Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials

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CRD summary
This review compared directly observed antiretroviral therapy with self administered treatment in patients with human immunodeficiency virus (HIV) infection. The authors concluded that there was no difference between the two interventions on viral suppression or overall adherence to treatment. This was a well-conducted review, but the poor quality of included trials means a cautious interpretation of the conclusion is warranted.

Authors’ objectives
To evaluate directly observed highly active antiretroviral therapy compared with self administered antiretroviral treatment in patients with human immunodeficiency virus (HIV) infection.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PsycINFO, LILACS, Current Controlled Trials and ClinicalTrials.gov were searched from inception to July 2009. In addition, websites of all conferences of the International AIDS Society (April 1985 to July 2009) and on Retroviruses and Opportunistic Infections (January 1997 to February 2009) were scanned for further articles of interest. Search terms were reported. Handsearching of abstracts from the International Conference on HIV Treatment Adherence (International Association of Physicians in AIDS Care, March 2006 to April 2009) was also carried out. The following lay publications and websites were searched between March and July 2009: The Body, Canadian AIDS Treatment Information Exchange publications, AIDS Treatment News, Google Scholar, and the Networked Digital Library of Theses and Dissertations. Bibliographies of relevant papers were scanned, and contacts were made with specialists and study authors. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) assessing directly observed therapy (the supervised swallowing of highly active antiretroviral therapy pills) to promote treatment adherence within any adult population or setting, were eligible for inclusion in the review. The primary outcome of interest was viral suppression (viral load) at trial endpoint. Secondary outcomes of interest were self-reported adherence, immunological progression (CD4 T-cells per mm), loss to follow-up, all-cause mortality, development of resistance mutations, and new or recurrent AIDS(acquired immune deficiency syndrome) defining illnesses.

The majority of included trials adopted partial direct observed therapy and all used self-administered treatment in the control group. There was variation in the measurement of viral load (range: less than 50 copies per mL to less than 400 copies per mL). The observers were health workers, community and peer supporters. Over half of the included trials involved more than 50% of men; the mean age across all trials (where reported) ranged from 33 to 47 years. Trials were conducted in the USA and/or Africa, with a duration of between six weeks and 24 months.

Two independent reviewers selected trials for inclusion in the review. Disagreements were resolved by consensus involving three reviewers, or by arbitration involving a fourth person.

Assessment of study quality
Trial quality was assessed on aspects of randomisation, adjustment of confounders, allocation concealment, blinding, objectivity of outcome measures, use of intention-to-treat analysis, and whether there was less than 20% loss to follow-up.

Two reviewers performed the quality assessment, and disagreements were resolved by involving a third reviewer.
Data extraction
Data were extracted on numbers of events to enable the calculation of relative risks (RR) and 95% confidence intervals (CI). Intention-to-treat data were used where possible, and the Haldane method of adding 0.5 to each trial group was applied in the case of zero events. Median (range) data were transformed to mean (plus standard deviation) data for changes in CD4 T-cell count. The weighted mean difference (WMD) was calculated for this outcome, using inverse variance weighting. Trial authors provided additional data for six papers that were reported as abstracts.

Two independent reviewers extracted the data.

Methods of synthesis
Relative risks and 95% confidence intervals were pooled in random-effects meta-analysis (DerSimonian and Laird). A method of weighting was used, but details were not reported. Heterogeneity was assessed using the $I^2$ statistic. A univariate sensitivity analysis was carried out for the primary outcome (using the $X^2$ test) to assess the effect of the following trial variables: groups at high risk of non-adherence versus the general population; intervention type (full versus partial directly observed therapy); allocation concealment, trial location, previous treatment experience, and trial duration (up to six months versus over six months). Trial results for secondary outcomes were presented in a table, and discussed in the text.

Results of the review
Twelve RCTs (n=2,255 patients) were included in the review. Sample sizes ranged from 43 to 500 patients. Quality assessment was possible in seven trials. Six trials reported the randomisation method, three trials reported allocation concealment, none were blinded, and four trial were based on intention-to-treat data. Five trials reported less than 20% of patients lost to follow-up. Follow-up (where reported) ranged from three to 24 months.

There was no statistically significant difference between intervention and control groups for viral suppression at study completion (10 RCTs, n= 1,862). This result was unaffected in sensitivity analysis, and similar mean event rates were recorded between groups. There was moderate heterogeneity ($I^2=53.8\%$).

In further sensitivity analyses, statistically significant increases in viral suppression were reported for patients at high risk of non-adherence (drug users and homeless people) (RR 1.31, 95% CI 1.00 to 1.71; $I^2=27.6\%$; four trials) and for trials with six months duration or less (RR 1.24, 95% CI 1.03 to 1.50; $I^2=32.5\%$; nine trials). There were no other statistically significant differences.

There were no statistically significant differences between groups on any secondary outcome. Adherence to treatment was high in both groups for directly observed therapy (mean 89%, standard deviation 12.7) and for self-administered treatment (mean 88%, standard deviation 11.6).

Authors' conclusions
There was no additional benefit of directly observed antiretroviral therapy compared with self-administered treatment in patients with HIV infection.

CRD commentary
The review question was clear, and this was supported by potentially reproducible inclusion criteria. The search strategy was extensive in its inclusion of sources for published and unpublished material. This, together with the absence of language restriction, means that efforts were made to minimise the potential for language and publication biases. The quality assessment criteria were appropriate to the included study design, and the review process was conducted with sufficient transparency to indicate the reliability of findings. Trial details were clearly presented. Heterogeneity was assessed and the chosen method of synthesis was appropriate. This was a well-conducted review, but the seemingly poor quality of trials warrants a cautious interpretation of the authors' conclusion.

Implications of the review for practice and research
Practice: The authors stated that widespread use of directly observed therapy in HIV patients is not justified.
Research: The authors stated that future research should investigate the potential for targeted interventions of finite duration for specific groups, and with acceptability for patients in mind. The reporting of differential effects of intervention delivery across various populations and the routine recording of mortality is also recommended.

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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.