Efficacy and tolerability of initial antiretroviral therapy: a systematic review

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CRD summary
This review concluded that many factors influenced antiretroviral therapy (ART) success. Didanosine was an effective option for initial ART, particularly in settings with limited resources. And ART guideline development may benefit from an ongoing systematic review of the evidence. These conclusions are appropriate in view of the limited duration and reporting of safety data in included studies.

Authors' objectives
To assess factors contributing to the efficacy and tolerability of initial antiretroviral therapy (ART) in patients with human immunodeficiency virus (HIV).

Searching
PubMed, Current Controlled Trials and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to December 2007. Websites for conferences of three relevant societies/meetings were searched for 2006 and 2007. Studies cited in treatment guidelines, drug labels, documents issued by the Food and Drug Administration, relevant meta-analyses and reviews and in study protocols were checked. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) and prospective cohort studies with a minimum duration of 24 weeks and that presented data for each regimen separately and assessed at least one ART regimen recommended in key guidelines published up to December 2007 were eligible for inclusion. Studies were required to conduct an intention-to-treat (ITT) analysis and to specify the type of analysis conducted. Studies of children and of primary HIV infection were excluded. Also excluded were studies that: evaluated only dual nucleoside analogue reverse transcriptase inhibitors (NRTIs); evaluated four drug regimens; assessed protease inhibitor only therapy; assessed alternating regimens; assessed more than one-third drug; and in which therapy was directly observed.

The primary outcome was the proportion of patients with undetectable plasma HIV viral load. Other outcomes were proportions of patients who ceased assigned therapy for adverse events, patient choice, loss to follow-up, virological failure or other reasons and various grade 2 or higher specified adverse events and combined adverse event incidence.

More than half of the studies were placebo controlled. Patients in included studies had a mean age of 36 years, 26% were female and 36% were nonwhites. The mean CD4 cell count was 286 cells/μl. The average number of pills prescribed per day was 8.1 over an average of 2.2 doses. Only 12.5% of patients were from Africa or Asia.

The authors did not state how papers were selected for the review.

Assessment of study quality
The studies were assessed for validity using criteria of description of the study as randomised and type of ITT analysis. The authors stated that blinding was not assessed; however, use of placebo control was included in the assessment. Study funding was noted and was assumed to be provided by a manufacturer unless stated otherwise.

One reviewer performed the validity assessment.

Data extraction
Data were extracted on the regimens employed and study inclusion criteria. Where a study evaluated both eligible and ineligible treatment groups, only data from eligible groups were considered. Data on treatment outcomes were extracted.

Data extraction was carried out by one author using two identical databases that were compared and discrepancies
resolved through comparison with the primary study report. Study authors and sponsors were contacted for further information.

Methods of synthesis
Multivariable regression analysis that incorporated all variables for which p<0.05 in univariate analysis was conducted. No imputations for missing data were conducted; only records with no missing data were included in the multivariable analysis. Heterogeneity was assessed using the F-test and Wald test.

Sensitivity analyses of RCTs only, published studies only and studies that reported week 48 outcome data only were conducted. Pearson's correlation weighted by study sizes was used to determine the association between treatment cessation and adverse events; no adjustments were made for multiple comparisons. Publication bias was assessed using funnel plot analysis.

Results of the review
Seventy-nine studies were included in the review: 64 RCTs and 15 cohort studies. There were 23,067 patients in 143 treatment groups. Mean follow-up was 14.3 months.

Efficacy: Treatment-related variables that were independently associated with higher treatment success were dosing relative to food (p=0.001), dual nucleoside backbone (favoured didanosine or tenofovir with emtricitabine or lamivudine) (p=0.002) and nonnucleoside analogue or ritonavir-boosted protease inhibitor as the third drug (p<0.0001).

Three factors related to population characteristics (nonwhites, exclusion for low haemoglobin, lower CD4 cell count) and shorter duration of follow-up were independently associated with higher treatment success. The model accounted for 79% of variability in rates of treatment success. Results of sensitivity analyses were similar to those of the primary analysis.

Tolerability: Adverse events were the most common reason for treatment cessation (9%), but were reported in only half of the included studies. The most common adverse events were diarrhoea (29%), nausea (25%), headache (18%), rash (15%) and fatigue (13%). Grade 2 or higher adverse events occurred in 21% of participants. The only adverse event significantly associated with lower efficacy was nausea (p=0.028).

There was no evidence of publication bias.

Authors' conclusions
Multiple factors influenced ART success in addition to the type of third drug; these should be considered in the design of future studies. Didanosine was an effective option for initial ART, particularly in settings with limited resources. ART guideline development may benefit from an ongoing systematic review of the evidence.

CRD commentary
The review question and inclusion criteria were clear. Several relevant databases and other sources were searched, which reduced the chances that relevant studies were omitted. The authors did not report that they used methods designed to reduce reviewer bias and error at any stage of the review process; data extraction was a partial exception. The assessment of study validity was limited and results were poorly reported. The analysis was reasonable and included attempts to assess and explore heterogeneity beyond the variables considered in the regression model.

The authors' conclusions largely related to the need for further research; in view of the short duration of many studies and the poor reporting of adverse effects this was appropriate.

Implications of the review for practice and research
Practice: The authors stated that didanosine was a largely ignored but effective, cheap and widely available option for initial ART with immediate relevance to settings with limited resources.
Research: The authors stated that an ongoing systematic review of all available data associated with ART could improve the development of ART guidelines. They also stated that future ART studies probably needed to have a longer duration and to report more adverse event data.

Funding
No funding.

Bibliographic details
Carr A, Amin J. Efficacy and tolerability of initial antiretroviral therapy: a systematic review. AIDS 2009; 23(3): 343-353

PubMedID
19114855

DOI
10.1097/QAD.0b013e32831db232

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Anti-HIV Agents /adverse effects /therapeutic use; Antiretroviral Therapy, Highly Active; CD4 Lymphocyte Count; Female; HIV Infections /drug therapy /immunology /virology; Humans; Male; Randomized Controlled Trials as Topic; Treatment Outcome; Viral Load

AccessionNumber
12009103246

Date bibliographic record published
07/10/2009

Date abstract record published
11/05/2011

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.