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CENTRAL NERVOUS SYSTEM AND COGNITION (SS SPUDICH, SECTION EDITOR)

Cerebrospinal Fluid HIV Escape from Antiretroviral Therapy

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Abstract CNS infection is a nearly constant facet of systemic CNS infection and is generally well controlled by suppressive systemic antiretroviral therapy (ART). However, there are instances when HIV can be detected in the cerebrospinal fluid (CSF) despite suppression of plasma viruses below the clinical limits of measurement. We review three types of CSF viral escape: *asymptomatic*, *neuro-symptomatic*, and *secondary*. The first, *asymptomatic CSF escape*, is seemingly benign and characterized by lack of discernable neurological deterioration or subsequent CNS disease progression. *Neuro-symptomatic CSF escape* is an uncommon, but important, entity characterized by new or progressive CNS disease that is critical to recognize clinically because of its management implications. Finally, *secondary CSF escape*, which may be even more uncommon, is defined by an increase of CSF HIV replication in association with a concomitant non-HIV infection, as a consequence of the local inflammatory response. Understanding these CSF escape settings not only is important for clinical diagnosis and management but also may provide insight into the CNS HIV reservoir.

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Keywords HIV · Cerebrospinal fluid (CSF) · Central nervous system (CNS) · Brain · Treatment · Encephalitis

Introduction

Central nervous system (CNS) infection is a nearly universal facet of HIV infection that begins at the time of primary infection [1–3] and continues thereafter in the absence of treatment so that HIV RNA can be measured in the cerebrospinal fluid (CSF) of nearly all viremic patients [4–6]. Overall, contemporary combination antiretroviral therapy (ART) is highly successful in reducing CSF HIV RNA levels to below clinical detection limits in individuals with effective plasma virus suppression [7, 8], and has also been highly effective in preventing the most severe complication of CNS HIV infection, HIV-associated dementia (HAD) related to HIV encephalitis [9, 10].

This review discusses three settings in which HIV RNA can be detected in CSF in the absence of comparable HIV RNA levels in plasma, i.e., three types of CSF "viral escape": asymptomatic, neuro-symptomatic, and secondary. These are listed in Table 1 along with some of their salient virological and clinical features. Before considering each of these in turn, we will first briefly discuss pertinent aspects of CNS HIV infection and antiretroviral treatment.

CNS HIV Infection and Treatment Effects

While individually variable, the CSF concentration of HIV RNA (the viral load, *VL*) averages about one tenth that of the plasma VL [11–13]. Figure 1 illustrates the relationship of CSF to plasma HIV in four clinical settings, and Fig. 1(A) uses previously published data from untreated patients [14] to illustrate this relationship. As with systemic infection, CNS

Table 1 Classification of CSF escape

	Biology	Neurological presentation	Plasma HIV RNA (copies/mL)	CSF HIV RNA	CSF WBC
Asymptomatic CSF escape	Equivalent to plasma blips?	Stable or asymptomatic; incidental finding in cohort or other study	<50	50–200*	Normal
Neuro-symptomatic CSF escape	Virological failure in CNS compartment	New or progressive CNS symptoms and signs	<50 or 50–500	>50 or >×2 plasma	Usually elevated
Secondary CSF escape	CNS viral replication related to another infection with inflammation	Reflects provoking infection	<50 or 50–500	>50 or >plasma	Elevated, as by provoking infection

*Occasionally higher

virus populations also evolve within the individual infected host and may change importantly as systemic disease progresses [15, 16, 13]. In general, CSF viruses in early infection derive largely or exclusively from those in blood, presumably carried by and amplified within trafficking CD4+ T cells and monocytes; this has been termed *non-compartmentalized* or *equilibrated* CSF infection. Although CSF and plasma HIV sequences are almost identical in the early, non-compartmentalized infection, local clonal amplification can result in some population differences between CSF and blood [17–19]. These early CSF viruses generally use the CCR5 co-receptor and predominately infect CD4+ T cells (R5 and T-tropic viruses) [20••, 21, 22]. Early infection appears to be largely centered within the meninges, and is frequently accompanied by a lymphocytic pleocytosis; hence, it is the cause of a type of aseptic meningitis, though almost always clinically silent [1, 3, 23].

As systemic infection progresses, CSF viruses may show more diverse compartmentalization involving R5 viruses that infect macrophages and related cells (referred to as M-tropic) [24–29]. While full formal proof of this remains to be shown, it is likely that these viruses are important in the development of encephalitis, in which productive infection can be identified in perivascular and parenchymal macrophages and microglial cells [30]. Whereas HAD is frequently the clinical correlate of HIV encephalitis, it is yet uncertain whether common less severe neurological impairment, manifesting in many patients without overt HAD, can relate to the effects of the T-tropic, largely meningeal infection, to minor populations of M-tropic viruses, or to other mechanisms.

Systemic ART is usually very effective in suppressing CSF HIV [3, 7, 8, 31, 32] and at both preventing and stopping the progression of HAD [33]. The rate of CSF viral decay after ART initiation may be similar to that of plasma or

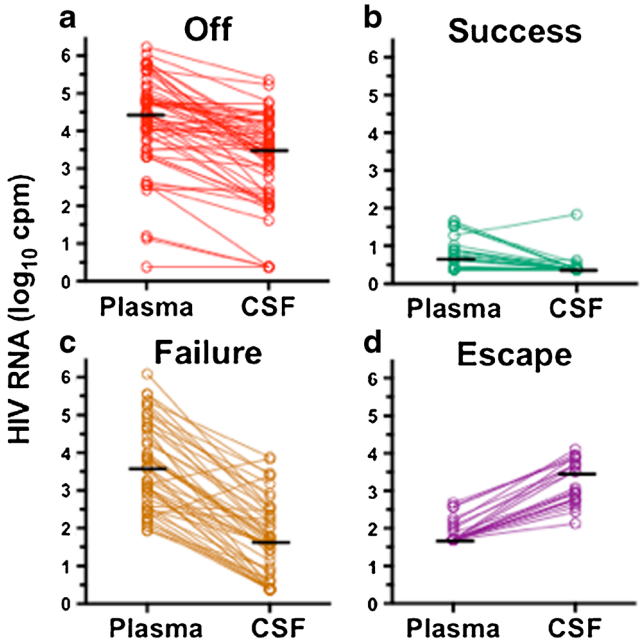

Fig. 1 The data in panels *A–C* are from a cohort study previously published (ref. [14]). The plasma and CSF HIV RNA levels were from the initial study visit when subjects were classified on the basis of treatment status (*A* off treatment, either naïve or off ART) and for those on treatment of plasma VLs below 50 copies/mL (*B* success) or above that level (*C* failure). For comparison, the data graphed in *D* include published data in two series describing neuro-symptomatic escape (refs. [57, 58])

substantially slower, likely depending on the main source of the virus: T-tropic CSF HIV predominating in earlier infection decays quickly, in parallel with plasma, while M-tropic CSF HIV found more commonly late in infection, particularly in HAD in which infected macrophages play a central role, decays more slowly. This likely relates to the different longevities of the cells supporting infection, short for T lymphocytes and longer for macrophages, and to different replication modalities within the two cell types [7, 24, 34–37]. This also may have implications for the demands of ART in suppressing CNS infections in the two settings: when derived and constantly renewed by systemic infection, systemically effective treatments may be fully capable of reducing CNS infection in parallel. However, compartmentalized infection may be more of a challenge and require that local concentrations of antiretroviral drugs are adequate to suppress the local CNS viral replication. This consideration also has potential implications for treatment of neuro-symptomatic escape.

Figure 1(B) shows the general effects of treatment, with most CSF values falling to the limit of detection in patients on chronic suppressive ART (in this study using a sensitive measure with a limit of 2.4 copies/mL), with only one CSF value substantially above this. Unexpectedly, in the patients with systemic treatment failure in Fig. 1(C) (plasma VL>50 copies/mL), while many of the CSF VLs were detected, the difference between CSF and plasma increased to nearly 2 logs, i.e., CSF was proportionally more suppressed than plasma in these patients with drug resistance and reduced adherence [14]. Figure 1(D) shows findings in patients with neuro-symptomatic escape that will be discussed later that contrast markedly with these more common relationships in treated patients.

In patients with plasma viral suppression, i.e., like those shown in Fig. 1(B), the use of a sensitive single copy assay with a detection limit of 0.3 copies/mL showed a 17 % frequency of detection in CSF and 57 % in plasma. Likewise, the median level in CSF was at the level of detection while that in plasma was 1 copy, underscoring the effectiveness of ART in suppressing CSF HIV in most patients, even to a larger extent than in plasma [38]. The origin of the small amounts of HIV RNA detected in CSF is uncertain; whether they are truly local or related to trafficking CD4+ T cells is unknown [38]. However, these observations emphasize how effective ART usually is in suppressing CSF HIV.

An additional issue of treatment relates to whether specific drugs or drug combinations have more favorable effects on CNS infection than others. Unfortunately, there are very limited data directly comparing the neurological or CNS virological efficacy of particular drug regimens. As an indirect approach to this issue, the pharmacological properties of various drugs and, in particular, the capacity of drugs to achieve therapeutic concentrations in the CNS, or as usually measured, in the CSF - "CNS penetration" - have been posited as a key property [39, 40]. Overall, it appears that most regimens are effective in suppressing CSF HIV when suppressing systemic infection and, as treatment regimens have evolved, this may have become less of an issue since many of the now-preferred regimens are assumed to be similar in their "CNS penetration" [41–44]. While the issue of drug penetration and efficacy may not be relevant for most patients in the treatment of systemic HIV, it may assume importance in those with compartmentalized CNS HIV infection and more clearly in patients with neuro-symptomatic escape, as discussed below.

Asymptomatic Escape: *CSF Blips?*

The designation of *asymptomatic CSF escape* refers to patients in whom low levels of CSF HIV above the clinical detection limit are detected in the absence of neurological symptoms or other clear indication of either new or progressive brain injury. Characteristically, these elevations are found incidentally in the course of cohort or other research studies sampling CSF outside of the diagnostic setting.

Eden and colleagues reported finding asymptomatic CSF escape in about 10 % of subjects in a cross-sectional cohort study of 69 individuals undergoing a single study lumbar puncture (LP) [45•]. These increases in CSF HIV VL appeared clinically benign, without evident neurological symptoms or progression. There was no accompanying CSF pleocytosis or biomarker evidence of neuronal injury, as indicated by similar levels of the CSF neuronal injury biomarker, neurofilament light chain protein (NFL), in patients with or without CSF escape. However, there were higher concentrations of CSF neopterin (a biomarker of local macrophage activation) in those with CSF escape, suggesting that CSF viral elevations might exert a biological effect, a mild host inflammatory response. These elevations did not appear to relate to any specific drug regimens or their aggregate CNS penetration and efficacy (CPE) scores [39, 40]. One hypothesis is that asymptomatic minor elevations of CSF HIV RNA are similar to plasma blips, and this is supported by the absence of progressive CSF escape in subjects with occasionally increased CSF viral load when followed longitudinally [46].

At present, the cellular origin and virological character of these elevations in CSF HIV RNA remain undefined, whether bursts of viruses from trafficking cells or signs that a CNS reservoir in macrophages or other cells periodically can produce HIV [47]. However, they are clearly different from neuro-symptomatic escape discussed next: clinically, in their lack of symptoms, signs, or discernable neurological deterioration, and biologically, in their lack of apparent cellular inflammatory response (Table 1). For practical management, the neuroasymptomatic CSF escape seems to have little therapeutic implication, including particularly no rationale for modifying therapy. However, whether it indicates a potential

pathogenetically important process that may take a toll on the CNS over the duration of treatment is uncertain.

A special issue related to asymptomatic CSF escape has been raised in the setting of ART simplification using two-drug or single-drug regimens such as ritonavir-boosted protease inhibitors (PI/r) monotherapy. In this setting, there is concern that uncontrolled CSF HIV replication, even at low levels, might theoretically lead to development of resistance and systemic viral failure. In addition to a few cases of symptomatic CSF escape, reported later [48–52], PI/r monotherapy was also associated with neuroasymptomatic CSF escape.

The prevalence of asymptomatic CSF escape (plasma HIV RNA<50 copies/mL, CSF HIV RNA>50 copies/mL) was 15 % (3/20 patients) in a pilot study of patients receiving long-term atazanavir/ritonavir (ATV/r) monotherapy (ATARITMO) [53], 19 % (4/21) in patients receiving lopinavir/ritonavir (LPV/r) monotherapy in a randomized controlled trial (compared to 5 %, 1/20 of patients receiving standard regimen) (MOST) [49•], and 7 % (1/14) among patients without overt neurological disease, but with neurocognitive impairment, as defined by a global deficit score of ≥0.5, in most of the cases, and receiving either darunavir/ritonavir (DRV/r) or LPV/r monotherapy (compared to 6 %, 1/16 of similarly cognitively impaired patients on LPV/r or DRV/r-based triple therapy) [55]. Using assays with a lower HIV RNA detection limit, estimated at 1 c/mL, the prevalence of asymptomatic CSF escape in the above study was 71 % (10/14) in monotherapy patients (compared to 50 %, 8/16 in patients on triple therapy [55]) and 11 % (2/17) in a cross-sectional study of patients receiving long-term LPV/r monotherapy (compared to none of 17 patients on LPV/r-based cART) [54].

In all the cases, there was no CSF pleocytosis and CSF HIV RNA levels, ranging between 75 and 6309 copies/mL at the time of the escape, returned below detection limit after reintensification with previously discontinued double nucleos(t)ide backbone [56]. Whether or not these patients would have gone on to neuro-symptomatic CSF escape described later is not certain.

Symptomatic Escape: *Isolated CNS Treatment Failure*

Quite distinct from asymptomatic CSF elevations is a syndrome characterized by "discordant" elevations of CSF HIV RNA in chronically ART-treated patients presenting clinically with overt neurological symptoms and signs, referred to here as *neuro-symptomatic CSF escape*. This entity was first clearly outlined in a case series of 11 patients reported by Canestri and colleagues [57••], subsequently supplemented by a second case series of 10 patients [58••], and by a number of individual reports [48, 50, 51, 59–65]. Overall, these cases support the concept that symptomatic CSF escape is an uncommon but real condition. Its boundaries, however, still remain to be clearly defined.

In almost all cases described so far, symptoms arose after a long-term ART regimen, from several months to years, with effective suppression of plasma replication. Table 1 includes some of the main features and tentative virological definitions of neuro-symptomatic CSF escape. Dissociation between CSF and plasma virus concentrations is the hallmark of this disorder. In those with plasma HIV RNA levels below detection limit, detectable CSF levels may be present, while in those with low but measureable plasma VLs, levels at least twice as high are characteristic (Fig. 1(D)). In understanding these CSF:plasma differences, it is relevant to refer to the usual ratios described earlier and illustrated in Fig. 1(A–C), in which plasma VLs are characteristically higher than CSF.

Neurological presentations of neuro-symptomatic CSF escape vary and may include focal or non-focal neurological symptoms and signs. Among the reported cases, most patients presented with insidious onset, over few weeks or months, of neurocognitive impairment [57••, 58••, 60, 61, 63], behavioral changes [60, 63], fatigue [60], headache [51, 57••, 62, 65], cerebellar dysfunction (including dysarthria, ataxia, or dizziness [50, 51, 57••, 58••, 59, 60]) and focal sensory or motor signs [51, 57••, 64, 61, 55, 44]. In most of these cases, the MRI correlate was of a diffuse white matter hyperintensity on the T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, without or with only subtle contrast enhancement. These abnormalities have been noted throughout cerebral, cerebellar, and brain stem white matter, with a predilection for periventricular areas, basal ganglia, cerebellum, and white matter (Fig. 2). These findings are reminiscent of those reported in pre-ART HIV encephalitis, but usually without displaying associated brain atrophy [66], though one case with atrophy has been reported with long-standing uncontrolled viral escape [61].

However, the onset of symptoms could be more acute, presenting within days with seizures [48], headache and stiff neck [48, 59, 65], and alterations of consciousness [57••]. Fever was also reported in some cases. MRI of these cases may show focal, contrast-enhancing, T2 hyperintense and T1 hypointense subcortical lesions [48, 58••], and meningeal thickening with contrast enhancement in T1-weighted sequences [58••, 62]. Some of these cases may remind of the acute meningoencephalitis cases observed during primary infection or in the context of the acute retroviral rebound syndrome following ART interruption [23, 67].

Table 2 summarizes some of the main laboratory features of this disorder, drawing on previous reports. These include relatively high blood CD4+ T cells (and high CD8+ cells, not shown), but low nadir blood CD4+ cell count. Unlike most treated patients, whether systemically suppressed or not, neuro-symptomatic escape patients characteristically exhibit

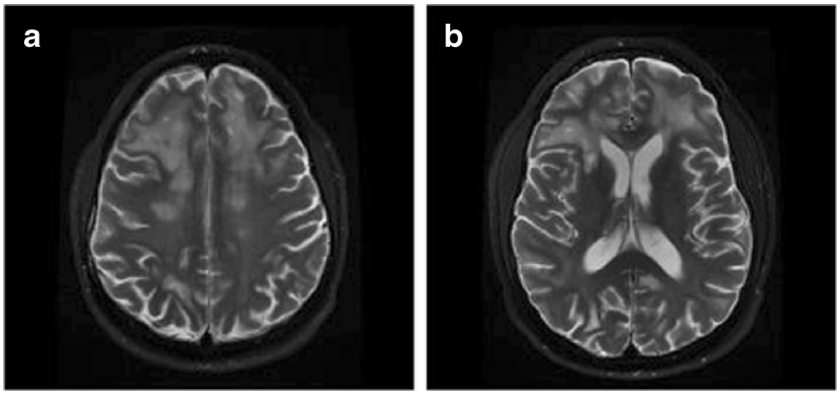

Fig. 2 **a**, **b** Axial T2-weighted sequences showing bilateral diffuse hyperintense signal alterations in the periventricular white matter in a case of neuro-symptomatic CSF viral escape. The patient was a 46-year-old man, who was admitted with behavioral and cognitive changes while on treatment with lamivudine, abacavir, and saquinavir. Blood and CSF examinations at admission showed plasma HIV RNA <40 c/mL, CSF HIV RNA 274 c/mL, CSF HIV genotyping M184V reverse transcriptase mutation, CSF white blood cells 68/μL, and CD4+ 545/μL

a CSF pleocytosis, indicating that it is an inflammatory disorder. Mean CSF HIV levels were near 1,000 copies/mL so that the usual CSF to plasma ratio was reversed with the former 10 times higher.

There is some overlap of these clinical cases with those classified pathologically as CD8+ cell encephalitis by Gray and colleagues [68••, 69] and similar forms previously described as demyelinating leukoencephalopathy [70••]. CD8+ cell encephalitis likely relates to the coexistence of HIV encephalitis and a relatively preserved or restored T cell population and differs in this way from HIV encephalitis in untreated patients in which blood T cells are often reduced late in systemic infection progression. Pathologically, CD8+ cell encephalitis is characterized by CD8+ lymphocyte perivascular and parenchymal infiltration, with sparse cells staining positively for HIV antigens, in contrast with the classical form sustained my macrophage-microglial cell predominance with abundance of HIV antigen-positive cells. Although several of the reported CD8+ cell encephalitis cases occurred in the same setting as that of neuro-symptomatic CSF escape [68••, 69], the spectrum of neuropathological abnormalities associated with this condition, and the respective role of inflammation and virus replication in sustaining the clinical picture, remains to be established.

What causes this isolated or disproportionate treatment failure in the CNS in the face of systemic treatment success? A number of factors, of varying importance, may contribute. Low CD4 nadir is a common background condition, perhaps laying the foundation through previous establishment and persistence of M-tropic CNS infection despite therapy. More immediately, two factors related to treatment are important. One is the development of drug resistance within the CNS, which may develop on a background of prior systemic resistance. Resistance of CSF viruses to components of the treatment regimen has been a common finding in the escape patients (Table 2) [48, 50, 51, 57••, 58••, 59, 60, 61, 62, 63, 64, 65]. The second factor relates to the penetration of the components of the regimen into the CNS, indeed providing the clearest setting where such penetration can be important. Treatment with drugs with limited CNS penetration, or with PI/r monotherapy or other simplified regimens, has also been a common finding in these cases. In addition, both drug resistance and relatively low CNS penetration may be fostered by incomplete treatment adherence. While one or the other of these factors may be predominant, they may operate together with the result, especially in a context of poor adherence, that the concentration of active drugs

Table 2 Characteristics of neuro-symptomatic CSF escape patients

Variable	Median (IQR)	Range
Blood CD4 (cells/μL)	520 (308–592)	107–660
Nadir blood CD4 (cells/μL)	55 (12–145)	2–250
CSF WBC (cells/μL)[a]	22 (10–55)	0–200
Plasma HIV (log_{10} copies/mL)	1.69 (1.69–2.68)	1.69–2.68
CSF HIV (log_{10} copies/mL)	3.01 (2.76–3.72)	2.13–4.11
CSF:plasma difference (log_{10} copies/mL)	1.25 (1.06–1.44)	0.44–2.23

Significant resistance was observed in 14 of 16 cases tested (70.6 %)

Values refer to refs [57, 58]

[a] Ref [57] only; ref. [58]: median 31, range 6–270

achieved in the CNS is inadequate to suppress the local, compartmentalized infection.

Biologically, the relative preservation of the systemic immune system with restored CD4 and high CD8 T cells characteristic of treated patients may be important in determining the phenotype of the disease with its CSF pleocytosis and frequent CD8 encephalitis.

Management of patients with neuro-symptomatic CSF escape starts with clinical suspicion at the onset of new CNS symptoms. MRI is important to document encephalitis and may reveal variable lesions, usually predominating in the white matter. CSF analysis is also essential, first to establish the inflammatory profile characteristic of the disease and then the presence of HIV RNA—and to exclude other CNS infections. CSF should also be used to assess local HIV drug resistance. In some medical facilities, it may be difficult to obtain CSF analysis of either the VL or drug resistance. With a high suspicion, every effort to obtain these assessments should be made since they are essential for diagnosis and rational management. If these cannot be done, then less certain diagnosis can be entertained and treatment adjustments made on an empirical basis [38, 40, 39].

The importance of HIV encephalitis as the etiological driver of this condition is supported by the arrest and reversal of neurological deficits in many of these patients when their ART regimens were changed. Such changes should take into account the two aspects of treatment contributing to the condition: drug resistance and CNS drug penetration. Thus, based on genotypic testing of CSF HIV and the history of the patient's prior treatments, the new regimen should include at least two drugs that the CSF HIV is sensitive to that also penetrate the CNS relatively well. Common candidate drug combinations may include either a tenofovir-emtricitabine, abacavir-lamivudine, or zidovudine-lamivudine nucleoside backbone (it is not clear whether one of these is more effective than the other in CNS infection) and, as third drug, the PI DRV/r bid or LPV/r [41–43], the integrase inhibitor dolutegravir [44], the entry inhibitor maraviroc, if additional information of CCR5 tropism of CSF virus is available or, less attractive because of lower barrier to resistance and possible CNS confounding side effects, the non-nucleoside reverse transcription inhibitor efavirenz. However, selections beyond these currently preferred regimens may be needed in the presence of more complex treatment and resistance histories. In cases where CSF escape occurs in the setting of monotherapy or simplification strategies, reintensification to a full triple-therapy regimen will likely suffice. It is essential, however, that ART optimization is combined with all the possible efforts to optimize adherence, including, in case, direct observed therapy. Lastly, patients with a histopathological diagnosis of CD8+ cell encephalitis, including a few with CSF viral escape, have been treated with high-dose intravenous steroids in association with ART optimization, with total or partial recovery in approximately two thirds of the cases [69]. At the moment, such an approach may find a rationale in case of potentially life-threatening acute inflammatory reaction.

Secondary Escape: *Epiphenomenon of Superimposed Infection or Inflammation*

In the third category, secondary CSF viral escape, CNS viral replication occurs in the context of another infection or inflammatory process that causes an influx of CD4+ cells susceptible to HIV infection into the CSF. This is uncommon and indeed may be more important as a theoretical construct than as a clinical problem. This mechanism involving secondary isolated CNS replication is often raised in the differential consideration of the neuro-symptomatic CSF escape syndrome discussed above and the question asked: "How can one be certain that the elevated CSF HIV RNA really is caused by primary CNS HIV infection rather than related to another infection that causes an inflammatory response that provides a foundation for local viral replication?"

The plausibility of disproportionate CSF HIV levels in treated patients with concomitant infections is in part predicated on observations of higher CSF than plasma VL concentrations in a number of nervous system infections in untreated patients, including neurosyphilis [71], herpes zoster [72, 73], and neuroborreliosis [74]. In treated patients, we have observed disproportional elevation in CSF compared to plasma VLs during herpes zoster [Hagberg L and Gisslen M, personal communication], and in a case of neuroborreliosis [74], suggesting that this type of escape can indeed be seen during some infections. This issue has not been consistently studied, and the frequency of this condition is uncertain. Because it likely parallels the course of inflammation related to the primary infection, CSF pleocytosis should be a consistent feature, and no ART adjustments necessary.

Conclusions

While CNS infection is usually very well controlled by ART, we have reviewed three exceptions. Asymptomatic escape shows that HIV can continue to reach the CNS (or, at least, the CSF) despite suppressive therapy. Whether that virus is simply being carried by trafficking cells or originates within the CNS is uncertain as is whether it is indeed replicating (with potential genetic evolution) or is simply released as considered for plasma blips. Clinically, the main question is whether asymptomatic escape is always benign or could be an actor in chronic inflammation and injury and neurocognitive impairment.

By contrast, neuro-symptomatic escape is clearly an important clinical entity related to an unusual form of treatment failure. It also raises the relevant issue of possible chronic

CNS persistence and hence a CNS viral reservoir, which may reactivate in the setting of inadequate local therapy. Its clinical morbidity demands early recognition followed by appropriate clinical evaluation that includes CSF analysis of HIV RNA levels and drug resistance testing. With appropriate ART adjustment, the majority of the reported cases have resolved with variable, but often substantial, improvement.

Secondary escape appears rare, but is of theoretical interest as it relates to or contrasts with the other two types of escape. Understanding the pathobiology of each of these three escape types has potential importance for better understanding the CNS reservoir and its release from ART control which, in turn, has implications for viral eradication.

Compliance with Ethics Guidelines

Conflict of Interest Francesca Ferretti declares payment from Bristol-Myers Squibb for educational presentation and travel expenses.

Magnus Gisslen declares payment for board memberships on the Scientific Advisory Boards from Gilead, Janssen, BMS, MSD, and GSK/ViiV, and honoraria payment for lectures from BMS, Gilead, Janssen, AbbVie, and GSK/ViiV, and declares travel expenses paid for by Gilead.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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