Modelling the long-term outcomes and costs of HIV antiretroviral therapy using HIV RNA levels: application to a clinical trial

Cook J, Dasbach E, Coplan P, Markson L, Yin D, Meibohm A, Nguyen B Y, Chodakewitz J, Mellors J

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
Anti-retroviral therapy (ART) for asymptomatic HIV-infected patients. The technologies, which compared surrogate marker response, were triple therapy with indinavir (IDV, 800mg every 8 hr) plus zidovudine (ZDV; 200 mg every 8 hr) plus lamivudine (3TC; 150mg twice a day) compared to double therapy with ZDV plus 3TC.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
HIV-infected patients who have not yet progressed to AIDS.

Setting
Hospital. The study was carried out in the USA.

Dates to which data relate
Effectiveness data were collected from studies published between 1991 and 1997. Cost data were derived from two studies published between 1993 and 1997.

Source of effectiveness data
Effectiveness data were derived from a review of the Literature.

Modelling
A 20-year semi-Markov decision analytic model was used to project the clinical and economic impact of ART over time. Three health states were used: pre-AIDS state, AIDS state, and death. Definitions were derived from the AIDS-defining illness index (index ADI).

Outcomes assessed in the review
The review assessed the following outcomes: CD4 count change, duration of HIV RNA suppression beyond trial period with ART, rate of decline following HIV RNA return towards baseline, risk of AIDS, and survival time.

Study designs and other criteria for inclusion in the review
Not stated.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Summary statistics from individual studies were used.

**Number of primary studies included**
At least 7 studies were included.

**Methods of combining primary studies**
Narrative method.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
If the patient's last observed HIV RNA level during the trial period is within 0.3 log base 10 copies per millilitre of their HIV RNA level at baseline or higher, the CD4 cell count was assumed to decline. For the remaining patients, the CD4 cell count was assumed to remain at the level of the last observed CD4 cell count until the time at which HIV RNA is projected to return towards the patient's HIV RNA level at baseline. \((\text{CD4 count})^2\) was assumed to decline linearly. An annual transition probability of 0.013 for death prior to developing AIDS was used. A constant hazard rate was used in the model.

**Methods used to derive estimates of effectiveness**
Expert opinion based on two panels consisting of 4 and 6 persons, respectively.

**Estimates of effectiveness and key assumptions**
For patients with HIV RNA above 500 copies/ml, it was assumed that HIV RNA will rebound to baseline in an average of 1 year after the end of the trial period. For patients whose last HIV RNA level was below 500 copies/ml, it was assumed that viral suppression will be maintained for an average of 2 years beyond the end of the trial period if the patient continues on ART.

**Measure of benefits used in the economic analysis**
The probability of survival and the mean survival time were used as the measures of benefit. Health benefits were discounted at an annual rate of 3%.

**Direct costs**
Direct costs were discounted at an annual rate of 3%. Quantities and costs were not reported separately. Direct costs included direct medical HIV/AIDS disease costs and the cost for ART. The quantity/cost boundary adopted was that of
the health service. The estimation of quantities and costs was based on actual data. Cost estimates for the pre-AIDS state were taken from a cost analysis of 1,164 HIV-positive patients during 1991 and 1992. ART costs were based on wholesale net prices. Costs were adjusted to 1996 US dollars using the medical consumer price indices from 1992 to 1996.

**Statistical analysis of costs**
Not reported.

**Indirect Costs**
Not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were conducted on the projected CD4 cell count profile, risk of AIDS, survival time following the index ADI, costs, and the annual discount rate.

**Estimated benefits used in the economic analysis**
ART with IDV plus ZDV plus 3TC will maintain CD4 cell counts above baseline levels for roughly 4.75 years, while therapy with ZDV plus 3TC will maintain CD4 cell counts above baseline for only 1.75 years.

At 5 years, IDV plus ZDV plus 3TC resulted in a significant 34% absolute increase relative to ZDV plus 3TC in the probability of remaining AIDS free (p<0.001).

Patients who received IDV plus ZDV plus 3TC are projected over 5 years to spend an average of 0.92 additional years AIDS free than had they received ZDV plus 3TC (p<0.001).

At 5 years, the probability of survival is projected to be 21% higher among patients receiving IDV plus ZDV plus 3TC compared with ZDV plus 3TC (p<0.001).

Over the 5-year horizon, patient receiving IDV plus ZDV plus 3TC were projected to survive an average of 0.37 years longer than patients receiving ZDV plus 3TC (p<0.001).

**Cost results**
Over the first 5 years, the total discounted costs of care were projected to be $5,054 lower per patient who received IDV plus ZDV plus 3TC than for those who received ZDV plus 3TC.

**Synthesis of costs and benefits**
The incremental cost-effectiveness ratio was estimated at $13,229 per additional discounted life year gained for patients receiving IDV plus ZDV plus 3TC relative to ZDV plus 3TC.

**Authors' conclusions**
Combination therapy with IDV plus ZDV plus 3TC is expected to be cost-effective relative to ZDV plus 3TC and is projected further to delay the progression of disease in the management of HIV patients prior to their index ADI.
CRD COMMENTARY - Selection of comparators
An implicit justification was given for the comparator used, namely it was the double therapy with ZDV plus 3TC. You, as a user of the database, should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of benefit
The authors did not state that a systematic review of the literature had been undertaken and they may, therefore, have used data from the available studies selectively. Additionally, the authors did not state whether or not they considered the impact of differences between primary studies when estimating effectiveness. Two expert panels were also used to derive estimates of effectiveness although the authors did not report the process by which these experts were selected. The effect of estimates were, however, investigated by sensitivity analysis. The ranges used appear to be appropriate. Estimation of benefits was obtained directly from the effectiveness analysis. The choice of benefit measures was justified although, as noted by the authors, surrogate markers have to be used in this population due to their asymptomatic status and the long follow-up needed to determine hard end-points.

Validity of estimate of costs
All categories of costs relevant to the perspective of the health service were included in the analysis. Indirect costs were not, however, considered although they would be relevant for a societal perspective. For each cost category, all relevant costs were included. Costs and quantities were not reported separately. A sensitivity analysis of quantities was not conducted and this may limit the interpretability of the study findings. A sensitivity analysis of prices was conducted, but the price year was not reported.

Other issues
The authors did not make appropriate comparisons of their findings with those from other studies, although this may be explained by the fact that the authors claimed that this was the first study of its kind. The issue of generalisability to other settings was addressed. The authors did not present their results selectively. The study analysed HIV-infected patients and this was reflected in the authors’ conclusions. As with economic evaluations of this kind, the model used had limitations imposed by the data used to develop the model, data inputs to the model, and uncertainties about future changes in treatment options.

Implications of the study
It would be desirable to model the change in HIV RNA over time and its impact on modifying the future rate of CD4 cell count change. It would also be desirable to subdivide the AIDS state according to the type of index ADI in order to estimate the costs and survival time more accurately.

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