Antiretroviral Therapy and Central Nervous System HIV Type 1 Infection

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Central nervous system (CNS) human immunodeficiency virus type 1 (HIV-1) infection begins during primary viremia and continues throughout the course of untreated systemic infection. Although frequently accompanied by local inflammatory reactions detectable in cerebrospinal fluid (CSF), CNS HIV-1 infection usually is not clinically apparent. In a minority of patients, CNS HIV-1 infection evolves into encephalitis during the late stages of systemic infection, which compromises brain function and presents clinically as acquired immunoodeficiency syndrome dementia complex (ADC). Combination antiretroviral therapy (ART) has had a major impact on all aspects of CNS HIV-1 infection and disease. In those with asymptomatic infection, ART usually effectively suppresses HIV-1 in CSF and markedly reduces the incidence of symptomatic ADC. In those presenting with ADC, ART characteristically prevents neurological progression and leads to variable, and at times substantial, recovery. Similarly, treatment has reduced CNS opportunistic infections. With better control of these severe disorders, attention has turned to the possible consequences of chronic silent infection and the issue of whether indolent, low-grade brain injury might require earlier treatment intervention.

The central nervous system (CNS) is a major target of HIV-1 infection and HIV-1–related diseases. Chronic CNS HIV-1 infection begins during primary systemic infection and continues in nearly all untreated seropositive individuals [1–5]. Late during the course of systemic infection, asymptomatic and seemingly benign CNS HIV-1 infection can progress to a more-invasive HIV-1 encephalitis (HIVE) that manifests as a clinical syndrome of cognitive, motor, and behavioral dysfunction known as AIDS dementia complex (ADC) [6–12]. In the late stages of systemic immunosuppression and AIDS, the CNS also is vulnerable to several severe opportunistic diseases. In the early years of the HIV-1 epidemic, these neurological conditions were characterized by high morbidity and mortality. This continues to be the case in resource-poor regions of the world currently devastated by the AIDS epidemic [13–16]. By contrast, in more highly developed countries, the widespread use of combination antiretroviral therapy (ART) has profoundly reduced this CNS disease burden [17].

This review will focus on the effects of antiviral therapy on CNS HIV-1 infection and disease, emphasizing the major accomplishments of ART in preventing CNS diseases, including both opportunistic infections and ADC/HIVE, and in arresting established ADC. Consideration will be given to the characteristics of chronic CNS HIV-1 infection and the effects of treatment, including the emerging issues of whether chronic, silent infection has long-term neurological sequelae and, if so, whether they can be treated. The adverse effects of therapy on the CNS will be briefly reviewed.

Before proceeding, 2 general caveats must be introduced. First, because clinical trials directly targeting CNS HIV-1 infection or ADC have been very difficult to implement, current treatment considerations derive largely from observational studies and from extrapolation of the results of systemic therapy within the theoretical context of CNS HIV-1 infection and neurological injury. In contrast to that for systemic treatment,
there is a dearth of direct empirical evidence to guide optimal treatment of CNS HIV-1 infection. On the other hand, progress in the prevention of neurological diseases during HIV-1 infection has clearly been substantial, and neurological disease-associated morbidity and mortality have been markedly reduced. Second, much of the current understanding of CNS HIV-1 infection and, in particular, its response to therapy derives from studies of cerebrospinal fluid (CSF). Although this accessible body fluid provides an invaluable window into the dynamics of brain infection and treatment [18, 19], it also can diverge in important ways from the brain. CSF constituents derive not only from the contiguous perivascular spaces and brain parenchyma involved in HIV but also from the choroid plexus, where this fluid is formed, and the surrounding leptomeninges, where it is subsequently modified.

**OVERALL IMPACT OF ART ON AIDS-RELATED NEUROLOGICAL DISEASES**

Before turning to some of the unresolved issues of HIV infection–related neurology, it is important first to consider the profound impact that combination ART has already exerted. During the early years of the HIV-1 epidemic, CNS diseases complicating late HIV-1 infection ranked high among those associated with the greatest morbidity and highest mortality. Several reasons accounted for these poor outcomes, including the absence of specific treatments. However, even treatable diseases, such as cryptococcal meningitis and cerebral toxoplasmosis, were associated with poor outcomes. This certainly was related in part to their onset during the late stage of systemic HIV-1 infection, but it is possible that their neurological sequelae increased patients’ vulnerability to other complications and also led caregivers, families, and patients to discontinue further therapeutic and supportive efforts.

The incidence of all AIDS-related CNS diseases is now markedly reduced. This was well documented in the EuroSIDA cohort, which showed a 10-fold decrease in CNS diseases that paralleled a decrease in systemic AIDS-related complications after protease inhibitors (PIs) and triple-drug therapy were introduced. Fewer cases of all the common CNS opportunistic diseases were observed, including cryptococcal meningitis, cerebral toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy (PML) [17].

Paradoxically, this reduction in the incidence of classic CNS complications of advanced HIV-1 infection has made neurological diagnosis more difficult in certain ways. Because the frequency of these familiar diseases has decreased markedly, the stereotyped, overwhelming neurological vulnerabilities of late-stage HIV-1 infection no longer have the same weight in diagnostic probabilities. HIV-related diseases now are intermixed with other disorders, including those affecting the general population (e.g., age-associated degeneration) and those related to comorbidities associated with the risk of acquisition of HIV-1 infection (e.g., complications of substance abuse). In addition, because of the difficulty of gaining admission to and remaining in treatment programs, patients troubled by substance abuse or mental illness now comprise a substantial proportion of those at highest risk for late-stage immunosuppression and its consequences. These patients often present with a more-complex neurological picture than do many of those seen during the pre-ART era. Immune reconstitution also may alter the presenting-disease phenotype.

The major CNS opportunistic diseases that had been common in the developed world remain a scourge in resource-poor settings, with some geographic variation in their relative frequency; diagnosis of these diseases also may be confounded by the high incidence of CNS infection by *Mycobacterium tuberculosis*, *Plasmodium* species, and other endogenous pathogens [16]. As many people in these regions transition to treatment at low blood CD4 cell counts, immune reconstitution inflammatory syndromes (IRISs) are likely to become more significant in disease presentation and management. All these issues are magnified by major deficiencies in diagnostic technology, most conspicuously with regard to modern neuroimaging modalities that critically influence the diagnosis and management of CNS disease in the developed world. In fact, diagnostic imprecision has impeded accurate epidemiological accounting of neurological diseases and limited treatment specificity in resource-limited settings.

**EFFECT OF ART ON ADC**

*Prevention of ADC.* With regard to major opportunistic infections, the widespread use of ART has markedly reduced the incidence of overt ADC (stages 1–4). In the EuroSIDA cohort, ADC was the most common severe CNS disease before ART and showed the greatest reduction in incidence between 1994 and 2002 [17]. This decline conforms to common clinical experience in the developed world. In our practice, subacute or progressive cognitive-motor decline similar to that encountered before ART are uncommon and confined almost exclusively to untreated patients or those experiencing treatment failure because of drug resistance or nonadherence. Both the disease presentation and the contextual background of immunosuppression are anachronistic in the current era. As commented earlier, these patients may present with additional diagnostic problems related to concurrent diseases and risks that obscure or confound diagnosis. The issues of continued prevalence of cognitive-motor impairment in treated patients who have not fully recovered neurologically and of the significance of milder, more-indolent brain injury may become increasingly important.

*Treatment of ADC.* Although it is clear that ART can arrest ADC and reverse its neurological disability, the general mag-
ntitude of this effect is variable and not precisely defined. Since an early AIDS Clinical Trials Group (ACTG) study (protocol 005) that showed the therapeutic benefit of zidovudine monotherapy for the treatment of ADC [20], there have been few controlled treatment studies [21–24]. Most reports document only anecdotal or observational experience or describe neurological or neuropsychological test results as secondary outcomes. In these studies, treatment regimens usually were not chosen to directly address specific neurological issues. Nonetheless, the aggregate experience that ART ameliorates ADC appears to be compelling and indicates that neurological dysfunction can be reversed. Although the magnitude of recovery can be dramatic, more frequently residual signs or symptoms remain. Figure 1 provides anecdotal evidence of the effects of ART on biological and neurological parameters in 2 patients with ADC seen in our practice [12, 26, 27]. These observations are similar to those reported by others [28].

**Pathogenesis of ADC.** These therapeutic effects are consistent with current views of ADC pathogenesis. Although fundamental questions regarding mechanistic details remain, the principal pathological substrate of severe ADC is HIV-E characterized by foci of infected macrophages and microglial cells, along with multinucleated cells derived from these cells by virus-related cell fusion [8, 10, 11, 29]. Other changes include widespread white-matter pallor, accompanied by microglial and astrocytic proliferation. HIV-1 infection in the brain manifests a predilection for the basal ganglia and deep white matter, providing a substrate for the subcortical type of dementia found in these patients [7]. However, specialized histological techniques and electron microscopy also show neuronal abnormalities [30–32].

These pathological changes indicate that HIV-1 is the pathogenetic “driver” of ADC/HIVE, and reversal of clinical disease by ART supports this hypothesis. Indeed, the extent of reversal suggests that a substantial share of neurological dysfunction relates to active, reversible toxic processes and that the disease

**Figure 1.** Effect of antiretroviral therapy (ART) on AIDS dementia complex (ADC). Graphs show the changes in plasma and cerebrospinal fluid (CSF) HIV-1 RNA levels (top), blood and CSF neopterin levels (middle), and composite quantitative neurological performance Z scores on 4 tests (QNPZ-4; bottom) [22, 25] for 2 patients with ADC after starting ART. Patient 4033 (left panels), a 38-year-old man with ADC stage 2, was treated with abacavir, lamivudine, nevirapine, and boosted indinavir, which led to a rapid decrease in both CSF and plasma HIV-1 RNA levels and in CSF neopterin levels from high baseline levels. During this same 3-month period, the patient improved neurologically (as documented by the increase in QNPZ-4), but he plateaued at an “impaired” level of approximately 1/1000, reflecting continued motor dysfunction that included a mild spastic gait. He was able to return to school and to acting. Patient 5002 (right panels), a 38-year-old man with ADC stage 3, was treated with abacavir, lamivudine, nevirapine, and nelfinavir. Although there was an initial delay in the decrease in CSF HIV-1 RNA concentration, it eventually fell to an undetectable level. Similarly, his CSF neopterin concentration decreased from a high baseline level. The QNPZ-4 score increased steadily over the first 3 months and continued improving over the remaining year, eventually reaching a normal level as he returned to a nearly asymptomatic functional level (ADC stage 0.5).
might be seen as a multifocal, microscopic, metabolic encephalopathy. An important factor is that HIV-1 infects extrinsic brain cells, particularly macrophages and microglia of bone marrow lineage, rather than inducing direct cytolytic infection of neurons, oligodendrocytes, or astrocytes, which are the major “functional elements” of the brain. For this reason, major theories of brain dysfunction and damage have focused on the indirect mechanisms of injury that involve both virus- and cell-coded signals and pathways [8, 32]. The role of macrophages is at the center of these theories, both as the major substrate for HIV-1 replication and as the source of important toxins coded signals and pathways [33, 34]. A plethora of putative signals and toxins have been implicated, and brain injury and clinical dysfunction are likely to involve several related or overlapping pathways [35–38].

**Diagnosis and evaluation of ADC and treatment outcomes.**

Despite its basic characterization >2 decades ago [6], the nosology and diagnosis of ADC are difficult in both clinical practice and clinical trials [24, 27, 39–41], in large part because ADC remains a phenotypic diagnosis that relies on recognition of the clinical syndrome and exclusion of alternative diagnoses, rather than on specific laboratory-based findings. Although slowed movements, spastic gait, and hyperactive deep-tendon reflexes may be particularly suggestive of ADC in an HIV-infected patient with slowed cognitive processing [6], these abnormalities are not diagnostically specific. A recently suggested revision in research terminology that uses the overall designation “HIV-associated neurocognitive disorder” (HAND) and that relies heavily on neuropsychological testing has added quantitative standardization to evaluation but does not add greater specificity to the diagnosis [42]. HAND also encompasses individuals with mild or without complaints of functional impairment who are identified by lower-than-normal test performance, which is likely to lower the specificity of identification of HIV-1-related brain injury. Because of this reliance on neuropsychological testing to define and categorize HAND, we continue to use the ADC terminology and staging in clinical practice [43].

Neuroimaging should be performed during the process of diagnostic evaluation of patients with AIDS and cognitive impairment. Certain findings with computed tomography (CT) or magnetic resonance imaging (MRI) are consistent with or even suggestive of ADC, including diffuse cerebral atrophy and subcortical or periventricular white-matter changes, which appear hypodense on CT scans or bright on T2 sequences on MRI scans. In the diagnostic evaluation of a patient with HIV infection and neurological impairment, neuroimaging is most useful as a means to exclude other common neurological conditions, since neither atrophy nor white-matter changes are sensitive or specific to ADC [44–46]. Among other techniques, single photon–emission CT, positron-emission tomography, and magnetic resonance spectroscopy have been investigated as tools for both diagnostic and pathogenetic studies of ADC [44, 46–48]. Although typical patterns of abnormalities have been documented in ADC cases by use of each method, none of these techniques has entered routine clinical practice. It is hoped that rapid advances in functional and anatomical neuroimaging eventually will prove more useful for diagnosis [49].

A second, related clinical shortcoming centers on the problem of distinguishing ongoing disease activity from static injury due to prior insults caused either by HIV-1 infection or by other conditions. This problem has caused particular difficulty in the structuring and evaluation of clinical trials of ADC treatment [24, 27]. Improvement in neurological function, as determined by use of quantitative performance testing, has been the mainstay of assessment of ART and other treatments [39], but more-objective measures of disease activity might improve treatment assessment, just as plasma HIV-1 RNA levels and blood CD4 cell counts have made the evaluation of systemic therapies more precise [27].

These considerations have rekindled interest in the use of CSF (or blood) biomarkers and biological measures obtained by magnetic resonance methodologies [49]. These methods have the potential to advance the study of CNS HIV-1 infection and ADC, both at the clinically overt and the more-subtle, subclinical levels. Among the promising CSF indicators are markers of neural injury and local immune activation. Levels of axonal neurofilament light-chain protein and the neuronal protein tau are frequently elevated in the CSF of patients with ADC/HIVE, may be detected before the development of ADC, and normalize with treatment [26, 50–52], while levels of CSF immunoactivation markers, such as neopterin and monocyte chemoattractant protein (MCP)–1 (chemokine [C-C motif] ligand 2 [CCL2]), and CSF HIV-1 RNA can be used to measure the effects of treatment on CNS intrathecal immunoactivation and viral replication [53–57]. Since these markers may be elevated during opportunistic infection of the nervous system or in neurodegenerative disorders other than ADC, none is specific enough to be used individually for the diagnosis of ADC. However, levels of markers of neuronal injury and intrathecal inflammation may be useful in monitoring the response to therapy, within the nervous system, once the diagnosis of ADC has been established. A combination approach that uses these different classes of biomarkers might override some of the issues of sensitivity and specificity that have limited previous approaches [27]. Further studies are needed to establish the applications and limitations of biomarkers for disease classification, diagnosis, and treatment assessment [49].

**CHRONIC CNS HIV-1 INFECTION**

It is useful to examine CNS HIV-1 infection and its treatment with the broader perspective of its protracted course from primary seeding onward.
General characterization of CNS HIV-1 infection. Infection of the CNS is a nearly constant component of the ecology of HIV-1 infection and has been characterized most clearly by studies analyzing CSF. Thus, chronic HIV-1 infection is detected within the CSF of nearly all those with infection, from the period of initial viremia after primary exposure through the course of neurollogically asymptomatic infection and in those developing ADC [2, 4, 5, 58]. A number of studies, most of which involved convenience cohorts, have provided a coherent picture of this infection, showing that it is nearly ubiquitous but variable in its magnitude and in its relation to plasma HIV-1 RNA level [5, 28, 57]. Figure 2 illustrates cross-sectional data derived from our own experience with 104 HIV-1–infected, untreated, neurologically asymptomatic subjects who underwent lumbar punctures in the context of research rather than for diagnosis; data from 8 untreated patients with ADC also are shown [5, 57]. In neurologically asymptomatic patients, the median plasma HIV-1 RNA level was 4.56 log_{10} copies/mL (intraquartile range [IQR], 4.02–5.16 log_{10} copies/mL), the median CSF HIV-1 RNA level was 3.50 log_{10} copies/mL (IQR, 2.44–4.18 log_{10} copies/mL), and the median plasma:CSF difference was 1.07 log_{10} copies/mL (IQR, 0.33–1.86 log_{10} copies/mL). Thus, in untreated individuals, CSF HIV-1 RNA levels are generally ~10-fold lower than plasma HIV-1 RNA levels, but the difference between viral concentrations in the 2 fluids varies considerably. Notably, CSF HIV-1 RNA concentrations in the patients with ADC were similar to those in the asymptomatic patients, particularly when considered in relation to their blood CD4 cell counts, which indicates that CSF HIV-1 RNA levels cannot be used to distinguish HIV-1–infected patients who are neurologically asymptomatic from patients with ADC [4, 5, 58].

Compartmentalization of CNS HIV-1 infection. One of the important features of CSF infection (and, more broadly, of CNS HIV-1 infection) is that its component viral populations can diverge from those in plasma. Genetic compartmentalization of CSF HIV-1 infection has been nicely demonstrated in a series of studies, by Swanstrom and colleagues [3, 60, 61], that used the heteroduplex tracking assay to compare blood and CSF viral populations cross-sectionally and longitudinally. These studies, as well as companion studies of simian immunodeficiency virus infection [62], have shown that, during acute infection, HIV-1 populations in CSF and blood may be identical, even as they change together over time. Subsequently, during chronic infection, the populations diverge, with the greatest divergence in patients with ADC/HIVE. This general picture of progressive compartmentalization of CSF and brain HIV-1 populations, in relation to the virus in plasma, also has been dissected by detailed clonal analysis of viral populations [63, 64].

Functional compartmentalization also has been shown with respect to drug resistance, chemokine-receptor utilization, and cell tropism. Differences in drug susceptibility between CSF and blood HIV-1 populations have been reported [65–68], and, although viral replication in CSF within an environment containing subtherapeutic drug concentrations might enhance the selection of resistance mutations [69–71], this is only rarely the

Figure 2. Cerebrospinal fluid (CSF) changes in HIV-1 infection. These cross-sectional data combine results from 2 cohorts [5, 57] and only include data for untreated HIV-infected subjects. With the exception of 8 patients presenting with AIDS dementia complex (filled symbols), the remaining subjects were neurologically asymptomatic. Graphs show the high prevalence of detectable CSF HIV-1 RNA levels across blood CD4 cell counts and their variable relationship to plasma HIV-1 RNA levels. The frequent presence of CSF pleocytosis also is shown. The vertical dotted lines mark a blood CD4 cell count of 50 cells/μL and show the generally high plasma and lower CSF HIV-1 RNA levels, the high plasma-CSF difference in HIV-1 RNA levels, and the lower incidence of pleocytosis. WBC, white blood cell.
cause of isolated viral escape in CSF [72]. Although utilization of chemokine receptors by HIV-1 populations in CSF and blood is most commonly concordant with a predominance of CCR5-using (R5) viruses, dual-tropic viruses can be found in CSF, either concordant or discordant with plasma viral populations [73]. Clonal analysis of receptor utilization suggests that viruses are exchanged between the 2 fluids in patients with chronic asymptomatic infection [73]. Perhaps the most important question in the pathogenesis of HIV-1–associated neurological disease is whether compartmentalized viruses are selected with respect to neurotropism or neuropathogenicity. A number of studies have suggested that certain envelope sequences may be important in ADC/HIVE, although data on specific genetic signatures are conflicting [74–76] and the analysis of patient samples for possible neuropathogenic sequences has not yet been proven for clinical use.

**Inflammation and immunoactivation.** CSF analysis also indicates that HIV-1 infection is associated with chronic intrathecal immunoactivation/inflammation, as indicated by frequent CSF pleocytosis and elevated levels of several soluble immunological markers [5, 59, 77]. As noted in figure 2, the mild elevation of white blood cell (WBC) counts in CSF is common during asymptomatic infection. Of these WBCs, 85%–95% are lymphocytes, with the majority being T cells and the remainder composed of monocytes. Our studies showed a median CSF WBC count of 4 cells/μL (IQR, 1–12 cells/μL) across a wide range of plasma CD4 cell counts, with the exception of markedly lower WBC counts in subjects with blood CD4 cell counts <50 cells/μL. This common, incidental CSF pleocytosis is important to consider in the interpretation of CSF findings from HIV-1–infected individuals undergoing diagnostic lumbar puncture for various reasons, such as for the diagnosis of neurosyphilis. From our studies, we derived some tentative guidelines for the interpretation of CSF cell counts (see the Appendix). Our subjects with pleocytosis did not have headaches or any other neurological symptoms. A similar absence of symptoms was particularly striking in a group of subjects who developed pleocytosis after treatment interruption [78, 79]. These observations also raise the question of whether to use the term “asymptomatic pleocytosis,” rather than “aseptic meningitis,” in this context.

Levels of a number of immunological markers are elevated in CSF during HIV-1 infection, including neopterin [80], β-2-microglobulin [81], quinolinic acid [82], interferon-γ-inducible protein (IP)–10 (chemokine [C-X-C motif] ligand 10) [83], and MCP-1 (CCL2) [53, 55], along with several others that have received less attention [84]. Frequent elevation of neopterin and IP-10 concentrations in asymptomatic subjects confirmed the presence of intrathecal immunoactivation as a relatively consistent finding in asymptomatic HIV-1 infection [54, 83]. Even higher levels of some markers, including neopterin and MCP-1, in patients with ADC/HIVE suggest that accelerated immunoactivation is involved in the genesis of brain injury and that these markers may be used diagnostically to identify ADC/HIVE or to predict its development [53, 85, 86].

**Brain injury in chronic asymptomatic infection.** The constant presence of HIV-1 and the associated immunoactivation and inflammation in CSF raise the important question of whether chronic asymptomatic infection is accompanied by ongoing, low-grade brain injury despite the lack of overt symptoms and signs. If this chronic inflammatory state leads to brain injury, will survivors show delayed neurological impairment years later? Will it provide a foundation for greater vulnerability to other neuropathologies that accumulate with age? Importantly, would earlier treatment ameliorate subclinical neurological injury and prevent later deterioration?

Parallel studies of neuropsychological test performance in HIV-1–infected populations have raised these same questions. Indeed, diminished group performance has led to the inclusion of the designation “HIV-associated asymptomatic neurological impairment” in the new HAND classification [42]. In this same classification, “mild neurocognitive disorder” is used when similar cognitive dysfunction is accompanied by neurological symptoms, whereas “HIV-associated dementia” is reserved for more-severe impairment, similar to the “ADC” designation. Although in one sense this terminology and the criteria for each of these subtypes represent an advancement in formal diagnosis, they remain dissociated from pathobiology-based disease characteristics [27, 49]. The new designations do not objectively separate any impairment unrelated to HIV-1 infection from that caused by the virus and do not clearly distinguish active from static brain injury.

Further studies will be needed to determine the long-term implications of subclinical brain injury and how to differentiate it from classic subacute ADC [87, 88]. Most importantly, studies will need to define whether injury will occur at blood CD4 cell counts greater than those defined by guidelines for the initiation of treatment and whether the damage will continue during treatment in the presence of low or undetectable CSF HIV-1 RNA levels [89]. With respect to the role of biomarkers, it will be critical to determine whether these markers can be used to detect ongoing injury and to predict future neurological deterioration.

**TREATMENT OF CNS HIV-1 INFECTION**

**Treatment effects on chronic CNS HIV-1 infection.** In general, CSF HIV-1 infection responds very well to ART [57, 90–92]; as HIV-1 RNA levels in plasma become undetectable, so do those in CSF. However, the relative rates of viral decay in the 2 compartments may differ in some patients, with HIV-1 RNA concentrations falling more slowly in CSF than in plasma. Slower decay has been noted in subjects with ADC and lower
blood CD4 cell counts but without CSF pleocytosis (figure 3) [5, 28, 93, 94]. These observations can be interpreted as being consistent with a simple model of compartmentalized CSF HIV-1 infection, with the lag in viral response in CSF due to either slow cell turnover and consequent prolonged viral release by macrophages or less-potent drug concentrations within CSF as a result of reduced drug entry. Indeed, this simple model emphasizes the potential importance of drug penetration in the CNS [70, 95].

Several observations, however, suggest that this simple model may not fully account for treatment effects in all settings. For example, it may not explain the overall effectiveness of a wide variety of drug regimens in the suppression of CSF HIV-1 RNA levels [91] or why cases of high CSF virus levels in the presence of suppressed plasma virus levels are rare. The very rapid decay of CSF HIV-1 is equivalent to that of plasma virus in some subjects, which also is difficult to explain when component drugs penetrate CSF so poorly that local drug concentrations are lower than those found in systemic tissues. We have noted that, in the presence of systemic treatment failure related to drug resistance, HIV-1 RNA levels in CSF were ∼100-fold lower than those in plasma, compared with a 10-fold difference between plasma and CSF HIV-1 RNA levels in untreated subjects [57]. Instead of serving as an isolated, treatment-refractory reservoir, CSF contains HIV-1 RNA levels that usually are more effectively treated than those in plasma.

The reason for this disproportionate response in CSF is unclear. It may relate to enhanced intracellular drug effects on CNS cells [96]. Because failed treatment reduces generalized systemic immune activation, compared with that in patients not receiving therapy [97], we speculate that immune activation may make an important contribution to both CSF HIV-1 RNA levels and their response to treatment [98]. Whatever the contributing mechanisms, these observations suggest the need for more-complex models of infection, to better characterize CSF infection and the salutary effects of ART.

Given these uncertainties, how should treatment be tailored to CNS HIV-1 infection? In neurologically asymptomatic patients—that is, most of those who initiate therapy—it is likely that the CNS warrants no special consideration. In patients presenting with symptomatic ADC or more-advanced immunosuppression, the basis for recommendations is less clear. In the absence of better evidence, we generally recommend that primary consideration be given to prescribing a potent regimen that suits the individual patient with ADC, by use of guidelines for systemic treatment, and that 4 rather than 3 drugs should be considered, to optimize treatment potency and accelerate viral suppression. Then, secondary consideration can be given to CNS drug penetration, with efforts to include ≥2 drugs with better-than-average penetration. Letendre et al. [70] have proposed a simple scheme for selecting drugs with these properties, rating them as 0 (low penetration), 0.5 (intermediate penetration), or 1 (high penetration). On the basis of a literature review, they rated tenofovir, didanosine, zalcitabine, nelfinavir, ritonavir-boosted and unboosted saquinavir, ritonavir, boosted tipeprevir, and enfuvirtide as 0; stavudine, lamivudine, emtricitabine, efavirenz, unboosted aprenavir and fosamprenavir, and unboosted atazanavir and indinavir as 0.5; and zidovudine,
abacavir, delavirdine, neviripine, and boosted aprenavir (and fosamprenavir), atazanavir, indinavir, and lopinavir as l. This list will likely be modified as more information about CNS drug penetration and its effect becomes available. Although this list represents a simple schematic, it also must be acknowledged that it is based largely on pharmacokinetic, rather than pharmacodynamic, data and that other drug properties, such as intracellular metabolism, may be important factors contributing to efficacy in the CNS. Hence, clinicians must recognize that the use of particular “CNS regimens” or of “neuro-ART” is not yet supported by clear empirical evidence.

**Treatment effects on CNS immunoactivation.** ART clearly suppresses CSF immunoactivation, as indicated by reduced CSF WBC counts and immunological markers. In our series, pleocytosis was mostly eliminated, not only by suppressive treatment but also by failed treatment related to drug resistance [5, 57]. This result underlies the recommendation that any pleocytosis in a patient receiving treatment should be considered clinically suspicious (see the Appendix). CSF neopterin concentrations also were reduced by treatment, with suppressive therapy having a greater effect than failed treatment. However, these levels do not always return to normal with suppressive treatment, indicating that low-level CNS immunoactivation can persist despite undetectable blood and CSF HIV-1 RNA levels [54, 99]. Whether this might be due to continued viral replication below levels of detection within the CNS or to residual immune activation (i.e., an immunological “scar”) is not yet known.

**Adjuvant treatment strategies.** Alternative treatment modalities have been suggested for ADC and milder cognitive impairments associated with HIV-1 infection [100–103]. These approaches, which are grouped together as adjuvant therapies, follow several rationales, including neuroprotection, immunomodulation, and symptom control. Results of a number of trials have been reviewed by Turchan et al. [104]. Overall, none has shown clear and substantial clinical effects. In part, this may relate to the great difficulty in structuring and implementing clinical trials to test adjuvant therapies while maintaining the best-available antiviral treatment [24]. However, when they are considered in relation to the sometimes dramatic and profound effect of ART on untreated ADC, it seems possible that these approaches are skirting the main treatment target, CNS HIV-1 infection, and are unlikely to compare favorably with direct ART. On the other hand, these strategies may help illuminate the mechanisms underlying disease pathophysiology and eventually may prove to have an accessory role, either by accelerating neurological improvement when ART is initiated or dampening the persistent immunopathological processes that follow viral clearance. They should not be regarded as alternatives to ART but as supplementary therapies.

**CNS ADVERSE EFFECTS OF ART**

Two types of CNS adverse reactions associated with ART should be considered: (1) direct drug toxicity and (2) immunopathology related to immune restoration and inflammation.

**Direct drug toxicity.** Peripheral nervous system and skeletal muscle toxicities of nucleoside reverse-transcriptase inhibitors are well recognized from early experience. Neuropathy related to the deoxynucleosides was appreciated as a dose-limiting toxicity during initial clinical trials [105] and proved to be a common toxicity, particularly when 2 drugs were used in combination [106]. Similarly, toxic myopathy complicated zidovudine therapy at doses higher than those now used [107]. These direct toxicities are attributed to drug effects on mtDNA polymerase [108–110]. Fortunately, there is little evidence to suggest that this class of drugs has similar toxic effects on the CNS. The same is true for PIs, which do not alter CNS function. The only drug that clearly and commonly affects the CNS is the nonnucleoside reverse-transcriptase inhibitor efavirenz [111], the effect of which most frequently manifests as vivid and, at times, dysphoric dreams; however, an array of other neuropsychiatric symptoms have been reported [112]. A prospective ACTG study that compared 200 HIV-infected patients taking efavirenz with ~100 control subjects noted no difference in neuropsychological test performance or formal measures of depression or anxiety between the 2 study arms [113]. The efavirenz group had more neurological symptoms, including bad dreams, during the first week but not during the subsequent weeks of treatment, and 6% of patients stopped taking efavirenz because of CNS-related symptoms. Although CNS-related symptoms characteristically resolve spontaneously after the initial weeks of treatment, in some patients these effects either persist or are sufficiently unpleasant to necessitate changing therapy. The mechanism of toxicity is uncertain; some studies have suggested a relationship to drug exposure as measured by plasma efavirenz levels [111, 114]. The ACTG study described above suggested an association between neurological symptoms during the first week of treatment and a genetically determined reduction in the metabolism of efavirenz [115]. One report also suggested an interactive effect of efavirenz and tenofovir on neuropsychiatric adverse effects [116]. Fortunately, these effects appear to be fully reversible with the discontinuation of treatment. As emphasized in a recent review by Cespedes and Aberg [111], severe neuropsychiatric symptoms associated with efavirenz should be managed by drug substitution and not dose adjustment. Lowering the dose may place patients at risk for virologic failure and resistance.

A recent report, by Robertson et al. [117], of an ACTG study of neuropsychological test performance in a group of subjects after treatment interruption has raised the question of whether ART impairs neurocognitive function. The study was designed to test whether the resurgence of viremia after treatment inter-
rupation is accompanied by deterioration in neuropsychological performance. Unexpectedly, the opposite was observed—that is, test performance improved after therapy was stopped. One interpretation of this observation is that the subjects, in fact, had been subclinically impaired by their treatment regimens and test performance returned to normal when treatment was stopped. An alternative interpretation is that the improvement was related to a practice effect from repetition of the neuropsychological tests. In our opinion, this is the more-plausible explanation. However, because no simultaneous control group was included in the study, a final interpretation remains uncertain.

**CNS HIV-1 infection–related IRIS.** Recently, there has been interest in the issue of whether IRIS provoked by CNS HIV-1 infection, rather than by infection with another opportunistic pathogen, may develop in patients beginning ART [118, 119]. The context for this speculation is provided by the clinically important model of IRIS in PML. PML is an opportunistic infection in the brain that is caused by the otherwise-benign JC virus (JCV) [120]. Although there is no specific treatment, clinical observations have indicated that PML remitted rarely if untreated [121]; however, with ART, the disease is arrested in most cases [122, 123]. This presumably relates to the restoration of anti-JCV immunity as part of the general immunological recovery induced by ART. Thus, immune reconstitution is the objective of treating PML. However, an unexpected number of PML cases develop when ART is started [124, 125]. Moreover, these cases may have atypical features, including local edema, inflammation, and contrast enhancement on neuroimaging. Because these reactions develop in the foci of PML, it is likely that JCV is the inciting antigen and that restored immunity leads to a local inflammatory response that can be extreme in some patients, to the point of causing accelerated immunopathological injury [126]. Although corticosteroids often are given, no formal trial has tested this or other treatment strategies. The outcome of PML/IRIS appears to be similar to that of classic noninflammatory PML [127].

This intense immunological reaction provides a possible precedent for cases of encephalitis with atypical features that develop in patients beginning ART, in which only HIV-1 can be implicated as the inciting antigen [118, 119]. These cases may show atypical robust perivascular inflammation and leukoencephalopathy [32, 118]. Given the large number of patients who begin ART with low CD4 cell counts, a clinically apparent reaction of atypical cognitive or functional decline in response to ART clearly is rare. However, if such a syndrome of atypical deterioration after initiation of ART indeed represents CNS HIV/IRIS, it is of considerable pathogenetic and clinical interest and warrants special treatment approaches.

**CONCLUSIONS**

Although there are a number of important treatment issues yet to be addressed, the advent of ART has had a profound impact on severe CNS disease as a complication of HIV-1 infection. This impact includes a marked reduction in the incidence of major CNS opportunistic infections and ADC and effective treatment for patients presenting with new-onset ADC. With this success, attention has turned to other aspects of CNS HIV-1 infection and particularly to the question of whether chronic infection is associated with more-indolent, subclinical brain injury, which may have long-term consequences. It is speculated that CNS HIV-1 infection and the associated local inflammation and immunoactivation may begin to damage the brain during the long period before treatment is initiated and may even continue in the presence of effective systemic viral suppression. Now that the most conspicuous and severe neurological complications of HIV-1 infection can be managed in most cases, the effects of therapy on this less-severe and more-subtle form of brain injury must be carefully considered and explored.

**Acknowledgments**

_Supplement sponsorship._ This article was published as part of a supplement entitled “Significant Challenges Facing HIV Practitioners,” sponsored by Bristol-Myers Squibb.

**APPENDIX**

**GUIDELINES FOR THE INTERPRETATION OF CEREBROSPINAL FLUID (CSF) WHITE BLOOD CELL (WBC) COUNTS IN HIV-1 INFECTION**

1. Mild mononuclear pleocytosis is very common in untreated, asymptomatic HIV-1–positive individuals with blood CD4 cell counts >50 cells/µL.

2. CSF pleocytosis should be regarded with suspicion and investigated when:
   a. CSF WBC counts are >20 cells/µL;
   b. CSF WBC counts are >5 cells/µL in patients with blood CD4 cell counts <50 cells/µL; or
   c. CSF WBC counts are >5 cells/µL in patients receiving antiretroviral therapy, regardless of whether HIV-1 in plasma is fully suppressed.

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