Cost-effectiveness of enfuvirtide for treatment-experienced patients with HIV in Italy
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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 combination of enfuvirtide (ENF) plus an optimised background (OB) antiretroviral regimen was compared with OB alone in the treatment of experienced patients with the human immunodeficiency virus (HIV). The OB regimen comprised one nucleoside reverse transcriptase inhibitor, one non nucleoside reverse transcriptase inhibitor, and two protease inhibitors.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis and cost-effectiveness analysis.

Study population
The study population comprised patients aged 43 years, with a CD4 count of 133 cells/mm3 and an HIV-1 viral load of 5.1 log10 HIV-1 RNA copies/mL.

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

Dates to which data relate
The effectiveness data were derived from studies published from 1998 to 2003. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from published and empirically derived mathematical models of disease progression produced during the highly active antiretroviral therapy era.

Modelling
A Markov model was developed to forecast the effect of therapy. The model linked the major clinical trial end points at week 48 to the subsequent occurrence of an AIDS-defining event (ADE) and mortality. The time horizon of the model was 10 years.

Outcomes assessed in the review
The outcomes assessed in the review were monthly transition probabilities to virological failure, immunological failure, ADE and death, and estimated quality of life.
Study designs and other criteria for inclusion in the review
Not reported.

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 seven studies were included in the review.

Methods of combining primary studies
The method used to combine the primary studies was not reported. Estimates for the transition probabilities to virological failure were derived from two Phase III clinical trials (TORO 1 and TORO 2; T-20 versus Optimised Regimen Only), which examined safety and efficacy of the ENF+OB regimen.

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

Results of the review
The cumulative virological failure rate was 17.5% in the ENF+OB arm and 36.8% in the OB arm after 2 months. During months 3 to 12, the average monthly failure rates were 3.9% (ENF+OB) and 4.6% (OB), respectively. These latter mean monthly failure rates for each arm were assumed to continue for the period subsequent to the 12-month trial period.

At a CD4 count of \( \leq 20 \) cells/mm\(^3\), the probability of an ADE was 5.68%, the mortality rate was 3.48%, and the quality of life estimate (utility) was 0.79.

At a CD4 count of 21 to 50 cells/mm\(^3\), the probability of an ADE was 2.20%, the mortality rate was 2.45%, and the quality of life estimate (utility) was 0.79.

At a CD4 count of 51 to 100 cells/mm\(^3\), the probability of an ADE was 0.92%, the mortality rate was 0.72%, and the quality of life estimate (utility) was 0.81.

At a CD4 count of 101 to 200 cells/mm\(^3\), the probability of an ADE was 0.37%, the mortality rate was 0.34%, and the quality of life estimate (utility) was 0.87.

At a CD4 count of 201 to 350 cells/mm\(^3\), the probability of an ADE was 0.13%, the mortality rate was 0.12%, and the quality of life estimate (utility) was 0.94.

At a CD4 count of >350 cells/mm\(^3\), the probability of an ADE was 0.06%, the mortality rate was 0.06%, and the quality of life estimate (utility) was 0.94.
Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). The utility estimates for each health state were derived from the literature. The authors assumed no direct effect of ENF administration on quality of life, as the TORO trials found no negative effect on quality of life when ENF was combined with OB.

Direct costs
The direct costs included were the pharmacological costs of antiretroviral therapy, non-pharmacological costs associated with the treatment of HIV patients, and the cost of treating an ADE. The non-pharmacological costs associated with HIV treatment included hospitalisation, day hospital, outpatient visits, laboratory tests and outpatient diagnostic procedures. An expert panel of physicians defined the composition of a standard OB regimen consistent with Italian current practice. The cost of ENF was derived from the Italian National Health Service. The costs of other drugs were based on published data on sales and hospital transfer prices. Non-pharmacological costs were derived from a study conducted in Italy. The mean cost for treating an ADE was calculated using diagnosis-related groups (DRG), with the cost of each DRG being weighted by the frequency of ADEs recorded in Italy. As the costs were incurred over a 10-year period, all future costs were discounted at an annual rate of 3%. The study reported the mean costs. The price year was 2004.

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

Indirect Costs
Inline with the perspective adopted, the indirect costs were not included.

Currency
Euros (EUR).

Sensitivity analysis
One-way sensitivity analyses were undertaken to evaluate uncertainty in the model parameters. The parameters investigated were treatment effectiveness, relevant progression probabilities, discount rates, medical care costs, the time horizon and utilities.

Two sub-group analyses were also undertaken. One assessed the effect of ENF when the virus had varying genotypic sensitivity to antiretroviral agents. The other assessed patients with baseline CD4 cell counts of less than and greater than 100/mm3.

Estimated benefits used in the economic analysis
The estimated discounted QALYs (undiscounted life-years) gained over a 10-year period were 5.5 (7.4) for patients in the ENF+OB arm and 4.0 (5.6) for patients in the OB arm.

Cost results
The mean discounted costs incurred over a 10-year period were EUR 126,487 for patients in the ENF+OB arm and EUR 84,416 for patients in the OB arm.

Synthesis of costs and benefits
The costs and benefits were combined using incremental cost-utility and cost-effectiveness ratios (i.e. the additional cost per QALY or life-year gained). The incremental cost per QALY gained with ENF+OB over OB was EUR 28,669. The incremental cost per life-year gained with ENF+OB over OB was EUR 23,721.
The results of the sensitivity analysis showed that the cost-effectiveness and cost-utility ratios were most sensitive to assumptions about the time horizon and baseline hazard of immunological failure. Based on the sub-group analysis, the model indicated that clinical and economic outcomes varied with the levels of resistance to the antiretroviral agents in the background regimen and by baseline CD4 cell count.

**Authors' conclusions**
Combination treatment with enfuvirtide had a cost-effectiveness ratio that was within accepted standards in Europe.

**CRD COMMENTARY - Selection of comparators**
A justification was given for using OB treatment alone as the comparator. It represented current practice in the authors’ settings. You should decide if the comparator used represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been undertaken. However, the literature used comprised recently published studies, and the main transition probabilities were derived from randomised clinical trials, which are considered to be the ‘gold’ standard study design when comparing health care interventions. Nevertheless, the authors provided very few details of the methodology undertaken in their review. This lack of detailed reporting made it difficult to ascertain whether the best available evidence had been used to populate the model.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled using a Markov model, which was appropriate. The authors reported benefits in terms of the life-years and QALYs gained, reporting all the utilities used for each health state. Since the benefits were incurred during a 10-year period, the QALYs were appropriately discounted.

**Validity of estimate of costs**
All the categories relevant to the health care system perspective adopted were included in the analysis, and no major relevant costs appear to have been omitted. Although the costs and the quantities were not reported separately, the authors provided a very detailed breakdown of the costs, which will increase the generalisability of the results to other settings. The unit costs were derived from published sources. Appropriate sensitivity analyses of the costs were undertaken. Discounting was relevant, as the costs could be incurred over 10 years, and was appropriately undertaken. The price year was reported, which will aid any future inflation exercises.

**Other issues**
The authors did not make appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, they projected finding of a 1-year randomised trial to determine implications over time. Second, the theoretical benefits of ENF still under investigation (e.g. continuing ENF in patients after viral failure while switching the underlying OB regimen) were omitted. Finally, there was a possible overestimation of the monthly costs due to the model structure.

**Implications of the study**
The authors did not make any recommendations as a result of their study. Based on their conclusions, it would appear that they recommend the use of the combined ENF+OB regimen in the treatment of experienced patients with HIV.

**Source of funding**
None stated.