

## Perspective

# Central Nervous System Complications in HIV Disease: HIV-Associated Neurocognitive Disorder

*HIV-associated neurocognitive disorder (HAND) is the result of neural damage caused by HIV replication and immune activation. Potent antiretroviral therapy has reduced the prevalence of severe HAND but not mild to moderate HAND. Brief symptom questionnaires, screening tests, and neuropsychological tests can be used with relative ease in the clinic to identify cognitive and neurologic deficits and to track patient status. Increasing data on pharmacokinetics of antiretrovirals in cerebrospinal fluid (CSF) have permitted formulation of central nervous system (CNS) penetration-effectiveness (CPE) rankings for single drugs and combinations. Available data indicate that regimens with higher CPE scores are associated with lower HIV RNA levels in CSF and improvement in neurocognitive functioning. This article summarizes a presentation by Scott Letendre, MD, at the IAS-USA live continuing medical education course held in San Francisco in May 2011.*

HIV enters the brain primarily by being carried in migrating monocytes and lymphocytes that cross the blood-brain barrier (BBB), a so-called “Trojan horse” mechanism. After crossing the BBB, HIV-infected monocytes can become perivascular macrophages. Activated perivascular macrophages and microglia can replicate HIV and express neurotoxic molecules (eg, soluble immune mediators) that can activate astrocytes and other cells. Astrocytes form an important component of the BBB by surrounding brain microvascular endothelial cells. When activated, astrocytes can lead to increased BBB permeability and monocyte and lymphocyte migration. Although it was once believed that astrocytes produced HIV-encoded proteins but not virus, there is now evidence that infected astrocytes can also produce virus. Eventually, the increase in brain concentrations of glutamate (a neurotransmitter that is an excitatory neurotoxin at high levels) and other neurotoxins results in neuronal injury, the proximal biological event underpinning clinical neurologic and cognitive disease.

The neurobehavioral disturbances resulting from HIV-mediated neural damage include emotional and other behavioral disturbances (eg, depression, anxiety, sleep disorders, mania,

and psychosis) and HIV-associated neurocognitive disorder (HAND). HAND consists of 3 subdisorders: (1) asymptomatic neurocognitive impairment (ANI), (2) mild neurocognitive disorder (MND), and (3) HIV-associated dementia (HAD). Secondary neurocognitive disorders consist of cognitive disorders that can accompany coinfections, cerebrovascular disease, malnutrition, and treatment-related disorders. The diagnosis of HAND requires the presence of acquired impairment in at least 2 cognitive abilities. Impairment is marked for a diagnosis of HAD, with the absence of any preexisting causes or strongly confounding conditions. For diagnosis of ANI, impairment does not interfere with daily function, whereas interference is mild for MND and marked for HAD.<sup>1</sup>

### HAND in the Current Antiretroviral Therapy Era

Combination (potent) antiretroviral therapy has reduced the prevalence of severe HAND but not the prevalence of mild to moderate HAND. A recent study compared data from the pre-antiretroviral therapy era from University of California San Diego with data from the current era from the CHARTER (CNS [central nervous system] HIV Antiviral Therapy Effects Research) study group. HAND was present in 36% of HIV-infected patients without AIDS in the combination antiretroviral therapy

era and in 29% in the pre-potent antiretroviral therapy era ( $P = .03$ ) and in 43% and 46% ( $P$  not significant) of AIDS patients, respectively. Prevalences of similar cognitive impairment in HIV-seronegative subjects were 19% in the pre-potent antiretroviral therapy era and 16% in the current era.<sup>2</sup>

In a study in the Swiss HIV Cohort, 27% of patients had spontaneous complaints about cognitive function and 73% did not, with neuropsychological testing showing neurocognitive impairment in 84% of those with complaints and 64% of those without complaints (69% of the total clinic population). Among those with spontaneous complaints, 24% had ANI, 52% had MND, and 8% had HAD, with 16% not having measurable impairment.<sup>3</sup>

### Risk Factors for HAND

The presence of risk factors for HAND should heighten clinical suspicion for the disorder, and include host factors, HIV disease factors, and comorbidities. Host factors include genetic predisposition, metabolic disorders, aging, vascular disease, anemia, and malnutrition. HIV disease factors include AIDS, immune activation, HIV subtype, neuroadaptation, and drug resistance. Comorbidity factors include stimulant use, hepatitis C virus (HCV) infection, and depression. Among the host factors, there is evidence of an association of HAND with apolipoprotein E e4 alleles (as in Alzheimer's disease) and with a polymorphism in a gene encoding the potent chemotactic protein MCP-1.<sup>4</sup> The CHARTER group has performed a genome-wide association study, and it is hoped that a brief testing panel may be available in the foreseeable future.

More important are the associations of HAND with metabolic disorders (eg, insulin resistance), aging, and vascular disease. There is evidence suggesting that vascular disease risk factors are more strongly associated with cogni-

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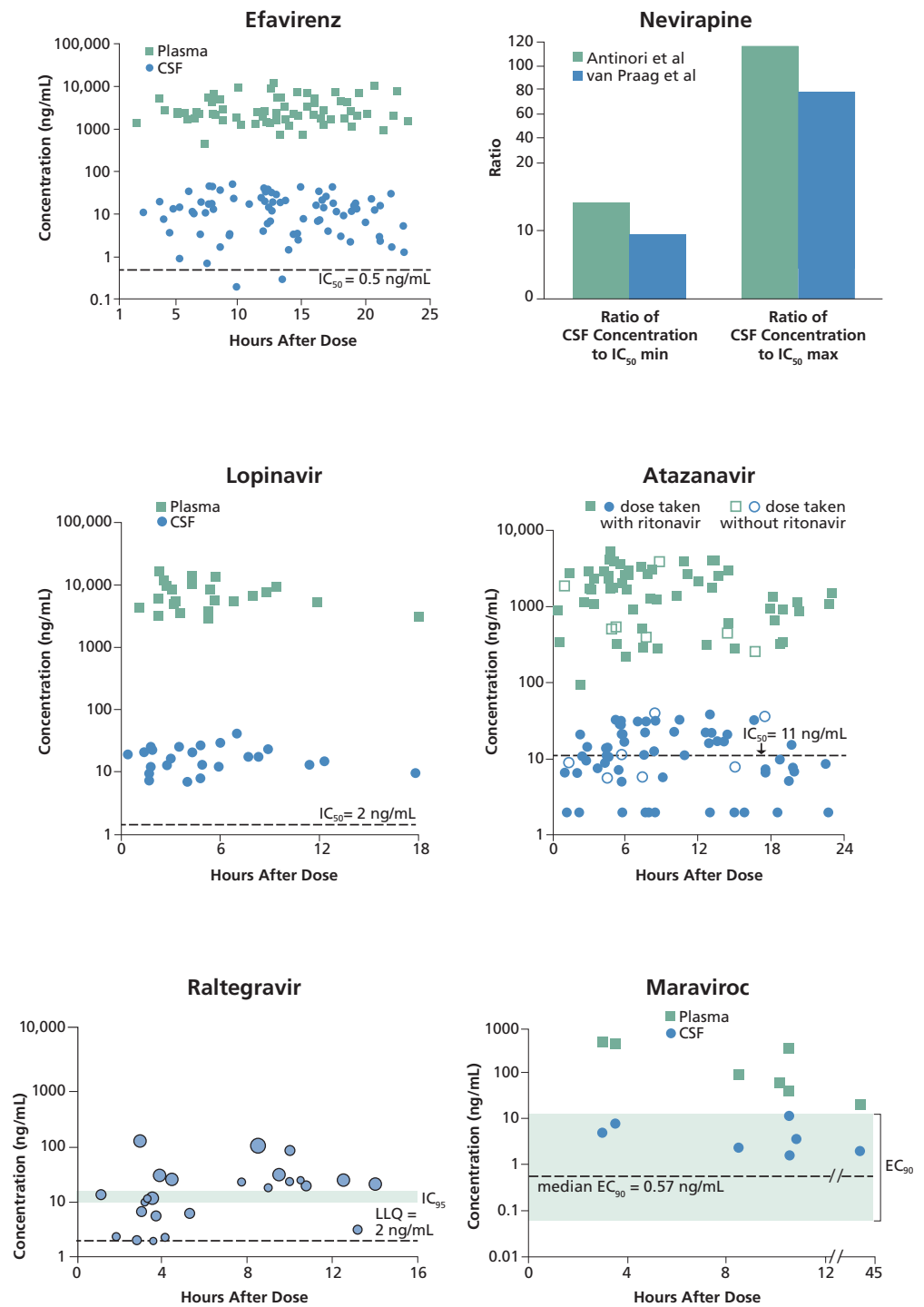
tive impairment than are such HIV disease risk factors as CD4+ count nadir and plasma HIV RNA level.<sup>5</sup> With regard to accelerated aging in HIV disease, there are data on phosphorylated Tau protein and other age-related markers in cerebrospinal fluid (CSF) indicating that HIV-infected patients have levels of these markers comparable to those in noninfected subjects who are 15 years to 20 years older.<sup>6</sup>

With regard to HIV disease factors, data from the CHARTER group indicate that CD4+ cell count nadir is strongly associated with risk for cognitive impairment, providing additional incentive to initiate antiretroviral therapy before CD4+ cell counts drop to below 200/ $\mu$ L.<sup>7</sup> Translocation of bacterial products, such as lipopolysaccharide, and resulting immune activation in people with HIV infection have been the topic of intensive investigation in recent years. Recent data have shown an association between impairment and blood levels of soluble CD14, the solubilized receptor for lipopolysaccharide.<sup>8</sup> This marker can be measured relatively inexpensively by an enzyme-linked immunosorbent assay, and may become a clinically useful biomarker of risk.

In terms of comorbidities, use of such drugs as methamphetamine and cocaine can have persistent adverse effects on the CNS.<sup>9</sup> HCV can infect glial cells. Although only approximately 10% of HCV-infected patients have detectable HCV RNA in the CSF (and typically at low levels), a much larger percentage of patients have relatively high levels of HCV core antigen.<sup>10</sup> The core antigen is highly immunogenic and may be a stimulus for brain injury.

## HAND Assessment in the Clinic

A range of tests are available for use in the clinic to assess neurocognitive function, with many being relatively simple and brief. Symptom questionnaires consist of the Medical Outcomes Study–HIV Health Survey<sup>11</sup> (MOS-HIV) and the somewhat more complex Patient's Assessment of Own Functioning Index<sup>12</sup> (PAOFI). Both are self-administered and can be completed by



**Figure 1.** Results of selected studies of antiretroviral pharmacokinetics in cerebrospinal fluid (CSF). Top left: Efavirenz plasma concentration and CSF concentration over time from dose. Adapted from Best et al.<sup>18</sup> Top right: Ratio of nevirapine CSF concentration to minimum 50% inhibitory concentration ( $IC_{50}$  min) and maximum 50% inhibitory concentration ( $IC_{50}$  max). Adapted from van Praag et al<sup>19</sup> and Antinori et al.<sup>20</sup> Middle: Plasma concentration and CSF concentration over time from dose for lopinavir (left, adapted from Capparelli et al<sup>21</sup>) and atazanavir/ritonavir (right, adapted from Best et al<sup>18</sup>). Bottom left: Raltegravir CSF concentration over time from dose. Size of data point indicates ratio of CSF concentration to serum albumin. LLQ indicates lower limit of quantitation;  $IC_{95}$ , 95% inhibitory concentration. Adapted from Yilmaz et al.<sup>23</sup> Bottom right: Maraviroc plasma concentration and CSF concentration over time from dose.  $EC_{90}$  indicates 90% effective concentration. Adapted from Yilmaz et al.<sup>24</sup>

the patient in the waiting room before meeting with the physician; results on the questionnaires serve as a baseline for subsequent follow-up.

Brief screening tests include the HIV Dementia Scale (which requires 5 to 10 minutes to complete), the International HIV Dementia Scale<sup>13</sup> (which requires even less time), and the Montreal Cognitive Assessment.<sup>14</sup> HIV clinicians may be reluctant to perform neuropsychologic testing, but brief tests are easy to administer. The ACTG (AIDS Clinical Trials Group) Longitudinal Linked Randomized Trial (ALLRT) Neurocognitive Screen consists of connect-the-dot tests and digit-symbol comparison tests.<sup>15</sup> The Grooved Pegboard test requires purchase of the grooved pegboard and is also not difficult to administer.<sup>16</sup> The Action Fluency test requires patients to name as many verbs as they can within a given time period.<sup>17</sup> Brief computerized tests that can be used in the clinic are also available. More comprehensive neuropsychologic testing requires assessment of at least 5 cognitive abilities, with at least 2 tests per ability.<sup>1</sup>

### Antiretrovirals and the Blood-Brain Barrier

The BBB features a number of unique elements that prevent passage of drugs or other substances into the brain. Brain microvascular endothelial cells are joined by tight-junction proteins (forming the “tight junction”) and are surrounded by a basement membrane. Abutting the basement membrane are astrocyte foot processes. Both the luminal and abluminal surfaces of the endothelial cells and astrocytes can express molecular drug pumps or transporters (eg, P-glycoprotein and organic anion transporters) that can limit the amount of drug that passes into the brain.

A number of drug characteristics influence penetration across the BBB. Perhaps most important is protein binding: drugs that are more highly bound to plasma proteins are less available to cross the BBB. Nucleoside analogue reverse transcriptase inhibitors (nRTIs) are the least protein-bound,

with protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) being roughly equally protein-bound and both more highly bound than nRTIs. PIs and NNRTIs exhibit greater fat solubility than nRTIs, a characteristic that favors crossing of the BBB. Low molecular weight also favors crossing of the barrier. Most of the antiretrovirals are relatively small molecules (with the exception of enfuvirtide), with nRTIs being smaller than NNRTIs, which are smaller than PIs. P-glycoprotein inhibits crossing of PIs, maraviroc, and raltegravir, and organic anion transporters inhibit crossing of nRTIs.

In the absence of measuring drug concentrations in the CSF, assessment of ability of antiretroviral drugs to cross the BBB was based on comparisons of the above characteristics, as well as their acid dissociation constants and estimates of the ability of CSF drug concentration to exceed the 50% inhibitory concentration ( $IC_{50}$ ) (derived by dividing the product of the unbound fraction and the plasma minimum concentration by the  $IC_{50}$ ). However, data on CSF pharmacokinetics of antiretroviral drugs are becoming increasingly available, in part through population pharmacokinetics studies. These studies involve sparse sampling of a large number of patients (rather than the intensive sampling of a smaller group performed in typical pharmacokinetics studies) to spare patients from having to undergo numerous lumbar punctures.

Examples of data from CSF pharmacokinetics studies are shown in Figure 1. For the NNRTI efavirenz, CSF penetration was 0.5% of plasma concentration, but exceeded the  $IC_{50}$  in the majority of measurements.<sup>18</sup> Nevirapine CSF penetration was approximately 29% to 63% of plasma drug concentration.<sup>19,20</sup> For the PI lopinavir, CSF penetration was 0.23% of plasma concentration, but all measured CSF concentrations exceeded the  $IC_{50}$ .<sup>21</sup> For atazanavir, CSF levels were 1% of plasma concentration, but only approximately 50% of measurements exceeded the  $IC_{50}$ .<sup>22</sup> Further, the variation in CSF levels was wide, and about 15%

of patients had atazanavir levels below the limit of detection, as measured by a highly sensitive assay. Among newer agents, maraviroc has exhibited CSF concentrations about 1  $\log_{10}$  lower than expected based on drug characteristics. Figure 1 shows CSF concentrations plotted against a range of 90% effective concentrations.<sup>23</sup> For raltegravir, Figure 1 shows CSF concentrations with the size of the data point indicating the CSF-to-serum albumin ratio, a marker of BBB permeability. Patients with more permeable BBBs generally had higher CSF drug concentrations.<sup>24</sup>

There are fewer data thus far on the pharmacodynamics of antiretrovirals in the CSF. Examples from extant data include the finding of statistically significant reductions in CSF HIV RNA levels in all patients receiving ritonavir-boosted (*r*) lopinavir monotherapy for 3 weeks.<sup>25</sup> Other studies have shown CSF viral load greater than 50 copies/mL in 1 of 11 patients with plasma viral load less than 50 copies/mL receiving lopinavir/*r* monotherapy, and in 3 of 20 patients receiving atazanavir/*r* monotherapy.<sup>26,27</sup> A study using an assay that detects HIV RNA down to a level of 2 copies/mL showed that in patients with plasma HIV RNA below detection limits, CSF viral load 2 copies/mL or greater was present in 25% of patients receiving lopinavir/*r* and in 75% of those receiving atazanavir or atazanavir/*r*.<sup>28</sup>

Using data from a population of approximately 1600 patients, some 80% of whom consented to lumbar puncture, the CHARTER group constructed a CNS Penetration-Effectiveness (CPE) ranking system for antiretrovirals (Table 1).<sup>29,30</sup> Higher numbers indicate better estimated penetration; for combination regimens, the scores for each drug are added. Using CSF viral load data from 615 patients, higher CPE scores were statistically significantly associated with lower CSF viral loads (see Figure 2).<sup>29</sup> Using a highly sensitive assay, a CPE score greater than the median of 7 was associated with a statistically significantly smaller proportion of patients having CSF viral load above 2 copies/mL, compared with a score of 7 or below.<sup>31</sup>

Table 1. Central Nervous System Penetration–Effectiveness Ranking

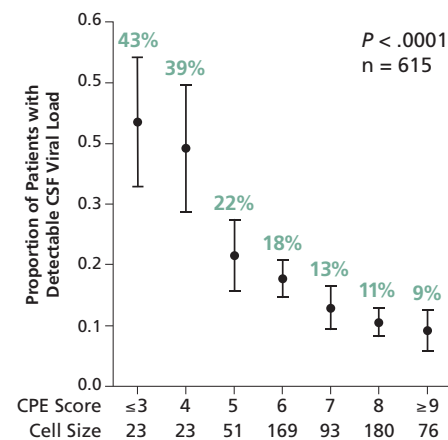
Drug Class	CPE Score			
	4	3	2	1
<b>Nucleoside Reverse Transcriptase Inhibitors</b>	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
<b>Nonnucleoside Reverse Transcriptase Inhibitors</b>	Nevirapine	Delavirdine Efavirenz	Etravirine	
<b>Protease Inhibitors</b>	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir/r Tipranavir/r
<b>Entry/Fusion Inhibitors</b>		Maraviroc		Enfuvirtide
<b>Integrase Strand Transfer Inhibitors</b>		Raltegravir		

CPE indicates central nervous system penetration effectiveness; /r, ritonavir-boosted. Larger CPE scores reflect estimates of better penetration or effectiveness in the central nervous system (eg, a ranking of 4 indicates the best penetration or effectiveness). Adapted from Letendre et al.<sup>30</sup>

Observational and uncontrolled interventional studies support the notion that antiretroviral regimens that better penetrate the CNS better reduce HIV RNA levels in the CSF. Most, but not all, studies also support the notion that antiretroviral regimens that better penetrate the CNS better protect the brain from HIV-related injury. It may be that better-penetrating antiretroviral therapy is a necessary condition for preventing or reducing CNS damage, but use of these regimens may not be sufficient in all individuals. Reducing HIV replication in the brain (through antiretroviral therapy) may not have effects on other processes involved in injury, including ongoing immune activation, comorbidities, and potential toxicities of antiretroviral drugs.

Prospective, uncontrolled, observational studies have assessed the association of antiretroviral regimen CPE score with outcomes on neuropsychological testing. For example, in a study of 37 patients, higher CPE of an antiretroviral regimen was associated with lower CSF viral load; patients were given 6 neuropsychological tests, and those receiving regimens

with higher CPE scores performed better than patients on regimens with lower CPE scores.<sup>32</sup> In a study of 185 patients in which CSF viral load was not measured, patients receiving regimens with higher CPE scores performed better on 16 neuropsychological tests given.<sup>33</sup>



In a third example, Ellis and colleagues found that higher CPE score was associated with better outcome on a total of 3 tests in 2636 patients (no measurement of CSF viral load was performed).<sup>34</sup> In a study of 26 patients, CPE score was associated with lower CSF viral load—but in contrast to other studies, patients who were cognitively impaired at baseline and received regimens with higher CPE scores had *less* improvement on a total of 4 tests than those receiving regimens with lower CPE scores.<sup>35</sup> The findings in the latter study raise the issue of potential neurologic toxicity of antiretroviral therapy and highlight the need for careful consideration of implementing treatment strategies based on better CNS penetration.

In addition to these published analyses of CSF viral load and neuropsychological functioning, regimens that appeared to have better distribution into the CNS were associated with better mood in the CHARTER cohort, even after accounting for antidepressant use and neuropsychological performance. Such regimens have also been associated with better survival in studies of nearly 20,000 patients in the United Kingdom,<sup>36</sup> more than 2000 perinatally-infected children,<sup>37</sup> and individuals with CNS opportunistic infections.<sup>38</sup>

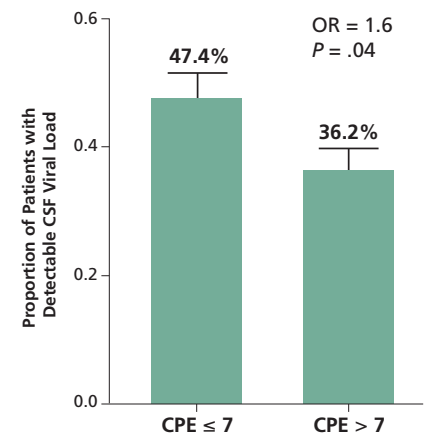


Figure 2. Left: Association of antiretroviral regimen CNS (central nervous system) Penetration-Effectiveness (CPE) score with proportion of patients with detectable HIV RNA in cerebrospinal fluid (CSF). Adapted from Letendre et al.<sup>29</sup> Right: Proportion of patients with CSF viral load between 2 copies/mL and 50 copies/mL, according to antiretroviral regimen CPE score of ≤ 7 or > 7 (the median value). OR indicates odds ratio. Adapted from Letendre et al.<sup>31</sup>



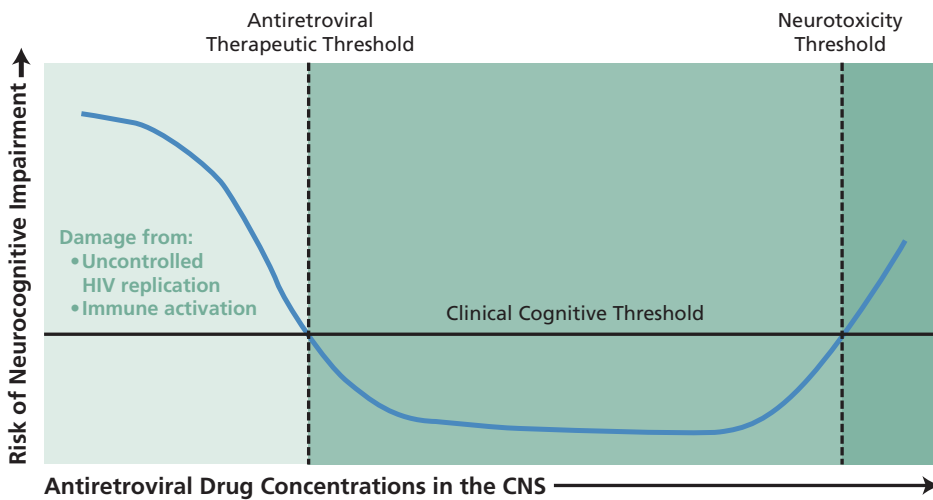


Figure 3. Conceptual therapeutic window for effectiveness of antiretroviral therapy in the central nervous system (CNS).

The goal of antiretroviral therapy, where risk for neurocognitive impairment is concerned, is to achieve adequate drug levels in the CNS without causing drug-related neurotoxic effects (see Figure 3). If drug levels in the CSF are too low, there is greater risk of damage caused by viral replication and ongoing immune activation, as well as a potential risk of drug resistance. However, biomarker and neuroimaging data support that subacute brain injury may continue despite adequate drug levels in the CNS. Such injury may not reach the point at which it is noticeable to the patient; many patients are asymptomatic despite having CNS injury that is detectable on neuropsychological testing. The therapeutic window for antiretroviral therapy in the CNS may thus be defined as the range of CNS drug concentrations that are associated with keeping damage below the clinical cognitive threshold and that do not expose patients to excessive risk of neurotoxicity.

## Summary

Patients should be counseled on HAND and on what is known about antiretroviral drug penetration to enable them to make informed treatment choices. Patients should be routinely questioned about cognitive symp-

toms, particularly at important clinical milestones, such as before initiating antiretroviral therapy. Brief testing improves the ability to correctly identify HAND. Other conditions that can cause CNS complaints (eg, syphilis, substance use, depression) should be screened for and treated. Physicians should consider using better-penetrating antiretroviral therapy, as accumulating data support that it better reduces HIV RNA levels in the CSF and leads to neurocognitive improvements. Patients should be continually monitored, as cognitive impairment might persist or present for the first time during antiretroviral therapy.

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