Lesions improvement in follow up MRI (B).

INSTI for PI in the other), according to the data in **Table 2**. All patients whose cART was optimized improved clinically.

The patient whose cART remained unchanged was lost to follow-up.

Five patients had CSF HIV viral load follow-up, all of which demonstrated reduced levels **(Figure 3).** Median $\log^{10}$ reduction of viral load was 1.25 ± 0.5.

## DISCUSSION

We report 12 cases of CNS HIV viral escape in the setting of patients on cART. These cases illustrate this clinical entity which is characterized by compartmentalization of HIV in the central nervous system.

Three types of CSF HIV escape have been defined: (a) asymptomatic, (b) neurosymptomatic and (3) secondary. The third category refers to CNS HIV replication in the context of another infection or inflammatory process [8]. HIV is thought to not only facilitate reactivation of latent infections and diseases through immunosuppression but also to facilitate the entry of several pathogens by increasing adhesion and invasion of brain microvascular endothelial cells[7,8]. Conversely, CNS infections appear to enhance the passage of HIV across blood-brain barrier (BBB) or might even sustain local production of the virus, since high viral load in CSF has been detected in patients with opportunistic neurological infections independent of plasma viral load [8]. In our series, most patients were neurologically or psychiatrically symptomatic and concomitant CNS infection was detected in 3 patients (2 co-infections with EBV and 1 patient with neurosyphilis). The clinical presentation of the cases described was variable from changes in behaviour to seizures, therefore representing different degrees of severity.

Narvid et al.[3] recognized imaging characteristics (patchy subcortical white matter intensities and a perivascular pattern of enhancement) in 6 patients with symptomatic escape. In our series, 5 out of 8 patients presented with white matter intensities

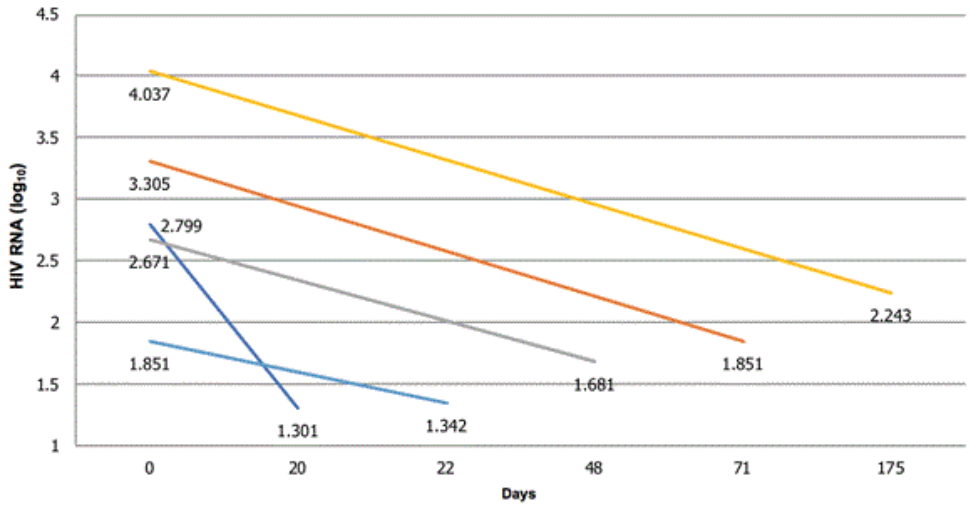


**Figure 3:** Evolution of HIV RNA levels in CSF of the 5 patients who had follow-up measurement. Day 0 represents the day the viral escape was detected and subsequent viral load determination is displayed on the respective day after day 0.

on imaging, while 2 presented concurrently abnormal perivascular enhancement. One patient demonstrated clinical and laboratory improvement as well as imaging amelioration.

The population we report comprises a sample of patients with long-term HIV infection (mean time since diagnosis of 9 years) and history of advanced immunosuppression (low median CD4+ T-cell count (47 cells/μL)) despite CD4+ T-cell count improvement at the time of viral escape (mean count 361 cells/μL). Both duration of HIV infection and low nadir CD4+ T-cell count have been previously identified as risk factors for CNS HIV viral escape[4]. One hypothesis of the mechanism through which viral escape occurs is that advanced immune suppression might ease the entry of HIV into CNS2. Moreover, previous studies have shown a higher prevalence of this entity among patients with LLV as compared to those with complete viral suppression[2]. Three quarters of our patients presented LLV (herein defined as plasma HIV viral load from 20 to 500 copies/mL) in the previous six months. It should be noted, however, that the definition of LLV is not consistent in all cohorts.

Another reason hypothesized for the discordance between CSF and plasma HIV RNA is the limited distribution of cART drugs into CNS, which could lead to subtherapeutic drug concentrations and hence HIV replication in this compartment, possibly with evolution of drug-resistant CSF HIV2. No patients in our series were on mono or dual-therapy and consisting of the current cART regimen of 2 NRTIs plus a ritonavir-boosted PI in 75% of the patients. With regard to CPE score, which intends to estimate drug penetration in the CNS [9], mean CPE value in our cohort was 7 (± 1), and only one patient had a CPE score under 6. In their series, Peluso et al. calculated an "adjusted CPE score", which attempted to assess effectiveness of cART in CNS taking into account viral isolate resistances, by arbitrarily designating "0" to a drug in the current regimen if a resistant-associated mutation to that particular drug was identified in the viral isolate genotypic test [10]. In 4 patients of our cohort, a CSF HIV genotypic test was possible, which allowed calculation of this "adjusted CPE score" (under 6 in 3 patients). It must be taken into consideration, however, that drugs might remain partially effective despite resistance-associated mutations, and in that manner this score might not truly reflect the actual CNS penetration, thus, its effectiveness.

All CSF viral genotypic tests (33% of the population) revealed new resistance-associated mutations, conferring resistance to at least one drug of the current regimen. The same amount of patients had previously documented resistance-associated mutations.

Modification of cART regimen was performed in 11 patients, achieving clinical improvement in most. In patients in whom CSF viral replication was subsequently evaluated, a reduction in RNA levels was also obtained.

This study is limited by its retrospective approach (in which data are based on chart reviews and complete neurological investigations may have been lacking) and by the limited follow-up data, since in many cases studies were not pursued after clinical improvement.

The real prevalence of CNS HIV viral escape in the general population of HIV-infected patients remains unclear, as there is a lack of prospective studies, which would identify asymptomatic cases of viral escape. We also hypothesize that patients with minor neurologic or psychiatric complaints might be less likely to undergo extensive CNS studies.

## CONCLUSION

This series emphasizes the need of considering the diagnosis of CNS HIV viral escape in patients on cART with virologic suppression or low level viremia who present with new neuropsychiatric signs or symptoms. Further studies are warranted to investigate the mechanisms and dynamics of HIV replication in the CNS compartment as well as to a better understanding of its consequences. The current approach for the appropriate management of CNS viral escape requires an individualized treatment regimen based on genotypic testing as well as cART penetration of the CNS compartment, while avoiding neurotoxicity.

## AUTHORS CONTRIBUTION

Patrocínio-Jesus R. was responsible for the protocol, revision of patient files and writing the manuscript, Flor-de-Lima B. was responsible for the protocol and manuscript revision; Casimiro C. revised the MRI images of the selected cases and contributed to the manuscript elaboration; Batista J, Silva J., Diva T. and Patricia P. revised the manuscript.

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