CD4+ guided antiretroviral treatment interruption in HIV infection: a meta-analysis
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CRD summary
This review concluded that antiretroviral treatment interruption in patients with human immunodeficiency virus infection increased the risk of developing AIDS or death, but this is reduced with higher CD4+ values. The risk difference was not statistically significant. Given the limitations with the included studies and potential for bias in the review, the authors’ conclusions should be interpreted with caution.

Authors' objectives
To assess the effects of CD4+ guided antiretroviral treatment interruption in patients with chronic human immunodeficiency virus (HIV) infection on the risk of death or acquired immune deficiency syndrome (AIDS)-defining events.

Searching
PubMed and The Cochrane Library were searched between January 2000 and December 2007 for full publications in English. Search terms were reported. A search of ClinicalTrials.gov was undertaken to identify ongoing and closed clinical trials. Reference lists of retrieved articles were searched manually.

Study selection
Studies that assessed a CD4+ guided interruption of antiretroviral therapy (maintenance of adequate CD4+ cell count during periods off therapy) in patients above 13 years of age with chronic HIV (CD4+ cell count >350 cells/mm$^3$) who were not taking concomitant immunomodulatory drugs were eligible for inclusion. Studies were categorised as randomised controlled trials (RCTs) and cohort studies. Eligible studies were required to have a follow-up duration of more than 100 person years and report the occurrence of AIDS-defining events and/or mortality as the primary outcome. Secondary outcomes of interest were occurrence of HIV-related non AIDS-defining events.

Some of the included studies were multicentre and conducted in Europe, North and South America, Africa, Asia and Australia; other studies were single centre and conducted in Europe, Argentina, Thailand or USA. The threshold to reinitiate therapy ranged from 200 to 400 cells/mm$^3$. Patients with interrupted therapy were compared to patients with continuing antiretroviral therapy. All-cause mortality rates were reported.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Two to three reviewers independently assessed the reporting standards of RCTs using the CONSORT 25-item checklist (which included clear reporting of randomisation, allocation concealment, blinding and statistical methods). Cohort studies were assessed using reporting standards from the STROBE statement. Kappa statistics were calculated to determine inter-rater agreement. Discrepancies were referred to a third reviewer.

Data extraction
Hazard ratios (HRs) or incidence rate ratios (IRRs) (corrected or uncorrected for potential confounders) were extracted to calculate relative risks (RRs) and risk differences (RDs)/absolute risk reduction and 95% confidence intervals (CIs). Studies that reported no events for outcomes were excluded from the meta-analysis. Primary authors were contacted for clarification on data, where necessary.

The authors did not state how many reviewers extracted data.

Methods of synthesis
A random-effects model was used to pool relative risks and risk differences and their 95% CIs. Studies were grouped by design (RCT or cohort study). Re-analysis was performed to correct for the latest CD4+ value, Statistical
heterogeneity was assessed with the $I^2$ statistic and Cochran’s Q test.

A sensibility analysis was carried out that classified deaths of unknown cause as 0, 50% or 100% AIDS-related and 0, 50% or 100% non-AIDS related. Where pooling was not possible, data were presented as a narrative synthesis and in tables.

Publication bias was assessed through visual inspection of a funnel plot.

**Results of the review**

Eighteen studies (n=7,552) were included: seven RCTs and 11 cohort studies. Follow-up rate in the interrupted treatment group ranged from 18 to 3,700 person years and in the control group ranged between 15 and 3,700 person years. Two RCTs clearly defined randomisation methodology; other RCTs provided limited details. Only one cohort study included sufficient efforts to address potential sources of bias. Three studies provided detail about reasons for non-participation. All cohort studies provided sufficient information on the source and methods of participant selection and clearly defined outcomes, exposures and confounders.

**RCTs**: There was a statistically significant increase in risk of AIDS-defining events or death in patients who underwent interrupted treatment compared with patients with continuing therapy (RR 2.50, 95% CI 1.87 to 3.34; three RCTs, $I^2=0\%$) and no statistically significant difference in risk difference (four RCTs, $I^2=91.5\%$). Correction for the latest CD4+ value did not significantly alter the findings.

There was an increased risk of death of any cause in the interrupted treatment group compared to the group with continuing therapy (RR 1.8, 95% CI 1.18 to 2.77, $I^2=0\%$) and a statistically significant risk difference (RD 0.01, 95% CI 0.001 to 0.012, $I^2=2.9\%$). A sensibility analysis was undertaken, but it was not possible to determine whether or not increased mortality was due to AIDS-related causes. Non AIDS-related events were increased in patients who interrupted treatment (23.2 events per 100 person years, 95% CI 20.5 to 26.1) compared with patients who received continuous treatment (11.9 events per 100 person years, 95% CI 9.4 to 14.9). Drug-related side effects were similar between treatment groups.

Publication bias could not be excluded.

The cumulative incidence of deaths or events in the cohort studies were reported in the review.

**Authors’ conclusions**

Antiretroviral treatment interruption in patients with HIV infection increased the risk of death or developing AIDS, but this was reduced with higher CD4+ values. The risk difference was not statistically significant.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. Two electronic databases were searched and limited attempts were made to locate unpublished studies. The search was restricted by language, so language bias may have been introduced. Publication bias was formally assessed and could not be excluded. The quality of reporting in the included studies appeared to be very limited, which suggested that they were not of high quality. The authors did not state how many reviewers extracted data, so reviewer error and bias could not be ruled out. Patient characteristics were not reported and few details on treatment regimens were described, which made it difficult to determine generalisability and whether pooling of the results was appropriate. Only a small number of RCTs were included in the meta-analysis and the findings from the cohort studies were somewhat limited. The influence of higher CD4+ counts to reinitiate therapy formed part of the authors’ conclusions, but as this was only mentioned in the review’s discussion and was not subjected to formal analysis, the reliability of this statement is uncertain.

Given the limitations with the included studies and the pooling of the studies and potential for bias in the review, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was needed to investigate how to initiate and possibly interrupt antiretroviral therapy and take into account influences that affected treatment interruption duration and occurrence of adverse events during treatment interruption.

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