A therapeutic HIV vaccine: how good is good enough

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
A hypothetical therapeutic vaccine for human immunodeficiency virus (HIV) was studied, in anticipation of clinical trials yet to be completed.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
In the model, a cohort of 1 million patients was simulated for each hypothetical vaccine. Patients entered the model with chronic HIV infection (mean CD4 cell count 500 cells/mm³, HIV RNA setpoint >30,000 copies/mL).

Setting
The setting was not explicitly reported. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence for a hypothetical vaccine was not informed by clinical studies but by the authors' expectations of a quality vaccine candidate (there were varied in the sensitivity analyses). Clinical trial results for ART came from studies reported in 1997 to 2000. Parameters for the natural history of the disease and rates of clinical events were derived from the Multicenter AIDS Cohort Study, which reported from 1995 to 1997. The utility weights were obtained from the HIV Cost and Services Utilization Study (1998 - 2002). Resource use in standard care was not directly reported, but was based on the AIDS Costs and Services Utilization Study (1998). The prices were all updated to 2001. (See Other Publications of Related Interest.)

Source of effectiveness data
Estimates of vaccine effectiveness were based on opinion, while the effectiveness of ART was modelled from 3 published randomised controlled trials (RCTs).

Modelling
In the absence of current clinical data, the authors designed a simulation model to explore the potential consequences of several hypothetical vaccine profiles. The model was a discrete event simulation model with a cohort size of 1 million hypothetical patients. This permitted the calculation of incremental gains in quality-adjusted life expectancy, incremental costs and cost-effectiveness ratios, across alternative intervention strategies (a hypothetical vaccine versus standard care).
Outcomes assessed in the review
The 'review' was not systematic. The effectiveness data for ART, the expected proportion of patients with HIV RNA suppression (to <500 copies/mL) in each line of therapy, were drawn from the RCT literature.

Study designs and other criteria for inclusion in the review
Clinical trials were selected to demonstrate the diminishing efficacy of ART.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The authors reported that 3 primary studies provided the effectiveness evidence for ART.

Methods of combining primary studies
The primary studies were not combined, but provided efficacy data for each line of therapy separately.

Investigation of differences between primary studies
The authors did not investigate differences between the primary studies, provide an explanation of differences between individual studies, or investigate how these differences affected the estimate of ART effectiveness.

Results of the review
HIV RNA suppression was estimated to be 70% of patients in first-line therapy at 48 weeks, 62% of patients in second-line therapy at 24 weeks, 34% of patients in third-line therapy at 12 weeks, and 22% of patients in fourth-line therapy at 12 weeks.

These suppression rates were standardised in the model to 24-week results, that is, 83% (first-line), 62% (second-line), 15% (third-line) and 7% (fourth-line).

Methods used to derive estimates of effectiveness
In the absence of reported trial data, the authors made assumptions to derive estimates of effectiveness for HIV vaccines.

Estimates of effectiveness and key assumptions
In the base-case, the vaccine series required 6 monthly injections to provide the presumed efficacy, based on current clinical trials that generally require numerous series of injections over time periods usually not exceeding 6 months. The vaccine was assumed to have a 0.5 log magnitude, with a penetrance of 25%, duration of effect of 3 years, and costs of $666.67 per patient per injection (total costs of $4,000). Assumptions about magnitude and penetrance were based on the potential effects of likely vaccine candidates that would be worthy of consideration. The cost was calculated to be approximately twice that of the most expensive vaccine (a pneumococcal vaccine named Prevnar) currently on the
market. It was assumed that vaccination occurred at a specified CD4 lymphocyte count (500 cells/mL) and that CD4 decline from this value occurred at an HIV RNA-dependent rate. It was assumed that no toxicity was associated with vaccination, and that no adverse effect of vaccination was produced in patients who did not realise the vaccine effect. The monthly rate of CD4 decline in nonresponders was set at 6.38 cells/mm3.

Measure of benefits used in the economic analysis
Life-years gained and quality-adjusted life-years (QALYs) were the outcome measures used in the economic analysis. The model assigned a quality of life weight for each CD4 cell count stratum and AIDS-related illness by applying the SF-6D utility scale to health status data from the HIV Cost and Services Utilization Study.

Direct costs
A discount rate of 3% was applied to the costs in the model. The quantities and the costs were not generally analysed separately. The charges for the treatment of opportunistic infections and routine HIV-and AIDS-related care were taken from the AIDS Costs and Services Utilization Study and converted to economic costs using a national cost-to-charge ratio for HIV/AIDS. The drug costs were obtained from the 2001 Red Book, while laboratory costs were obtained from the Medicare Fee Schedule (accessed in 2003). The medical care component of the Consumer Price Index was used to update costs to 2001 US dollars.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
Despite the fact that the authors stated that the study had been carried out from a societal perspective, the indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
In the main multivariate sensitivity analyses, the authors varied the vaccination costs ($2,000 to $10,000), vaccine magnitude (log 0.5 to log 1.5), vaccine penetrance (0 to 100%), vaccine durability (0.5 to 10 years), and changes in the rate of CD4 decline in nonresponders (6.38 to 7.03 cells/mm3). They also examined the following:

alternative HIV RNA setpoints;
amplified heterogeneity of vaccine response;
increase in ART efficacy;
effect on ART efficacy (zero in the base-case);
alternative CD4 cell count thresholds for initiating ART (350 to 500 cells/mm3);
plausible rates of toxicity; and
changes in the discount rate.

The authors made assumptions in the selection of ranges.
Estimated benefits used in the economic analysis
In the base-case, compared with optimal standard care, the addition of the specified vaccine increased life expectancy by 0.50 quality-adjusted life-months, on average, across 1 million simulated patients. Vaccination also delayed time to the initiation of ART by 1.12 months.

Cost results
The total cost per patient was $140,800 for vaccination and $137,000 for optimal standard care.

The costs of adverse effects of vaccination were not included in the base-case, but were analysed in a sensitivity analysis.

Synthesis of costs and benefits
The estimated benefits and costs were combined in an incremental cost-effectiveness ratio (ICER; incremental cost per QALY).

A comparison of the base-case vaccination strategy versus optimal standard of care gave an ICER of $89,900 per QALY gained.

If patients received sub-optimal (i.e. only first-line) ART, the ICER reduced to $74,600 per QALY gained.

In a best-case scenario (vaccine 1.5 log magnitude, 100% penetrance and $2,000 cost), therapeutic vaccination was cost-saving. In the worst-case scenario (0.5 log magnitude, 25% penetrance and $10,000 cost), the ICER became $230,500 per QALY gained.

In general, cost-effectiveness ratios below $100,000 per QALY were achieved when at least one of the following was true: the cost was less than or equal to $4,000 per series, penetrance was at least 75%, or magnitude was at least 1.5 log.

The majority of possible combinations explored (54 out of 60) achieved cost-effectiveness ratios below $100,000 per QALY.

Authors' conclusions
Clinically useful vaccines should have either moderate results in four domains (change in viral setpoint, magnitude, penetrance, and cost), or excellent outcomes in one domain and more modest results in the others. The authors suggested that a therapeutic vaccine, even if only moderately effective, could confer an overall survival advantage in comparison with no vaccine and compare favourably with other means of treating human immunodeficiency virus (HIV). Even very expensive vaccines, up to US$10,000 per series, may be reasonably cost-effective in countries willing to spend up to $100,000 per quality-adjusted life-year (QALY) gained.

CRD COMMENTARY - Selection of comparators
The authors chose standard care for HIV as a comparator for the hypothetical intervention. The choice was implicitly justified as it represented current best practice. You should decide whether optimal ART plus opportunistic infection prophylaxis represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not justify their assumptions with reference to the medical literature, although very little clinical data were available at the time. The authors appear to have based several assumptions on the “reasonable” results they expected such inputs to engender within the model. The model, while useful for examining scenarios in a forecasting situation, does not, in its present form, report clinically relevant results, but rather an indication of effectiveness thresholds. For decision-making purposes it would be necessary to update the model with clinical trial data. The estimates were varied in sensitivity analyses but the ranges used were also based on authors' assumptions.
Validity of estimate of measure of benefit
The estimation of benefit (QALYs gained) was modelled. The instrument used to derive a measure of health benefit, the SF-6D, was appropriate.

Validity of estimate of costs
Although the authors reported that the costs were estimated from a societal perspective, only the direct medical costs were included. The indirect costs were ignored. The costs and the quantities were generally not reported separately, making it difficult to update or transfer the study to another setting. Sensitivity analyses were not conducted for resource use, thus limiting the interpretation of the study findings. However, resource use was derived from a published source (a large national survey), which provides more credible backing to this model input than most others in the study. The prices were taken from recognised published sources, although sensitivity analyses were not conducted except on the price of the hypothetical vaccine. Charges were converted to costs using an appropriate method, while the costs were updated to a single price year using a suitable health price index.

Other issues
The authors made appropriate comparisons with other studies in this therapeutic area, though stating that few studies exist. The authors' conclusions reflected the scope of the analysis, but recognised the limitations in the absence of clinical trial data on HIV vaccine efficacy and on outcomes in patients already on ART. The authors did not present their results selectively and tabulated the main ICER results. Generalisability was discussed, in that the authors included an analysis exploring a comparator of sub-optimal ART, such as might occur in less developed countries than the USA. They noted that the model did not attempt to estimate possible public health benefits accruing from a diminished HIV RNA setpoint in terms of decreasing HIV transmission. Finally, they noted that the model design was limited to therapeutic, rather than preventive vaccines.

Implications of the study
The authors' primary recommendation emphasised the need for further research to discover worthy HIV vaccine candidates and to quantify their beneficial effects. The authors drew attention to the fact that, alongside the potential benefits of vaccination, there are several important and plausible downsides. The value of any HIV vaccine thus depends critically on the generation of credible clinical data.

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Other publications of related interest


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