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# Effects of Switching To Protease Inhibitor Monotherapy on Nucleoside Analogue-Related Adverse Events

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## Abstract

***Switching from triple combination treatment to protease inhibitor monotherapy may increase the risk of elevations in HIV RNA, and is not recommended in most international treatment guidelines. However, the use of protease inhibitor monotherapy could prevent or reverse adverse events related to long-term use of nucleoside analogues, such as lipoatrophy, renal adverse events, osteopenia, and anemia. A detailed MEDLINE search was conducted to identify randomized clinical trials of triple-combination treatment versus protease inhibitor monotherapy with detailed analyses of safety. Summary results from analysis of changes in body composition, changes in lipids, renal adverse events, and anemia were evaluated for patients taking either protease inhibitor monotherapy or triple therapy. In six trials with dual-energy X-ray absorptiometry data available, the percentage of patients with lipoatrophy was significantly lower in the protease inhibitor monotherapy arms than the triple therapy arms (p = 0.03). In these trials there was also no significant difference in the risk of lipohypertrophy between protease inhibitor monotherapy and triple therapy arms. In one trial there was a higher risk of renal adverse events for patients taking tenofovir in the triple therapy arm. In two trials there were rises in total cholesterol when patients stopped taking tenofovir in the protease inhibitor monotherapy arms. In conclusion, there is a mixed pattern of changes in nucleoside analogue-related adverse events after switching from triple therapy to protease inhibitor therapy. The potential for safety benefits of stopping nucleoside analogues needs to be set against a higher risk of HIV RNA elevations during protease inhibitor monotherapy.*** **(AIDS Rev. 2014;16:236-45)**

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## Key words

***Protease inhibitor. Darunavir. Lopinavir. Nucleoside analogue. Lipoatrophy. Creatinine clearance. Cholesterol. Bone mineral density.***

## Introduction

Nucleoside analogue treatment has been associated with a range of mitochondrial toxicities: zidovudine is associated with anemia, neutropenia, and lipoatrophy[1]. Zidovudine and abacavir have both been associated with rises in lipids. Tenofovir treatment has lowered total cholesterol in studies in healthy volunteers[2]. However, tenofovir is also associated with renal toxicities such as reduced creatinine clearance, proteinuria, and proximal tubule dysfunction[3].

Antiretroviral treatment normally includes two nucleoside analogues combined with either a protease inhibitor (PI), nonnucleoside, or integrase inhibitor. Direct comparisons between nucleoside analogues in randomized trials have shown differences: for example, a lower risk of lipoatrophy for tenofovir compared with zidovudine, or a higher risk of lipid elevations for zidovudine or abacavir compared with tenofovir. However, it may be difficult to evaluate the overall effects of mitochondrial toxicity in clinical trials where all patients are receiving nucleoside analogues. Several randomized clinical trials of PI monotherapy versus triple combination

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therapy have been conducted[4,5]. These trials have generally shown a slightly higher risk of elevation in HIV RNA for PI monotherapy compared with triple combination treatment. However, patients who are intensified with nucleoside analogues after these HIV RNA elevations tend to show long-term re-suppression. There has been no additional risk of HIV drug resistance shown in trials of PI monotherapy[6-9].

These studies allow the evaluation of adverse events in people taking nucleoside analogues versus those not taking them. The purpose of this review is to evaluate published safety analyses from randomized trials of PI monotherapy. The risk of nucleoside analogue-related adverse events was compared between the triple therapy and PI monotherapy arms in each trial. Effects of stopping different nucleoside analogues (tenofovir, abacavir, zidovudine) were also evaluated.

The results of two previous systematic reviews were used to identify randomized clinical trials of PI monotherapy versus triple combination therapy, which included detailed analyses of safety endpoints[4,5]. Trials could assess maintenance, whereby patients were simplified to PI monotherapy after HIV RNA suppression, or could evaluate PI monotherapy as an induction strategy in antiretroviral-naive patients. MEDLINE was searched to obtain further publications or conference presentations for the identified clinical trials. For evaluation, results from Week 48 were used where possible since this was the time point most frequently studied across the clinical trials.

The primary outcomes for this review were: (i) median change in body in limb and trunk fat from baseline to Week 48; (ii) proportion of patients with a 20% decrease from baseline in Week 48 in limb fat (lipoatrophy); (iii) proportion of patients with a 20% increase from baseline to Week 48 in trunk fat (lipohypertrophy); (iv) median changes in lipids (total cholesterol, low-density lipoprotein [LDL] cholesterol, and high-density lipoprotein [HDL] cholesterol); and (v) proportion of patients discontinuing treatment for adverse events. Changes in body composition (outcomes i, ii, and iii) were measured by DXA (dual-energy X-ray absorptiometry). In addition, measures of renal function and bone mineral density (BMD) were described where available.

Review Manager 5.2 was used to analyze the data[10]. For binary outcomes (outcomes ii, iii, and v) the risk difference (RD) between the PI monotherapy arm and triple-therapy arm was calculated with 95% confidence intervals (CI). The meta-analysis was conducted using inverse variance weighting. The $I^2$ statistic, a measure of variation across trials, was used to measure statistical heterogeneity among the trials in each analysis. However, in order to present a conservative analysis, studies were pooled using a random-effects model for all outcomes. The results for outcomes (i) and (iv) were presented as median change (from baseline to Week 48) and interquartile range (IQR) where possible; if unavailable, mean and standard deviation were presented. Due to differences in reporting, the results for these outcomes were not pooled; instead a narrative overview was undertaken in which the results from each trial were individually evaluated.

## Clinical trials of PI monotherapy

Eight trials were identified that matched the inclusion criteria; summary data are shown in table 1. Of these eight trials, five evaluated lopinavir/ritonavir monotherapy, all at the dose of 400/100 mg twice daily. Three trials evaluated darunavir/ritonavir monotherapy, one at the dose of 600/100 mg twice daily (MONOI), and the other two at the dose of 800/100 mg once daily (Monarch and MONET). For seven of the eight trials, the control arm was the same boosted PI plus two nucleoside analogues; for the other trial (Abbott 613), the control arm included the non-nucleoside efavirenz.

Three trials used a fixed nucleoside analogue backbone in the control arm (zidovudine/lamivudine for the Abbott 613 and Monark trials, abacavir/lamivudine for the KRETA trial). The other five trials allowed investigator-selected nucleoside analogues in the control arm. For these five trials, the percentage of patients using zidovudine in the control arms was 38% in Kalesolo, 21% in MONOI, 10% in MONET, and 0% in Monarch; zidovudine was one of the most common nucleosides in the OK-04 study, but the proportion is not given (Table 1).

Of the eight trials included in the meta-analysis, six measured changes in body composition by DXA analysis; in total 471/1,281 randomized patients (37%) had DXA measurements (471/820, 57%, from the six trials with DXA analysis). Results from the 48-week analysis were used for five trials, and the 96-week results were used for one trial (Abbott 613).

More details of the eight individual trials are shown below:

– The Abbott 613 trial[9,11] recruited 156 treatment-naive patients in a 2:1 ratio to either (i) zidovudine/lamivudine/lopinavir/ritonavir followed by lopinavir/ritonavir monotherapy (once the HIV RNA had

**Table 1. Baseline characteristics of trials included in meta-analysis**

| Trial (reference) | Design | Follow-up time | Treatment arms | Patients | DXA |
|---|---|---|---|---|---|
| Abbott 613[9,11] | Induction/ maintenance | 96 weeks | LPV/r + ZDV/3TC, with simplification to LPV/r after HIV RNA suppression<br>EFV + ZDV/3TC | n = 104* (92 simplified)<br>n = 51* | n = 74<br>n = 32 |
| Monark[12,13] | Naive | 48 weeks | LPV/r monotherapy<br>LPV/r + ZDV/3TC | n = 83<br>n = 53 | n = 41<br>n = 22 |
| Kalesolo[14] | Maintenance | 48 weeks | LPV/r monotherapy<br>LPV/r + 2 NRTIs (38% ZDV) | n = 87<br>n = 99 | n = 19<br>n = 23 |
| MONOI[15,16] | Maintenance | 48 weeks | DRV/r monotherapy<br>DRV/r +2 NRTIs (21% ZDV) | n = 112<br>n = 113 | n = 75<br>n = 81 |
| Monarch[17,18] | Maintenance | 48 weeks | DRV/r monotherapy<br>DRV/r + 2 NRTIs (0% ZDV) | n = 15<br>n = 15 | n = 15<br>n = 15 |
| KRETA[19] | Maintenance | 48 weeks | LPV/r monotherapy<br>LPV/r + ABC/3TC | n = 44<br>n = 44 | n = 34<br>n = 40 |
| MONET[6,20] | Maintenance | 144 weeks | DRV/r monotherapy<br>DRV/r + 2 NRTIs | n = 127<br>n = 129 | NA<br>NA |
| OK-04[8] | Maintenance | 96 weeks | LPV/r monotherapy<br>LPV/r + 2 NRTIs | n = 103<br>n = 102 | NA<br>NA |

*One patient was randomized but did not receive any drug in the study.
DXA: dual-energy X-ray absorptiometry; LPV/r: lopinavir/ritonavir; ZDV: zidovudine; 3TC: lamivudine; NRTI: nucleoside reverse transcriptase inhibitor; DRV: darunavir; ABC: abacavir; NA: data unavailable.

fallen to < 50 copies/ml and maintained for three months), or (ii) the control arm of zidovudine/lamivudine/efavirenz for 96 weeks. Results from DXA analyses were available at both baseline and Week 96 for 106/156 patients (68%).

- The Monark trial[12,13] recruited 136 treatment-naive patients in a 2:1 ratio to receive either lopinavir/ritonavir monotherapy or zidovudine/lamivudine/lopinavir/ritonavir for 96 weeks. There were 63 patients (46%) with DXA results at both the baseline and Week 48 visits.
- The Kalesolo trial[14] recruited 186 patients with HIV RNA < 50 copies/ml and no history of virological failure on PIs. Patients were randomized in a 1:1 ratio to receive either lopinavir/ritonavir monotherapy, or two investigator-selected nucleoside analogues plus lopinavir/ritonavir. The DXA results were available at baseline and Week 48 for 42/186 patients (23%).
- The MONOI trial[15,16] recruited 225 patients with HIV RNA < 50 copies/ml and no history of virological failure on PIs. Patients were randomized in a 1:1 ratio to receive either darunavir/ritonavir monotherapy or two investigator-selected nucleoside analogues plus darunavir/ritonavir. The DXA results were available at Week 48 for 156/225 patients (69%).
- The Monarch trial[17,18] recruited 30 patients with HIV RNA < 50 copies/ml and no history of virological failure on PIs. Patients were randomized in a 1:1 ratio to receive either darunavir/ritonavir monotherapy or two investigator-selected nucleoside analogues plus darunavir/ritonavir. The DXA results were available at Week 48 for all 30 patients (100%).
- The KRETA trial[19] recruited 88 patients with HIV RNA < 50 copies/ml and moderate-to-severe lipoatrophy while taking zidovudine/abacavir/lamivudine. The patients were then randomized in a 1:1 ratio to either lopinavir/ritonavir or abacavir/lamivudine plus lopinavir/ritonavir for 96 weeks. The DXA results were available at baseline and Week 48 for 74/88 patients (84%).

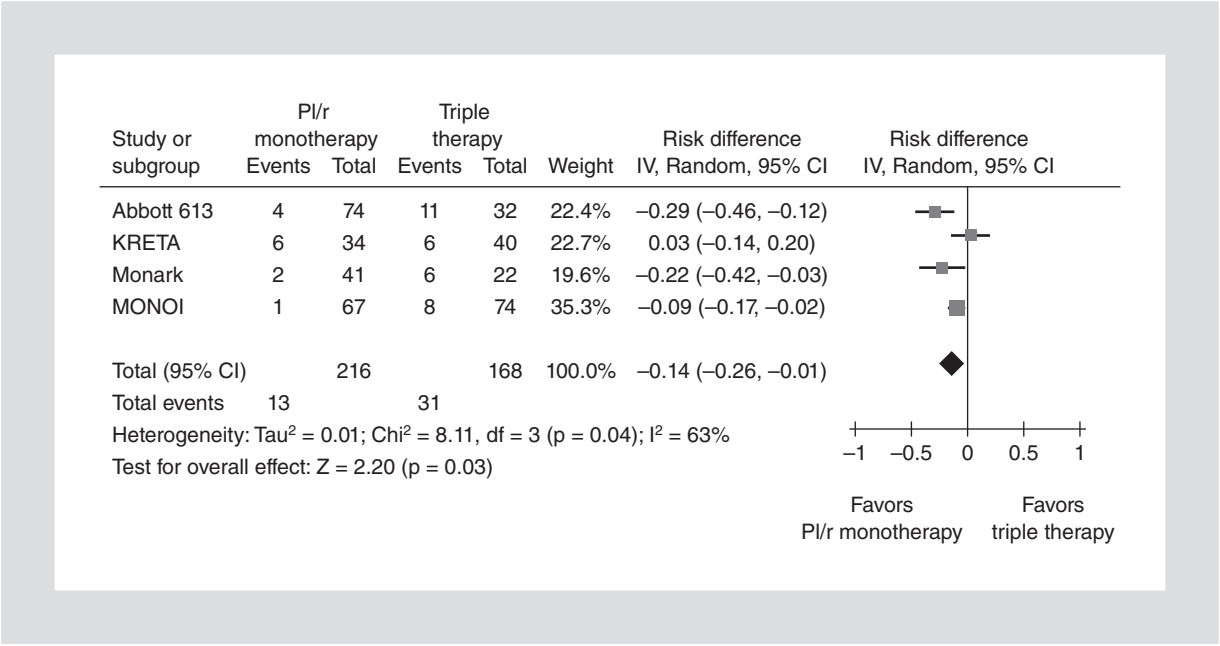


**Figure 1.** *Forest plot of risk difference: Patients with lipoatrophy by treatment arm. PI/r: ritonavir boosted protease inhibitor.*

- The MONET trial[6,20] recruited 256 patients in a 1:1 ratio to receive either darunavir/ritonavir as monotherapy or with two nucleoside analogues. At enrolment, patients had HIV RNA levels < 50 copies/ml on a stable triple antiretroviral therapy (ART) regimen, and had no history of virological failure.
- Finally, the OK-04 study[8] recruited patients who had been taking lopinavir/ritonavir for at least four weeks as part of a triple-therapy regimen. The 205 patients were randomly assigned in a 1:1 ratio to either stop or continue the nucleoside backbone. Patients had a viral load of < 50 copies HIV RNA/ml for six months prior to enrolment and had no history of virological failure.

## Changes in body composition

Six of the eight trials included data on the changes in body fat (limb and trunk) from baseline to Week 48. In the limb fat analysis, a statistically significant difference was observed between the two treatment arms in four of the six trials (Abbott 613, Kalesolo, Monark, and MONOI). In these trials, there was a significantly greater rise in limb fat for patients treated with PI monotherapy, compared with triple therapy from baseline to Week 48.

However, the significant difference in change in limb fat in the MONOI study (median +0.34 kg; IQR: –0.04, +1.14 vs. –0.02 IQR: –0.53, +0.52, monotherapy vs. triple, respectively) observed at Week 48 was not maintained through to Week 96. Similarly, there was no significant difference between the two arms in limb fat change at Week 96 in the KRETA study. These results contrast with the Abbott 613 study in which the difference was highly significant at Week 96 ($p < 0.001$).

In a subgroup analysis of the triple-therapy arm in the MONOI study, patients receiving only tenofovir or abacavir in the nucleoside analogue backbone observed no change in limb fat in the first 48 weeks (median +0.04 kg; IQR: –0.45, +0.67 kg) compared to those who continued thymidine analogue or didanosine-containing regimens who experienced a decrease (median –0.18 kg; IQR: –0.57, +0.30 kg), but this difference was not significant.

The analysis of the percentage of patients with lipoatrophy, defined as a 20% or greater loss in limb fat, included results from four trials (Fig. 1). There were significantly fewer patients with lipoatrophy in the PI-monotherapy arms compared to the control arms for three or the four trials analyzed individually ($p < 0.05$), and for the overall meta-analysis (RD: –0.14; 95% CI: 0.26 to –0.01; $p = 0.03$).

No significant differences were observed in change in trunk fat from baseline to Week 48 between the PI-monotherapy and triple-therapy arms (non-significant

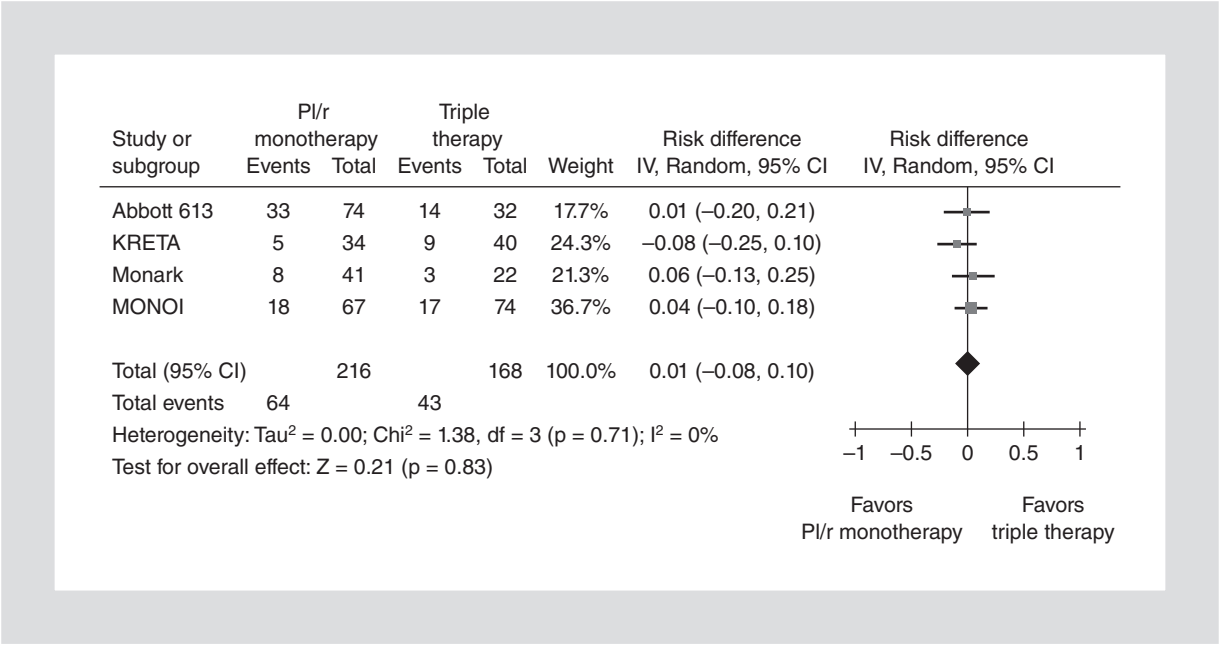


**Figure 2.** *Forest plot of risk difference: Patients with lipohypertrophy by treatment arm. PI/r: ritonavir boosted protease inhibitor.*

difference for all six trials). Furthermore, in the analysis of lipohypertrophy (Fig. 2), there were no significant differences between the arms, either for individual trials or the meta-analysis (RD: +0.01; 95% CI: –0.08 to +0.10; p = 0.83).

## Bone mineral density

Changes in BMD were reported in four of the six trials. In the two trials that enrolled ART-naive patients (Monark and Abbott 613), significant bone loss was observed in both treatment groups from baseline to point of assessment (Week 48 and 96 for Monark and Abbott 613, respectively). The changes in BMD were similar for both treatment regimens (Table 2). Similarly, in the Kalesolo trial the evolution of BMD did not differ between the treatment groups for both males and females (Table 2). In the MONOI study, at Week 96, osteoporosis was observed in 12% of patients and osteopenia in 37%, with no difference between the treatment groups. Compared to abacavir exposure, current exposure to tenofovir was associated with a higher risk of a smaller T-score or Z-score in total hip but not in lumbar spine (p = 0.009).

Interestingly, in the Monarch study an increase in lumbar and femur BMD was observed after discontinuation of tenofovir/emtricitabine in the monotherapy arm; the change in lumbar BMD was significantly more pronounced in the monotherapy arm compared to the triple-therapy (p = 0.029). Importantly however, more patients in the monotherapy arm were taking tenofovir at baseline (n =14 vs. 9).

## Lipid elevations

Six trials had information relating to total cholesterol, LDL cholesterol, and HDL cholesterol (Table 3). A statistically significant within-group change from baseline to Week 96 was observed for total cholesterol, HDL cholesterol, and LDL cholesterol for both treatment groups in the Abbott 613 study. In the KRETA study a significant increase was observed in HDL cholesterol fat both 48 weeks (p = 0.03) and 96 weeks (p = 0.01) in the monotherapy arm; this increase drove a statistically significant reduction in the total cholesterol/HDL cholesterol ratio at weeks 48 and 96 (p = 0.002 and p = 0.007, respectively). No statistically significant intra-group changes were observed in the triple-therapy arm. In the MONOI study no significant changes were observed within treatment groups with regard to total cholesterol, HDL cholesterol, and LDL cholesterol.

Regarding differences between treatment groups, fasting total cholesterol increased significantly more in the PI/r monotherapy arm than the triple-therapy arm in the Kalesolo and Monarch trials (Table 3). Additionally,

**Table 2. Median changes (interquartile range) from baseline in bone mineral density by treatment arm**

| Trial | Median change (IQR) at Week 48 | | p value between arms |
|---|---|---|---|
| | PI/r monotherapy arm | Triple-therapy arm | |
| **Lumbar spine (g/cm$^3$)** | | | |
| Abbott 613* | NA | NA | NA |
| Kalesolo | –0.013 (–0.01, 0.009) | –0.004 (–0.02, 0.009) | NS |
| Monarch | +0.01 (–0.01, 0.04) | 0.00 (–0.01, 0.04) | NS |
| Monark† | –4.4% (–2.1%, –5.1%) | –4.0% (–1.7%, –5.0%) | NS |
| **Neck of femur (g/cm$^3$)** | | | |
| Abbott 613* | NA | NA | NA |
| Kalesolo | –0.001 (–0.01, 0.015) | –0.002 (–0.01, 0.011) | NS |
| Monarch | +0.02 (–0.02, 0.04) | 0.00 (–0.03, 0.02) | 0.03* |
| Monark | NA | NA | NS |
| **Total hip (g/cm$^3$)** | | | |
| Abbott 613*‡ § | –2.5% (–3.4%, –1.4%) | –2.3% (–3.8%, –0.8%) | NS |
| Kalesolo | 0.001 (–0.01, 0.011) | 0.002 (–0.01, 0.011) | NS |
| Monarch¶ | +0.01 (0.00, 0.04) | +0.01 (–0.02, 0.02) | NS |
| Monark† | –3.7% (–0.9%, –5.3%) | –3.1% (–2.4%, –4.9%) | NS |

*Week 96 analysis.
†Percent median change (IQR) from baseline.
‡Percent mean change (95% confidence interval) from baseline.
§Total bone mineral density
¶Body bone mineral density.
IQR: interquartile range; PI/r: protease inhibitor/ritonavir; ns: non-significant; NA: data unavailable.

in the KRETA trial a statistically significant reduction in the total cholesterol/HDL cholesterol ratio (mean difference: 20.91; 95% CI: 21.38, 0.23; p = 0.006) in favor of the monotherapy group was observed. No significant intra-group changes were observed among lipid parameters in the Abbott 613, MONOI, or OK-04 studies. In Abbott 613 more patients in the monotherapy group experienced grade 3 or 4 cholesterol abnormalities (> 7.8 mmol/l) through to week 96, but this difference was not significant (13 vs. 4%; p = 0.145). In the MONOI study only one participant (in the triple-therapy group) experienced a grade 3/4 cholesterol event, and similarly, there was no significant difference in patients experiencing grade 3/4 cholesterol events in the OK-04 study.

In the MONET trial, at Week 96, the number of people with sustained elevations in total cholesterol was six in the monotherapy arm and three in the triple-therapy arm; furthermore, there was a trend for a rise in total cholesterol early in the trial in the monotherapy arm in patients who stopped taking tenofovir (0.5 mmol/l)[21]. In those that switched to tenofovir in the triple-therapy arm, there was a corresponding fall in total cholesterol.

## Renal toxicity

In the Kalesolo study, the only trial that detailed creatinine clearance, the rate of clearance did not differ between treatment groups and no patients experienced a creatinine clearance < 30 ml/min during follow-up. In this trial two patients discontinued treatment for altered renal function; both patients were in the triple-therapy arm.

The 96-week analysis of the MONET trial provides detailed data comparing renal toxicity between the two regimens. In the triple-therapy arm 70 patients received tenofovir; the remaining 59 patients in the triple-therapy arm, and all the 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 versus those not using tenofovir (45 vs. 33%; p = 0.0297, adjusting for gender). Glucosuria and proteinuria was also more common for tenofovir-treated patients versus those not taking tenofovir (11.7 vs. 5.4%; p = 0.054 and 5.4 vs. 4.6%; p = 0.060, respectively). There were 12 reports of Grade 1-4 hematuria as a clinical adverse event in the triple-therapy arm: eight of these patients

**Table 3. Median changes (interquartile range) from baseline in cholesterol by treatment arm**

| Trial | Median change (IQR) at Week 48 | | p value between arms |
|---|---|---|---|
| | PI/r monotherapy arm | Triple-therapy arm | |
| **LDL cholesterol (mg/gl)** | | | |
| Abbott 613*† | +32.0 (±3.9) | +20.1 (±6.2) | NS |
| Kalesolo | NA | NA | NS |
| KRETA‡ | +0.3 (±30.4) | +16.6 (±41) | NS |
| Monarch | +14 | +5 | Sig |
| MONOI | +7 (–23, +22) | +2 (–26, +25) | NS |
| OK-04 | NA | NA | NS |
| **HDL cholesterol (mg/dl)** | | | |
| Abbott 613*† | +13.9 (±1.5) | +15.1 (±2.3) | NS |
| Kalesolo | NA | NA | NS |
| KRETA‡ | 5 (±10.5) | –0.6 (±19.2) | NS |
| Monarch | NA | NA | NA |
| MONOI | 0 (–5, +6) | –1 (–6, +8) | NS |
| OK-04 | NA | NA | NS |
| **Total cholesterol (mg/dl)** | | | |
| Abbott 613*† | +57.2 (±6.2) | +42.1 (±8.9) | NS |
| Kalesolo | +16.2 | +3.1 | 0.04* |
| KRETA‡ | –7 (±36) | 10.2 (±46) | NS |
| Monarch | +26 | +7 | Sig |
| MONOI | +6 (–15, +30) | +3 (–23, +17) | NS |
| OK-04 | NA | NA | NS |

*Week 96 analysis.
†Mean (±SE).
‡Mean (±SD).
IQR: interquartile range; PI/r: protease inhibitor/ritonavir; NS: non-significant; Sig: significant but value unavailable; NA: data unavailable; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

were receiving tenofovir and six cases were classified as Grade 3 (severe). There were four cases of Grade 1-4 hematuria in the darunavir/ritonavir monotherapy arm, of which one was Grade 3: this patient had stopped taking tenofovir at the baseline visit. Clinical diagnosis of hematuria was significantly more common for patients taking tenofovir (p = 0.03).

## Other adverse events

Discontinuation of treatment for adverse events by Week 48 was documented for both arms in six trials (Fig. 3). There was no significant difference between the two treatment arms in all trials except in KRETA where discontinuation was statistically more frequent in the monotherapy arm group (8 [18%] vs. 2 [5%]; p = 0.044). In the overall meta-analysis there was no difference in discontinuation for adverse events between the monotherapy and triple-therapy arms (RD: 0%; 95% CI: –0.03%, +0.03%). The reasons for discontinuation in the monotherapy arms of all trials (except MONET) were hypertriglyceridemia (n = 5), gastrointestinal toxicity (n = 2), central nervous system disorders (n = 2), lipodystrophy (n = 1), hyperglycemia (n = 1), and dyslipidemia (n = 1). In the triple-therapy arm the reasons for discontinuation were diarrhea (n = 3), lipodystrophy (n = 2), hypertriglyceridemia (n = 2), liver toxicity (n = 2), altered renal function (n = 2), asthenia (n = 1), and insomnia (n = 1). Details of discontinuation for adverse events were not given in the MONET trial, but in this trial the majority of patients discontinued for gastrointestinal adverse events.

In the KRETA trial discontinuations for adverse events were significantly higher in the monotherapy arm at Week 96 (p = 0.047), but there was no difference between the two treatment arms for either serious adverse events or drug-related adverse events. Similarly, there was no difference between arms in Grade 3 to 4 clinical events or laboratory abnormalities in the MONOI, Abbott 613, and Kalesolo trials.

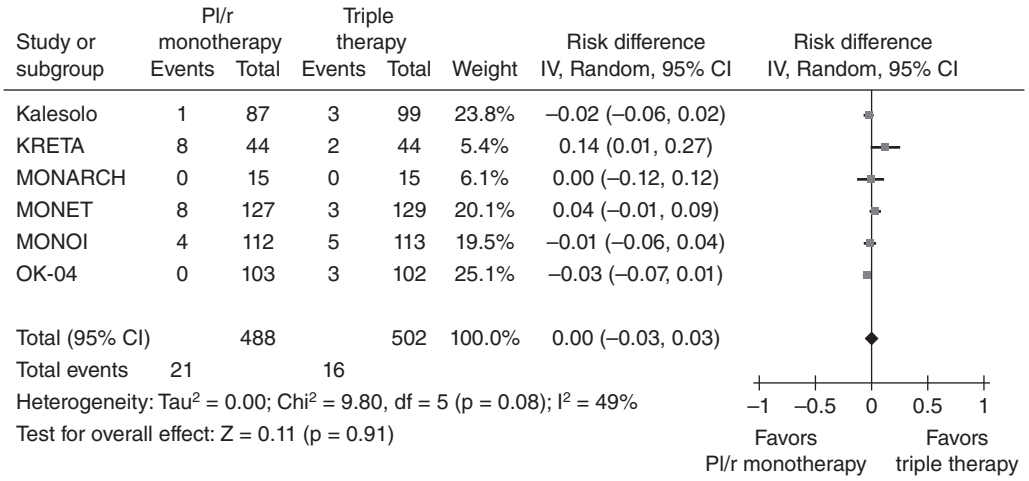


**Figure 3.** *Forest plot of comparison: Patients discontinuing treatment for adverse events by treatment arm. PI/r: ritonavir boosted protease inhibitor.*

## Conclusions

Randomized trials of PI monotherapy versus triple therapy allow assessment of the independent effects of nucleoside analogues on a range of adverse events. In this meta-analysis of eight randomized trials, there was a significantly lower risk of lipoatrophy for patients treated with PI monotherapy compared to triple therapy including two nucleoside analogues. There was no difference in trunk fat or lipohypertrophy between the PI monotherapy and triple-therapy arms. In the majority of studies, changes in BMD did not differ significantly between PI monotherapy and triple therapy. Low BMD has been previously associated with PI use[22], but the results of this review indicate that PI monotherapy does not adversely affect the BMD profile[22]. Similarly, in the majority of studies there was no difference in changes in cholesterol measures. In the MONET and MONARCH studies, switching to a PI/r monotherapy led to increased cholesterol levels. Tenofovir is known to have a lipid-lowering effect, and this difference is likely to have been driven by changes in tenofovir usage; tenofovir was discontinued at baseline in most of the patients simplified to darunavir/ritonavir in the MONET study[20] and all of the patients simplified to darunavir/ritonavir in the MONARCH study[23]. Data from the MONET analysis indicates that PI/r monotherapy can lead to a reduction in renal toxicity and could therefore be beneficial for patients experiencing tenofovir-related renal toxicity[24]. Overall, there were no significant differences between PI monotherapy and triple therapy in the risk of discontinuation for adverse events.

There are four main limitations to this meta-analysis. Firstly, in the six trials included in the meta-analysis with DXA measurements, 471/821 randomized patients (57%) were tested for changes in body shape by DXA: the subset who were sampled at baseline and at the end of the trial may not be representative of the overall population of randomized patients. Secondly, only four trials included estimates of the percentage of patients with lipoatrophy or lipohypertrophy. Thirdly, the control arm was zidovudine/lamivudine in two of the trials. This combination is now rarely used in Europe, given the evidence for improved tolerability and a lower risk of lipoatrophy when using tenofovir/emtricitabine or abacavir/lamivudine[25-27]. In the MONOI trial there was a statistically significant difference in lipoatrophy between the PI monotherapy and triple-therapy arms, despite only 21% of patients in the triple therapy arm using zidovudine/lamivudine. However, in the KRETA trial this difference was not found when lopinavir/ritonavir monotherapy was compared to lopinavir/ritonavir plus abacavir and lamivudine.

Finally, the meta-analysis included trials of both first-line treatment and maintenance treatment with PI monotherapy. Whilst most of the tests for heterogeneity of treatment effect did not show differences between the trials, the tests for lipoatrophy presented an $I^2$ value indicative of significant heterogeneity between the studies.

Boosted-PI monotherapy is not recommended for treatment of antiretroviral-naive patients due to its lower efficacy compared with triple-drug HAART[9,18]. However, some antiretroviral treatment guidelines[28-30] include an option for switching patients to PI monotherapy when they have full HIV RNA suppression on triple combination treatment, based on the more favorable results from switching studies[6-8]. Consequently, an important question for clinicians is whether using PI monotherapy for maintenance of viral suppression could be associated with a lower risk of limb fat, BMD, and lipid changes than triple-drug HAART. This meta-analysis shows that boosted-PI monotherapy is associated with larger limb fat increases than triple-drug HAART including zidovudine. However, since only one trial (KRETA) had a comparator arm including only non-thymidine nucleoside analogues (abacavir plus lamivudine), this meta-analysis cannot answer the question of whether boosted-PI monotherapy compared to triple-drug HAART containing abacavir/lamivudine or tenofovir/emtricitabine is more beneficial with regard to limb-fat changes. Additionally, PI monotherapy could provide a beneficial profile in terms of renal toxicities and could be a possible strategy for patients with tenofovir-related toxicities. The removal of the nucleoside analogue backbone does not seem to have a significant impact on cholesterol levels and BMD, but long-term data are required to confirm the findings of this analysis. In addition, these analyses should be repeated for other nucleoside analogue-sparing strategies, such as dual combinations of PIs with integrase inhibitors.

The role of PI monotherapy in future treatment may be highly restricted. The PI monotherapy has shown significantly lower efficacy than triple therapy in studies of patients who failed prior treatment with detectable viremia at baseline[31,32]. In studies of people with undetectable HIV RNA levels switching to PI monotherapy, predictors of virological failure include low CD4 nadir, coinfection with hepatitis C and poor adherence[33-35]. The subset of people who are highly adherent to treatment, with high nadir CD4 counts (> 200 cells/ul) and who have not failed virologically in the past could therefore be considered as candidates for PI monotherapy, but patients should be regularly monitored for HIV RNA, to detect elevations as early as possible.

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