Analysis of treatment costs for HIV RNA reductions and CD4 increases for darunavir versus other antiretrovirals in treatment-experienced, HIV-infected patients

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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 study examined several antiretroviral treatments for patients infected with the human immunodeficiency virus (HIV). These were:

- darunavir plus ritonavir (DRV/r);
- fosemprenavir plus ritonavir (fAPV/r);
- lopinavir plus ritonavir (LPV/r);
- atazanavir plus ritonavir (ATV/r);
- zidovudine (ZDV) alone;
- zidovudine plus lamivudine (ZDV/3TC);
- tipranavir plus ritonavir (TPV/r);
- a nucleoside reverse transcriptase inhibitor (NRTI);
- NRTI plus abacavir (NRTI/ABC);
- optimised background plus tenofovir (OB/TDF); and
- OB plus enfuvitide (OB/T-20).

The daily dosage of DRV/r, which was the new treatment mainly investigated in this study, was 600 mg darunavir and 100 mg ritonavir.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of treatment-experienced, HIV-infected patients. Patients receiving a new treatment had to have been pre-treated with antiretrovirals of the same class (e.g. new PIs in PI-experienced patients etc.).
Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
Clinical and resource use data were derived from studies published between 1997 and 2006. The price year was 2006.

Source of effectiveness data
The clinical data used in the analysis were the log reduction in HIV RNA and the mean increase in CD4 count (at week 24). Both end points were considered measures of treatment effectiveness.

Sources searched to identify primary studies
The clinical trials used to derive the effectiveness data were as follows:
- Gilead 907 for TDF versus placebo,
- CNA3021 for ABC versus placebo,
- BMS-045 for ATV/r versus LPV/r,
- CONTEXT for fAPV/r versus LPV/r,
- TORO-1 and TORO-2 for T-20 versus placebo,
- CAESAR for ZDV/3TC versus placebo,
- RESIST-1 and RESIST-2 for TVP/r versus PI/r, and
- POWER 1 and POWER 2 for DRV/r versus PI/r.

Baseline characteristics (sample size, CD4 count at baseline) of the patients included in the clinical trials were presented.

Methods used to judge relevance and validity, and for extracting data
The authors stated that a literature search was performed, which included US Food and Drug Administration product labels in order to identify data on the effectiveness of the treatments under examination. Results from intention to treat analyses were used for all trials with 24-week data. The reasons why two published studies were excluded were reported. Other details of the review were not given.

Measure of benefits used in the economic analysis
The summary benefit measure was the additional percentage of patients reaching undetectable viral load levels (RNA <50) over 24 weeks. This was derived directly from the literature.

Direct costs
The perspective of the study was that of the payer. However, the analysis of the costs was restricted to drug acquisition expenses, which were estimated using average wholesale prices. Resource consumption was based on data derived from the clinical trials. Details of resource use were presented together with the annual costs of all drugs. Discounting was not relevant as the costs were incurred during less than 1 year. The price year was 2006.

Statistical analysis of costs
No statistical analyses of the costs were performed.

**Indirect Costs**
Productivity costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
A deterministic univariate sensitivity analysis was carried out to test the hypothesis of a high cost of DRV, assuming that the control PI component of the control arm of the POWER trials had no efficacy.

**Estimated benefits used in the economic analysis**
The additional percentage of patients reaching undetectable viral load levels (RNA <50) over 24 weeks was as follows:

- 22% with TDF and 1% with placebo in the Gilead 907 trial (difference 21%);
- 20% with ABC and 2% with placebo in the CNA3021 trial (difference 18%);
- no benefit differences in the comparison between ATV/r and LPV/r in the BMS-045 trial;
- no benefit differences in the comparison between fAPV/r and LPV/r in the CONTEXT trial;
- 20% with T-20 and 7% with placebo in the TORO-1 trial (difference 13%);
- 12% with T-20 and 5% with placebo in the TORO-2 trial (difference 7%);
- no data available for the comparison between 3TC and placebo in the CAESAR trial;
- 25% with TPV/r and 10% with PI/r in the RESIST-1 trial (difference 15%);
- 23% with TVP/r and 9% with PI/r in the RESIST-2 trial (difference 14%);
- 45% with DRV/r and 12% with PI/r in the POWER 1 and 2 trials (difference 33%).

**Cost results**
The cost-difference was:

- $5,384 with TDF versus placebo in the Gilead 907 trial;
- $4,787 with ABC versus placebo in the CNA3021 trial;
- $22,537 with T-20 versus placebo in both TORO-1 and TORO-2 trials;
- $5,510 with TVP/r versus PI/r in both RESIST-1 and RESIST-2 trials;
- $427 with DRV/r versus PI/r in the POWER 1 and 2 trials.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative strategies.
The incremental cost per additional patient with an HIV RNA <50 copy response over 24 weeks was:

- $25,638 with TDF versus placebo in the Gilead 907 trial;
- $26,594 with ABC versus placebo in the CNA3021 trial;
- $173,362 with T-20 versus placebo in TORO-1 trial;
- $321,957 with T-20 versus placebo in TORO-2 trial;
- $36,733 with TVP/r versus PI/r in RESIST-1 trial;
- $39,357 with TVP/r versus PI/r in RESIST-2 trial;
- $1,294 with DRV/r versus PI/r in the POWER 1 and 2 trials.

The sensitivity analysis showed that, even when the control PI component of the control arm of the POWER trials had no efficacy and the cost of DRV increased, the incremental cost-effectiveness ratio associated with DRV remained favourable ($31,433).

**Authors' conclusions**
The cost-effectiveness of darunavir plus ritonavir (DRV/r) over its control treatment for human immunodeficiency virus (HIV)-infected, antiretroviral-experienced patients was better than that of other antiretroviral treatments (in comparison with their respective control treatments). This was due to the higher improvement in efficacy.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear in that all available approved antiretroviral treatments were included in the analysis. Individual comparisons were based on published evidence. Some treatments were excluded from the cost-effectiveness comparison as the drugs showed no benefit over placebo (or the direct comparator). You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The use of a review of the literature to identify relevant clinical studies was appropriate. The review included only randomised trials, which usually represent a valid source of data given their high internal validity. Official product labels were also used to derive clinical data. Some information on the baseline characteristics of the trials was reported. For example, sample size, CD4 count, HIV RNA long copies and drug classes used were explicitly reported. Each trial was used to obtain data on a single treatment and the estimates were not combined. However, the authors noted that clinical trials might differ with respect to entry criteria, baseline characteristics and concomitant antiretroviral use.

**Validity of estimate of measure of benefit**
The benefit measure represents a disease-specific measure since it is valid only for HIV-infected patients. It represents an intermediate measure of the impact of the interventions on patient health, although it is widely used as an end point of antiretroviral treatments.

**Validity of estimate of costs**
The analysis of the costs was restricted to the drugs under examination. Other resources associated with HIV treatment were not considered as the analysis focused on drugs. The unit costs were not presented, whereas the annual treatment costs and the number of daily pills were. Statistical analyses of the costs were not performed and the cost estimates were not varied in the sensitivity analysis. The price year was reported, which will assist if replicating the analysis in other time periods.

**Other issues**
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. The very limited use of sensitivity analysis reduces the external
validity of the study. The authors noted some potential limitations to the analysis. For example, it was pointed out that patients enrolled in the clinical trials were usually highly treatment-experienced patients, which limits the applicability of the study results to patients undergoing earlier lines of treatment. Moreover, the analysis did not account for differences in toxicity, use of concomitant medications, or adherence to treatment.

**Implications of the study**
The study results suggest that DRV/r would appear to be a cost-effective treatment for HIV-infected, treatment-experienced patients. The authors stated that new clinical trials evaluating economic aspects of treatments alongside their clinical impact are underway.

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None stated.

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