Cost-effectiveness of lopinavir/ritonavir versus nelfinavir as the first-line highly active antiretroviral therapy regimen for HIV infection


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 use of protease inhibitors, lopinavir coformulated with ritonavir (LPV/r) versus nelfinavir (NFV), as a first-line highly active antiretroviral therapy (HAART) regimen for human immunodeficiency virus (HIV). The two treatment regimens compared were LPV/r plus stavudine (d4T) plus lamivudine (3TC) (intervention group) and NFV plus d4T plus 3TC (control group).

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of people with HIV who were, on average, aged 37 years old and were naive to ART.

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

Dates to which data relate
The effectiveness data were derived from studies published between 2001 and 2004. The resource use data were derived from a study published in 2001. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from published and unpublished studies, and from the authors’ own assumptions.

Modelling
The decision analytic model used in the study was based on a three-compartment Markov model. Patients entered the model as ART-naive patients (Stage 1) and started either LPV/r or NFV, plus two nucleoside transcriptase inhibitors (NTRIs). ART was initiated with a CD4 cell count below 500 cells/microL and detectable viral load (VL) in excess of 400 copies/mL. Patients entered Stage 2 when they were switched to a new protease inhibitor regimen because of treatment failure, defined as a health state with CD4 less than 500 cells/microL and detectable VL (at least 400 copies/mL). Patients then progressed through 12 health states in Stage 2 until they reached a health state that represented failure of second-line therapy or death. Patients then entered Stage 3 where they were switched to a new regimen composed of two protease inhibitors plus two NRTIs because of treatment failure, defined as CD4 less than 350 cells/microL and detectable VL. Patients then progressed through the health state in Stage 3 until they entered the
death health state. The model ran until 50% of patients had reached the death health state. In the model, HIV sufferers were at risk of common opportunistic infection and other HIV events. This risk varied by 12 health states defined by CD4 cell count and VL levels.

The model assumed that only one type of opportunistic infection event can occur to the same patient at any one time. In addition, the model assumed that there was no additional divergence in the survival curve of VL breakthrough between the two study arms. The progression through the three stages in the model assumed that the relevant pattern of ART included two HAART regimens plus salvage therapy, with the decision to switch to new therapy depending on ART history.

**Outcomes assessed in the review**
The authors derived the following 48-week results of a clinical trial evaluating LPV/r versus NFV:

- the median baseline VL and CD4 cell count,
- the dropout rate of any cause, and
- the VL and the CD4 cell change from baseline.

From other studies the authors derived:

- the risk of HIV-related events,
- the quality-adjusted life-year (QALY) weight attached to each health state by CD4 cell count and VL, and
- the percentage of all HIV-related acquired immune deficiency syndrome (AIDS) events by disease or other adverse event (e.g. candidiasis, cervical cancer, cytomegalovirus infection, dementia, tuberculosis, wasting syndrome, herpes).

The authors also derived the transition probabilities for moving in and between states in the model.

**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 7 primary studies were included in the review.

**Methods of combining primary studies**
Some effectiveness parameters derived from the primary studies were combined using a narrative method.
Investigation of differences between primary studies
Potential differences between the primary studies were not discussed in the analysis.

Results of the review
The median baseline VL (RNA copies/mL) was 5.01 log10 copies/mL for patients in the LPV/r group, and 4.98 log10 copies/mL for patients in the NFV group.

The median baseline CD4 count was 232 cells/microL in both groups.

The 48-week results of the clinical trial evaluating LPV/r versus NFV were as follows.

The dropout rate for any cause was 17% in patients receiving LPV/r and 24% in patients receiving NFV.

The proportion of patients with a VL less than 400 copies/mL was 75% in patients treated with LPV/r when the analysis was undertaken on an intention to treat basis, and 63% in patients treated with NFV.

The proportion of patients with a VL less than 50 copies/mL was 67% (intention to treat) in patients treated with LPV/r and 52% in patients treated with NFV.

The CD4 cell count change from baseline was +207 cells/microL in patients treated with LPV/r and +195 cells/microL in patients treated with NFV.

The authors derived the following outcomes from other literature.

The risk of AIDS events was found to increase by falls in the CD4 cell count and by rises in the VL.

In a health state with CD4 cell count of more than 500, and where VL was lower than 400, the risk of HIV-related events was 1.71. This risk increased to 2.18 when the VL at least 400 and the CD4 cell count was greater than 500.

With CD4 cell counts of 351 to 500 the risk was also between 1.71 and 2.18, depending on VL. When CD4 cell count dropped to between 201 and 350, the risk of HIV-related events ranged from 2.84 to 4.25, again depending on VL. At CD4 cell counts between 50 and 200, the risk of HIV-related events ranged from 5.11 to 14.47, increasing to 17.87 when CD4 cell counts were lower than 50 (in this case, irrespective of VL).

The utility placed on each of the 12 health states (as determined by CD4 counts and VL) fell with lower CD4 cell counts and higher VL.

The proportion of all HIV-related AIDS events due to specific diseases was 22.8% wasting syndrome, 20.1% pneumonia, 13.0% pneumocystic pneumonia, 9.0% candidiasis, 5.8% mycobacterium avium complex, 4.9% tuberculosis and 4.5% cytomegalovirus retinitis.

Other HIV-related events such as cervical cancer, HIV-dementia, and herpes simplex accounted for less than 4% of events.

Methods used to derive estimates of effectiveness
The authors made several assumptions to try and capture different best clinical practices in HIV disease.

Estimates of effectiveness and key assumptions
The authors made the following assumptions.

The response rates to second-line HAART in the model assumed an average increase of 50 CD4 cells/microL and an undetectable VL rate (below 400 copies/microL) of 70%.
The response rates to third-line HAART in the model assumed an average increase of 30 CD4 cells/microL and an undetectable VL rate (below 400 copies/microL) of 30%.

The protease inhibitor resistance through 48 weeks was assumed to be 33% for NFV versus 0% for LPV/r.

**Measure of benefits used in the economic analysis**
The measures of benefits used were the life-years and QALYs gained. Health-related quality of life was estimated for each health state, based on an analysis of data from about 21,000 clinical trial patients assessed by the EuroQol quality of life instrument (EQ-5D). The preference weight modelling transformation developed by Dolan was used to transform the original questionnaire responses. The health benefits were discounted at an annual rate of 3%.

**Direct costs**
The direct costs included in the analysis were those to the health system. These were the costs of routine HIV care, switching ART regimens and treatment for opportunistic infections. The inpatient costs were derived from Medicare billing and were adjusted to approximate opportunity costs by using reported HIV-specific cost-to-charge ratios. The costs of care for opportunistic infections were based on the average cost per year observed in a Medicaid cohort, multiplied by the average survival time for patients with that condition. The routine costs of HIV care included routine visits and laboratory tests at the HIV clinic. Daily antiretroviral drug costs were derived from the wholesale acquisition costs reported by PriceProbe for 2002. The authors reported that they did not include the costs of any changes in a HAART regimen due to toxicities and the treatment of toxicities. Discounting was necessary, as the costs were incurred over the lifetime of the patient, and was performed at an annual rate of 3%. The study reported the total costs for 100 patients. The price year was 2002.

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

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
In a series of one-way sensitivity analyses, the point value of cost or probability parameters were varied to test their impact on the overall cost and event rates. A clinically relevant range over which to vary the values of the parameters under investigation was derived from references sources.

**Estimated benefits used in the economic analysis**
The added survival (undiscounted) of treating patients with LPV/r rather than NFV was 25.4 years over the patients’ lifetime. When protease inhibitor resistance was included in the model, the lifetime-added years of survival of using LPV/r over NFV was 27.4 years.

The authors did not report the additional QALYs gained when patients were treated with LPV/r as opposed to NFV.

**Cost results**
The total (undiscounted) costs of treating 100 patients with LPV/r and NFV over the patients’ lifetime were $28,526,301 and $28,237,473, respectively. The incremental cost was $288,828 (undiscounted). When protease
inhibitor resistance was included into the model, LPV/r was found to cost less than NFV over the patients' lifetime, generating cost-savings of $61,100.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the additional cost per life-year gained) and an incremental cost-utility ratio (i.e. the additional cost per QALY gained). When compared with NFV, the (discounted) incremental cost-effectiveness ratio of LPV/r was $6,376 per life-year gained, and the (discounted) incremental cost-utility ratio was $6,653 per QALY gained. When protease inhibitor resistance was included in the model, LPV/r was found to be dominant over NFV, meaning it was both more effective and cheaper.

Variations in the utility values (50 to 100%) and the clinical event (opportunistic infection) rates per health state (50 to 200%) did not alter the conclusions of the base-case analysis. When the costs for opportunistic infection events were varied from 50 to 200% of the baseline cost, a 20% increase in costs was observed. This resulted in an approximately 5% decrease in the cost-utility ratio, to $6,019 per QALY gained. The authors found that the cost per daily dose of LPV/r was the only parameter that affected the conclusions of the analysis. If the LPV/r cost per daily dose was equivalent to NFV, then the undiscounted incremental cost-effectiveness ratio of LPV/r over NFV would be $11,389 and the corresponding cost per QALY would be $12,058. This indicated that LPV/r therapy would still be cost-effective in comparison with NFV therapy.

**Authors' conclusions**
When treatment options are being considered, the use of lopinavir and ritonavir (LPV/r) in the first antiretroviral regimen was cost-effective based on improved efficacy and resistance in comparison with nelfinavir (NFV).

**CRD COMMENTARY - Selection of comparators**
Although no explicit justification was given for using nelfinavir 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 whether a systematic review of the literature had been undertaken to identify all relevant research and minimise biases. However, the studies included in the review were up to date, published no later than 2001, and the authors also included data from unpublished trials. The authors failed to provide the methodology used in their review. They also did not report all the parameters used in the model, probably because they were derived from unpublished data. Data from the trials was supplemented with the authors' own assumptions. All assumptions and parameters used were appropriately varied in the sensitivity analyses using very wide ranges.

**Validity of estimate of measure of benefit**
The measure of benefits was derived from a Markov model, which was appropriate for the study question. As benefits could be incurred over a patients' lifetime, future benefits were appropriately discounted.

**Validity of estimate of costs**
All the categories of cost relevant to the health system perspective adopted were included in the review. All the major relevant costs appear to have been included in the analysis. However, the authors reported that some costs, such as the costs of any changes in a HAART regimen due to toxicities, were not included in the analysis. Such omissions are unlikely to have affected the authors' results. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The costs were derived primarily from Medicare and Medicaid charges, as well as from the literature. The authors adjusted these charges, so as to approximate them to true opportunity costs, using reported HIV-specific cost-to-charge ratios. The costs were appropriately varied in sensitivity analyses using wide ranges. As the costs could be incurred over a patients' lifetime, future costs were appropriately discounted. The price year was reported, which will aid any possible future inflation exercises.
Other issues
The authors made appropriate comparisons of their findings with those from other studies. They reported that the cost-effectiveness ratio of LPV/r versus NFV compared favourably with those of other therapies used in HIV disease. The issue of generalisability to other settings was partially addressed in the sensitivity analyses. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. However, more transparent details of the review methodology and data used to populate the model would have been desirable. The authors stated that the main limitation of the study was that their model greatly simplified the sequence of treatment decisions for a person with HIV, especially after the diagnosis of AIDS. However, their model improved on previous models by incorporating VL into the health state definition and by capturing the effects of a sequential ART regimen.

Implications of the study
The authors appeared to recommend the use of LPV/r as the first-line HAART regimen for HIV infection, at least in the developed world, owing to its cost-effectiveness. The authors argued that the cost-effectiveness was well below the threshold for cost-effective innovation in developed countries.

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