Low-dose ritonavir-boosted darunavir in virologically suppressed HIV-1-infected adults: an open-label trial (ANRS 165 Darulight)

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Objectives: To assess whether low-dose ritonavir-boosted darunavir (darunavir/r) in combination with two NRTIs could maintain virological suppression in patients on a standard regimen of darunavir/r + two NRTIs.

Design: A multicentre, Phase II, non-comparative, single-arm, open-label study.

Setting: Tertiary care hospitals in France.

Subjects: One hundred HIV-1-infected adults with no darunavir or NRTI resistance-associated mutations (RAMs) and a plasma HIV RNA level <50 copies/mL for ≥12 months on once-daily darunavir/r (800/100 mg) + two NRTIs for ≥6 months were switched to darunavir/r 400/100 mg with the same NRTIs.

Primary outcome measure: Proportion of patients with treatment success: plasma HIV RNA level <50 copies/mL up to 48 weeks without any change in the study regimen, in a modified ITT (mITT) analysis.

Results: At baseline, most patients were male (78%), with a median age of 43 years, median duration of HIV RNA <50 copies/mL of 35 months and median CD4 T cell count of 633 cells/mm3. Seventy-six percent received tenofovir/emtricitabine and 24% abacavir/lamivudine. Five patients were excluded from the mITT analysis. The rate of treatment success through to week 48 was 91.6% (87/95; 95% CI 84.1%–96.3%). No RAM was detected in three amplifiable genotypes. A total of 212 adverse events (AEs) occurred in 64 patients (64%); 9 AEs were serious, none leading to treatment discontinuation.

Conclusions: In HIV-infected patients well suppressed with darunavir/r (800/100 mg) and two NRTIs, a reduction of the darunavir dose to 400 mg/day maintained virological efficacy and was safe over 48 weeks.

Introduction

Continuous improvements in the treatment of HIV infection have led to high rates of sustained virological suppression and good tolerability, thereby reducing morbidity and mortality.1 However, because treatment is life-long, simplified regimens are needed to improve convenience and adherence, and to reduce drug-related adverse events (AEs) and cost.2–3 Among current strategies being assessed to improve antiretroviral therapies, such as co-formulation of multiple agents in a single pill and dual therapy or long-acting injectable agents, dose reduction of antiretroviral agents has been less frequently investigated.4–6 WHO has, however, recently updated its guidelines to recommend low-dose efavirenz (400 mg daily instead of 600 mg) as an alternative first-line regimen in low- and middle-income countries, following the results of a large randomized trial.1–9

PIs, despite a unique high genetic barrier to the development of resistance when boosted with low-dose ritonavir (r), have been moved to alternative or second-line regimens because of their
imperfect tolerability profile and high cost.\textsuperscript{7–10} Pioneering studies that demonstrated that lower doses of ritonavir-boosted indinavir induced and maintained adequate virological suppression with improved safety and adequate PK established an interest in examining lowered doses of boosted PIs.\textsuperscript{11–13} Few studies thereafter have assessed the safety and efficacy of low-dose second-generation PIs in combination with other antiretroviral agents, which might improve tolerability and reduce costs.\textsuperscript{14–16}

Once-daily ritonavir-boosted darunavir (darunavir/r) at the dose of 800/100 mg has demonstrated durable efficacy in both treatment-naïve and treatment-experienced patients with no darunavir resistance-associated mutations (RAMs), and a better tolerability profile than ritonavir-boosted atazanavir.\textsuperscript{17–21} We wished to investigate a reduced dose of darunavir (400 mg) in combination with ritonavir in well-suppressed patients on the standard dose of once-daily darunavir/r + two NRTIs.

Patients and methods

Patient population

Patients enrolled in the ANRS 165 Darulight study were treatment-experienced, HIV-1-infected adults (\geq 18 years), with a plasma HIV-1 RNA \leq 50 copies/mL for at least 12 months, no previous virological failure, defined as a plasma HIV RNA \geq 200 copies/mL, CD4 cell count > 300 cells/mm\textsuperscript{3} and none of the 11 darunavir (V11I, V32I, L33F, I47V, I50V, L54I, L54M, T74P, L76V, I84V and L89V) or NRTI RAMs detected by a resistance genotyping test before treatment initiation.\textsuperscript{22} Patients needed to be receiving a stable darunavir-containing regimen for \geq 6 months at screening with once-daily darunavir/r (800/100 mg) + two NRTIs [tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC)]. Patients with chronic hepatitis B and/or C infection were allowed to enrol if their condition was clinically stable and they were not expected to require treatment during the study period. Other exclusion criteria included HIV-2 infection, the presence of any active AIDS-defining illness, use of disallowed concomitant therapy, pregnancy/breastfeeding, and laboratory abnormalities (ALT or AST levels > 2-fold the upper limit of normal, haemoglobin level < 11 g/dL, platelet count < 150000/mm\textsuperscript{3}, or estimated CrCl using the Cockcroft–Gault equation < 60 mL/min if tenofovir disoproxil fumarate was used.

Study design

ANRS 165 Darulight was a multicentre Phase II, non-comparative, single-arm, open-label study assessing the efficacy, safety and tolerability of switching from once-daily darunavir/r 800/100 mg + two NRTIs to once-daily darunavir/r 400/100 mg with the same two NRTIs, over 48 weeks in well-suppressed treatment-experienced patients with no darunavir or NRTI RAMs. Study treatments were delivered every 2 months at each hospital visit. Other exclusion criteria included HIV-2 infection, the presence of any active AIDS-defining illness, use of disallowed concomitant therapy, pregnancy/breastfeeding, and laboratory abnormalities (ALT or AST levels > 2-fold the upper limit of normal, haemoglobin level < 11 g/dL, platelet count < 150000/mm\textsuperscript{3}, or estimated CrCl using the Cockcroft–Gault equation < 60 mL/min if tenofovir disoproxil fumarate was used. The trial consisted of a screening period (up to 4 weeks), a 48 week treatment period, and an extended follow-up of 24 weeks up to week 72 until the last participant completed the 48 week visit.

The primary objective was to establish the proportion of patients with treatment success through to 48 weeks, defined as plasma HIV RNA levels \leq 50 copies/mL without any change in the darunavir/r dose, in a modified ITT (mITT) analysis.

The primary analysis was performed when all actively enrolled patients had completed 48 weeks.

Written informed consent was obtained from all study participants. The study protocol was reviewed and approved by the Paris Saint-Louis ethics committee (Comité de Protection des Personnes) and health authority (EudraCT number 2014-001505-40), was conducted in accordance with good clinical practice and the Declaration of Helsinki, and was registered at ClinicalTrials.gov (NCT02384967).

Study evaluations and statistical methods

Plasma HIV-1 RNA measurements and safety assessments were performed at screening, baseline and each visit (weeks 8, 12, 16, 24, 32, 36, 40, 48, 60 and 72 or withdrawal). The mITT population included all enrolled patients who took one or more doses of trial medication, with no major violation of inclusion criteria, irrespective of protocol compliance.

A minimum of 94 patients had to be enrolled to detect a difference in success rate from 80% (H0) to 90% (H1) with a type I error rate of 5% and a statistical power of 85%, through to 48 weeks in an mITT analysis.

HIV RNA levels in plasma were quantified at each timepoint using the HIV-1 Cobas TaqMan v2.0 test (Roche, Meylan, France) with a detection threshold of 20 copies/mL or the Abbott Real Time HIV-1 assay with a threshold of 40 copies/mL, using for each patient the same test during follow-up.

Virological failure was defined as a confirmed plasma HIV RNA level \geq 50 copies/mL with the confirmatory sample taken at least 2 weeks after the first sample. Genotypic resistance tests were centralized and performed on samples with virological failure. Genotypic tests were performed using the ANRS PCR and sequencing procedure and resistance interpretation was done using the French ANRS algorithm.\textsuperscript{24} Virological blip was defined as a single plasma HIV RNA level \geq 50 copies/mL without confirmation. Risk factors for blips and virological failures were assessed using patients’ baseline characteristics and adherence in a multivariate analysis.

Change over time in CD4 cell count from baseline to week 48 was calculated using observed data.

Patient adherence was assessed at weeks 0, 12, 24, 36 and 48 using the ANRS self-report questionnaire about the number of missed doses over the last 4 days. Patients were defined as either fully adherent (no missed doses at any questionnaire) or non-fully adherent.

The ITT population including all enrolled patients was used for the safety analysis. Safety was assessed using AE data, clinical laboratory tests (haematology and biochemistry) and physical examination. An independent Data and Safety Monitoring Board was implemented for continued review of the safety data. AEs and laboratory abnormalities were graded according to the ANRS Grading Table and causality was assessed by the study investigators.\textsuperscript{25}

In addition, patients’ self-reported gastrointestinal symptoms (diarrhoea, nausea, pain, flatulence, constipation) were assessed at baseline and weeks 12, 24, 36 and 48 using a self-administered questionnaire based on the Gastrointestinal Symptom Rating Scale.\textsuperscript{26} Changes from baseline in these parameters were assessed by generalized linear models incorporating a subject effect.

A PK sub-study of darunavir and ritonavir was performed at baseline and week 12 in 15 volunteers who had a PK blood sampling over 24 h at 0, 1, 3, 5, 8 and 24 h.\textsuperscript{27} The full results of this PK sub-study will be reported separately.

Results

Patient demographics and baseline characteristics

From March to October 2015, 113 patients were screened at 13 sites in university hospitals in France and 100 patients were enrolled (Figure 1).

Baseline patient characteristics are shown in Table 1. Most patients were male (78%); median age was 43 years, median duration of plasma HIV RNA \leq 50 copies/mL was 35 months and median CD4 T cell count was 633 cells/mm\textsuperscript{3}. The NRTIs used were
113 patients were assessed for eligibility

- 13 were excluded
  - 12 did not meet inclusion criteria
  - 1 was lost to follow-up

100 patients started open-label darunavir/ritonavir (400/100 mg once daily) + 2 NRTIs

95 patients included in the mITT analysis

Attendance at clinic visits

<table>
<thead>
<tr>
<th>Week</th>
<th>Patients Present</th>
<th>Attendance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>95/95</td>
<td>100%</td>
</tr>
<tr>
<td>12</td>
<td>87/95</td>
<td>91.6%</td>
</tr>
<tr>
<td>16</td>
<td>87/95</td>
<td>91.6%</td>
</tr>
<tr>
<td>24</td>
<td>87/95</td>
<td>91.6%</td>
</tr>
<tr>
<td>32</td>
<td>87/95</td>
<td>91.6%</td>
</tr>
<tr>
<td>36</td>
<td>87/95</td>
<td>91.6%</td>
</tr>
<tr>
<td>40</td>
<td>87/95</td>
<td>91.6%</td>
</tr>
<tr>
<td>48</td>
<td>87/95</td>
<td>91.6%</td>
</tr>
</tbody>
</table>

8 patients discontinued darunavir/ritonavir (400/100 mg)

- 6 experienced virological failure up to week 48
- 1 became pregnant
- 1 physician decision

*All patients switched back to darunavir/r 800/100mg once daily; none experienced virological failure while on darunavir/r (400/100mg once daily).

Figure 1. Patient disposition up to week 48.
TDF/FTC (76%) and ABC/3TC (24%). At baseline, one patient had a plasma HIV RNA > 50 copies/mL, which was not confirmed on follow-up testing.

Five patients were excluded from the mITT analysis: three because they experienced previous virological failure (two with RAMs) and one because of pregnancy, all of whom switched back to the 800/100 mg dose of darunavir/r, and one because of consent withdrawal before starting the low-dose darunavir/r regimen.

Eight out of 95 (8.4%) patients enrolled in the mITT analysis prematurely discontinued darunavir/r 400/100 mg during the first 48 weeks of follow-up: one because of pregnancy, one due to physician decision and six because of a confirmed plasma HIV RNA level > 50 copies/mL. No patient discontinued the study because of AEs or loss to follow-up.

**Efficacy through to week 48**

Through to week 48, 87 out of 95 patients maintained a plasma HIV RNA level < 50 copies/mL, with a treatment success rate of 91.6% (87/95; 95% CI 84.1%–96.3%); therefore, excluding the null hypothesis of an efficacy of only 80%.

There was a moderate increase in median CD4 cell count from baseline to week 48 of 40 cells/mm³ (P = 0.049).

Six patients (6.3%) experienced virological failure during the first 48 weeks of the trial, with a confirmed plasma HIV RNA level > 50 copies/mL. Only two patients had confirmed plasma HIV RNA levels > 200 copies/mL and in these two patients there was obvious non-adherence to the study regimen, with treatment discontinuation for several weeks.

Genotypic resistance testing was attempted in cases of virological failure using all plasma samples with > 50 copies/mL. The reverse transcriptase and protease genes were amplifiable in only three subjects, including the two subjects that had confirmed plasma HIV RNA levels > 200 copies/mL; none of them showed PI or NRTI RAMs.

Efficacy during extended follow-up

Sixty-eight patients extended follow-up beyond week 48 by a median of 91 days (range 84–186).

During extended follow-up, two additional patients presented with virological failure; only one of them had a plasma HIV RNA level above the 200 copies/mL threshold, and in this patient no RAM was detected on the resistance genotypic test. This patient was not fully adherent to the treatment regimen.

**Adherence**

Based on self-administered questionnaires, 73/95 (76.8%) patients were fully adherent to their study drugs at all visits during the first 48 weeks of follow-up. The three patients who failed during the entire study follow-up, with a plasma HIV RNA level > 200 copies/mL, were all non-fully adherent to their regimen.

**Safety**

Sixty-four patients presented a total of 212 AEs, most being gastrointestinal AEs (23%) (Table 3). Serious AEs were reported in only nine patients: cerebrovascular ischaemia, endocarditis, neutropenia, dog bite, sciatricgia, prostate cancer, diarrhoea, iatrogenic Cushing syndrome, post-traumatic bone fracture and abdominal

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**Table 1.** Patient baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (IQR) or n (%) (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 (37–48)</td>
</tr>
<tr>
<td>Male sex</td>
<td>78 (78)</td>
</tr>
<tr>
<td>MSM</td>
<td>55 (55)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>72.5 (67–82.5)</td>
</tr>
<tr>
<td>History of AIDS</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Duration of ART (months)</td>
<td>46 (31–63)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>633 (513–770)</td>
</tr>
<tr>
<td>CD4 cell count nadir (cells/mm³)</td>
<td>297 (201–376)</td>
</tr>
<tr>
<td>Peak plasma HIV RNA level (log10 copies/mL)</td>
<td>4.9 (4.4–5.4)</td>
</tr>
<tr>
<td>Duration of HIV RNA plasma levels &lt; 50 copies/mL (months)</td>
<td>35 (22–52)</td>
</tr>
<tr>
<td>Hepatitis B or C co-infection</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Tenofovir + emtricitabine</td>
<td>76 (76)</td>
</tr>
<tr>
<td>Abacavir + lamivudine</td>
<td>24 (24)</td>
</tr>
</tbody>
</table>

**Table 2.** Risk factors for plasma HIV RNA levels ≥50 copies/mL (blips and virological failure) during the first 48 weeks of follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.98 (0.92–1.04)</td>
<td>0.54</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.19 (0.34–4.15)</td>
<td>0.78</td>
</tr>
<tr>
<td>Sexual orientation other than MSM</td>
<td>1.53 (0.54–4.40)</td>
<td>0.43</td>
</tr>
<tr>
<td>Body weight</td>
<td>0.98 (0.94–1.03)</td>
<td>0.47</td>
</tr>
<tr>
<td>Duration of ART (months)</td>
<td>0.99 (0.96–1.01)</td>
<td>0.25</td>
</tr>
<tr>
<td>Baseline CD4 cell count (per 100 cells/mm³)</td>
<td>1.03 (0.82–1.29)</td>
<td>0.79</td>
</tr>
<tr>
<td>Screen and/or baseline plasma HIV RNA above assay threshold⁹</td>
<td>4.76 (1.47–15.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Peak plasma HIV RNA level (log10 copies/mL)</td>
<td>2.06 (1.00–4.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of plasma HIV RNA ≥50 copies/mL (months)</td>
<td>0.98 (0.95–1.01)</td>
<td>0.17</td>
</tr>
<tr>
<td>Fully therapy adherent at all visits</td>
<td>0.67 (0.21–2.16)</td>
<td>0.50</td>
</tr>
<tr>
<td>TDF/FTC versus ABC/3TC</td>
<td>2.42 (0.51–11.5)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

⁹ 88 patients were tested with the Roche assay (threshold of 20 copies/mL) and 12 with the Abbott assay (threshold of 40 copies/mL).
Low-dose darunavir in HIV infection

Table 3. Summary of safety

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Once-daily darunavir/ritonavir 400/100 mg (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE</td>
<td>64</td>
</tr>
<tr>
<td>≥1 serious AE</td>
<td>9</td>
</tr>
<tr>
<td>≥1 AE leading to discontinuation</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal AEs</td>
<td>23</td>
</tr>
<tr>
<td>nausea/vomiting</td>
<td>2</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>9</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>5</td>
</tr>
<tr>
<td>Laboratory abnormalities grade 2–3</td>
<td>14</td>
</tr>
<tr>
<td>neutrophils &lt;1,000/mm³</td>
<td>4a</td>
</tr>
<tr>
<td>white blood cells &lt;2,000/mm³</td>
<td>1</td>
</tr>
<tr>
<td>total cholesterol &gt;7.75 mmol/L</td>
<td>1</td>
</tr>
<tr>
<td>triglycerides &gt;4.5 mmol/L</td>
<td>2</td>
</tr>
<tr>
<td>phosphatemia &lt;1.5 mmol/L</td>
<td>2</td>
</tr>
<tr>
<td>glucose &gt;7 mmol/L</td>
<td>3</td>
</tr>
<tr>
<td>ALT ≥ 2.5 × ULN</td>
<td>2a</td>
</tr>
<tr>
<td>AST ≥ 2.5 × ULN</td>
<td>1</td>
</tr>
<tr>
<td>γ-glutamyl transferase ≥ 2.5 × ULN</td>
<td>1</td>
</tr>
</tbody>
</table>

ULN, upper limit of normal.

aOne grade 3 event.

Patients enrolled in the ANRS 165 Darulight study had a long history of treatment with a median of 46 months of antiretroviral therapy, were virologically suppressed for a median of 35 months and had high CD4 cell counts at baseline.

These results are consistent with a subset analysis of the POWER 1 and 2 studies in patients with HIV strains susceptible to darunavir, which showed similar virological response rates with once-daily darunavir/r 400/100 and 800/100 mg (78% and 74%, respectively, at week 24). In addition, clinical trials of darunavir/r in PI-naïve or -experienced patients have shown no correlation between PK exposure to darunavir and plasma HIV RNA suppression, when HIV-1 was susceptible to darunavir, suggesting that the optimal dose of darunavir in patients with a susceptible strain is as yet unknown. It is also reassuring that preliminary PK data reported from the ANRS 165 Darulight study showed a similar AUC of darunavir at the dose of 800/100 or 400/100 mg, with an increase in ritonavir AUC with the low darunavir dose probably because of lower induction on ritonavir.

In addition, two small pilot studies have also reported high virological suppression rates of 88.5%–90% in patients using once-daily darunavir/r at the 600/100 mg dose. This strategy of low-dose boosted PIs has also been successful with another PI (atazanavir) in the setting of a large randomized trial, and it would be interesting to confirm the efficacy of the low-dose darunavir/r 400/100 mg in a randomized trial. Such a trial is currently ongoing in South Africa (NCT02671383) evaluating, in well-suppressed patients on a PI-based second-line therapy with lopinavir/ritonavir, the non-inferiority of a switch to darunavir/r (400/100 mg) + two NRTIs.

Should this trial confirm our findings, this strategy could lead to significant savings for second-line therapy in low- and middle-income countries. In addition, some tolerability benefits could be also associated with this reduced dose, as shown in our study, with a slight reduction in self-reported diarrhoea.

Discussion

The results from this single-arm, Phase II, open-label trial in well-suppressed treatment-experienced patients with no darunavir or NRTI RAMs and no previous virological failure demonstrated that over 48 weeks of treatment a switch from once-daily darunavir/r 800/100 mg to darunavir/r 400/100 mg with the same two NRTIs was associated with a high rate of virological suppression of 91.6%.

Changes from baseline to week 48 in fasting lipid-related laboratory parameters (total cholesterol, HDL and LDL cholesterol and triglycerides), glycaemia and plasma CLCR were minimal and non-significant (data not shown).

Analysis of self-reported gastrointestinal tolerability questionnaires showed a small but significant improvement from baseline in diarrhoea with the reduction in darunavir dose (Figure 2, P = 0.01). No patient died during the study. The two pregnant women who switched back to darunavir/r 800/100 mg delivered healthy non-HIV-infected babies.

The overall incidence of laboratory abnormalities was low, with most being grade 1 or 2 in severity, and only 14 patients experienced grade 2 or worse laboratory abnormalities, with two grade 3 events (one episode of neutropenia and one episode of ALT elevation) (Table 3). The most frequently reported treatment-emergent grade 2–3 laboratory abnormalities were neutropenia, hyperglycaemia and lipid abnormalities.

Changes from baseline to week 48 in fasting lipid-related laboratory parameters (total cholesterol, HDL and LDL cholesterol and triglycerides), glycaemia and plasma CLCR were minimal and non-significant (data not shown).

Discussion

The results from this single-arm, Phase II, open-label trial in well-suppressed treatment-experienced patients with no darunavir or NRTI RAMs and no previous virological failure demonstrated that over 48 weeks of treatment a switch from once-daily darunavir/r 800/100 mg to darunavir/r 400/100 mg with the same two NRTIs was associated with a high rate of virological suppression of 91.6%.
select for drug RAMs due to the high genetic barrier for the development of resistance to boosted PIs, a number of trials with boosted PIs used a higher plasma HIV RNA threshold to define virological failure, ranging from 200 to 400 copies/mL. Indeed, in our study over the 72 weeks of follow-up only three of eight patients with plasma HIV RNA >50 copies/mL had a plasma viral load above the assay threshold at baseline or screening, suggesting that these patients did not have full suppression of viral replication.

Nevertheless, this rate of virological failure at 48 weeks in our study seems higher than that reported in more recent switch trials with single-tablet cobicistat-boosted darunavir/tenofovir/emtricitabine in the EMERALD study (2.1% virological failure), or in the STRATEGY-PI trial, where patients maintaining a ritonavir-boosted PI regimen had a 1.4% rate of virological failure, and the results of well-powered randomized trials with low-dose darunavir/r are awaited. In addition, our results could not be extrapolated to the combination of darunavir with cobicistat because a PK study has reported a 30% reduction in darunavir Cmin levels when boosted with cobicistat as compared with ritonavir, which represents another limitation of our findings because darunavir is now coformulated with cobicistat.

In conclusion, our pilot study suggests that among well-suppressed patients under a once-daily darunavir/r-based regimen at the standard dose of 800/100 mg with two NRTIs, with no previous virological failure and no darunavir or NRTI RAMS, a switch to a reduced dose of darunavir/r (400/100 mg) is associated with a high rate of virological suppression through to 48 weeks and has a
favourable safety and tolerability profile. These results need confirmation in a large randomized trial before this reduced dose of darunavir/r can be recommended in clinical practice.

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Members of the ANRS 165 Darulight Study Team

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Members of the DSMR included: Dr P. De Truchis, I. Charrue, Dr L. Bocquet, Prof. V. Lemoing and G. Point.

Members of the scientific committee included: Prof. J. M. Molina, Prof. S. Chevret, E. M. El Abbassi, Dr S. Gallien, Prof. P. Tattevin, Dr G. Gras, Dr M. L. Choix, Dr G. Peytavin, J. Saillard, S. Couffin-Cadiergues, I. Madelaine, A. Diallo and S. Gibowski.

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Author contributions

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References


