Cytotoxic T-lymphocyte responses to canarypox vector-based HIV vaccines in HIV-seronegative individuals: a meta-analysis of published studies

Edupuganti S, Weber D, Poole C

CRD summary
This review determined overall CD8+ cytotoxic T-lymphocyte (CTL) responses to canarypox vector-based human immunodeficiency virus vaccines. The authors concluded that further studies are required to identify the dose or immunisation schedule to maximise CTL response. Insufficient details of the review methods and the restriction to English language publications make it difficult to comment on the strength of the evidence underpinning the authors’ conclusions.

Authors' objectives
To determine the overall CD8+ cytotoxic T-lymphocyte (CTL) responses to canarypox vector-based human immunodeficiency virus (ALVAC-HIV) vaccines and to explore factors influencing CTL responses.

Searching
MEDLINE (via OVID and PubMed), the Cochrane Controlled Trials Register, BIOSIS Previews, Web of Science and ClinicalTrials.gov were searched from 1966 to August 2004 for reports in English; the search terms were reported. The reference lists of reviews and published clinical trials and bibliographies cited at www.hvtn.gov and www.iavi.org were also checked.

Study selection
Study designs of evaluations included in the review
Inclusion criteria were not specified in terms of the study design. Two studies that did not specify a control group were excluded. All of the included studies were double-blind, placebo-controlled, randomised controlled trials (RCTs).

Specific interventions included in the review
Studies of ALVAC-HIV vaccines were eligible for inclusion. The included studies all used intramuscular injections of vaccines but different ALVAC-HIV constructs, different numbers of immunisations, different vaccine doses, different vaccinations regimens and different vaccination schedules (details were reported). All but two of the included studies used ALVAC-RG with or without HIV-1 rgp120 as control vaccinations; one study used saline, while the other used either saline or ALVAC-RG as the control.

Participants included in the review
Studies of HIV-seronegative volunteers were included. Most of the studies included volunteers with low-risk behaviour for HIV; two studies included people with high- and low-risk HIV behaviour.

Outcomes assessed in the review
Studies reporting CTL responses were eligible for inclusion. The review assessed cumulative CTL responses, defined as a positive CTL response to any of the HIV proteins derived from env, gag, pol or nef at one or more time points during the study. All of the included studies reported CTL responses to env or gag; one study also reported the response to pol and nef.

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

Assessment of study quality
Data on randomisation, blinding and presence of a control group, and percentage loss to follow-up were recorded. The
authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the number of patients who developed cumulative CTL responses to env, gag, pol or nef, and the number lost to follow-up were extracted.

The risk difference (RD) of any CTL response between vaccine and control was calculated, along with its 95% confidence interval (CI), for each study.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a meta-analysis. The pooled RD with 95% CI was calculated, using a random-effects model, for vaccine versus placebo. Publication bias was assessed using a funnel plot and using the tests of Begg and Muzumdar and Egger.

How were differences between studies investigated?
Statistical heterogeneity was assessed using Cochrane’s Q statistic and a forest plot was presented. A stratified random-effects meta-regression was used to explore the influence on the results of the following factors:

- the number of immunisations (4 or more than 4);
- log10 vaccine dose (dose lower than 1E6.42 or higher than 1E6.52); the type of ALVAC-HIV constructs used for immunisation (vCP125, vCP205 and vCP300); the length of follow-up after last vaccination (less than 6 months or more than 6 months);
- vaccine combination (ALVAC-HIV only or ALVAC-HIV plus rgp 120 groups);
- immunisation schedule (monthly or weekly increments);
- control group vaccine (ALVAC-RG boosted with rgp120, ALVAC-RG alone or saline);
- type of volunteers (low risk or high and low risk); and
- the percentage of participants lost to follow-up.

One study in which the vaccine titre fell during the study was classified in the lower dose of vaccine dose group; the meta-analysis was repeated with this study allocated to the higher vaccine dose group. An influence analysis was conducted by repeating the meta-analysis after excluding each study in turn.

**Results of the review**
Eight double-blind, placebo-controlled, RCTs were included in the meta-analysis (n=703). Two studies published as abstracts did not provide adequate detail and were excluded from the meta-analysis.

Vaccination was associated with a 32% absolute increase in the risk of CTL response compared with control (RD 0.32, 95% CI: 0.26, 0.39). No statistically significant heterogeneity was detected (P=0.21). No one study greatly influenced any of the analyses.

The funnel plot was symmetrical and tests also showed little evidence for publication bias (P=0.6 and P=0.8). The meta-regression identified only two factors that were associated with response. Participants given more than four vaccinations had a higher average RD than those given only four vaccinations. Higher doses of vaccine were associated with higher RD. Vaccine dose and number of vaccines were highly associated with each other, but it was
not possible to explore possible confounding because of the small number of studies.

Authors' conclusions
Further studies are required to identify the dose and immunisation schedule that would maximise the CTL response.

CRD commentary
The review stated a clear research question. However, the inclusion criteria were explicit for interventions and outcomes only. Several relevant sources were searched and attempts were made to locate unpublished studies, thus limiting the possibility of publication bias. Appropriate methods were used to assess the presence of publication bias, and no evidence of it was found. No attempts were made to minimise language bias; the restriction to English language studies might have resulted in the loss of some relevant data. The methods used to select the studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Methodological characteristics pertinent to study quality were recorded. The data were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. A meta-regression was used to explore the influence of a number of factors on the results. The evidence presented appeared to show that responses varied considerably between the studies. The authors were unable to determine the regimen associated with the best effect, owing to the small number of studies, and the lack of reporting on the review methods makes it difficult to comment on the strength of the evidence presented. However, the authors' conclusions appear appropriately cautious.

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

Research: The authors stated that more trials are needed to determine what dose or immunisation schedule would elicit the maximum CTL response. They further stated that future meta-analyses of CTL responses should compare ALVAC-HIV only with ALVAC-HIV plus rgp 120 groups to determine the association between rgp120 and CTL responses.

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