Protease inhibitor monotherapy and the CNS: peace of mind?

Ignacio Perez-Valero1, Carmen Bayon2, Irene Cambron2, Alicia Gonzalez1 and Jose R. Arribas1*

1Servicio de Medicina Interna, Unidad VIH, Hospital La Paz, IdiPAZ, Madrid, Spain; 2Servicio de Psiquiatría, Hospital La Paz, IdiPAZ, Madrid, Spain

*Corresponding author. Consulta Medicina Interna 2, Hospital La Paz, Poseo de la Castellana 261, 28046, Madrid, Spain. Tel: +34-91-207-1676; Fax: +34-91-729-0033; E-mail: jrarribas.hulp@salud.madrid.org

Boosted protease inhibitor (bPI) monotherapy has demonstrated high efficacy for maintaining viral suppression in the blood. bPI monotherapy has the theoretical advantage of avoiding the long-term toxicity associated with the use of nucleoside reverse transcriptase inhibitors. Concern about the efficacy of bPI monotherapy in preventing HIV replication in the CNS is one reason that has precluded the widespread use of this therapeutic strategy. In several studies, a low CNS penetration-effectiveness (CPE) score has been associated with a higher risk of virological failure in the CNS and with neurocognitive impairment. Since the CPE score is substantially lower for bPI monotherapy than for triple-drug highly active antiretroviral therapy (HAART), it has been postulated that bPI monotherapy might have a higher risk for CNS virological failure and neurocognitive impairment. However, the available evidence, although limited, does not support this notion. Lopinavir and darunavir achieve CSF drug levels that are sufficient to fully suppress HIV replication. In clinical trials, when compared with triple-drug HAART, patients receiving bPI monotherapy with lopinavir and darunavir who maintain full virological suppression in plasma do not appear to be at a higher risk of discordant HIV replication in the CSF or of neuropsychiatric adverse events. It should be noted that several studies have suggested that nucleoside reverse transcriptase inhibitors might have neurotoxic effects and, consequently, bPI monotherapy might be able to avoid the CNS toxicity induced by nucleosides. It is clear that more studies including detailed neurocognitive testing are needed to completely establish the risk/benefit ratio of bPI monotherapy or triple-drug HAART for preserving neurocognitive function in HIV-infected patients.

Keywords: PIs, CNS, HIV

Introduction

Triple-drug highly active antiretroviral therapy (HAART) is the gold standard for the initial therapy of HIV-infected patients.1 Using three antiretroviral drugs avoids the selection of drug-resistant HIV natural mutants that pre-exist in antiretroviral-naive patients with high levels of viral replication. However, when HIV suppression has been achieved, do we still need to continue treatment with three drugs? The results of several clinical trials1,3 have suggested that the use of boosted protease inhibitor (bPI) monotherapy can be almost as efficacious as triple therapy in maintaining viral suppression in the blood.5,5

The main reasons for treating HIV-infected patients with a single antiretroviral instead of triple-drug HAART are to avoid drug-related toxicity and to reduce treatment costs.6 The main objective of a lifetime treatment such as HAART has to be a trade-off between the efficacy and long-term toxicity. We still do not know for an individual patient what the right number of antiretrovirals is that offers the optimal balance between long-term efficacy and toxicity.

HIV, HAART and the CNS

HIV is a neurotropic virus that can cause a spectrum of neurocognitive disorders, globally denominated HIV-associated neurocognitive disorders (HAND).7 Despite the global uptake of HAART, the frequency of HAND has not decreased in the HAART era.8 If HAND is occurring in patients receiving triple-drug HAART, it is logical that one of the main concerns among clinicians and researchers about bPI monotherapy is its possible lower ability to protect patients from the effects of HIV in the CNS reservoir.

Reservoirs are anatomical sites or cell types in which replication-competent HIV accumulates and persists, despite the effects of HAART. HAART suppresses HIV replication in plasma if adequate drug concentrations are achieved. However, it is unclear whether HAART can uniformly suppress HIV replication in anatomical reservoirs such as the CNS. Complete HIV suppression in plasma but not in the CNS has been described (Table 1). A lack of efficacy in HAART controlling HIV replication in the CNS has been associated with HAND.9 Active HIV replication releases neurotoxic proteins, such as Tat and
gp120. Microglial cells infected with HIV release proinflammatory cytokines, and infected oligodendrocytes release low concentrations of glutamate, nitric oxide and calcium. These mechanisms might contribute to HAND. It has been estimated that ~50% of HIV-infected patients suffer HAND in the HAART era.

HAART prevents HAND and appears to be more efficacious when it is started in patients who still have high CD4 cell counts. It has been suggested that when the CD4 cell count drops, HIV has fewer available lymphocytes to infect. In an environment depleted of CD4 cells, HIV increases its avidity for cells expressing low levels of HIV receptors, such as microglial cells and oligodendrocytes. Subsequently, the number of cells infected in the CNS rises, increasing proinflammatory cytokines, neuronal dysfunction and CNS cell destruction.

The efficacy of HAART in preventing HAND probably relies on its ability to achieve HIV suppression in plasma and in the CNS. Suppression in plasma avoids the trafficking of HIV towards the CNS and suppression in the CNS avoids local HIV replication. The concentrations of antiretrovirals in the CNS depend on the capacity of antiretroviral drugs to cross the blood–brain barrier (BBB) and the ability of the BBB to expel antiretrovirals outside the CNS. Antiretroviral concentrations and HIV replication are not directly measurable in the brain; therefore, drug concentrations are measured in the CSF. Since antiretroviral concentrations and HIV replication in the brain and in the CSF seem to be related, CSF has been used as a valid substitute of brain tissue for evaluating the effect of antiretrovirals suppressing HIV replication.

### CPE score, bPI monotherapy and HAND

Detectable HIV RNA in the CSF has been associated with a higher risk of HAND development and/or progression. The CHARTER group has postulated that when levels of antiretrovirals in the CNS are not sufficient to fully suppress HIV, local viral replication in the CSF could be ongoing while suppressed in plasma. Based on studies that have measured the pharmacokinetic profile of antiretrovirals in the CSF, along with other characteristics of the drugs, the CHARTER group had proposed a CPE score for antiretrovirals as a tool to predict the risk of HIV replication in CSF and neurocognitive impairment.

The CPE score for a specific HAART regimen is calculated by adding up the individual value of each antiretroviral included in the regimen. The CHARTER group and others have reported that patients receiving a HAART regimen with a low CPE score have a higher risk of HAND and HIV virological failure in CSF. However, other studies have communicated conflicting results. The ALLRT cohort only confirmed the CPE score utility in patients receiving more than three antiretrovirals. A recent update of the CHARTER cohort, including a higher number of patients, did not confirm the results observed previously.

The CPE score of bPI monotherapy is considerably lower than that of triple-drug HAART. Given these large differences, it appears logical to hypothesize that bPI monotherapy might be associated with a higher risk of CNS virological failure and HAND. It is important to emphasize that one important caveat of the studies evaluating the CPE score is that typically they have included a diverse population of patients, with both active and suppressed HIV replication in plasma.

### Levels of PIs in the CSF, CSF viral suppression and bPI monotherapy

The ability of antiretroviral therapy to inhibit HIV viral replication in the CSF depends on several factors: the origin of the HIV viral load detected in the CSF; the levels of free drug achieved in the CSF; and the IC_{50} for antiretrovirals in the CSF.

---

**Table 1.** Studies including data on the percentage of patients on conventional antiretroviral treatment with detectable HIV RNA levels in the CSF and HIV RNA <50 copies/mL in plasma

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>HIV RNA cut-off used in CSF (copies/mL)</th>
<th>Percentage of patients above HIV RNA cut-off in CSF and &lt;50 HIV RNA copies/mL in plasma</th>
<th>CPE score predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eden et al.</td>
<td>69</td>
<td>50</td>
<td>10</td>
<td>no</td>
</tr>
<tr>
<td>Letendre et al.</td>
<td>300</td>
<td>2</td>
<td>26</td>
<td>NA</td>
</tr>
<tr>
<td>Letendre et al.</td>
<td>842</td>
<td>50</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Marra et al.</td>
<td>NA</td>
<td>50</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Yilmaz et al.</td>
<td>94</td>
<td>50</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Antinori et al.</td>
<td>107</td>
<td>50</td>
<td>15.2</td>
<td>yes</td>
</tr>
</tbody>
</table>

NA, not available.

*This study included only neuro-asymptomatic patients.
It has not been clarified whether the HIV viral load in the CSF derives mainly from plasma HIV replication or is the result of local production in the CNS. CD4 cells trafficking from plasma seem to be responsible for most of the HIV viral load detected in the CSF. Local active HIV replication in the CNS is increased in advanced patients with a low nadir CD4 cell count. The CSF antiretroviral levels needed to fully suppress HIV replication in patients with a low level of local CNS HIV replication could be lower than the antiretroviral levels needed when local CNS HIV replication is high.

The levels of antiretrovirals achieved in the CSF depend on different factors. Antiretroviral penetration into the CSF is modulated by the blood–CSF barrier (BCB). Different factors, such as molecular size, lipophilicity, ionization and plasma protein binding, modify antiretroviral penetration across the BCB. The CSF/plasma ratio for an antiretroviral is used to measure the effect of factors favouring drug penetration or making drug penetration difficult into the CSF.

Total CSF levels for an antiretroviral drug depend on the total plasma concentration for that antiretroviral and its CSF/plasma ratio. Antiretroviral levels in plasma are variable, depending on adherence, drug interactions and other factors. The CSF/plasma ratio remains constant, except in the presence of conditions that alter the permeability of the BBB and the BCB, such as CNS infections.

The total level of an antiretroviral in a biological fluid represents a proportion of the drug bound to proteins and a proportion of unbound free drug. Only the free drug component is active against HIV replication. More relevant than the CSF/plasma ratio for total antiretroviral levels is the CSF/plasma ratio for an antiretroviral.
The IC50, the concentration of an antiretroviral that inhibits the replication of HIV in 50% of infected cells, is the cut-off used to evaluate the capacity of an antiretroviral to suppress HIV replication in the CSF. The IC50 is typically assessed in a protein-free medium (PFM) and in the presence of plasma. Values for the IC50 are lower when assessed in PFM than when assessed with plasma, because in PFM there is a higher proportion of unbound drug.

The IC50 in the presence of CSF is normally not assessed because of methodological problems. Therefore, a precise activity cut-off for total antiretroviral levels in the CSF, a low-protein fluid, is not available. To solve this problem, three approaches have been tried. First, to compare the total level of the antiretroviral in the CSF with the IC50 in plasma; second, to compare the total level of the antiretroviral in the CSF with the IC50 in PFM; and third, if the unbound antiretroviral levels in the CSF can be measured, to compare the unbound level of the antiretroviral in the CSF with the IC50 in PFM. This last option is the most accurate, because it compares the effect of the drug under the same testing conditions (in a PFM).

bPIs are large lipophilic molecules that are highly bound to plasma proteins.29–31 The CSF/plasma ratio of total levels of PIs tested as monotherapy31–33 are low and, subsequently, concentrations achieved in the CSF are also low.31,32,36 However, the IC50 in PFM for the PIs used as monotherapy is also very low (~1–2 ng/mL).32,35,36 Although total levels of PIs in the CSF are low, they might be theoretically sufficient to exceed the IC50 in PFM in most cases (Table 3).

Factors interfering with antiretroviral drug levels in plasma, such as adherence or the presence of drug interactions, are very relevant when bPI monotherapy is used. The reduction of PI levels in plasma induces the reduction in levels of the antiretroviral in the CSF. To prevent this situation, it is very important for a bPI monotherapy that CSF levels of free drug are, in standard situations, several fold greater than the IC50 in PFM.

Several studies have evaluated the pharmacokinetic profile of the PIs tested as monotherapy (Table 3). These and other studies presented below have evaluated if the drug levels achieved in the CSF when atazanavir/ritonavir, lopinavir/ritonavir and darunavir/ritonavir are used as bPI monotherapy are enough to suppress the HIV viral load.

### Atazanavir/ritonavir

Best et al.36 studied 11 CSF/plasma sample pairs for patients receiving atazanavir and 68 for patients receiving atazanavir/ritonavir. Median CSF concentrations for atazanavir/ritonavir and atazanavir were 10.3 ng/mL (interquartile range (IQR) <5–38 ng/mL) and 7.9 ng/mL (IQR <5–40 ng/mL), respectively. Eleven of the paired samples (16%) had undetectable atazanavir levels in the CSF. Compared with patients with detectable atazanavir levels in the CSF, patients with undetectable levels were more likely to have detectable HIV RNA in the CSF (20% versus 37%).

In the ATARITMO trial, CSF viral suppression was analysed in 20 patients who remained with suppressed HIV replication in plasma after 24 weeks of treatment with atazanavir/ritonavir monotherapy.33 Three patients (15%) had a detectable viral load in the CSF without evidence of genotypic resistance mutations. This proportion of patients was consistent with the 16% of patients without detectable levels in the CSF in the study performed by Best et al.36 The lower IQR of the atazanavir concentrations measured in CSF in the ATARITMO trial was less than the IC50 in PFM for atazanavir.

### Lopinavir/ritonavir

Capparelli et al.32 performed a study with 24 CSF/plasma sample pairs to analyse if CSF concentrations of lopinavir exceeded the IC50 in PFM. After excluding seven pairs for poor adherence, results showed a median lopinavir CSF concentration of 17 ng/mL. The measured CSF concentration exceeded the IC50 in PFM for lopinavir by a median of 5.3-fold. Similar results were obtained by Yilmaz et al.37 in 12 patients, 12 and 48 weeks after starting lopinavir/ritonavir-based HAART. The mean concentration of lopinavir in the CSF in those patients was 25 ng/mL.

CSF viral suppression in patients receiving lopinavir/ritonavir monotherapy was analysed in three studies. In the first study, published by Letendre et al.,38 a reduction in the CSF viral load was observed after 3 weeks of lopinavir/ritonavir monotherapy in all 10 patients assessed. In the substudy of the IMANI-II

### Table 3. PIs used as monotherapy: relevant characteristics with regard to activity in the CNS reservoir

<table>
<thead>
<tr>
<th>PI</th>
<th>CPE score</th>
<th>Protein binding</th>
<th>CSF/plasma level ratio</th>
<th>CSF drug level, IQR (ng/mL)</th>
<th>IC50 (ng/mL) PFM</th>
<th>IC50 (ng/mL) plasma</th>
<th>CSF concentration above PFM IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/ritonavir</td>
<td>225</td>
<td>86%60</td>
<td>NA</td>
<td>&lt;5–3816</td>
<td>116</td>
<td>116</td>
<td>NA</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>325</td>
<td>98%–99%59</td>
<td>NA</td>
<td>12.1–22.752</td>
<td>272</td>
<td>NA</td>
<td>5-fold42</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>325</td>
<td>95%31</td>
<td>&lt;10%83</td>
<td>39.6–80.531</td>
<td>0.6–2.835</td>
<td>12–5535</td>
<td>18.5-fold35a</td>
</tr>
</tbody>
</table>

NA, not available.

aThese values are for unbound levels of darunavir instead of total darunavir levels.
clinical trial, the CSF HIV suppression rate was evaluated in 11 patients suppressed in plasma after 24 weeks of lopinavir/ritonavir monotherapy. Virological failure without evidence of genetic resistance mutations was observed in only one patient, who had high expression of MPC-1, a molecule related to the recruitment of blood lymphocytes and monocytes into the CNS. In this study, lopinavir/ritonavir concentrations exceeded at least three times the IC50 in PFM in all patients. Lastly, the MOST clinical trial was designed to compare, after 48 weeks of follow-up, CSF virological suppression in patients receiving lopinavir/ritonavir monotherapy or triple-drug therapy. Unexpectedly, the MOST trial was suspended prematurely after six patients (21%) receiving lopinavir/ritonavir monotherapy had a virological failure in plasma without development of genotypic resistance. Five of these six patients also had a detectable CSF viral load and four of these patients had symptoms consistent with acute retroviral syndrome.

Although the MOST study appears to suggest that the risk of discordant HIV replication (active replication in CSF while replication is suppressed in plasma) might be higher for patients receiving lopinavir/ritonavir monotherapy, a closer look at the data does not support this notion. Indeed, in the group of patients fully suppressed in plasma (HIV RNA <50 copies/mL), 4/29 patients in the monotherapy arm and 4/31 patients in the triple-drug HAART arm had a detectable CSF viral load. Only one patient receiving lopinavir/ritonavir monotherapy fulfilled the criteria of CSF virological failure defined in the study.

Darunavir/ritonavir

The CSF pharmacokinetic profile of darunavir/ritonavir was analysed in three studies. The first study, published by Yilmaz et al., included 14 CSF/plasma paired samples and the other two, presented by the CHARTER group, both included 29 CSF/plasma paired samples. The Yilmaz et al. study included patients receiving darunavir/ritonavir during a median of 12.5 weeks. All 14 CSF samples showed detectable levels of darunavir with a median concentration of 34.2 ng/mL (range 15.9–212 ng/mL). All concentrations were above the IC50 in PFM estimated for this study (2.75 ng/mL). Results from the CHARTER group, first presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy and at the 18th Conference on Retroviruses and Opportunistic Infections, were very similar and are presented together. Total darunavir concentrations (IQR 39.6–80.5 ng/mL) and the unbound concentration (IQR 36–73.6 ng/mL) in the CSF were detectable in all samples. Unbound CSF darunavir was a median of 18.5-fold above the IC50 in PFM for darunavir. This study was the first where the IC50 in PFM was compared with the unbound instead of the total drug concentration in the CSF, ensuring that the CSF protein rate did not interfere with the results.

In the Yilmaz et al. study, the CSF HIV viral load was analysed in the 14 CSF samples. Eleven patients had undetectable HIV RNA in the CSF. Detectable CSF viral load was associated with a shorter period of receiving triple-drug HAART including darunavir/ritonavir (1 week for two patients and 5 weeks for the third patient, whose CSF viral load was close to being undetectable). Unfortunately, there are no studies published that have evaluated the ability of darunavir/ritonavir to suppress HIV viral replication in the CSF. In MONOIF, two patients with CSF virological failure without emergence of genotypic mutations were reported in the presence of mild acute neurological symptoms.

Fosamprenavir/ritonavir

Fosamprenavir/ritonavir monotherapy has been tested unsuccessfully recently. The study was stopped prematurely due to a high proportion of HIV virological failure in plasma at 48 weeks (45%). The CSF HIV viral load was tested in 10 patients with an undetectable HIV viral load in plasma at week 24. All patients had undetectable HIV viral loads in the CSF using a cut-off of <40 copies/mL.

Neuropsychiatric events in bPI monotherapy trials

Neuropsychiatric events have been explored as part of the safety analysis of bPI monotherapy clinical trials. Although clinical neuropsychiatric events are less sensitive for detecting neurocognitive impairment than neurocognitive tests, no gross negative effects of bPI monotherapy in cognitive performance have been detected (Table 2). Of note, in most of these trials the actual proportion of patients with CNS adverse events was not reported, probably due to the low number of events.

Atazanavir/ritonavir

All atazanavir/ritonavir monotherapy clinical trials have been designed as single-arm studies. This design does not allow us to compare the rate of neuropsychiatric adverse events between atazanavir/ritonavir monotherapy and triple-drug HAART based on atazanavir/ritonavir. Neuropsychiatric adverse events in atazanavir/ritonavir monotherapy trials were low (Table 2).

Lopinavir/ritonavir

In the OK04 trial, patients randomized to receive lopinavir/ritonavir monotherapy did not have an increased incidence of neuropsychiatric events after 2 years of follow-up. A case of neurocognitive impairment associated with HIV virological failure in plasma was described in a single patient included in a single-arm trial of lopinavir/ritonavir monotherapy in Brazil after a year of follow-up. Neurological recovery was observed after the patient regained suppression after adding two nucleoside reverse transcriptase inhibitors (NRTIs). A CSF assessment returned normal results. Unfortunately, the CSF viral load was not available. Transient areas of cerebral hypoperfusion were detected in a scintigraphy with 99mTc-ECD.

In the MOST trial, four of the six patients in the monotherapy arm with virological failure in plasma presented with neurological symptoms as part of an acute retroviral syndrome. Interestingly, in the MOST study changes in neuropsychological test results did not differ between patients receiving triple-drug HAART or lopinavir/ritonavir monotherapy, or between patients who had detectable HIV RNA in CSF versus those with suppressed RNA in CSF. Neurological symptoms after loss of virological
suppression have not been reported in other bPI monotherapy trials or trials evaluating the interruption of triple-drug HAART.49

**Darunavir/ritonavir**

The MONOJ44 and MONET48 trial patients randomized to receive darunavir/ritonavir as bPI monotherapy had a similar incidence of neuropsychiatric events after 2 years of follow-up when compared with patients receiving triple-drug HAART. In the MONOJ trial, two patients in the monotherapy arm presented with neurological symptoms (one case of unusual headaches in a woman and one case of seizures in a known epileptic patient) with low levels of viral load in the CSF (HIV RNA 330 and 580 copies/mL). The addition of abacavir and lamivudine to darunavir/ritonavir in the two patients led to an improvement in clinical symptoms and a decrease in the CSF viral load to the lower limit of quantification (<200 copies/mL).

The MONET study included a memory and concentration self-scored assessment as a part of the Functional Assessment of HIV Infection (FAHI) quality of life questionnaire.49 Results of this self-scored questionnaire were used to evaluate cognitive functioning, clarity of thought, memory and ability to concentrate. Of the 206 patients who completed the FAHI questionnaire at weeks 0, 24 and 48, there were no differences at baseline or the 206 patients who completed the FAHI questionnaire at weeks 0, 24 and 48, there were no differences at baseline or week 48 between patients included in the bPI monotherapy arm or in the triple-drug HAART arm (Table 2).

The MONET study also included a small substudy in which six patients underwent computerized neurocognitive assessment (CogState29) and cerebral proton magnetic resonance spectroscopy.50 Three patients in the monotherapy arm and two in the triple-drug arm completed all procedures. An improvement in neurocognitive performance tests was observed in both treatment groups after 48 weeks of follow-up, without differences between groups. Improvements in brain inflammatory markers (choline and myo-inositol) but not in neuronal integrity markers [N-acetyl aspartate (NAA)] were observed in all patients after follow-up, without differences between groups. The absence of differences between groups could be related to the small number of patients included in the study. The decrease in the inflammatory markers after darunavir/ritonavir was started either as bPI monotherapy or as part of triple-drug therapy could be related to a better CPE score of darunavir/ritonavir compared with the PI used previously (atazanavir/ritonavir and saquinavir/ritonavir).

**The other side of the coin: possible CNS toxicity of NRTIs**

While the concern about the capacity of bPI monotherapy to suppress HIV replication in the CNS has been frequently postulated as a limitation before this strategy becomes more generally used, the potential benefit of removing NRTI toxicity in the CNS has not usually been taken into account.

There are two studies suggesting that HAART including drugs with good CNS penetration might be associated with worse neurocognitive function. Recently, the ACTG 5170 study47 reported that neuropsychological tests improved for up to 96 weeks in a group of treated patients with preserved immune function after HAART interruption. These results raise the possibility that all or some of the antiretroviral drugs may have a negative effect on neuropsychological function. Marra et al.22 performed a study in 101 patients to determine whether antiretroviral regimens with good CNS penetration give better control of HIV replication in CSF and improve cognition. Marra et al. reported that, as expected, regimens with a higher CPE score achieved better control of CSF HIV replication. Surprisingly, these regimens with good CNS penetration were associated with poorer neurocognitive performance. Although it is true that other studies19–21 have established a correlation between triple-drug therapy with high CPE scores and better neurocognitive function, the ACTG 5170 and Marra et al. studies cast some doubts about the general principle that better CNS penetration and higher CPE scores imply better neurocognitive functioning.

A number of NRTIs, such as stavudine or didanosine, might induce a negative effect on brain tissue by causing mitochondrial toxicity. In 18 HIV-infected patients who were analysed by magnetic resonance spectroscopy, stavudine and didanosine were associated with a reduction in NAA, which is a marker sensitive to alterations in mitochondrial integrity.51 Lower levels of NAA were also observed in patients receiving zidovudine plus lamivudine or in untreated patients compared with non-HIV subjects.

Neuronal toxicity has been tested in vitro for antiretroviral drugs.52 In one study of neuronal cultures, the addition of any of 15 antiretroviral drugs (NRTIs, non-nucleoside reverse transcriptase inhibitors, PIs and maraviroc) was associated with neuronal lesion and destruction. Of note, doses of abacavir, didanosine, etravirine and nevirapine that are considered neurotoxic fell within the range of CSF concentrations seen in patients receiving antiretroviral therapy. It is possible that the penetration of some antiretroviral drugs into the brain at concentrations sufficient to suppress HIV replication would carry some risk of neuronal damage. If this risk is relevant, then the use of bPI monotherapy would probably reduce the neuronal toxicity associated with triple-drug antiretroviral therapy.

**Conclusions**

The current evidence is insufficient to conclude whether, compared with triple-drug HAART, bPI monotherapy entails a higher risk of discordant CSF HIV replication and worse neurocognitive performance.

The existence of HIV active replication in the CSF while HIV replication is suppressed in plasma (CSF viral escape) is not exclusive to bPI monotherapy. Discordant replication in the CSF in patients who are suppressed in the blood has been reported in patients receiving triple therapy (Table 1). At present, we lack comparative data to conclude if the risk of discordant CSF HIV replication is higher in patients treated with bPI monotherapy than in patients receiving triple-drug HAART.

Current evidence does not suggest that bPI monotherapy with lapinavir/ritonavir or darunavir/ritonavir is associated with worse neurocognitive outcomes than triple-drug HAART. However, it should be noted that this issue cannot be definitively solved until we have available results of detailed neuropsychological testing in clinical trials comparing bPI monotherapy and triple-drug HAART. An ongoing study, the PIVOT clinical trial,53 will be the first study where neurocognitive performance will be compared between bPI monotherapy and triple-drug HAART.
as a secondary endpoint using more detailed neurocognitive testing. Other ongoing prospective studies are designed to compare neurocognitive performance between bPI monotherapy and triple-drug HAART. The results of these studies will be available in the following years. \(^5\)

Lopinavir/ritonavir and darunavir/ritonavir used as bPI monotherapy achieve concentrations in the CSF that are sufficient to suppress CSF HIV replication in adherent patients not harbouring PI-resistant isolates. The evidence that atazanavir/ritonavir as bPI monotherapy achieve sufficient concentrations in the CSF to ensure CSF HIV suppression appears more questionable. In patients fully suppressed in plasma, the risk of neuropsychiatric events assessed as adverse events in clinical trials with lopinavir/ritonavir or darunavir/ritonavir bPI monotherapy is low and similar to the risk of these adverse events observed with triple-drug HAART including lopinavir/ritonavir or darunavir/ritonavir.

We suggest that when detailed neurocognitive testing and virological suppression data obtained from patients treated with bPI monotherapy are available, these data would have to be taken into account for new revisions of the CPE score. In the future, the results of detailed neuropsychological testing, rates of suppression of HIV replication in the CSF and the possible neurotoxic effects of antiretrovirals would be important outcomes to capture in studies planning to compare triple-drug HAART, bPI monotherapy and other NRTI-sparing strategies. These data would be essential to establish if different therapeutic strategies are equally protective of the deleterious effects of HIV infection in the brain.

**Funding**

This work was supported by a ‘Fondo de Investigaciones Sanitarias (FIS)’ grant from the Spanish Ministry of Health, FIS P10/00483. I. P.-V. is supported by a grant from the FIS Rio Hortega programme (CM09/00228) and J. R. A. is an investigator from the ‘Programa de Intensificación de la Actividad Investigadora en el SNS’ (I3SNS).

**Transparency declarations**


**References**


