96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline

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Background: In virologically suppressed patients, switching to darunavir/ritonavir monotherapy could avoid resistance and adverse events from continuing nucleoside analogues.

Methods: Two hundred and fifty-six patients with HIV RNA <50 copies/mL on current antiretrovirals were switched to darunavir/ritonavir 800/100 mg once daily, either as monotherapy (n=127) or with two nucleoside analogues (n=129). Treatment failure was defined as two consecutive HIV RNA levels at least 50 copies/mL by week 96, or discontinuation of study drugs. The trial had 80% power to show non-inferiority (δ=−12%) at week 48.

Results: Patients were 81% male, 91% Caucasian, and had a median baseline CD4 count of 575 cells/mm3. There were more patients with hepatitis C co-infection at baseline in the monotherapy arm (18%) compared with the triple therapy arm (12%). In the efficacy analysis, HIV RNA <50 copies/mL by week 96 (per protocol, time to loss of virological response, switch equals failure) was 78% versus 82% in the monotherapy and triple therapy arms (difference 4.2%, 95% confidence interval (CI) −14.3% to +5.8%); in a switch included analysis, HIV RNA <50 copies/mL was 93% versus 92% (difference +1.6%, 95% CI −5.0% to +8.1%). The percentage of patients with HIV RNA <5 copies/mL (optical density from the sample equal to the negative control) remained constant over time in both treatment arms.

Conclusions: In the week 96 analysis of the MONotherapy in Europe with TMC114 (MONET) trial, switching to darunavir/ritonavir monotherapy showed non-inferior efficacy to darunavir/ritonavir plus two nucleoside analogues in the switch included and observed failure analyses, but not in the main switch equals failure analysis.

Keywords: protease inhibitor monotherapy, clinical trials, HIV drug resistance, renal adverse events

Introduction
The primary aim of antiretroviral treatment is suppression of HIV RNA levels <50 copies/mL, and current treatment guidelines recommend continuing combinations of at least three antiretrovirals for a patient’s lifetime, even after full HIV RNA suppression <50 copies/mL has been achieved.1,2 However, recently published European HIV treatment guidelines have introduced the option for a switch to protease inhibitor (PI) monotherapy (either with darunavir/ritonavir once daily or lopinavir/ritonavir twice daily) for patients who have HIV RNA levels sustained <50 copies/mL and no history of virological failure.3 The MONotherapy in Europe with TMC114 (MONET) and MONOI trials were designed to evaluate whether darunavir/ritonavir monotherapy could show non-inferior efficacy, compared with a triple therapy arm of two nucleoside analogues plus darunavir/ritonavir.1,6 Both trials recruited patients with HIV RNA levels <50 copies/mL at screening, while taking triple combination therapy. The primary efficacy analyses of both trials were conducted at 48 weeks. In the primary efficacy analysis of the MONET trial (n=256), the percentage of patients with HIV RNA suppression <50 copies/mL at week 48 was 86.2% versus 87.8% in the monotherapy and triple therapy arms, respectively [difference −1.6%, 95% confidence interval (CI)
In the primary efficacy analysis of the MONOI trial ($n=225$), the percentage of patients with HIV RNA $<400$ copies/mL at week 48 was 94.1% versus 99.0% in the monotherapy and triple therapy arms, respectively (difference $-4.9\%$, 90% CI $-0.8\%$ to $-9.1\%$).

For patients with HIV RNA already suppressed $<50$ copies/mL, a switch to darunavir/ritonavir monotherapy could avoid the adverse events, resistance and costs of using additional drug classes, in particular nucleoside analogues. This paper presents results from a pre-planned follow-up analysis at week 96 in the MONET study, to evaluate the durability of HIV RNA suppression to darunavir/ritonavir monotherapy and the longer-term safety profile.

**Patients and methods**

MONET is an ongoing, 144 week, randomized, controlled, open-label Phase 3b trial, with data obtained from 256 patients in 11 European countries, Russia and Israel. Patients were randomized between June 2007 and March 2008. The results from the 48 week analysis were published previously.

The trial recruited patients who had HIV RNA levels $<50$ copies/mL on a stable triple antiretroviral regimen, for at least 24 weeks, and no history of virological failure since first starting antiretrovirals. All patients were naive to darunavir/ritonavir treatment at screening.

Patients were randomized to receive darunavir/ritonavir 800/100 mg once daily, either as monotherapy (monotherapy arm) or with two nucleoside analogues (triple therapy arm). The randomization was stratified for the use of boosted PIs at screening. Darunavir was administered as 400 mg tablets and ritonavir as 100 mg soft gelatin capsules. The nucleoside analogues used during the MONET trial were selected by the investigators and could be changed either at screening or during the trial, to improve tolerability.

**Efficacy and safety assessments**

Patients attended study visits at screening, baseline, weeks 4 and 12, and then every 12 weeks to week 96. Plasma HIV RNA was measured using the Roche Amplicor HIV-1 Monitor assay (version 1.5, Roche Molecular Systems, Branchburg, USA). For samples with HIV RNA $<50$ copies/mL, this assay can produce two different results. Either no HIV RNA is detected (the optical density from the sample is the same as from the negative control) or traces of HIV RNA that are below the limit of 50 copies/mL can be detected. The HIV RNA data were re-analysed at baseline and week 96, using this additional classification, to test whether traces of HIV RNA, in the range of 5–50 copies/mL, were more likely to be detected when patients took darunavir/ritonavir monotherapy.

Any patient with an HIV RNA result $>50$ copies/mL attended a confirmation visit for repeated testing of HIV RNA, drug resistance and plasma drug levels. If a patient had two consecutive HIV RNA levels $>50$ copies/mL, investigators could intensify or change antiretrovirals. Viral genotypic tests were performed using Virco TYPE HIV-1 assays (Virco BVBA, Mechelen, Belgium). The number of patients with treatment-emergent primary International AIDS Society–USA (IAS–USA) PI mutations was analysed by treatment arm.

Clinical and laboratory abnormalities were classified using the Division of AIDS 2004 grading tables. The adverse events were then classified by the System Organ Class (SOC). Adverse events in the SOC of 'Nervous System' or 'Psychiatric Disorder' were tabulated by treatment arm, using the Medical Dictionary for Regulatory Activities (medDRA) coding dictionary (www.meddramsso.com). Adherence to randomized medication was evaluated using the Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire.

Urinalysis was conducted at a central laboratory at baseline and at study visits to week 96. Haematuria was assessed by clinical diagnosis and from urinalysis. The percentage of patients with haematuria (clinical diagnosis), urine occult blood, glucosuria and proteinuria was compared between the treatment arms and by use of tenofovir, either at baseline or during the trial (Cochran Mantel–Haenszel test). Changes in plasma creatinine were also compared between treatment arms, using analysis of covariance.

Written informed consent was obtained from all participating patients before the study started. Study protocols were reviewed and approved by the appropriate institutional ethics committees and health authorities, and were undertaken in accordance with Good Clinical Practice and the Declaration of Helsinki. The ClinicalTrials.gov identifier is NCT00458302.

**Statistical methods**

The MONET trial was designed to show non-inferior efficacy of the monotherapy arm versus the triple therapy arm at week 48, with a non-inferiority margin of $-12\%$. The sample size calculations assumed 80% power, a one-sided significance level of 0.025, a 90% overall response rate and 10% of patients excluded from the per protocol population. The primary efficacy parameter, treatment failure, was defined as two consecutive HIV RNA levels $>50$ copies/mL at week 48, or discontinuation of randomized treatment [commonly known as time to loss of virological response (TLOVR)]. A protocol amendment was made to extend the trial to 96 and then 144 weeks of randomized treatment. The main analyses at week 96 used the same endpoint as the original week 48 analysis; no adjustments were made for multiple comparisons in this non-inferiority design. Patients were classified as virological failures even if they subsequently withdrew from the trial for adverse events or other reasons.

In the primary analysis, switches of treatment classified as failure were as follows: (i) stopping darunavir/ritonavir; (ii) starting nucleoside analogues in the monotherapy arm; and (iii) stopping all nucleoside analogues in the triple therapy arm. Patients were allowed to switch nucleoside analogues for reasons of toxicity in the triple therapy arm.

The per protocol population was used for the main efficacy analysis at week 96: this population excluded patients with major protocol violations, such as a history of virological failure or incorrect randomization. The analyses were then repeated for the intent to treat (ITT) population, including all randomized patients.

In the ITT switch included analysis, patients who had HIV RNA levels $<50$ copies/mL at week 96 were counted as successes, even if they had confirmed HIV RNA elevations and had subsequently intensified treatment with nucleoside analogues. In addition, the main analysis was repeated, including only the observed virological endpoints (observed failure analysis).

**Results**

Of 293 patients screened, 256 were randomized and treated (127 in the darunavir/ritonavir arm and 129 in the triple therapy arm) and were included in the ITT analysis. Eleven patients were excluded from the per protocol population (5 from the monotherapy arm, 6 from the triple therapy arm). Eight of these patients had a history of virological failure before the trial, one patient was imprisoned, one left the investigational site indefinitely and one was excluded for other reasons.

Data from 245 patients (122 in the monotherapy arm and 123 in the triple therapy arm) were thus included in the per protocol population. Figure 1 shows a flow chart of patient disposition during the trial.
Baseline characteristics

Baseline characteristics were previously presented and were generally well balanced between the treatment arms. Patients were 81% male with a mean age of 44 years, mean weight of 73 kg and mean CD4 count of 575 cells/mm³. The patients had a median 8 years of known HIV infection, and had been treated with antiretrovirals for a median of 6.5 years.

At the screening visit, 57% of the patients were receiving PIs and 43% were receiving a non-nucleoside reverse transcriptase inhibitor. By hepatitis C serology, 23/127 patients (18%) had hepatitis C antibodies in the monotherapy arm and 15/129 (12%) in the triple therapy arm. At baseline, 13 patients had HIV RNA levels >400 copies/mL (9 in the monotherapy arm and 4 in the triple therapy arm), despite having results <50 copies/mL at screening; two of these elevations were >400 copies/mL.

Nucleoside analogues used at baseline in the triple therapy arm were tenofovir plus emtricitabine (46%), tenofovir plus lamivudine (7%), abacavir plus lamivudine (31%) or zidovudine plus lamivudine (10%), with 6% taking other combinations.

Efficacy

Figure 2 shows the percentage of patients with HIV RNA levels in different ranges of viral load during the trial: <5, 5–50, 50–400 and >400 copies/mL (observed data). The percentage of patients with this HIV RNA suppression in the categories of <5 copies/mL and 5–50 copies/mL remained constant in both treatment arms between the visits at baseline and week 96. Higher HIV RNA levels were in the range of 50–200 copies/mL. Including data from all patient visits to week 96, HIV RNA was >50 copies/mL in 69/1009 samples (6.9%) in the darunavir/
MONET trial: darunavir/ritonavir monotherapy

Table 1. Summary of efficacy at week 96 by treatment arm

<table>
<thead>
<tr>
<th>Efficacy endpoint, week 96</th>
<th>Monotherapy n=129</th>
<th>Triple therapy n=127</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL, switch = failure, TLOVR, per protocol</td>
<td>95/122 (78%)</td>
<td>101/123 (82%)</td>
<td>−4.2% (−14.3%, +5.8%)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL, switch = failure, TLOVR,ITT</td>
<td>95/127 (75%)</td>
<td>104/129 (81%)</td>
<td>−5.8% (−16%, +4.4%)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL, observed failure, per protocol</td>
<td>108/122 (89%)</td>
<td>112/123 (91%)</td>
<td>−2.5% (−10.1%, +5.1%)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL, switch included, per protocol</td>
<td>114/122 (93%)</td>
<td>113/123 (92%)</td>
<td>+1.6% (−5%, +8.1%)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

ritonavir monotherapy arm versus 47/1051 samples (4.5%) in the triple therapy arm.

Table 1 shows the comparison of efficacy between the two treatment arms at week 96. In the per protocol, switch equals failure analysis, 95/122 patients (78%) had HIV RNA <50 copies/mL at week 96 in the monotherapy arm versus 101/123 patients (82%) in the triple therapy arm. In the ITT, switch equals failure analysis, 95/127 patients (75%) in the monotherapy arm and 104/129 patients (81%) in the triple therapy arm had HIV RNA <50 copies/mL at week 96. These treatment comparisons did not meet the pre-defined criteria to show non-inferiority for monotherapy versus the triple therapy arm, but there was no statistically significant difference between the arms for either comparison (Table 1). In the per protocol, switch included analysis, 114/122 patients (93%) in the monotherapy arm and 113/123 patients (92%) in the triple therapy arm had HIV RNA levels <50 copies/mL at the week 96 visit. The observed failure analysis, including only the virological endpoints (per protocol population), showed HIV RNA suppression rates <50 copies/mL of 108/122 (89%) in the monotherapy arm and 112/123 (91%) in the triple therapy arm. The treatment comparisons for the switch included and observed failure analyses met the criteria for non-inferiority (Table 1). Median CD4 counts remained stable over time in both treatment arms.

In a multivariate analysis, hepatitis C co-infection was a significant predictor of confirmed HIV RNA elevations (P=0.01). At baseline, 23/127 patients (18%) were HCV antibody positive in the darunavir/ritonavir arm versus 15/129 patients (12%) in the triple therapy arm. For patients infected only with HIV at baseline, the percentage with HIV RNA <50 copies/mL at week 96 (per protocol population, TLOVR switch equals failure) was 85.1% (86/101) in the monotherapy arm versus 84.5% (93/110) in the triple therapy arm. For patients who were antibody positive for both HIV and HCV at baseline, the percentage with HIV RNA <50 copies/mL at week 96 was 42.9% (9/21) in the monotherapy arm versus 66.7% (8/12) in the triple therapy arm. Four additional patients had acute HCV infection during the trial (in the monotherapy arm): three of these patients had HIV RNA elevations at the time of acute HCV infection (Table 2). Ninety percent of patients with hepatitis C co-infection were former intravenous (IV) drug users, some of whom were actively using heroin or cocaine during the trial. The patients with HCV co-infection at baseline had significantly lower adherence than patients with HIV infection alone. In multivariate analyses of efficacy, there was a strong correlation between elevations in HIV RNA and either IV drug use or hepatitis C co-infection.

Table 2 shows the outcome for each individual patient with protocol-defined virological failure (ITT population). Of the 15 patients with confirmed HIV RNA elevations >50 copies/mL in the monotherapy arm, 11 (73%) had HIV RNA levels <50 copies/mL either at week 96 or their most recent visit (Table 2). The other four patients had a low level of HIV RNA at the last visit, ranging from 100 to 231 copies/mL.

Of the 11 patients with confirmed HIV RNA elevations >50 copies/mL in the triple therapy arm, 10 (91%) had HIV RNA levels <50 copies/mL either at week 96 or their most recent visit (Table 2). In both treatment arms, most of the HIV RNA elevations were transient, in the range of 50–200 copies/mL, and occurred at times of poor adherence or intercurrent infections (Table 2). In the monotherapy arm, 9 of the 15 patients with confirmed HIV RNA elevations changed their antiretrovirals as recommended in the trial protocol, either by adding nucleoside reverse transcriptase inhibitors (NRTIs) or switching back to their pre-trial antiretrovirals. None of the 11 patients in the triple therapy arm with confirmed HIV RNA elevations changed their antiretroviral treatment.

In the darunavir/ritonavir monotherapy arm, 17 patients withdrew from the trial before week 96 without prior virological failure: all 17 patients had follow-up HIV RNA levels <50 copies/mL at their most recent visit. In the triple therapy arm there were 14 discontinuations before week 96. Twelve of these 14 patients had HIV RNA <50 copies/mL at their most recent follow-up visit; 1 patient had an HIV RNA level of 112 copies/mL and 1 had missing data.

Drug resistance

Seventy-six patients (41 on monotherapy, 35 on triple therapy) had at least one HIV RNA result >50 copies/mL during the trial and were genotyped. Genotyping was successful for 48 patients (21 and 27 patients in the monotherapy and triple therapy arms, respectively). Forty-six of these 48 patients (96%) showed genotypic and phenotypic sensitivity to all boosted PIs and NRTIs. Major IAS–USA PI mutations were detected in one patient per treatment arm, during short-term elevations in HIV RNA. In the monotherapy arm, the L33F mutation was detected at a single visit, when the HIV RNA level was 63 copies/mL. In the triple therapy arm, PI mutations detected before the trial re-emerged, when the HIV RNA level was 78 and 50 copies/mL during an interruption of
treatment. Both patients remained phenotypically sensitive to darunavir during follow-up, with sustained HIV RNA ≤ 50 copies/mL during the trial and no change in antiretroviral treatment.

Safety

No new or unexpected safety events occurred, and adverse events were not treatment-limiting in most cases. Serious adverse events were seen in 26 patients (13 in each treatment arm). The most common grade 2–4 drug-related clinical adverse events were gastrointestinal. No patients died during the trial. Neurological or psychiatric adverse events were analysed in detail, given concerns over the central nervous system (CNS) penetration of protease inhibitors: results are shown in Table 3. Grade 1–4 adverse events of the nervous system and psychiatric adverse events were seen in a similar percentage of patients in each treatment arm (Table 3). There was one grade 3 nervous system or psychiatric adverse event in the monotherapy arm—a patient who discontinued treatment for headache. In the triple therapy arm there were two patients with grade 3 nervous system or psychiatric disorders: one patient had grade 3 depression and one had a loss of libido. There were no reported neuropsychiatric adverse events in either arm that would suggest CNS viraemia.

The most common laboratory abnormalities were elevations in lipids, liver enzymes and haematological abnormalities, which are shown in Table 3. Elevations in alanine transaminase and aspartate transaminase were associated with acute or chronic infection with hepatitis A or hepatitis C. The percentage of patients with elevations in liver enzymes remained stable during the trial. There was an apparent difference between the arms for grade 3 elevations in total cholesterol. However, eight of the 14 patients in the monotherapy arm showed these elevations at only a single timepoint. The number of patients with sustained elevations in total cholesterol was six in the monotherapy arm versus three in the triple therapy arm. There was a trend for total cholesterol to rise in the monotherapy arm, early in the trial, for patients who stopped taking tenofovir. The rise was 0.5 mmol/L for these patients. There was a

Table 2. Outcomes of confirmed HIV RNA elevations in the darunavir/ritonavir monotherapy arm and the triple therapy arm

<table>
<thead>
<tr>
<th>Patient (hepatitis C)</th>
<th>HIV RNA blips</th>
<th>Changed antiretroviral/comments a</th>
<th>Last HIV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy arm (n=15): ITT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (HCV−)</td>
<td>140, 133</td>
<td>none/sinusitis</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>2 (HCV−)</td>
<td>59, 214</td>
<td>ZDV/3TC/NVP</td>
<td>&lt;50 (week 128)</td>
</tr>
<tr>
<td>3 (HCV−)</td>
<td>539, 862</td>
<td>TDF/FTC/EFV</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>4 (HCV−)</td>
<td>158, 140</td>
<td>ABC/3TC/DRV/r</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>5 (HCV−)</td>
<td>215, 427</td>
<td>none</td>
<td>158 (week 112)</td>
</tr>
<tr>
<td>6 (HCV+)</td>
<td>810, 605</td>
<td>TDF/FTC/DRV/r</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>7 (HCV+)</td>
<td>40500, 628</td>
<td>none (stopped antiretrovirals)</td>
<td>&lt;50 (week 112)</td>
</tr>
<tr>
<td>8 (HCV+)</td>
<td>134, 79</td>
<td>none</td>
<td>108 (week 96)</td>
</tr>
<tr>
<td>9 (HCV+)</td>
<td>722, 157</td>
<td>TDF/FTC/DRV/r</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>10 (HCV+)</td>
<td>288, 3880</td>
<td>TDF/FTC/DRV/r</td>
<td>&lt;50 (week 112)</td>
</tr>
<tr>
<td>11 (HCV+)</td>
<td>779, 267</td>
<td>ABC/3TC/DRV/r</td>
<td>&lt;50 (week 112)</td>
</tr>
<tr>
<td>12 (HCV+)</td>
<td>154, 100</td>
<td>none</td>
<td>100 (week 96)</td>
</tr>
<tr>
<td>13 (ACUTE)</td>
<td>132, 139</td>
<td>LPV/r monotherapy</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>14 (ACUTE)</td>
<td>51, 80</td>
<td>no change</td>
<td>&lt;50 (week 112)</td>
</tr>
<tr>
<td>15 (ACUTE)</td>
<td>106, 268</td>
<td>TDF/FTC/DRV/r</td>
<td>231 (week 116)</td>
</tr>
<tr>
<td>Triple therapy arm (n=11): ITT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (HCV−)</td>
<td>55, 616</td>
<td>none</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>2 (HCV−)</td>
<td>305, 69</td>
<td>none</td>
<td>&lt;50 (week 112)</td>
</tr>
<tr>
<td>3 (HCV−)</td>
<td>9240, 612</td>
<td>adverse event</td>
<td>397 (week 96)</td>
</tr>
<tr>
<td>4 (HCV−)</td>
<td>294, 116</td>
<td>none/heroin use</td>
<td>&lt;50 (week 112)</td>
</tr>
<tr>
<td>5 (HCV−)</td>
<td>78, 50</td>
<td>none/stopped antiretrovirals</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>6 (HCV−)</td>
<td>164, 67</td>
<td>none</td>
<td>&lt;50 (week 60)</td>
</tr>
<tr>
<td>7 (HCV−)</td>
<td>989, 59</td>
<td>none</td>
<td>&lt;50 (week 84)</td>
</tr>
<tr>
<td>8 (HCV−)</td>
<td>746, 2230</td>
<td>none/poor adherence</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>9 (HCV−)</td>
<td>128, 548</td>
<td>none/poor adherence</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>10 (HCV+)</td>
<td>54000, 3400</td>
<td>none/cocaine use</td>
<td>&lt;50 (week 96)</td>
</tr>
<tr>
<td>11 (HCV+)</td>
<td>87, 135</td>
<td>none</td>
<td>&lt;50 (week 96)</td>
</tr>
</tbody>
</table>

HCV−, HCV antibody negative at baseline; HCV+, HCV antibody positive at baseline; ACUTE, acute infection with HCV during the trial; TDF, tenofovir; FTC, emtricitabine; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir; NVP, nevirapine; EFV, efavirenz; DRV/r, darunavir/ritonavir; LPV/r, lopinavir/ritonavir.

aThe investigators were asked to comment on why HIV RNA was elevated in their patients.
corresponding fall in total cholesterol for patients who switched to tenofovir in the triple therapy arm.

There were 70 patients in the triple therapy arm who received tenofovir during the MONET trial. The remaining 59 patients in the triple therapy arm and all patients in the monotherapy arm did not receive tenofovir. Overall in the trial, detectable urine occult blood was significantly more common for patients taking tenofovir in the triple therapy arm (45%) than in those not using tenofovir (33%) \( (P=0.0297, \text{ adjusting for gender}) \). Glucosuria and proteinuria were also more common in tenofovir-treated patients (11.7% and 25%) than in those not taking tenofovir (5.4% and 4.6%) \( (P=0.054 \text{ and } P=0.060, \text{ respectively}) \). There were 12 reports of grade 1–4 haematuria as a clinical adverse event in the triple therapy arm: 8 of these patients were receiving tenofovir and 6 of these cases were classified as grade 3 (severe). There were four cases of grade 1–4 haematuria in the darunavir/ritonavir arm, of which one was grade 3: this patient had stopped taking tenofovir at the baseline visit. Clinical diagnosis of haematuria was significantly more common for patients taking tenofovir \( (P=0.03) \).

### Discussion

In the MONET study for patients with HIV RNA <50 copies/mL at baseline, slightly more patients showed confirmed elevations in

HIV RNA in the darunavir/ritonavir monotherapy arm (15 patients, 11.6%) compared with the triple therapy arm (11 patients, 8.7%). However, patients in both treatment arms could be re-suppressed <50 copies/mL either by remaining on their current treatment or after switching back to triple combination therapy. Similarly, all patients who withdrew from the trial had follow-up HIV RNA levels <50 copies/mL. There was only one patient in each arm with evidence of drug resistance during a temporary episode of viraemia in the trial—both patients remained phenotypically sensitive to darunavir and had sustained re-suppression of HIV RNA <50 copies/mL after long-term follow-up. Most of the elevations in HIV RNA were low-level, in the region of 50–200 copies/mL. In the most recent treatment guidelines from the US Department for Health and Social Security, low-level viraemia in the range of 50–200 copies/mL was not found to be associated with treatment failure. If these guidelines had been followed in the MONET trial, very few patients with protocol-defined endpoints would have been intensified with nucleoside analogues or switched.

At week 96, non-inferiority was not demonstrated in the efficacy analysis, which classified temporary elevations in HIV RNA or switches in treatment as failures. The imbalance in hepatitis C co-infection at baseline between the treatment arms, and acute HCV infections during the trial, may have contributed to this result. In addition, the triple therapy arm included a higher percentage of patients taking their first antiretroviral regimen, fewer had baseline HIV RNA levels >50 copies/mL and more were naive to PI treatment. There was a close correlation between hepatitis C co-infection and IV drug use as a risk factor for HIV infection in the MONET trial. The exact reason why hepatitis C co-infected patients were more likely to show elevations in HIV RNA in the MONET trial is unknown, but may be related to adherence. Co-infection with hepatitis C has been correlated with treatment failure in other studies. Importantly, however, most elevations were transient and the vast majority of patients showed HIV RNA suppression <50 copies/mL at their week 96 visit.

The risk of treatment-emergent drug resistance during darunavir/ritonavir monotherapy in the MONET trial was low. This risk needs to be put in perspective, given the risks of developing resistance to nucleoside analogues, non-nucleosides or integrase inhibitors during standard triple combination treatment. In the MONET trial, all samples with HIV RNA levels >50 copies/mL were evaluated for genotypic drug resistance. This very detailed, systematic analysis of drug resistance is not normally undertaken in other trials, which normally evaluate resistance only in patients with two consecutive HIV RNA levels >400–1000 copies/mL. The potential risks of switching to darunavir/ritonavir in this trial appear to be small: patients with elevations in HIV RNA can be re-suppressed with intensified treatment, there is no additional risk of developing drug resistance and there is no increase in the risk of CNS adverse events. Darunavir does show levels in the CNS above the EC50. These potential risks should be set against the issues with prolonged use of nucleoside analogues, in terms of adverse events, drug resistance and costs. The MONET trial was not powered to detect a safety benefit from discontinuing nucleoside analogues in the monotherapy arm. Even so, there was some evidence for excess
renal toxicity in the triple therapy arm for the patients receiving tenofovir. Large cohort studies have also shown an excess risk of renal adverse events from prolonged use of tenofovir.\textsuperscript{19,20} In addition, there is the risk of other adverse events from nucleoside analogues; e.g. in the MONOI trial, patients in the triple therapy arm showed a higher risk of lipopathy compared with those in the darunavir/ritonavir monotherapy arm.\textsuperscript{21}

These results suggest that the strategy of switching to darunavir/ritonavir monotherapy can be considered in treatment-experienced patients who have a history of HIV RNA levels <50 copies/mL on other treatments, but who wish to avoid toxicities related to nucleoside analogues, non-nucleosides or other antiretrovirals. If necessary, patients who show low-level elevations in HIV RNA during darunavir/ritonavir monotherapy can be successfully re-intensified with nucleoside analogues to re-suppress HIV RNA below detectable levels.

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\section*{Transparency declarations}
C. M. and Y. D. are employees of Janssen. A. H. and J. A. have received consultancy payments from Janssen. The other authors have nothing to declare.

\section*{Author contributions}
A. H. had full access to the data and guarantees the quality of the database. N. C., A. R., D. B., W. S. and J. A. were trial investigators who also provided comments on the original protocol the presentation of the data and the manuscript. C. M. and Y. D. coordinated the clinical trial, as well as reviewing the trial protocol and manuscript. The corresponding author, N. C., had the final responsibility to submit the manuscript for publication.

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