Objectives: Long-term results at week 96 are needed to evaluate the capacity of the darunavir/ritonavir monotherapy strategy to maintain a sustained control of the HIV-1 viral load.

Methods: MONOI is a prospective, open-label, non-inferiority, randomized, 96 week trial comparing darunavir/ritonavir monotherapy versus a darunavir/ritonavir triple-therapy strategy to maintain HIV-1 viral load suppression in HIV-1-infected patients. Clinical trial registration: NCT00412551.

Results: From 225 randomized patients, 219 patients reached the 48 week follow-up and 211 reached the 96 week follow-up (106 patients in the darunavir monotherapy arm and 105 in the darunavir triple-therapy arm). Baseline characteristics were well balanced between the two treatment groups. At week 96, in intent-to-treat analysis, 91/103 patients (88%, 95% CI 81–94) allocated to the darunavir/ritonavir monotherapy arm and 87/104 patients (84%, 95% CI 75–90) allocated to the darunavir triple-therapy arm achieved an HIV-1 viral load <50 copies/mL, with no statistical difference between the two groups. Throughout the 96 week follow-up, 66/112 patients (59%, 95% CI 49–68) and 79/113 patients (70%, 95% CI 61–78) consistently had HIV-1 RNA <50 copies/mL with darunavir/ritonavir monotherapy and darunavir/ritonavir triple therapy, respectively.

Conclusions: The MONOI study establishes darunavir/ritonavir monotherapy as durable and efficacious for maintaining virological suppression in HIV-1 patients. Darunavir/ritonavir monotherapy should be considered as a (tailored) treatment option for standard triple-therapy patients who have had a substantial period of viral suppression.

Keywords: darunavir, protease inhibitor monotherapy, clinical trials, MONOI study, virological suppression
Introduction

Two randomized studies—the MONET and MONOI studies—have established the capacity of darunavir/ritonavir monotherapy (monotherapy arm) to maintain viral suppression compared with darunavir/ritonavir plus two nucleoside analogues (triple-therapy arm) in patients with suppressed viraemia. In the MONET study, 86.2% of monotherapy-arm patients had a plasma viral load (pVL) $\leq$50 copies/mL by week 48, similar to patients in the triple-therapy arm (87.8%). At week 96, this rate was 74.8% in the darunavir/ritonavir monotherapy arm. The MONOI ANRS 136 study showed a 99% treatment success rate with darunavir/ritonavir triple-therapy versus a 94% success rate in those receiving darunavir/ritonavir monotherapy ($d = -4.9\%, 90\% CI -9.1$ to $-0.8$) in a per-protocol population. The results were not different from the intent-to-treat (ITT) population, albeit that, in the ITT analysis, non-inferiority was not reached.

Durable viral suppression is a key consideration in the choice of antiretroviral maintenance strategy. Thus, the long-term efficacy of darunavir/ritonavir monotherapy was evaluated in the final 96th week of the MONOI ANRS 136 study.

Methods

Study design

The MONOI trial (NCT00412551) is a randomized, open-label study. To be enrolled, patients were on a stable regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), with a pVL $\leq$400 copies/mL for $\geq$18 months and screening pVL $\leq$50 copies/mL. Patients with a history of HIV-related neurological disease or with hepatitis B coinfection could not participate. After an initial phase of 8 weeks during which patients received darunavir/ritonavir (600/100 mg twice daily) in combination with two NRTIs, patients were randomly assigned, 1:1, to either continue the triple-drug regimen (triple-therapy arm) or to discontinue the two NRTIs (monotherapy arm). At week 48 in the two arms, in patients with pVL $<50$ copies/mL, 600/100 mg of darunavir/ritonavir twice daily was switched to 800/100 mg once daily until week 96. Monitoring assessments were carried out at 8 week intervals between weeks 48 and 96. All patients provided their written informed consent. The protocol was approved by the appropriate independent ethics committees and was conducted according to the Declaration of Helsinki.

A genotypic resistance test was performed in all patients with two consecutive pVLs $>50$ copies/mL. Sequences of protease and reverse transcriptase genes on RNA at the time of virological failure were determined using ANRS consensus-technique primer sequences, as described at http://www.hivfrenchresistance.org.

Treatment failure was defined as either two consecutive measurements of pVL $>400$ copies/mL within 2 weeks or treatment modification, defined as any modification of antiretroviral therapy or discontinuation. The primary efficacy endpoint was the percentage of patients who were successfully treated by week 48. Secondary efficacy endpoints included the percentage of patients with pVL $<50$ copies/mL at each timepoint until week 96. For these secondary endpoints, missing data due to missed evaluations were ignored.

Figure 1. Flow chart of patient treatments in the study. DRV/r, darunavir/ritonavir.

- Withdrew consent: 17 pts
- Treatment discontinuation: 11 pts
  - Viral load increase ($<400$ copies/mL): 3 pts
  - Adverse event: 4 pts
  - Other: 3 pts

- 98 patients continued randomized treatment
  - Withdrew consent: 3 pts
  - Treatment discontinuation: 8 pts
  - Viral load increase ($<400$ copies/mL): 6 pts
  - Virological failure ($>400$ copies/mL): 2 pts

- 106 pts at week 96
  - 90 patients continued randomized treatment

- Withdrew consent: 3 pts
  - Treatment discontinuation: 5 pts
  - Adverse event: 6 pts
  - Virological failure: 4 pts

- 105 pts at week 96
  - 91 patients continued randomized treatment

- Withdrew consent: 3 pts
  - Treatment discontinuation: 8 pts
  - Virological failure ($>400$ copies/mL): 2 pts

- 110 pts at week 48
  - 104 patients continued randomized treatment

- Withdrew consent: 3 pts
  - Treatment discontinuation: 6 pts
  - Adverse event: 5 pts
  - Other: 1 pt

- 113 pts allocated to the DRV/r triple-therapy regimen

- 109 pts at week 48
  - 98 patients continued randomized treatment

- Withdrew consent: 3 pts
  - Treatment discontinuation: 8 pts
  - Virological failure ($>400$ copies/mL): 2 pts
  - Viral load increase ($<400$ copies/mL): 6 pts

Statistical methods

Between-group comparisons were carried out using the Kruskal–Wallis test for continuous variables and using the Fisher’s exact test for categorical variables.
Results

Population

Overall, from the baseline ITT population of 225 randomized patients, 219 patients reached the 48 week follow-up and 211 patients reached the 96 week follow-up, with 106 patients in the monotherapy arm and 105 in the triple-therapy arm (Figure 1).

Baseline characteristics were well balanced between the two arms, with a median duration of 8.3 years (IQR 3.7–11.3) of anti-retroviral therapy and a median of 587 CD4 cells/µL (IQR 446–749). At screening, 69.5% of patients were receiving a PI and 19.1% an NNRTI.

Virological response

By week 96, in the ITT analysis, 91 of the 103 patients (88%, 95% CI 81–94) (95% in the on-treatment analysis) allocated to the monotherapy arm and 87/104 (84%, 95% CI 75–90) (90% in the on-treatment analysis) receiving darunavir/ritonavir triple therapy had a pVL <50 copies/mL (P = 0.42) (Figure 2). Throughout the 96 week follow-up, 66/112 patients (59%, 95% CI 49–68) and 79/113 patients (70%, 95% CI 61–78) consistently had a pVL <50 copies/mL with the darunavir/ritonavir monotherapy and the darunavir/ritonavir triple therapy, respectively (P = 0.10).

Until week 48, three patients experienced virological failure in the monotherapy arm versus none in the triple-therapy arm (pVL = 2722 and 411 copies/mL with darunavir trough concentrations of 1120 and 3480 ng/mL, respectively; and pVL = 484569 copies/mL corresponding to a treatment discontinuation). From weeks 48 to 96, virological failure occurred in six patients: two in the monotherapy arm and four in the triple-therapy arm. The main causes of the virological failure were poor compliance (in the monotherapy arm, pVL = 471 copies/mL and low darunavir plasma level) and treatment discontinuation (pVL = 5134, 240000 and 58200 copies/mL). In the remaining two patients, one in each arm, the darunavir trough concentration was within the normal range (2517 and 2967 ng/mL) despite an increase in the pVL (722 and 848 copies/mL). In all patients included in the monotherapy

![Graph](image_url)

Figure 2. Proportion of patients with an HIV-1 RNA <50 copies/mL by week 96 (ITT and on-treatment analysis).
arm, therapeutic resumption of the initial two NRTIs led to pVL <50 copies/mL. No associated darunavir resistance mutations or accumulation of reverse transcriptase mutations were found in the nine patients at failure.

At week 96, the overall median CD4 cell count was 626 cells/μL (IQR 448 to +835), with a median increase of +70 cells/μL (IQR −46 to +165) in the monotherapy arm and +39 cells/μL (IQR −55 to +146) in the triple-therapy arm (P=0.33).

Adverse events

Overall, 34 patients experienced serious adverse events between weeks 48 and 96; 12 in the monotherapy arm and 22 in the triple-therapy arm. The most serious adverse events were related to bacterial infections (n=8), cardiovascular events (n=4) and malignant diseases (n=3). One patient in each treatment group died; one from hepatocarcinoma in the darunavir/ritonavir monotherapy arm and the other drowned. No neurological events were recorded between weeks 48 and 96 in the monotherapy arm.

Discussion

The results of this 96 week analysis from the randomized MONOI study confirm and extend those observed at 48 weeks. Overall, at week 96, the rate of virological success was in the range of standard antiretroviral therapy; 85% of the patients had a sustained pVL with darunavir/ritonavir monotherapy. Importantly, in a recent analysis of the MONOI study, using an ultrasensitive RNA assay and quantification of DNA viraemia, we were able to show that patients who adhered to therapy, with the lowest RNA values and DNA viraemia, were the best candidates for PI monotherapy.

In conclusion, the MONOI study establishes that darunavir/ritonavir monotherapy appears to be an efficacious virological strategy to contain viral replication in the long-term management of HIV-infected patients. In the era of long exposure to antiretroviral NRTIs, the choice of using PI monotherapy offers the potential to reduce cumulative NRTI-associated toxicities and should be considered as a treatment option for patients who have had a substantial period of viral suppression.

Acknowledgements

We thank the investigators, study coordinators, site and data managers, and the patients for their contributions. We thank Janssen-Cilag for providing darunavir for this trial.

Members of the MONOI ANRS 136 Study Group


Participating centres and investigators (all in France)

Funding

This work was supported by Agence Nationale de Recherche sur le SIDA et les Hépatites Virales, Paris, France (ANRS-MONOI ANRS 136 trial) and Janssen-Cilag provided darunavir for this trial.

Transparency declarations

M. A. V., P. F., L. M.-J., A. Cabiè, J. L. M., L. Slama, L. C., A. G. M. and C. K. have received travel grants, fees for conference attendance or consultancy fees from various pharmaceutical companies, such as Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck/Schering-Plough and Viiv Healthcare. All other authors: none to declare.

Author contributions

M. A. V., P. F. and C. K. designed the study and wrote the manuscript. P. F. did the data analysis and revised the manuscript. S. L.-N., L. M.-J. and A. G. M. did the laboratory work. A. Cabiè, J. L. M., D. P., F. A., L. Slama, A. Curjol, L. C. and L. Schneider provided samples and clinical data. A. M. T. acted as a pharmaceutical adviser.

References


