HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review

Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA

CRD summary
This review concluded that the overall efficacy of ritonavir-boosted protease inhibitor monotherapy was inferior to highly active antiretroviral therapy in HIV treatment. Efficacy improved in patients started on monotherapy after HIV-RNA suppression for at least six months. These conclusions reflected the results of the review, but the uncertain quality of included studies mean they should be interpreted with caution.

Authors' objectives
To assess the efficacy of ritonavir-boosted protease inhibitor monotherapy in the treatment of HIV.

Searching
MEDLINE, EMBASE (both from 1982 to May 2008) and the Cochrane Database of Systematic Reviews were searched; search terms were reported. Abstracts from three relevant international conferences were also reviewed. Experts in the field were contacted. Only studies that had been published in a peer-reviewed journal or presented at a conference were eligible for inclusion in the review.

Study selection
All studies of ritonavir-boosted protease inhibitor monotherapy for HIV were eligible for inclusion.

The primary outcome assessed was HIV-ribonucleic acid (RNA) suppression. Therapy failure was defined as an HIV-RNA level of more than 50 copies/mL at study end using intention-to-treat data. Intention-to-treat was defined as including all patients receiving at least one dose of study medication.

Included studies assessed ritonavir monotherapy boosted with atazanavir, indinavir, lopinavir and saquinavir. Studies of both suppressed and unsuppressed HIV-RNA patients were included. Where applicable, the comparator was highly active antiretroviral therapy. Baseline viral load, whether patients were already on protease inhibitor monotherapy varied considerably.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted to permit the calculation of odds ratios (OR) with 95% confidence intervals (CI) for intention-to-treat and as-treated populations. Patients discontinuing treatment for reasons other than virological failure were not included in the as-treated population. Studies were categorised as being in suppressed HIV-RNA patients or in patients with unsuppressed HIV-RNA.

The authors did not state how many reviewer performed the data extraction.

Methods of synthesis
All trial data were combined in a meta-analysis using in a fixed-effect model; if significant statistical heterogeneity was detected, a random-effects model was adopted. Pooled odds ratios with 95% confidence intervals were calculated.

Separate analyses were used for trials in suppressed and unsuppressed HIV-RNA patients.

Randomised controlled trials (RCTs) were also analysed in a separate meta-analysis.
Results of the review
Twenty-two studies were included in the review. Sixteen studies were classed as prospective trials (including six RCTs). Fourteen studies were in patients with suppressed HIV-RNA. Eight studies were in patients with unsuppressed HIV-RNA. Duration of follow-up varied considerably.

The analysis of intention-to-treat data from the RCTs showed a statistically significantly greater rate of therapy failure in those treated with ritonavir-boosted protease inhibitor monotherapy compared with those treated with highly active antiretroviral therapy (OR 1.48, 95% CI: 1.02 to 2.13, 6 RCTs). The as-treated analysis showed similar trends.

At the end of follow-up, the percentage of patients with undetectable HIV-RNA ranged from 33.3 to 90.0%; overall 67.9% patients had undetectable HIV-RNA based on the intention-to-treat analysis, with similar proportions reported for patients with suppressed and unsuppressed HIV-RNA at trial inception. Results of the as-treated analysis were also reported.

Fifty-eight of 570 patients experienced treatment failure; 10 of these patients had virological failure, experiencing major protease inhibitor mutations.

Authors’ conclusions
The overall efficacy of ritonavir-boosted protease inhibitor monotherapy was inferior to that of highly active antiretroviral therapy. Efficacy improved in patients started on monotherapy after HIV-RNA suppression for at least six months. Ten percent of patients experience viral rebound, with HIV-RNA levels between 50 and 500 copies/mL.

CRD commentary
The review question was clear, although only some of the inclusion criteria were specified. The authors searched three relevant databases and other additional sources. However the requirement for studies to be published in peer-reviewed journals or be presented at conferences may have increased the chances of publication bias. The authors did not report using methods to reduce reviewer bias and error at any stage of the review process.

The authors did not report whether they assessed study quality; the lack of a validity assessment made it difficult to determine the strength of the evidence contributed by the included studies. It was appropriate to conduct a separate analysis of the RCTs; it was not clear how informative the overall analysis of all trials was likely to be.

The authors’ conclusions reflected the results of the review and may be reliable, but the uncertain quality of the included studies means that they should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that the majority of patients with prolonged viral suppression on highly active antiretroviral therapy can successfully be treated with protease inhibitor monotherapy.

Research: The authors did not state any implications for further research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.