Meta-analysis of prophylactic treatments against Pneumocystis carinii pneumonia and toxoplasma encephalitis in HIV-infected patients

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Authors' objectives
To examine the efficacy of prophylactic treatments for Pneumocystis (P.) carinii pneumonia and toxoplasma encephalitis in patients with HIV infections in reducing opportunistic infections and mortality.

Searching
MEDLINE, AIDSLINE, AIDSTRIALS and AIDSDRUGS were searched, as were the Proceedings of the International and European Conferences on AIDS. Bibliographies of identified trials were screened and experts in the field contacted.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials were included; trials comparing any prophylactic regimen with placebo were excluded.

Specific interventions included in the review
Aerosolised pentamidine, trimethoprim-sulfamethoxazole, dapsone or dapsone/pyrimethamine.

Participants included in the review
HIV-infected patients were included.

Outcomes assessed in the review
The end points considered for analysis were opportunistic infections with P. carinii pneumonia, toxoplasma encephalitis or both, death and drug-limiting toxicity requiring the change to another prophylactic treatment.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of the trials was rated with a quality score ranging from 0 (lowest) to 1 (highest) based on the assessment of 30 characteristics of the study design, randomisation, blinding, statistical analysis and reporting of the study results. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. However, it is reported that when specific information on baseline characteristics, duration of follow up or outcomes was missing, the authors of the primary studies were contacted for additional information.

Methods of synthesis
How were the studies combined?
Risk ratios were calculated for three pairs of comparisons: trimethoprim-sulfamethoxazole with aerosolised pentamidine, dapsone/pyrimethamine or dapsone with aerosolised pentamidine and trimethoprim-sulfamethoxazole.
with dapsone or dapsone/pyrimethoamine. Summary estimates with 95% confidence intervals (CI) for risk ratios were calculated using a random-effects method and two-tailed p values were reported. Summary incidence rate ratios for progression to any end point, using events by patient-years of follow-up, were also calculated but not reported as the results were similar to single counts of events.

How were differences between studies investigated?
Subgroup analyses were conducted to examine outcomes in relation to duration of follow-up and severity of HIV infection. In addition, dose relations for efficacy and drug-limiting toxicity were also examined. An average effect size for each subgroup was calculated.

Results of the review
A total of 22 randomised controlled trials (RCTs) (n=4870) were included in the review.

8 compared trimethoprim-sulfamethoxazole with aerosolised pentamidine and 1 compared trimethoprim-sulfamethoxazole with aerosolised pentamidine/pyrimethamine.

5 compared dapsone/pyrimethamine or dapsone with aerosolized pentamidine.

4 trials included three treatment arms; 3 compared either dapsone or dapsone/pyrimethamine with trimethoprim-sulfamethoxazole and aerosolised pentamidine, and 1 trial compared dapsone/pyrimethamine with trimethoprim-sulfamethoxazole and aerosolised pentamidine/pyrimethamine.

4 trials compared trimethoprim-sulfamethoxazole with dapsone/pyrimethamine.

The mean quality score for all studies was 0.56 (range, 0.27, 0.78).

For dapsone/pyrimethamine versus aerosolised pentamidine, the risk ratio for P. carinii pneumonia was 0.90 (95% CI, 0.71, 1.15) and for toxoplasma encephalitis it was 0.72 (95% CI, 0.54, 0.97). The risk ratio for mortality was not reported.

For trimethoprim-sulfamethoxazole versus aerosolised pentamidine, the risk ratio for P. carinii pneumonia was 0.59 (95% CI, 0.45, 0.76) and for toxoplasma encephalitis it was 0.78 (95% CI, 0.55, 1.11). For mortality it was 0.88 (95% CI, 0.74-1.06).

For trimethoprim-sulfamethoxazole versus dapsone/pyrimethamine, the risk ratio for P. carinii pneumonia was 0.49 (95% CI, 0.26, 0.92) and for toxoplasma encephalitis it was 1.17 (95% CI, 0.68, 2.04). The risk ratio for mortality was 0.98 (95% CI, 0.80, 1.08).

Authors' conclusions
Although current evidence does not allow a definitive recommendation, administration of trimethoprim-sulfamethoxazole for prophylaxis of P. carinii pneumonia and toxoplasmosis in HIV-infected patients is consistent with available data.

CRD commentary
The objective of the review is clear, as are the inclusion criteria. The literature search is thorough, although no time period or keywords are reported. Further details of the processes by which the data were extracted and relevance and quality were assessed may have enhanced the review. The data analysis is methodologically sound and well-discussed.

Implications of the review for practice and research
The authors state that this meta-analysis highlights the need for additional research in optimising prophylactic regimens. Investigators in subsequent trials should directly address issues of quality of life and consider studying the benefits of staged regimens.
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Other publications of related interest

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Record Status
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.