Efficacy of inactivated hepatitis a vaccine in HIV-infected patients: a hierarchical Bayesian meta-analysis

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CRD summary
This review measured the response rate to the hepatitis A virus vaccine in human immunodeficiency virus-1 (HIV)-infected patients. The authors concluded that up to half of all HIV-infected patients may be nonresponders. However, given the weaknesses in study methodology, the likelihood of publication bias, and differences between the studies, this result may not be reliable.

Authors' objectives
To measure the response to the hepatitis A virus (HAV) vaccine in human immunodeficiency virus-1 (HIV)-infected patients using Bayesian meta-analysis.

Searching
MEDLINE, the American Association for the Study of Liver Diseases database, and abstracts from Conferences on Retroviruses and Opportunistic Infections (1997 to 2004) were searched for English language papers; the search terms were reported. In addition, recent issues of relevant journals were handsearched.

Study selection
Study designs of evaluations included in the review
Eligible study designs were not specified, with the exception that non-controlled studies were eligible for inclusion.

Specific interventions included in the review
Studies of the HAV vaccine were eligible for inclusion. In the included studies, the vaccine given was mostly Havrix (720 ELISA units at 0, 1 and 6 months, or 1,440 ELISA units up to 12 months apart); one study evaluated VAQTA (dose not provided). In some of the studies the participants were also receiving HIV treatment.

Participants included in the review
Trials that evaluated HIV-infected patients were eligible for inclusion. Non HIV-positive immunocompromised participants were excluded. The studies included mostly or all men with a median age ranging from 21 to 42 years. However, one study included paediatric and adult patients.

Outcomes assessed in the review
The primary outcome was the rate of response to the HAV vaccine. Trials had to report the number or percentage of patients who responded to HAV treatment to be eligible for inclusion. The included studies evaluated the response rate from 4.5 up to 12 months after the first vaccination. Studies used a variety of definitions for response, including development of detectable antibody if absent at baseline, concentration of antibody at a protective level, or four-fold increase in antibody concentration if antibodies measurable at baseline.

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
The authors stated that quality was assessed by how well a study described the vaccine dose and timing, timing of serology follow-up, study population, eligibility criteria, participation rate, covariates and confounders with appropriate techniques for control, and statistical methodology. The authors did not state how many reviewers assessed validity.

Data extraction
One reviewer extracted the data. Data were extracted to enable both intention-to-treat (ITT) and per-protocol (PP) analyses. Response rates and, when available, covariates including CD4+/CD8+ counts, HIV viral load, stage of HIV
disease progression and geometric mean anti-HIV titres were extracted from the studies.

**Methods of synthesis**

How were the studies combined?
A Bayesian hierarchical random-effects model using non informative priors was used to analyse the data. Both ITT and PP meta-analyses were undertaken, with patients lost to follow-up in the ITT analysis assumed to be nonresponders. Gibbs sampling was used for estimation. The Brooks-Gelman-Rubin diagnostic was used to assess convergence of the model. Publication bias was explored using Kendall’s rank correlation and Egger’s test.

How were differences between studies investigated?
Heterogeneity was assessed by examining likelihood ratios for random-effects versus fixed-effect models. The Bayesian model was used to estimate if rates of response in participants lost to follow-up would change the overall results. Sensitivity analysis was undertaken by changing the prior distribution parameters and assessing model fit. Subgroup analysis was conducted by running the model with pre-highly active antiretroviral therapy (HAART: 1996 or prior) studies, and by excluding the study with paediatric participants. The reviewers also explored the data by analysing only full manuscripts.

**Results of the review**

Eight trials (n=458) were included; the study types were not reported.

The HAV vaccine demonstrated an overall response rate of 0.64 (95% confidence interval, CI: 0.52, 0.75) when the analysis was based on ITT (individual study results ranged from 36.8 to 93.9%) and 0.71 (95% CI: 0.60, 0.80) when based on PP (individual study results ranged from 38.5 to 93.9%). There was significant heterogeneity amongst the study results.

There was no significant difference in response rate when assessing pre-HAART and post-HAART only studies, when excluding paediatric studies, or when assessing full manuscripts only.

Egger’s test showed evidence of a negative correlation between effect size and study precision, suggesting possible publication bias.

**Authors’ conclusions**
The overall response rate is lower than typically cited: up to half of HIV-infected patients may be nonresponders.

**CRD commentary**
The research question was well-defined in terms of the intervention and outcome but less so for the participants and study design. Two databases, conference abstracts and relevant journals were searched, but no attempt was made to identify unpublished studies and this introduces the potential for publication bias. Publication bias was assessed and some evidence of it was found. In addition, the search was restricted to English language papers only, thus introducing the potential for language bias. The authors did not describe how papers were selected for the review, nor did they take steps to minimise reviewer error (only one reviewer extracted the data from the studies). Some aspects of validity were assessed, but it is not clear whether these criteria were robust enough for the types of studies included in the review. Details of the included studies, apart from study design, were presented. The authors used appropriate techniques to explore the data, and conducted sensitivity and subgroup analyses. However, given the heterogeneity and unknown study quality, the appropriateness of pooling the results is questionable. The weaknesses in study methodology, the likelihood of publication bias, and the debatable appropriateness of pooling the studies mean that the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

Practice: Scrutiny of current vaccination practices in high-risk populations is warranted.

Research: Future research is required to better understand the correlates of response.
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