Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136

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Background: Darunavir/ritonavir (darunavir/r) maintenance strategy, in patients with suppressed HIV RNA viremia, is a potential long-term strategy to avoid nucleoside analogue toxicities and to reduce costs.

Methods: MONOtherapy Inhibitor protease is a prospective, open-label, noninferiority, 96-week safety and efficacy trial in virologically suppressed patients on triple therapy who were randomized to a darunavir/r triple drug regimen or darunavir/r monotherapy. The primary endpoint was the proportion of patients with HIV RNA less than 400 copies/ml at week 48; treatment failure was defined as two consecutive HIV RNA more than 400 copies/ml (time to loss of virologic response) or any change in treatment. The trial had 80% power to show noninferiority for the monotherapy arm ($\delta = -10\%$, 90% confidence interval).

Results: A total of 242 patients were screened, 225 of whom were randomized. In the per protocol efficacy analysis, treatment success was 99% on darunavir/r triple drug versus 94% on darunavir/r monotherapy ($\delta = -4.9\%$, 90% confidence interval, from -9.1 to -0.8). Similar results were found in intent-to-treat population (92 versus 87.5%, $\delta = -4.5\%$, 90% confidence interval from -11.2 to 2.1). Three patients experienced virologic failure on darunavir/monotherapy and none on darunavir/r triple drug. No resistance to protease inhibitor emerged in patients with plasma viral load above 50 copies/ml. The two groups did not differ in the number of serious adverse events.

Conclusion: Darunavir/r monotherapy exhibited efficacy rate over 85% with concordant results in the magnitude of difference with darunavir/r triple drug regimen in both intent-to-treat and per protocol analyses, but discordant conclusions with respect to the noninferiority margin. Patients failing on darunavir/r monotherapy had no emergence of new darunavir resistance mutations preserving future treatment options.

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Introduction

The standard and commonly accepted regimens for the initial treatment of HIV-1 infection involve the use of three drugs from two different classes: two nucleoside reverse transcriptase inhibitors (NRTIs) with either one boosted protease inhibitor or one nonnucleoside reverse transcriptase inhibitor (NNRTI) [1]. Although the regular use of combined antiretroviral therapy has substantially reduced AIDS-related morbidity and mortality, the inability to eradicate HIV with such a regimen requires their prolonged use for a lifetime, making long-term toxicity and cost critical issues in the management of HIV-infected patients [2]. In order to treat the largest number of patients worldwide, a continued search for alternative, effective, safe and affordable long-term therapy is necessary.

The use of NRTI is associated with several adverse effects, including mitochondrial toxicity, lipoatrophy and renal impairment [3–6]. Attempt to limit drug exposure as a strategy has been unsuccessful investigated by structured treatment interruptions [7]. Studies investigating monotherapy such as lopinavir/ritonavir or atazanavir/ritonavir have provided some promising results [8–11]. Monotherapy with a boosted protease inhibitor as a maintenance strategy is attractive because it spares other classes of drugs and reduces toxicity and cost [12]. Darunavir/ritonavir (darunavir/r) is an appropriate candidate for protease inhibitor monotherapy due to its high genetic barrier [13], high potency in wild-type and resistant HIV strains [14] and good pharmacokinetic profile [15,16]. Trials investigating maintenance or first-line therapy with protease inhibitor monotherapy have demonstrated a slightly higher proportion of patients with intermittent viremia, raising the concern about selecting resistance mutations [17,18]. Recent data have shown that the selection of darunavir-resistant mutations from wild-type strains is slower and more difficult than for other protease inhibitors [13,19,20]. Our objective was to evaluate whether monotherapy with darunavir/r could be noninferior in terms of efficacy in comparison with a standard triple drug therapy comprising two NRTIs and darunavir/r.

Methods

MONOtherapy Inhibitor protease (MONOI) is an ongoing, 96-week, multicenter, randomized, open-label trial with a primary endpoint at week 48, performed at 32 Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS) sites in France. This study included a first phase in which darunavir 600/100 mg twice daily was introduced for 8 weeks as a component of a triple drug regimen in replacement of the protease inhibitor, NNRTI or third NRTI. Patients whose HIV viral load remained lower than 50 copies/ml 4 weeks after darunavir induction (W-4) and who had no severe adverse event (SAE) or darunavir-related toxicity were randomly assigned 1 : 1 to continue the triple drug darunavir-containing regimen (darunavir triple therapy) or to stop the two NRTIs (darunavir monotherapy). Randomization was centralized and stratified by HIV-1 RNA level (<versus ≥100 000 copies/ml) prior to first antiretroviral treatment and whether or not the center participates to the body composition substudy. The protocol was amended in June 2007 to allow patients with missing HIV-1 RNA before treatment initiation to be enrolled and randomized in the strata HIV-1 RNA at least 100 000 copies/ml.

The study population consisted of HIV-1-infected patients at least 18 years of age receiving a triple antiretroviral drug regimen. All patients had plasma HIV-1 RNA less than 400 copies/ml for the past 18 months, based on at least four viral load measurements, and less than 50 copies/ml at screening. Patients had no history of virologic failure while receiving a protease inhibitor-containing regimen, a documented CD4 lymphocytes nadir greater than 50 cells/μl and acceptable laboratory results at screening. Patients with a history of HIV-related neurological disease or with hepatitis B coinfection could not be enrolled.

Efficacy and safety assessments

After screening (W-10), study evaluations were completed before trial entry (W-8 and W-4), at randomization and at weeks 4, 8 and every 8 weeks thereafter for the duration of the study. Virologic assessments were performed at local laboratories, all from the HIV virology and resistance network of ANRS. A genotypic resistance test was performed in all patients with a plasma HIV-1 RNA level more than 400 copies/ml confirmed in a second sample within 2 weeks or with two plasma HIV-1 RNA levels more than 50 copies/ml obtained in two consecutive visits. Sequences of the protease and reverse transcriptase genes were determined in each laboratory using the ANRS consensus technique (http://www.hiv-frenchresistance.org). Darunavir resistance mutations (V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V) were identified from the International AIDS Society-USA resistance testing panel [21].

Laboratory analyses, including CD4 cell count were measured at screening, at entry and every 8 weeks thereafter. Patients' adherence to study-drug regimen was assessed by standardized self-report questionnaires at entry, weeks 4, 24 and 48 [22]. The adherence questionnaire included a 4-day recall. An adherence rate of 100% was defined as no missed doses declared during the previous 4 days at entry, weeks 4, 24 and 48. Adverse clinical and laboratory events were assessed by site

investigators and were scored with the use of the adverse-event grading scale of the ANRS. An independent Data and Safety Monitoring Board (DSMB) reviewed interim efficacy and safety results.

The primary endpoint measure was the proportion of patients with treatment success by week 48. Treatment failure was defined as any of the following events: virologic failure; treatment modification or discontinuation; and withdrawal. Virologic failure was defined as two consecutive measurements of HIV-1 RNA more than 400 copies/ml within 2 weeks. Patients with a single value of HIV-1 RNA more than 400 copies/ml and a missing second HIV-1 RNA measurement were also considered as failures. Treatment modification was defined as any modification of antiretroviral therapy.

Secondary efficacy endpoints included the proportion of patients with HIV-1 RNA level less than 50 copies/ml and less than 400 copies/ml at each study visit, changes in the CD4 cell count and emergence of resistance mutations. For these secondary endpoints, missing data due to missed evaluations were ignored.

The protocol was approved by the ethics committee Comité de protection des personnes (CPP) Paris VI Pitié-Salpêtrière and by the Agence Française de Sécurité Sanitaire des Produits de Santé (23 January 2007). All patients provided written informed consent.

Statistical analysis

Prespecified criteria stated that darunavir monotherapy would be judged noninferior to darunavir triple therapy if the lower limit of the two-sided 90% confidence interval (CI) of the difference in percentage of patients in therapeutic success (monotherapy − triple therapy) was greater than 10%. On this basis, assuming a 90% success rate in both treatment arms, a total of 110 patients per arm would provide approximately 80% power (one-sided, $\alpha = 0.05$) to assess the noninferiority of darunavir monotherapy compared with darunavir triple therapy.

All patients who underwent randomization and received at least one day of study treatment were included in the intent-to-treat (ITT) population. The per protocol population included all patients from the ITT population except those who did not fulfill the inclusion criteria or withdrew from the study or discontinued study treatment without virologic failure or SAE. Analysis of the primary efficacy endpoint was performed with both per protocol and ITT populations. A secondary analysis was performed stratified according to the level of viral load before treatment initiation. Except for the primary endpoint, all other CIs are given at 95%. An exploratory analysis compared patients who maintained HIV-1 RNA below 50 copies/ml throughout the study to those experiencing at least one HIV-1 RNA level above 50 copies/ml.

The study was designed and conducted by members of the ANRS, Paris, France (MONOI ANRS 136 trial). Janssen-Cilag provided darunavir for this trial.

Results

A total of 242 patients were enrolled in the first phase from March 2007 to April 2008 (Fig. 1). Sixteen patients discontinued the study during this phase for the following reasons: SAE in three patients; darunavir-related toxicity in three patients; patient's decision in six patients; HIV-1 RNA more than 50 copies/ml at W-4 in three patients and lost-to-follow-up in one patient.

The ITT population included 225 randomized patients who received the study treatment and the per protocol population involved 204 patients (102 patients in each arm). Twenty-one patients were not included in the per protocol population for the following reasons: study withdrawal without virologic failure or SAE in six patients; modification of darunavir or any NRTI or treatment intensification without virologic failure or SAE in 10 patients; and violation of inclusion criteria in five patients.

Baseline characteristics were well balanced between the two treatment groups (Table 1). At screening, 69, 19, 10 and 2% of patients were receiving a triple therapy comprising a protease inhibitor, a NNRTI, three NRTIs and another combination therapy, respectively. Main combinations of NRTIs consisted of tenofovir/emtricitabine (33%), zidovudine/lamivudine (24%) or abacavir/lamivudine (16%).

Primary endpoint

At week 48, in the per protocol population, the proportion of patients with treatment success was 101 of 102 patients (99%) in the darunavir/r triple therapy arm and 96 of 102 patients (94%) in the darunavir/r monotherapy arm (Table 2). The difference between the two groups was −4.9% (90%CI from −9.1 to −0.8), thereby establishing noninferiority of darunavir/r monotherapy to darunavir/r triple therapy. In the ITT population, the proportion of response to therapy was 92% with darunavir/r triple therapy and 87.5% with darunavir/r monotherapy. The difference between the two groups was of same magnitude (−4.5%), but with a larger 90%CI (−11.2 to 2.1), excluding noninferiority. The stratified analysis, on 153 patients with available pretreatment viral load, showed a larger difference in efficacy for patients randomized in the strata with a high level of HIV RNA (Table 2).

Outcomes of treatment failures

Three patients experienced virologic failure in the darunavir/r monotherapy group. One patient with a

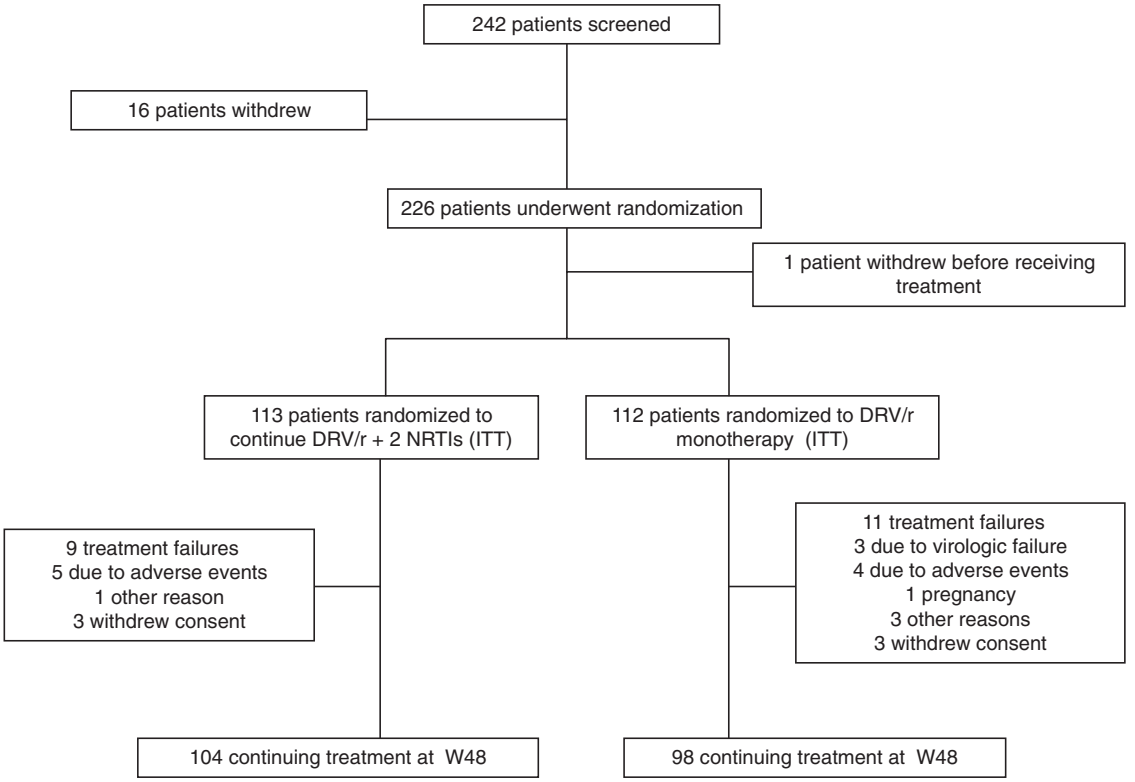

Fig. 1. Trial profile. DRV/r, darunavir/ritonavir; ITT, intent-to-treat; NRTIs, nucleoside reverse transcriptase inhibitors.

plasma viral load at week 8 of 2722 copies/ml admitted to low adherence to therapy with a darunavir trough concentration of 1120 ng/ml. The second patient had a viral load at week 24 of 411 copies/ml with an adequate darunavir trough concentration of 3480 ng/ml. The third patient had discontinued therapy at week 32 with a viral load of 484 569 copies/ml. All three patients re-suppressed HIV-1 RNA after the addition of two NRTIs.

Response to treatment

At week 48, the proportions of patients with plasma HIV-1 RNA less than 50 copies/ml and less than 400 copies/ml were 94.5% (95%CI 90–99) and 100%, respectively on darunavir/r triple therapy, and 89% (95%CI 83–95) and 97.3% (95%CI 94–100) on darunavir/r monotherapy (Fig. 2a and b). Over the 48 weeks, 91 (81%) and 82 patients (73%) from the ITT population had consistent plasma HIV-1 RNA measurements less than 50 copies/ml on darunavir/r triple therapy and on darunavir/r monotherapy, respectively (Table 3). Concordant results were found for the per protocol analysis. When analysis was stratified on pretreatment viral load, a much lower difference between the two treatment groups was observed in the strata with a low level of HIV-1 RNA for both ITT and per protocol analyses (Table 3).

At week 48, the median CD4 cell count was 574 cells/μl [interquartile range (IQR) 452–825, median increase 36 cells/μl, IQR −71–100] on darunavir/r triple therapy and 621 cells/μl (IQR 481–778, median increase 6 cells/μl, IQR −53–93) on darunavir/r monotherapy ($P = 0.58$ by the Wilcoxon rank-sum test).

Overall, 74 (33%) patients reported having missed at least one dose over the four evaluations; there were no significant differences among the randomized groups. In terms of primary endpoint, there was no difference between patients with 100% adherence and those with a lower rate of adherence ($P = 0.15$). However, adherence and the HIV-1 RNA level at baseline were significant predictors of consistent HIV-1 RNA measurements less than 50 copies/ml. Indeed, 19% of patients with 100% adherence had at least one HIV-1 RNA measurement more than 50 copies/ml compared with 32% in patients with a lower rate of adherence ($P = 0.03$). All eight patients with an HIV-1 RNA level between 50 and 400 copies/ml at baseline had at least one further HIV-1 RNA level more than 50 copies/ml compared with 20% of the patients with HIV-1 RNA level less than 50 copies/ml at baseline ($P < 0.0001$). A multivariate model including both adherence and HIV-1 RNA level at baseline could not be estimated due to difficulty in the likelihood estimation. Our data, however, suggest that the two variables were independent predictors of consistent HIV-1 RNA measurements less than 50 copies/ml as there was no association between adherence and HIV-1 RNA level at baseline (from the eight patients with an HIV-1 RNA level between 50 and 400 copies/ml at

Table 1. Baseline characteristics.

	Darunavir/r triple therapy $N=113$	Darunavir/r monotherapy $N=112$
Age (years)		
Median (IQR)	45 (39–56)	46 (41–51)
Male sex, *n* (%)	87 (77)	83 (74)
BMI, kg (IQR)	24.7 (22.4–26.8)	23.2 (21.9–24.9)
Route of HIV infection, *n* (%)		
Homo-bisexual sex	61 (55)	54 (49)
Heterosexual sex	42 (38)	43 (39)
Injection-drug use	3 (3)	10 (9)
Other	5 (4.5)	4 (4)
CDC stage, *n* (%)		
A	75 (66)	81 (72)
B	16 (14)	16 (14)
C	22 (19)	15 (13)
CD4 cells/μl, median (IQR)		
Baseline	582 (390–780)	585 (457–757)
Nadir	212 (147–283)	223 (150–320)
Hepatitis B-positive, *n* (%)	0	0
Hepatitis C-positive, *n* (%)	3 (3)	5 (4)
Number of previous, median (IQR)		
NRTI	4 (2–5)	4 (2–5)
NNRTI	1 (0–1)	1 (0–1)
PI	1 (1–2)	1 (1–2)
3 class experience, *n* (%)	49 (43)	43 (38)
Duration of HIV infection, years		
Median (IQR)	8.9 (4.2–15.6)	11.7 (6.5–15.9)
Duration of ART, years		
Median (IQR)	7.8 (3.0–11.3)	8.7 (4.6–11.3)
Prior PI exposure, *n* (%)	101 (89)	93 (83)
Regimen at screening, *n* (%)		
2 NRTIs + PI	83 (73.5)	72 (64.3)
2 NRTIs + NNRTI	21 (18.6)	22 (19.6)
3 NRTIs	7 (6.2)	16 (14.3)

IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

baseline, four patients had 100% adherence and four patients had a lower rate of adherence).

Resistance to HIV drugs

From the three observed virologic failures, one patient had the V11I mutation at failure, but the mutation was also found retrospectively in a previous sample 7 years prior to study entry. No darunavir resistance-associated mutations were found in the other two patients at failure. No darunavir resistance mutations were also found in the 13 other patients having two consecutive plasma HIV-1 RNA more than 50 copies/ml (11 in the darunavir/r monotherapy group and two in the darunavir/r triple therapy).

Adverse events

Adverse events leading to discontinuation of study drugs occurred in five patients in the triple therapy arm and in four patients in the monotherapy arm (Table 4). There was no difference between arms in grade 3–4 clinical events and laboratory abnormalities. Two patients on darunavir/r monotherapy experienced mild neurological transient symptoms – unusual headaches in a 36-year-old woman and seizures in a 66-year-old man with known

Table 2. Primary endpoint.

	Darunavir/r triple therapy	Darunavir/r monotherapy	Difference (%)	90% Confidence interval
Therapeutic success (PP)	101/102 (99.0%)	96/102 (94.1%)	−4.9	−9.1 to −0.8
Therapeutic success (ITT)	104/113 (92.0%)	98/112 (87.5%)	−4.5	−11.2 to 2.1
				95% Confidence interval
Therapeutic success (PP)				
Strata < 100 000 copies/ml	42/43 (97.7%)	39/39 (100%)	+2.3	−2 to 6.8
Strata > 100 000 copies/ml	33/33 (100%)	25/29 (86.2%)	−13.8	−26 to −1.2
Therapeutic success (ITT)				
Strata < 100 000 copies/ml	43/45 (95.6%)	40/44 (90.9%)	−4.7	−15 to −6
Strata > 100 000 copies/ml	33/34 (97.1%)	25/30 (83.3%)	−13.7	−28 to 0.1

Primary endpoint was measured by week 48. ITT, intent-to-treat; PP, per protocol.

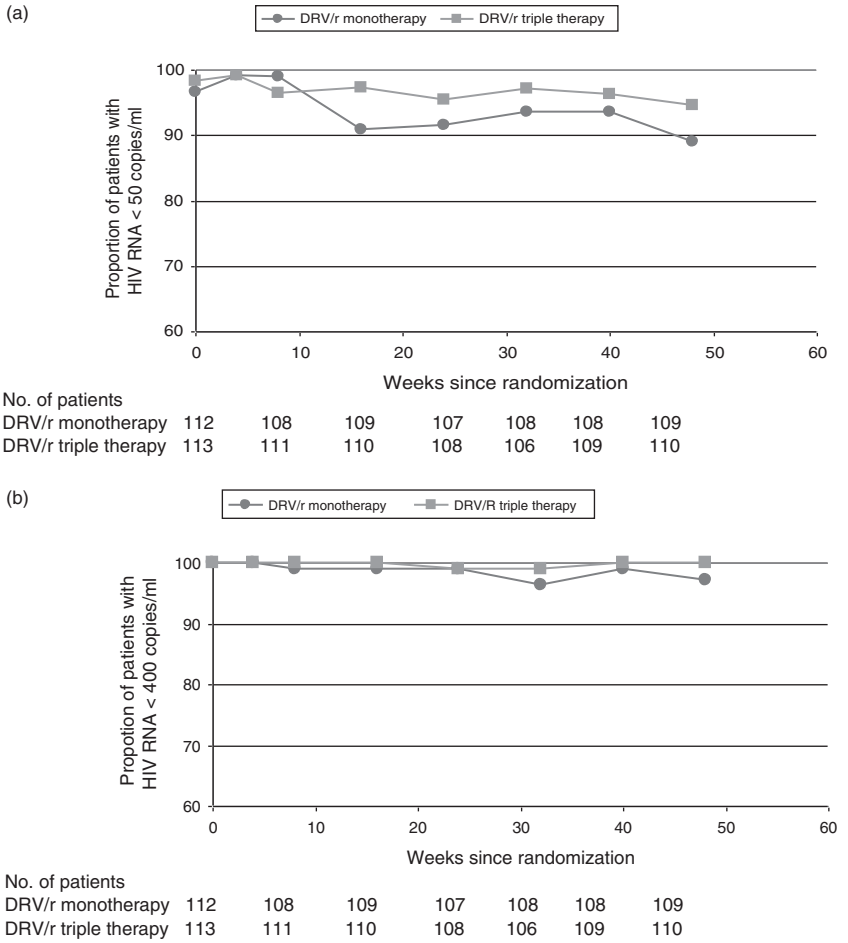

Fig. 2. Proportions of patients with HIV-1 RNA < 50 and 400 copies/ml. (a) Proportion of patients with plasma HIV RNA levels less than 50 copies/ml, intent-to-treat (ITT) observed analysis. (b) Proportion of patients with plasma HIV RNA levels less than 400 copies/ml, ITT observed analysis.

untreated epilepsy. Cerebrospinal fluid (CSF) investigation showed no abnormality – neither in cell number nor in protein level – other than a CSF viral load of 330 and 580 copies/ml, respectively, contrasting with a suppressed plasma viremia less than 50 copies/ml. Addition of abacavir and lamivudine to darunavir in the two patients led to improvement in clinical symptoms and decrease in CSF viral load to the lower limit of quantification below 200 copies/ml.

Discussion

The randomized MONOI study confirmed the high efficacy rate of a darunavir monotherapy strategy in experienced patients with an overall proportion over 85% patients maintaining suppressed viremia at week 48. Results were concordant in the magnitude of difference in efficacy between the two randomized arms in both ITT and per protocol analyses, but conclusions were

Table 3. HIV-1 RNA response to treatment.

	Darunavir/r triple therapy	Darunavir/r monotherapy	Difference	95% Confidence interval
All HIV-1 RNA <50 copies/ml (PP)	82/102 (80.4)	75/102 (73.5)	−6.86	−18.4 to 4.7
All HIV-1 RNA <50 copies/ml (ITT)	91/113 (80.5)	82/112 (73.2)	−7.32	−18.3 to 3.7
All HIV-1 RNA <50 copies/ml (PP)				
Strata <100 000 copies/ml	33/43 (76.7)	29/39 (74.4)	−2.39	−21.0 to 16.3
Strata >100 000 copies/ml	28/33 (84.8)	20/29 (69.0)	−15.1	−36.7 to 4.9
All HIV-1 RNA <50 copies/ml (ITT)				
Strata <100 000 copies/ml	35/45 (77.8)	32/44 (72.7)	−5.05	−23.0 to 12.9
Strata >100 000 copies/ml	29/34 (85.3)	21/30 (70.0)	−15.3	−35.6 to 5.0

ITT, intent-to-treat; PP, per protocol.

Table 4. Adverse events.

	Darunavir/r monotherapy $N=112$	Darunavir/r triple therapy $N=113$
Treatment-limiting event, *n* (%)		
CNS disorders	2 (2)	0
Hepatic aminotransferase >5 times ULN	0	1 (1)
Lipodystrophy	1 (1)	1 (1)
Hyperglycemia	1 (1)	0
Hypertriglyceridemia	0	1 (1)
Diarrhea	0	1 (1)
Asthenia	0	1 (1)
Grade 3 or 4 clinical event		
Any new sign or symptom	13 (12%)	11 (10)
Infectious disease events	3 (3)	2 (2)
Cardiovascular events	1 (1)	2 (2)
Grade 3 or 4 laboratory abnormality		
Hepatic aminotransferase >5 times ULN	1 (1)	2 (2)
Creatine kinase >5 times ULN	0	1 (1)
Fasting triglycerides >750 mg/dl	1 (1)	0
Fasting cholesterol >400 mg/dl	0	1 (1)

CNS, central nervous system; ULN, upper limit of normal.

discordant with respect to the noninferiority margin. Although the difference in efficacy was even lower in the ITT analysis (−4.5%) compared with the per protocol analysis (−4.9%), the former analysis did not demonstrate noninferiority due to a larger CI. Indeed, proportions of treatment success in each arm were lower in the ITT analysis, leading to larger variances, compared with the per protocol analysis. To our knowledge, this is the first time that such discordant conclusions between these two standard analyses occurred in an HIV noninferiority trial. It is admitted that when both analyses lead to the same conclusion, confidence in the trial results is increased [23]. In our study, despite high proportions of patients in treatment success on darunavir/r monotherapy in both ITT and per protocol analyses, we cannot simply conclude to the noninferiority of darunavir/r monotherapy to darunavir/r triple therapy.

Guidance on statistical principles for noninferiority clinical trials indicates that non-ITT analyses might be desirable as a protection from falsely concluding noninferiority from ITT analysis [23]. In general, ITT analysis leads to smaller observed treatment effects than if all patients had fully adhered to both the protocol and the study treatments. Then, in noninferiority trials, ITT analysis will often increase the risk of falsely claiming noninferiority. In our study, although the difference in efficacy was smaller for the ITT analysis compared with the per protocol analysis, the former analysis failed to demonstrate the noninferiority of darunavir/r monotherapy to darunavir/r triple therapy, whereas the per protocol analysis showed noninferiority. Recently, a study with similar treatment groups showed that darunavir/r monotherapy was noninferior to a triple drug regimen including darunavir/r in both ITT and per protocol analyses [24]. One of the main differences between the two studies was the use of a different threshold value to define virologic failure: 50 copies/ml in the MONOtherapy in Europe with TMC114 (MONET) trial and 400 copies/ml in the MONOI trial [24]. Recent data suggested that a theshold of 50 copies/ml falsely declared virologic failure for an unacceptably high number of patients who ultimately re-suppress <50 copies/ml without a change in antiretroviral treatment [Poster 580 CROI 2009]. In the AIDS Clinical Trials Group study (ACTG) 5202, virologic failure was defined as a confirmed HIV-1 RNA level of at least 1000 copies/ml at or after 16 weeks and before 24 weeks or at least 200 copies/ml at or after 24 weeks [25]. This may be particularly relevant in the context of strategies using drugs with high genetic barrier to resistance.

Interestingly, the stratified analysis showed that the difference in efficacy between the two treatment groups was larger in patients with a high level of pretherapy HIV-1 RNA. These results indicated that patients, with a known HIV-1 RNA below 100 000 copies/ml before treatment initiation and after achieving a durable period of HIV-1 RNA suppression, might be eligible for darunavir/monotherapy. In addition, the three patients who experienced a virologic failure on darunavir/r monotherapy had no evidence of emergence of new darunavir resistance mutations and re-suppressed after re-introduction of two NRTIs.

A higher proportion of intermittent viremia was seen in the patients randomized to darunavir/r monotherapy (Fig. 2), a feature observed not only in maintenance studies of lopinavir/r monotherapy [8,17], but also in a study on antiretroviral-naive patients [26]. In a large majority of patients, these elevations were transient and subsequent HIV-RNA levels were less than 50 copies/ml without any treatment modification. Prolonged periods of low-level viremia might favor the development of resistance mutations as seen with antiretroviral naive patients on lopinavir/r monotherapy [27]. In our study,

no new darunavir resistance mutations were found in the virus of patients experiencing two successive measurements of HIV- 1 RNA more than 50 copies/ml. This is of great importance that preserves future treatment options for patients receiving such a strategy. However, longer follow-up is necessary to consolidate the robustness of the strategy. The cause of these episodes of intermittent viremia is not completely clear, though low adherence has been associated with HIV-1 RNA elevations or virologic failure [28,29]. Adherence to therapy in a context of monotherapy is even more crucial than in triple therapy as suggested in our results in which patients who reported missing doses were more likely to have intermittent viremia.

There are now several randomized studies to suggest that protease inhibitor monotherapy could be a valuable maintenance strategy in virologically suppressed patients. Most of them had involved lopinavir/r and had shown similar efficacy to triple drug therapy [8,17]. As in our study, HIV RNA elevations were mainly transient, in the range of 50–200 copies/ml and did not generally lead to treatment emergent drug resistance.

Because HIV replication has to be optimally controlled, there has been concern that a protease inhibitor monotherapy may not be sufficient in all compartments and reservoirs of HIV. In a study of paired CSF/plasma samples from eight HIV-infected patients, median concentration of darunavir was 34 ng/ml, above the IC50 [15]. In our study, the two patients on darunavir/r monotherapy with discordant CSF plasma HIV RNA had undetectable CSF darunavir concentrations, which might explain the low level HIV replication in the CSF. Furthermore, we recently reported several cases of neurological symptoms and discordant plasma/CSF viral replication in patients receiving standard triple therapy reported as adequate penetrations in CSF [30]. Protease inhibitor monotherapy with darunavir offers an effective alternative strategy for long-term control of HIV infection as considering both ITT and per protocol analyses, 87–94% of patients on darunavir/r monotherapy and 92–99% of patients on darunavir/r triple therapy were on treatment success at week 48. Confidence intervals and noninferiority margin were such that noninferiority could not be demonstrated in both ITT and per protocol analyses. Patients failing darunavir/r monotherapy had no emergence of new darunavir resistance mutations, thus preserving all subsequent therapeutic options, including restarting the previously used NRTIs.

Long-term management of antiretroviral therapy over decades will require different strategies for different patient profiles. We think that protease inhibitor monotherapy, and particularly darunavir monotherapy, has proved itself sufficiently to be progressively introduced in clinical practice. The impact of such strategies on fat distribution and potential other benefits of an NRTI-sparing strategy are under evaluation.

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