

The Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy (PIVOT) trial: a randomised controlled trial of a protease inhibitor monotherapy strategy for long-term management of human immunodeficiency virus infection

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Scientific summary

The PIVOT trial

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Scientific summary

Background

Standard-of-care antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection uses a combination of drugs, an approach until now considered essential to minimise treatment failure and development of drug resistance. The 2013 British HIV Association (BHIVA) treatment guidelines recommend that an initial treatment regimen should contain two nucleoside reverse transcriptase inhibitors (NRTIs) together with a non-NRTI (NNRTI) drug (efavirenz), a ritonavir-boosted protease inhibitor (PI) [atazanavir or darunavir (DRV)] or an integrase strand-transfer inhibitor (raltegravir). In practice, the most commonly used third drug (on the backbone of two NRTIs) prescribed in the UK has been efavirenz.

Protease inhibitors have very high antiviral activity, have the highest genetic barrier to resistance of all HIV drugs and are the only drugs that act at multiple steps of the HIV lifecycle, thus giving them the potential to be used alone as monotherapy. A randomised controlled trial that examined the use of PI monotherapy in treatment-naïve patients showed clearly inferior performance with the generation of substantial drug resistance. However, several other trials in which patients switched to PI monotherapy after achieving full viral load (VL) suppression have produced more encouraging results, in some cases demonstrating non-inferiority compared with standard-of-care (for a primary outcome of short-term VL suppression). However, these trials have used a single protocol-specified PI, lopinavir/ritonavir or DRV/ritonavir, usually mandated for both the monotherapy and the standard-of-care group (thus not resembling standard practice in the UK). Furthermore, the trials have been based on a primary end point of short-term VL suppression (usually at 48 weeks), whereas it is the preservation of adequate future treatment options and the minimisation of toxicity that really matter in long-term HIV care. Although data supporting longer-term meaningful outcomes are limited, PI monotherapy is being increasingly used in clinical practice in the UK and in some European countries.

Objective

To compare the effectiveness, toxicity profile and cost-effectiveness of PI monotherapy with those of standard-of-care triple therapy in a pragmatic long-term clinical trial based in routine clinical care.

Design

Open-label, parallel-group, randomised controlled trial.

Setting

Forty-three HIV clinical centres in the UK NHS with wide geographical representation and including diverse patient populations (14 centres in London, 29 outside London).

Participants

The trial enrolled HIV-positive adults aged > 18 years who had been on ART consisting of two NRTIs and one NNRTI or a PI for at least 24 weeks with no change in the previous 12 weeks and who had a VL of < 50 copies/ml at, and for at least 24 weeks before, screening. The main exclusion criteria were known major PI resistance mutation(s) on previous resistance testing; previous ART change for unsatisfactory virological response; concomitant medication with PI interactions; and central nervous system disease, cardiovascular disease or diabetes.

Interventions

Participants were randomised to maintain ongoing triple therapy (OT) or switch to a strategy of physician-selected ritonavir-boosted PI monotherapy (PI-mono) with prompt return to combination therapy (reintroduction of NRTIs, switch of PI to NNRTI discretionary) in the event of VL rebound (defined as three consecutive tests at > 50 copies/ml, including one repeat on the first sample if available). VL was monitored every 12 weeks.

Protease inhibitor substitution was allowed for toxicity or convenience.

Main outcome measures

The primary outcome was loss of future drug options, defined as new intermediate-/high-level resistance to one or more drugs to which the patient's virus was considered to be sensitive at trial entry (non-inferiority comparison, 10% margin). The primary analysis included all resistance mutations detected, whereas a predefined sensitivity analysis excluded resistance mutations that were detected to classes of drugs that the patient was not receiving during the trial (and which likely were archived mutations). Secondary outcomes included confirmed VL rebound, serious drug- or disease-related complications, total grade 3 or 4 adverse events (AEs), neurocognitive function change (using a standardised test battery assessing five neurocognitive domains), cluster of differentiation 4 (CD4) cell count change, change in health-related quality of life, cardiovascular risk change, health-care costs and health economic analysis.

Results

In total, 587 participants were randomised (77% male, 68% white) to OT ($n = 291$) or PI-mono ($n = 296$) and followed for a median of 44 months, of whom 2.7% withdrew/were lost to follow-up. One or more episodes of confirmed VL rebound were observed in eight patients (Kaplan–Meier estimate 3.2%) in the OT group and 95 patients (35.0%) in the PI-mono group [absolute risk difference 31.8%, 95% confidence interval (CI) 24.6% to 39.0%; $p < 0.001$]. PI-mono patients who changed to combination ART after VL rebound all resuppressed (median 3.5 weeks). The proportions of participants with loss of a future drug option at 3 years were 0.7% in the OT group and 2.1% in the PI-mono group [difference 1.4% (95% CI -0.4% to 3.4%); non-inferiority demonstrated]. In the prespecified sensitivity analysis, in which mutations that were likely archived were excluded, the proportions of patients with loss of a future drug option at the end of trial follow-up were 1.5% in the OT group and 1.0% in the PI-mono group [difference -0.4% (95% CI -2.1% to 1.4%); non-inferiority also demonstrated]. Only one participant in the PI-mono group developed resistance to the PI that they were taking: a participant taking atazanavir monotherapy who developed the I50L mutation, predicted to confer high-level resistance to atazanavir.

There were no significant differences in serious drug- or disease-related complications between the groups. Although there were more deaths in the PI-mono group (six vs. one), these were of diverse aetiology, often with clear non-HIV-related risk factors present, and the numerical difference was not statistically significant. The numbers of serious adverse events and clinical grade 3 and 4 AEs did not differ between the groups, but there were fewer total grade 3 or 4 AEs in the PI-mono group, the difference reflecting fewer laboratory events. Fewer patients in the PI-mono group experienced an estimated glomerular filtration rate below 60 ml/minute/1.73 m² during follow-up (10% OT group vs. 5% PI-mono group; difference -4.6%, 95% CI -8.8% to -0.4%; $p = 0.033$). There were no differences between the groups in the proportions of patients with symptomatic peripheral neuropathy, facial lipoatrophy or abdominal fat accumulation or in the summary scores for neurocognitive function, cardiovascular disease risk or quality of life or in the mean CD4 cell count change.

Overall, the PI-mono strategy was shown to be cost-effective compared with OT under most scenarios explored. The PI-mono strategy was cost saving because of large savings in ART drug costs while being no less effective in terms of quality-adjusted life-years in the within-trial analysis and only marginally less effective with modelling.

Conclusions

Protease inhibitor monotherapy, with regular VL monitoring and prompt reintroduction of combination therapy for VL rebound, was non-inferior to combination therapy in preserving future treatment options and is an acceptable and cost-effective alternative for long-term management of HIV infection.

Trial registration

This trial is registered as ISRCTN04857074.

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