Cost-effectiveness of enfuvirtide in treatment-experienced patients with advanced HIV disease


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
The study compared the use of enfuvirtide (ENF) in combination with an optimised background regimen (OBR) with an OBR alone in treatment-experienced patients with advanced human immunodeficiency virus (HIV) disease.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of HIV patients. The cohort had the same patient characteristics as those in the T-20 versus Optimized Regimen Only (TORO) 1 and 2 trials. Specifically, the mean age was 42 years, 90% of the cohort was male and the mean CD4 cell count was 133 cells/mm3.

Setting
The study setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1995 and 2003. The costs were updated to 2001 prices.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, supplemented by the authors' own assumptions that had been based on the literature.

Modelling
The authors used a published state-transition model of HIV disease to simulate the TORO studies and to project the short-term trial results into long-term outcomes (e.g. life expectancy, quality-adjusted life expectancy, costs and cost-effectiveness).

Outcomes assessed in the review
The outcomes from the review were:

- the efficacy of OBR alone and ENF+OBR in HIV RNA suppression and CD4 cell count increase;
the incidence of primary and secondary opportunistic infections (OIs), death related to OIs, and chronic HIV-related
deaths; and
the quality of life associated with each CD4 cell count stratum.

**Study designs and other criteria for inclusion in the review**
The efficacy data for each of the treatment interventions were derived from the trial results for each study arm in the
TORO studies. No other details on the study designs or other inclusion criteria were given.

**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**
Approximately 13 primary studies were included in the review.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
The authors did not report whether differences between the primary studies were investigated.

**Results of the review**
The following probabilities were derived from the review.

HIV RNA suppression was achieved in 12.0% (range: 6.0 - 30.0) of patients receiving OBR alone and 30.4% (range:
21.2 - 76.4) of patients receiving ENF+OBR, at 48 weeks.

An average CD4 cell increase of 45 cells/mm³ (range: 23 - 113) in patients receiving OBR alone and 91 cells/mm³
(range: 68 - 206) in patients receiving ENF+OBR was achieved at 48 weeks.

The authors did not report any other outcomes of the review.

**Methods used to derive estimates of effectiveness**
The results from the review of the literature were supplemented with the authors’ own assumptions. Such assumptions
were based on the literature.

**Estimates of effectiveness and key assumptions**
To reflect the emerging data demonstrating a protective effect of antiretroviral therapy, independent of the current CD4
cell count, the authors assumed that the CD4 cell count-specific risks of developing an OI and of acquired immune
deficiency syndrome (AIDS)-related death for patients receiving antiretroviral therapy were 54% of that of untreated patients with the same cell count.

The authors also reported that although 81% of the patients in the TORO studies were reported to have had prior AIDS-defining illnesses, they assumed that such illnesses were clinically mild or currently inactive to reflect the generally stable state of health of patients eligible for entry into clinical trials.

**Measure of benefits used in the economic analysis**

The measure of health benefits used was the number of quality-adjusted life-years (QALYs) gained. Quality of life weights for the model were derived by applying the short form-6D (SF-6D) utility scale to the Medical Outcomes Study-HIV data from the HIV Cost and Services Utilization Survey. Each CD4 cell count stratum was assigned a baseline quality of life weight on a scale from 0 (death) to 1 (perfect health). Decrements were applied to this CD4 cell count-specific baseline on drug toxicity events and history of OIs. The utility weights for each health state were not reported.

**Direct costs**

The direct costs included in the analysis were those to the health care system. These included the costs of antiretroviral therapy, OI treatment, OI prophylaxis, and other CD4 cell count-specific, HIV-related care not related to OIs or antiretroviral drugs, such as monitoring tests and palliative care. The drug costs were obtained from the Drug Topics Red Book, laboratory costs from Medicare fee schedules, and other costs from the AIDS Cost and Services Utilization Survey. As the costs could be incurred over the lifetime of a patient, future costs were discounted at an annual rate of 3%. The average costs per patient were reported in the study. All the costs were updated to 2001 prices using the medical care component of the Consumer Price Index.

**Statistical analysis of costs**

The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**

Inline with the authors' stated perspective, the indirect costs were not included.

**Currency**

US dollars ($).

**Sensitivity analysis**

To explore the strength of the conclusions under alternative parameter estimates, the authors performed a series of sensitivity analyses using wide ranges of plausible input data. These analyses considered:

- the virologic and immunologic efficiency of ENF and OBR;
- the cost of ENF;
- the continuation of ENF after the HIV RNA level returned to baseline;
- the reduction in OI risk afforded by receiving antiretroviral therapy independent of the CD4 cell count and by having no prior history of OIs;
- the OI history of the cohort at baseline; and
- the quality of life decrement associated with ENF.
**Estimated benefits used in the economic analysis**
The mean discounted (undiscounted) life expectancy per patient was 55.7 (61.6) months for those in the OBR alone group and 66.8 (75.2) months for those in the ENF+OBR group.

The mean discounted (undiscounted) quality-adjusted life expectancy, in quality-adjusted life-months, was 45.4 (50.0) for those in the OBR alone group and 54.9 (61.6) for those in the ENF+OBR group.

**Cost results**
The total discounted lifetime cost was $205,900 per patient for those receiving ENF+OBR compared with $151,000 per patient for those receiving OBR alone.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained). When ENF plus OBR was compared with OBR alone, the additional cost per QALY gained was $69,500.

The results of the sensitivity analyses showed that when 48-week virologic suppression rates for ENF+OBR were varied from a 50% decrease to a 250% increase in the suppression rate attributable to ENF, the cost-utility ratios ranged from $97,900 to $52,300 per QALY, respectively. The analysis also showed that if ENF was continued after the HIV RNA levels return to the pre-treatment baseline, the cost-utility ratio increased to $168,200 per QALY. The cost-effectiveness of ENF was also found to be sensitive to the price of the drug. The cost-utility ratio of ENF plus OBR was found to be greater than $50,000 per QALY gained unless the price of ENF fell to approximately $9,300 per year.

**Authors’ conclusions**
Although enfuvirtide (ENF) plus an optimised background regimen (OBR) was less cost-effective than other commonly used interventions in human immunodeficiency virus (HIV) disease, its use could be justified, given the poor prognosis of advance HIV disease patients and their otherwise limited options for antiretroviral therapy.

**CRD COMMENTARY - Selection of comparators**
Although no explicit justification was given for using OBR as the comparator, it would appear to represent current practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not report that a systematic review of the literature had been undertaken to identify relevant research and minimise biases. Only limited details of the trials and their study designs were included in the review. For example, although the authors provided the baseline characteristics (in terms of age, gender, mean cell CD4 cell count and HIV RNA level) of patients in the TORO studies, they gave very few details of this trial, which was used to derive data on the efficacy of both the interventions being assessed. The authors also failed to report the methodology used in the review of the literature and synthesis of evidence. The authors made several assumptions, based on the literature, which were appropriately tested in the sensitivity analysis. Given the lack of detail reported, it was difficult to ascertain if the best available evidence had been used in the model.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The model used was appropriate for the study question.

**Validity of estimate of costs**
The authors did not report the perspective adopted in the economic analysis. However, it would appear that all the cost categories and cost relevant to the interventions being assessed were all included in the analyses. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The costs were...
derived from a variety of published sources and appropriate sensitivity analyses were conducted. All the costs were updated to current prices using appropriate inflation indices which took medical care inflation into account. Since the costs were incurred over the lifetime of the patient, all future costs were appropriately discounted. For some costs (i.e. laboratory costs), charges from Medicare were used to proxy prices. These charges might not reflect the true cost of providing the service.

Other issues
The authors compared the cost-effectiveness of ENF+OBR with other HIV and non-HIV interventions. They found that the cost-effectiveness of ENF+OBR was lower than that of other HIV and non-HIV interventions. The issue of generalisability to other settings was addressed in the exhaustive sensitivity analyses. The authors do not appear to have presented their results selectively. However, in their conclusions, the authors recommended the use of ENF+OBR for treatment-experienced patients with advanced HIV disease, despite the poor cost-effectiveness of this intervention. In the USA, the cost-effectiveness threshold is approximately $50,000 per QALY gained, substantially lower than the cost-effectiveness of ENF+OBR.

The authors reported a number of further limitations to their study. First, there was little information about the long-term clinical benefits or toxicity of ENF. Second, there was some evidence to suggest that resistance to ENF may result in reduced viral fitness. Finally, the authors did not assess the cost-effectiveness of ENF if used in patients with earlier stage HIV disease.

Implications of the study
Although the authors recommended the use of ENF+OBR for patients with advanced HIV disease, its use would not appear to be cost-effective in comparison with OBR because of its high cost-utility ratio, approximately $69,500 per QALY gained.

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Other publications of related interest


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