AIDS Rev. 2014;16:101-8

Central Nervous System Penetration and Effectiveness of Darunavir/Ritonavir Monotherapy

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Abstract

Darunavir/ritonavir monotherapy is an experimental switching strategy for virologically suppressed patients without protease inhibitor resistance to avoid nucleos(t)ide-related toxicities. This therapy maintains virological suppression in most patients, but at slightly lower rates than standard therapy that includes two nucleos(t)ides. Patients experiencing virological failure are generally re-suppressed without emergence of resistance with the resumption of two nucleos(t)ides. Reports of cerebrospinal fluid viral escape has been observed in patients receiving protease inhibitor monotherapy, and concerns exist regarding the capacity of protease inhibitor monotherapy to control HIV infection in the brain and to prevent neurocognitive decline. In the current report we have pooled together available evidence regarding the capacity of darunavir/ritonavir monotherapy to control HIV replication in cerebrospinal fluid and to prevent neurocognitive decline. **(AIDS Rev. 2014;16:101-8)**

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Key words

HIV. Darunavir. Protease inhibitor monotherapy. CSF viral escape. Neurocognitive performance.

Introduction

Standard HIV therapy includes the daily administration of two nucleos(t)ides - abacavir/lamivudine or tenofovir/emtricitabine plus a third drug (a nonnucleoside reverse transcription inhibitor, a ritonavir-boosted protease inhibitor, or an integrase inhibitor) for life[1]. Despite the fact that these combinations are generally well tolerated, there is a group of patients who present renal, bone, or cardiovascular comorbidities, and who are not good candidates for receiving abacavir or tenofovir. For this reason, several nucleos(t)ide-sparing regimens of a boosted protease inhibitor (PI) alone[2] or with a second drug (an integrase inhibitor[3] or lamivudine[4]) or dual combinations of an integrase inhibitor and a non-reverse transcription inhibitor[5] have been evaluated as alternatives to conventional antiretroviral therapy (ART) in these patients.

Simplification to darunavir/ritonavir[6,7] or to lopinavir/ritonavir[8] monotherapy appears as experimental alternatives to conventional ART for virologically suppressed patients having abacavir or tenofovir toxicities. In most patients, PI monotherapy maintains virological suppression, but at slightly lower rates than triple therapy that includes two nucleos(t)ides. Patients experiencing virological failure are generally re-suppressed with the resumption of two nucleos(t)ides and rarely compromise future therapeutic options[9]. Despite that darunavir/ritonavir and lopinavir/ritonavir monotherapies have not been compared in clinical trials, findings from an observational study suggest that both strategies have similar efficacy, but darunavir/ritonavir monotherapy appears as the better-tolerated option[10].

There is not a consensus about the convenience of use of PI monotherapy. The 2014 United States Department of Health and Human Services (DHHS) guidelines disallowed a widespread use of PI monotherapy[1]. The 2013 European AIDS Clinical Society (EACS) guidelines indicated that lopinavir/ritonavir and darunavir/ritonavir monotherapy might represent an option for

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simplification in selected patients with intolerance to nucleos(t)ide analogues[11]. The 2012 International Antiviral Society (IAS) HIV guidelines also disallowed darunavir/ritonavir monotherapy due, in addition to other reasons, to concerns about poor central nervous system (CNS) penetration and the report of discordant plasma and cerebrospinal fluid (CSF) viral loads[12].

The CNS penetration effectiveness of protease inhibitor monotherapy in general and of darunavir/ritonavir in particular is currently one of the major concerns regarding the safety of PI monotherapy. In recent years, several studies have evaluated the capacity of this strategy to control HIV replication in CSF and protect neurocognitive decline. In the present review we have pooled together all these studies and specifically analyzed those results concerning darunavir/ritonavir monotherapy.

Selection of studies

We selected articles indexed in PUBMED from January, 2003 to May, 2014 and congress communications presented at the CROI, at the EACS conferences, at the HIV Drug Therapy conferences, at the IAS conferences, and at the AIDS world congresses during the same period of time. We used the following selection criteria: articles and communications presenting comparative data about CNS side effects, neurocognitive performance, and HIV RNA concentrations in CSF and in plasma of patients receiving PI monotherapy.

Brain infection, central nervous system penetration, and neurocognitive decline

The HIV passes through the blood brain barrier, infecting CNS cells, generally perivascular macrophages and microglia[13]. This CNS infection produces, in certain patients, a wide spectrum of neurocognitive alterations that are known as HIV-associated neurocognitive disorders (HAND)[14]. Comorbidities, such as hepatitis C coinfection, use of illicit drugs, other CNS infections, and a variety of medical conditions, may also produce neurocognitive impairment in patients living with HIV[14]. In many cases, differentiating whether neurocognitive deficits are due to CNS HIV infection, comorbidities, or both is extremely difficult.

When immunity is preserved, HIV is commonly detected in the CSF, but not always in the brain parenchyma[15]. At these stages, HAND may be detected generally as a mild condition. When immunity declines[16], HIV clades with high avidity for infecting macrophages and the microglia start to be predominant inside the CNS and HIV may compartmentalize[17,18]. At that stage, HIV encephalitis (HIVE) appears, producing HIV dementia[19].

In patients presenting mild HAND, ART has a minimal impact on recovery of cognition. In patients with HIVE and HIV dementia, the ART has a tremendous impact on improving cognition[20,21], but in many cases ART is not able to recover cognition completely[22]. Partial effectiveness of ART may be due to the association of other comorbidities, the release of neurotoxic viral proteins from chronically infected astrocytes[23], or because ART does not penetrate into the CNS in enough concentration to suppress local HIV replication[24].

Antiretroviral concentrations and HIV replication are not measurable directly in the brain parenchyma and have to be measured in the CSF[25]. To guide the selection of ART regimens with good CNS penetration and effectiveness, the CHARTER group, based on molecular, pharmacokinetic, and pharmacodynamic characteristics, developed a CNS penetration and effectiveness (CPE) rank for each antiretroviral[26]. Ranks of each antiretroviral included in an ART regimen were added in order to obtain a prediction of the capacity of this ART to control HIV replication inside the CSF. This additive approach was sustained by previous studies that associated the number of antiretrovirals with good CNS penetrators used with the ART capacity to control HIV replication in the CSF[24]. The reliability of the CPE ranking to predict HIV replication in the CSF[21,25-29], especially in patients with HIV suppression in plasma[30-33], and neurocognitive impairment[29,34] is questioned due to conflicting results.

Caveats regarding central nervous system concerns on darunavir/ritonavir monotherapy

Darunavir/ritonavir monotherapy has a considerably lower CPE score of 3, lower than any conventional ART. Due to this low CPE score, concerns arose about the capacity of this strategy to control HIV replication in the CNS and prevent neurocognitive impairment. Several caveats question the validity of the CPE score to predict the CNS safety of the PI monotherapy.

First, the CPE score has been validated in studies that include a diverse population of patients, both with active and suppressed HIV replication in plasma[21,26-28]. Protease inhibitor monotherapy is only allowed in patients with persistent HIV suppression in plasma and it is mandatory to stop it and re-intensify therapy in the presence of confirmed loss of viral suppression[11].

Table 1. Studies including data on the percentage of patients on conventional antiretroviral treatment with cerebrospinal fluid viral escape: detectable HIV RNA levels in the cerebrospinal fluid and HIV RNA < 50 copies/ml in plasma

Study	(n)	HIV RNA cutoff used in CSF (copies/ml)	Percentage of CSF viral escape	Incidence of CSF viral escape	CPE score predictive value	Risk factors associated with CSF viral escape
Eden, et al.[31*]	69	50	10.0	NA	No	ART duration, neopterin levels, ART interruptions
Letendre, et al.[57]	300	2	26.0	NA	NA	NA
Marra, et al.[58]	NA	50	0	NA	NA	NA
Yilmaz, et al.[56]	94	50	2.0	NA	NA	NA
Antinori, et al.[55]	107	50	15.2	Yes	Yes	CPE score
Perez-Valero, et al.[32†]	1,209	50	4.4	NA	No	Protease inhibitors use, CSF pleocytosis, times in HIV diagnosis, platelet level, serum protein level
Perez-Valero, et al.[33]	849	50	NA	37.4 per 1,000 person-years	No	Protease inhibitor use, plasma HIV RNA within 20-50 cop/ml, CSF pleocytosis
Rawson, et al.[46]	69	200	13.0		Yes[‡]	CPE score
Pinnetti, et al.[47]	302	50	10.3		No	Gender, CD4 cell count, atazanavir, abacavir/lamivudine
Perez Valero, et al.[50]	30	50	6.6	NA	No	NA

CFS: cerebrospinal fluid; CPE: CNS penetration and effectiveness; NA: not available; ART: antiretroviral therapy.
*This study included only neuro-asymptomatic patients.
†Patients underwent lumbar punctures due to clinical research exclusively.
‡Only in patients with HIV encephalopathy.

Therefore, only those studies that have evaluated the CNS penetration effectiveness in patients with viral suppression in plasma apply to PI monotherapy[30-33]. Detection of HIV RNA in CSF in patients with viral suppression in plasma, known as CSF viral escape, as we will see in detail later, is an infrequent event (Table 1). The CPE score has failed to demonstrate association with the presence of CSF viral escape in all studies[31-33] except one published by Antinori, et al.[30].

Second, the benefits of using several drugs with good CPE to control HIV infection in CNS derived from classical studies that analyzed antiretrovirals with low antiviral potency that are currently withdrawn[24]. None of these studies contemplated the possibility that a single drug with high antiviral activity and a high barrier of resistance could control HIV replication alone. Similarly, several studies have failed to demonstrate benefits in terms of improving HIV control in CSF, brain protection, or neurocognitive performance of adding another antiretroviral with good CNS penetration in patients already suppressed in blood[35,36].

Finally, the CPE score did not take into account the deleterious neurotoxic effect that the addition of antiretrovirals may have on the brain tissue and subsequently on neurocognitive performance[37].

Levels of darunavir/ritonavir achieved in cerebrospinal fluid

Darunavir is a large lipophilic molecule, which is highly bound to plasma proteins[38], and subsequently the capacity of darunavir free drug component to cross

the blood-brain barrier is limited. However, darunavir exhibited potent anti-HIV activity, with a low 50% effective concentration (EC_{50}) of 1.0-8.5 nM and a 90% effective concentration of 2.7-13.0 nM[39]. Therefore, although concentrations of darunavir that reached the CSF are low, they are generally enough to control local HIV replication.

Three studies have evaluated the pharmacokinetic profile of darunavir/ritonavir in the CSF, two with the 600/100 mg twice-daily dosing[38,40] and one with the 800/100 mg once-daily dosing[41]. The first study published by Yilmaz, et al[38] evaluated 14 CSF-plasma paired samples from patients receiving darunavir/ritonavir 600/100 mg twice-daily during a median of 12.5 weeks. All 14 CSF samples showed detectable levels of darunavir several folds above the inhibitory concentration (IC) 50 estimated in protein-free medium (2.75 ng/ml) with a median total darunavir concentration of 34.2 ng/ml (range: 15.9-212).

The second study published by the CHARTER group[40] analyzed the unbound levels of darunavir in the CSF in 29 CSF-plasma samples from 16 subjects also receiving darunavir/ritonavir 600/100 mg twice-daily for a median of 9.4 months. Total darunavir concentrations (median 55.8 ng/ml; IQR: 39.5-79.1) and unbound concentrations (50.2 ng/ml; IQR: 35.0-72.6) in CSF were detectable in all but one CSF sample (3%). The subject with the undetectable CSF darunavir concentration had the lowest plasma darunavir concentration and high plasma and CSF HIV RNA values, all suggesting potential ART nonadherence. All unbound darunavir concentrations except for the single sample with undetectable levels of darunavir in CSF exceeded by at least eightfold the IC_{90} for wild-type HIV.

Finally, the third study[41] compared CSF darunavir and ritonavir concentrations in 41 patients receiving darunavir/ritonavir 800/100 mg once-daily or 600/100 mg twice-daily. Levels of darunavir in patients receiving the once-daily dosing were significantly lower (CSF darunavir trough of 10.7 ng/ml; range, 6.7-23.0) than in patients receiving the twice-daily dosing (38.2, range 30.2-52.3; $p = 0.0004$). Three patients (11.6%) in the once-daily arm had CSF darunavir concentrations below the median IC_{50} (2.75 ng/ml) compared to none in the twice-daily arm. These low concentrations were associated with an AA genotype in SLCO1A2 at position 38. These results might suggest that the once-daily dosage of darunavir/ritonavir may be inappropriate in patients who require an increased pharmacological coverage in the CNS due to neurological disorders and/or risk of compartmental HIV replication.

Despite that the darunavir concentration in CSF achieved suppressive concentrations in the majority of cases, certain factors, such as the administration of darunavir without food that decreased darunavir levels by 30%[42] or the use of darunavir/ritonavir without tenofovir/emtricitabine that reduced darunavir concentrations by 36%[43], might acquire special relevance when darunavir/ritonavir is administered as monotherapy. Another factor that may impact darunavir concentrations in the CSF in patients receiving monotherapy is adherence to therapy. In a study of 17 healthy volunteers performed to evaluate the effect of forgotten and delayed dosing of darunavir/ritonavir 800/100 mg once-daily, 82% of the subjects did not achieve therapeutic doses of darunavir in plasma after missing a single dose[44]. In addition, selective adherence to darunavir due to ritonavir-related side effects may reduce darunavir concentrations up to 14-fold[45].

In summary, darunavir/ritonavir achieves therapeutic concentrations in a majority of patients with optimal adherence. In some cases that require increased pharmacological coverage in the CNS due to neurological disorders and/or risk of compartmental HIV replication, twice-daily dosage of darunavir/ritonavir 600/100 mg is preferable to ensure therapeutic levels in CSF. The potential impact of the AA genotype in SLCO1A2 over levels of darunavir in CSF in patients receiving darunavir/ritonavir 800/100 mg once-daily dosage monotherapy deserves special attention.

Darunavir/ritonavir monotherapy and cerebrospinal fluid viral escape

Cerebrospinal viral escape has been defined as the presence of levels of HIV RNA above the limit of quantification in CSF and below this limit in plasma, as a level of HIV RNA 1 $\log_{10}$ higher in CSF than in plasma, or as both[30-33,46]. In a prospective study performed in 849 aviremic HIV-infected patients followed for a median of 2.5 months in two large US cohorts that included, as a predefined routine procedure, the assessment of neurocognitive performance and the determination of HIV RNA in plasma and CSF every six months, CSF viral escape was uncommon (37.4 cases per 1,000 person-years) and generally a transient event (90%), mostly reported in CNS asymptomatic patients and not clearly associated with progression to neurocognitive decline[33].

Several factors, including the use of PIs and the detection of low-level viremia in plasma (within 20-50 copies/ml), were associated with CSF viral escape[32,47].

Table 2. Clinical trials and prospective studies of darunavir/ritonavir monotherapy: Neurocognitive outcomes

Study	Group (n)	Neurocognitive performance, mean + SD (weeks of follow-up)	Percentage of patients with CNS adverse events (week of follow-up)
MONET[6]	Darunavir/r (127)	8.9 + 2.8 (48)†	16% (48) - 21% (96)
	Darunavir/r + 2 NRTI (129)	9.0 + 2.6 (48)†	16% (48) - 19% (96)
MONOI[7]	Darunavir/r (103)	NA	NA‡
	Darunavir/r + 2 NRTI (104)	NA	NA
PICASSO[51]	Darunavir/r (43/30)	21% (0)§ Mean GDS change: –0.06 (48)	NA
	Darunavir/r + 2 NRTI (25/20)	36% (0)§ Mean GDS change: –0.05 (48)	NA
PIVOT[9]	PI monotherapy (296)¶	Mean NPZ-5 change: +0.51 (187)	NA
	PI triple therapy (291)	Mean NPZ-5 change: +0.50 (187)	NA

SD: standard deviation; CNS: central nervous system; NA: not available; r: ritonavir; GDS: Global Deficit Score; NPZ-5: neurocognitive performance Z-Score 5.
*Intent-to-treat, missing and switches equal failure.
†FAHI score used to measure neurocognitive performance.
‡Transient acute neurological symptoms (seizures in an epileptic patient and atypical headache) in two patients in the monotherapy arm resolved after re-induction with two NRTIs.
§Proportion of neurocognitive impairment.
¶79% of patients received darunavir/ritonavir.

Considering that low-level viral load rebounds are more frequently observed in patients receiving PI monotherapy, higher rates of CSF viral escape might be expected in patients receiving darunavir/ritonavir monotherapy. Unfortunately, rates of CSF viral escape in patients receiving darunavir/ritonavir monotherapy or triple therapy have not been compared in clinical trials.

Outside clinical trials, only two cases of asymptomatic CSF viral escape have been reported by Gisslen, et al.[48]: a 27-year-old black woman and a 51-year-old man with low nadir CD4 T-cell counts of 170 and 160 cell/µl, respectively, and both asymptomatic while receiving darunavir/ritonavir 800/100 mg. Levels of HIV RNA were assessed as part of a study protocol in both cases, showing 709 and 478 copies/ml in CSF and 114 and 46 copies/ml. Patients did not develope HIV resistance in CSF, were successfully re-suppressed with tenofovir/emtricitabine and abacavir/lamivudine, and their HIV RNA levels in CSF decreased to 56 and below 20 copies/ml.

Infrequently, CSF viral escape has been observed in patients presenting neurological symptoms as a persistent condition sometimes associated with compartmentalization of resistant HIV clades[49]. These cases have been rarely reported, both in patients receiving triple therapy and PI monotherapy. Symptomatic CSF viral escape in patients receiving darunavir/ritonavir monotherapy has only been reported, to our knowledge, in two patients enrolled in the MONOI clinical trial[7] (a 36-year-old woman who experienced unusual headaches and a 66-year-old man with known untreated epilepsy) and in a 47-year-old subject with persistent headache[49]. Levels of HIV RNA in CSF were, respectively, 330, 508, and 580 copies/ml. The three cases were successfully re-suppressed with abacavir/lamivudine and darunavir/ritonavir and symptoms disappeared. Interestingly, the last patient had an undetectable darunavir concentration in CSF (< 5) while it was under normal limits in plasma (3,522 ng/ml).

Finally in the PICASSO study[50], a prospective study designed to compare neurocognitive performance between PI-based monotherapy and triple therapy, HIV RNA in CSF was assessed in some patients diagnosed with neurocognitive impairment. Using the conventional cutoff of 50 copies/ml, CSF viral escape was detected in one patient (HIV RNA in CSF 370 copies/ml) receiving triple therapy of darunavir/ritonavir plus tenofovir/emtricitabine. Using a qualitative nested-PCR able to detect any trace of HIV RNA, residual CSF HIV RNA was detected in four out of five patients (80%) receiving darunavir/ritonavir monotherapy and in two out of five (40%) receiving triple therapy (p = 0.39).

In light of these results, available evidence is not enough to confirm if darunavir/ritonavir monotherapy is or is not associated with higher risk of CSF viral escape than triple therapy. Although, considering the limited number of cases reported after more than 10 years of use of PI monotherapy, it seems unlikely that darunavir/

ritonavir monotherapy is associated with high risk of CSF viral escape.

Darunavir/ritonavir monotherapy and the neurocognitive performance

Neurocognitive performance has been compared in patients receiving darunavir/ritonavir as monotherapy or as triple therapy in two studies: the PICASSO study[51] and the PIVOT clinical trial[9] (Table 2). The PICASSO study is a one-year prospective study designed to compare, using a comprehensive battery of 14 tests covering seven neurocognitive domains, the neurocognitive performance in a clinical setting of aviremic patients on stable therapy (> 1 year) with darunavir/ritonavir or lopinavir/ritonavir prescribed by clinical decision as monotherapy or as triple therapy. The PIVOT study is a five-year clinical trial designed to compare the loss of therapeutic options in patients randomized to receive PI monotherapy or triple therapy that also compared, using an abbreviated battery of five tests, the neurocognitive performance of patients. Both studies are complimentary and have added relevant information about the capacity of PI monotherapy to preserve neurocognitive performance.

The PICASSO study[51] included 96 patients on monotherapy and 95 on triple therapy at baseline. Of them, 43 received darunavir/ritonavir as monotherapy and 25 as part of a triple therapy. The prevalence of neurocognitive impairment was similar (p = 0.17) between patients treated with darunavir/ritonavir monotherapy (21%) or darunavir/ritonavir and two nucleos(t)ides (36%). At follow-up, 134 patients agreed to neurocognitive reassessment. Thirty of them received darunavir/ritonavir monotherapy and 20 darunavir/ritonavir and two nucleos(t)ides. In this subgroup of patients, the evolution of the neurocognitive performance measured using the global deficit score was almost identical (p = 0.84) in patients receiving darunavir/ritonavir as monotherapy (mean –0.06; 95% CI: -0.17-0.05) or as triple therapy (mean –0.05; 95% CI: –0.18-0.09).

The PIVOT clinical trial[9] included 296 patients treated with PI monotherapy and 291 with a PI and two nucleos(t)ides. In almost 80% of the cases the PI selected was darunavir/ritonavir. Neurocognitive function measured as the mean change in NPZ-5 from baseline improved progressively and in an almost identical way in patients that received monotherapy and triple therapy after 3.6 years of follow-up (p = 0.06).

In addition to these two large studies, a small neurocognitive substudy of six patients was included in the MONET clinical trial[52]. Three patients in the monotherapy arm and two in the triple-therapy arm underwent neurocognitive assessment using a computerized battery (CogState™). These five patients improved cognition after 48 weeks in the same way. Absence of differences between the groups could be related to the small number of patients included in the study.

In summary, the results of these two studies, one of them randomized with more than three years of follow-up and the other prospective including detailed neurocognitive assessment, have showed almost identical evolution of neurocognitive function in patients receiving monotherapy or triple therapy

Darunavir/ritonavir monotherapy and adverse events in clinical trials

Neuropsychiatric adverse events have been explored in patients treated with darunavir/ritonavir as monotherapy and as triple therapy in the MONOI[7] and the MONET[6] clinical trials. In both studies, neuropsychiatric adverse events were uncommon and appeared in similar proportions after 96 weeks of follow-up in both clinical trials. Due to the fact that neuropsychiatric events could be another form of expression of brain dysfunction, we should expect higher rates of neuropsychiatric events in patients receiving monotherapy than those on triple therapy if darunavir/ritonavir monotherapy is unable to control HIV replication in the CNS.

Darunavir/ritonavir monotherapy and functional complaints in clinical trials

While in the MONOI study functional complaints were not recorded, in the MONET study functional complaints were assessed using the Functional Assessment of HIV Infection (FAHI) quality of life questionnaire[53]. The self-reported FAHI questionnaire evaluated cognitive functional complaints regarding clarity of thought, memory, and ability to concentrate. Similar proportions of patients presented cognitive functional complaints at baseline and after 48 weeks of follow-up of darunavir/ritonavir monotherapy or triple therapy (Table 2).

Dual therapies with darunavir/ritonavir and the central nervous system

Another strategy to avoid abacavir and tenofovir-related toxicities is dual therapy with a PI and a second drug such as lamivudine[4] or raltegravir[3]. From a CNS

point of view, the addition of a second drug might increase the PI capacity to control CNS HIV replication. However, concerns exist about the capacity of dual therapy to cover patients who are not good candidates to receive PI monotherapy due to suboptimal adherence, low CD4 nadir, or previous CNS infections. In those cases, if the PI alone does not control CNS HIV replication, dual therapies will expose patients to a functional monotherapy with a drug with low genetic barrier and, therefore, in such circumstances HIV would become resistant and would compartmentalize.

Currently, there are no specific data regarding the CNS safety of these dual therapies. Until now, clinical trials did not report cases of CSF viral escape. Neurocognitive performance has only been evaluated in the ATLAS study[54], a single-arm study investigating the safety of switching to conventional ART of atazanavir/ritonavir plus lamivudine in aviremic patients. Despite the majority of patients improving during the study, this result may be due to the learning effect. Further studies are needed to evaluate the CNS safety of dual therapies.

Conclusion

Darunavir concentrations in the CSF are enough to suppress CSF HIV replication in the majority of the patients not harboring PI-resistant isolates. Subtherapeutic concentrations of darunavir in CSF have been associated with the presence of the AA genotype in SLCO1A2 in patients treated with darunavir/ritonavir 800/100 mg once-daily. Whether this polymorphism is associated with a higher risk of CSF viral escape in patients receiving darunavir/ritonavir monotherapy deserves further investigation.

Cases of CSF viral escape are rare in patients receiving darunavir/ritonavir monotherapy. Adverse events reported in clinical trials do not support the existence of a higher prevalence of symptomatic CSF viral escape in patients receiving darunavir/ritonavir monotherapy than in patients receiving darunavir/ritonavir plus two nucleos(t)ides. Asymptomatic cases of CSF viral escape have not been detected in higher proportions in patients receiving darunavir/ritonavir monotherapy. However, considering the limited number of patients that have been assessed, this possibility cannot be completely ruled out.

Finally, the prevalence of neurocognitive impairment and the evolution of neurocognitive performance after several years of receiving darunavir/ritonavir monotherapy as well as other PI monotherapies or conventional ART are comparable.

Conflict of Interest

Ignacio Pérez-Valero is free of conflict of interest for the present work. Outside this work, he is member of the Gilead's Speaker Bureau and has received honoraria from MSD, Gilead Sciences S.A., Janssen-Cilag S.A. VIIV and BMS for lectures.

Alicia González-Baeza, has no conflict of interest.

M.ª Luisa Montes-Ramírez, has no conflict related to this manuscript. Outside this work, has received consulting fees from Abbott Pharmaceuticals, Boehringer Ingelheim, Janssen, Gilead Sciences and ViiV. Payment for lectures from Abbott Pharmaceuticals, Bristol-Myers Squibb and Roche.

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