Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity

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
Genotyping for human leukocyte antigen (HLA) B*5701 was examined.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with and without abacavir hypersensitivity. Hypersensitivity was defined as the occurrence of at least two of rash, fever, respiratory or gastrointestinal symptoms, within 6 weeks of starting abacavir.

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

Dates to which data relate
The dates of the effectiveness evidence and resources used from the authors' own study were not reported. The costs were valued in 2002 prices. The two other efficacy studies in the pooled analysis were published in 2002.

Source of effectiveness data
The authors conducted a single study and then pooled the results with two completed studies.

Link between effectiveness and cost data
The costing of a hypersensitivity reaction was carried out retrospectively using average resource use estimated from a sample (n=16) of consecutive patients attending the authors' setting. It was not declared whether any or all of these patients also participated in the efficacy study.

Study sample
No sample size was determined in the planning phase of the study. In addition, power calculations were not performed retrospectively. The patient population for the efficacy study was selected from the HIV clinic at North Manchester General Hospital in the UK. Patients were eligible for inclusion as hypersensitivity cases if features of hypersensitivity were identified in their record and considered definitive. Definite hypersensitivity occurred when a patient had been exposed to other drugs at the same time as abacavir and they had had a negative rechallenge to the other drugs, in particular nevirapine and efavirenz. Patients were eligible for inclusion as controls if they had been taking abacavir for
12 months without any evidence of hypersensitivity.

Twenty patients with symptoms indicative of hypersensitivity were identified, of which 7 were excluded because they did not meet the authors' predefined criteria. This left 13 patients (median age 34 years, range: 22 - 45; 2 females) who were all Caucasians with definite hypersensitivity. They were compared with 51 controls (median age 37 years, range: 27 - 66; 5 females, 4 non-Caucasians) who had been exposed to abacavir for at least 1 year without hypersensitivity.

**Study design**
This was a case-control study that was carried out in a single centre. No blinding of the outcome assessment was reported.

**Analysis of effectiveness**
All of the patients included in the study appear to have been accounted for in the analysis. The primary health outcome was the proportion of HLA B*5701-positive patients. For the genotyping, a statistical analysis was performed using Fisher’s exact test and 95% confidence intervals (CIs) for the odds ratios (ORs) were calculated by Gart’s method.

**Effectiveness results**
Six (46%) of the abacavir hypersensitive patients were HLA B*5701-positive, compared with 5 (10%) of the non-hypersensitive patients (OR 7.9, 95% CI: 1.5 - 41.4; p=0.006).

**Clinical conclusions**
The authors concluded that their study showed a strong association between abacavir hypersensitivity and HLA B*5701 in a UK cohort. This emphasised the robustness of this genetic association, shown previously in Mallal et al. 2002 and Hetherington et al. 2002.

**Modelling**
A decision-analytic model was used to analyse the costs and consequences of testing. In the no-test branch (current practice), patients were given abacavir-containing regimens without genotyping. In the test branch, patients were prescribed antiretroviral therapy regimens according to the test result. Following an abacavir hypersensitivity reaction in either branch, it was assumed that a patient received appropriate treatment and was switched to an alternative non-abacavir-containing regimen. The time horizon was 6 months.

**Outcomes assessed in the review**
The outcomes included:

- the test characteristics (sensitivity and specificity),
- the probability of testing positive for the presence of HLA B*5701,
- the prevalence of HLA B*5701, and
- the timing of when hypersensitivity occurred following the initiation of abacavir therapy.

The probability of testing positive for HLA B*5701 was determined by pooling the authors’ data with further published data. Other inputs for the economic model were assessed from the literature.

**Study designs and other criteria for inclusion in the review**
Two cohort studies (Mallal et al. 2002 and Hetherington et al. 2002) were included in the pooled analysis to assess the probability of testing positive for HLA B*5701. The probability of occurrence of hypersensitivity reactions was taken
from a study of 5,332 patients in which 197 patients experienced a reaction (Symonds et al. 2002, see ‘Other Publications of Related Interest’ below for bibliographic details). The timing of the occurrence of hypersensitivity following the initiation of abacavir therapy was drawn from data relating to 636 cases of hypersensitivity reactions (Hetherington et al. 2001, see ‘Other Publications of Related Interest’ below for bibliographic details). No further description of these studies was provided.

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
Four studies were provided.

Methods of combining primary studies
The authors pooled their genotyping results with those of Mallal et al. 2002 and Hetherington et al. 2002, using a random-effects model.

Investigation of differences between primary studies
It was unclear whether any differences between the primary studies were investigated and explained, nor whether any differences might have affected the estimate of the effectiveness of the technology.

Results of the review
The pooling analysis resulted in a pooled DerSimonian-Laird OR of 29 (95% CI: 6.4 - 132.3; chi-squared 191, d.f.=1, p<0.0001).

Using the pooled data from 3 studies, the test sensitivity was 0.51 (95% CI: 0.45 - 0.56) and the test specificity was 0.96 (95% CI: 0.94 - 0.98).

The positive predictive value was 82% (95% CI: 71 - 90) and the negative predictive value was 85% (95% CI: 81 - 88).

The probability of occurrence of reaction was given as a prevalence of 3.7%.

The median time to reaction was 11 days, but some reactions still occurred up to 6 months after starting abacavir. Therefore, a 6-month time horizon was adopted in the model.

Methods used to derive estimates of effectiveness
Authors’ assumptions (citing 4 clinical trial references) were used.

Estimates of effectiveness and key assumptions
The authors assumed that all treatment regimens considered in the model (i.e. those containing abacavir and those not containing abacavir) were therapeutically equivalent and differed only in their cost.
Measure of benefits used in the economic analysis
The economic analysis calculated the hypersensitivity reactions avoided.

Direct costs
Discounting was irrelevant in a short time horizon. The quantities and the costs were analysed separately. The perspective of the UK NHS was taken, covering direct medical costs only. The resources measured included the cost of drugs for each alternative therapy regimen, the cost of genotyping and the cost of treating a hypersensitivity reaction. The latter was derived from data in the authors' setting for 16 hypersensitivity patients. It encompassed drug costs, inpatient stays, outpatient clinic visits and the cost of other tests (e.g. chemical pathology, haematology, serology, radiology and cultures). The cost of the various therapy regimens was calculated on the basis of 6 months of the appropriate drugs and doses. The price year was 2002. The sources included the British National Formulary and the respective departments or the accounting department of the Manchester hospital. Thus, charges were used to approximate the costs.

Statistical analysis of costs
There was a large inter-individual variance in the costs of treating hypersensitivity reactions (median Euro2,611, range: 0 - 11,857). The costs of treating hypersensitivity reactions were sampled from a log-normal distribution, having first tested the transformed cost data for normality using the Shapiro-Wilk test.

Indirect Costs
No indirect costs were included.

Currency
UK pounds sterling (€). These were converted to Euros (Euro). The exchange rate was Euro1 = 0.70.

Sensitivity analysis
The uncertainty surrounding model inputs was characterised by assigning probability distributions. Uncertainty associated with test sensitivity and specificity, prevalence of hypersensitivity and probability of a positive test result were represented by independent beta prior distributions for binomial proportions. Monte Carlo simulations (1,000) were performed to determine the ceiling ratio at which the test was certain of being cost-effective. These were repeated for each alternative to abacavir-containing regimens. A multiple univariate analysis was performed for a base-case scenario which assumed a single cost for alternative regimens. A threshold analysis was conducted to explore the relationship between the cost of alternative regimens, the decision-makers' willingness to pay to avoid hypersensitivity reactions and the probability of adopting routine testing as a strategy. The method used to select the ranges was not discussed.

Estimated benefits used in the economic analysis
In the base-case, the number of hypersensitivity reactions per 1,000 patients was 19 when testing was implemented, versus 37 in the absence of testing. Therefore, testing was associated with 18 hypersensitivity reactions avoided per 1,000 patients.

Cost results
Depending on the abacavir-containing and non-abacavir-containing regimens chosen, the 6-month cost of implementing testing varied from Euro 2.03 million to Euro 5.59 million per 1,000 patients. The 6-month cost when testing was not implemented varied from Euro 2.13 million to Euro 6.14 million per 1,000 patients.
Synthesis of costs and benefits
The estimated benefits and costs were combined in an incremental cost-effectiveness ratio (ICER). Depending on the choice of comparator regimens, routine testing for HLA B*5701 ranged from being a dominant strategy (i.e. less expensive and more beneficial) to an ICER versus no testing of Euro22,811 per hypersensitivity reaction avoided. Routine adoption of testing was the dominant strategy when the cost of alternative non-abacavir-containing regimens was low.

The results of the probabilistic sensitivity analysis suggested ceiling ratios ranging from Euro 0 to Euro 37,776 depending on the alternative regimen. The results of the univariate sensitivity analysis suggested that the cost of the alternative regimen was most influential on the ICER, followed by the probability of developing a hypersensitivity reaction. Increasing to higher prevalence resulted in more favourable (for testing) ICERs.

Authors' conclusions
Pre-prescription genotyping prior to the initiation of abacavir therapy may be a cost-effective use of health care resources.

CRD COMMENTARY - Selection of comparators
The comparator (no HLA B*5701 genotyping) was justified on the grounds that it was current practice. You should decide if this is the case in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a case-control study design, which was appropriate for the study question. It is unknown whether the study sample was representative of the population where the population was defined as any person requiring antiretroviral treatment. The sample was drawn from patients who were already attending a Manchester clinic and receiving therapy. The patient groups were shown to be reasonably comparable at analysis, although only sociodemographic factors were compared. Ethnicity appears to have varied between cases and controls, but no significance testing was performed on the differences. An appropriate statistical analysis of the outcomes was not undertaken to account for potential systematic bias. In additional, the sample size was small, limiting interpretation and the weight of the findings.

In searching for effectiveness data, the authors did not state if the review was conducted systematically to identify all relevant research and to minimise bias. Certain effectiveness estimates from the literature were combined with the results of the authors' own study. This was done by pooling the results via a random-effects model, weighting to reflect the differing importance (sizes) of the studies. The authors do not appear to have fully considered the impact of differences between the primary studies when including them in the model. The authors assumed that all antiretroviral regimens were therapeutically equivalent, justifying this assumption by reference to the clinical trials literature. They also stated that modelling HIV treatments was outside the scope of this work. This assumption was not varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of benefits (hypersensitivity reactions avoided) was modelled. The authors derived the results appropriately, with the estimates of effectiveness entering a Markov model as probability distributions.

Validity of estimate of costs
All the categories of cost relevant to the NHS perspective were included in the analysis. The costs and the quantities were analysed separately but not reported separately. The resource use quantities were taken from a single study conducted at the authors' setting. A statistical analysis of the quantities was performed and resource use entered the model as an appropriate probability distribution. The drug prices were taken from a standard published source. Other medical resource prices were taken from the authors' hospital setting. The price year (2002) was reported, which will enhance any future inflation exercises. Statistical or sensitivity analyses of the prices were not performed. The authors
performed currency conversions from pounds sterling to Euros, but did not explain why. Hospital charges reported by financial departments were used to proxy costs; such charges do not reflect true opportunity costs (due to profit margin) and (in the absence of a cost-to-charge ratio) may limit the generalisability of the results beyond the authors' clinical setting.

Other issues
The authors compared their clinical findings with those from other studies. It is not known whether other cost-effectiveness studies exist as no reference was made. The issue of generalisability to other settings was addressed only in so far as the authors acknowledged that the analysis relates to Caucasian patients and not to those of other ethnicities. The authors did not present their results selectively. The results were presented for a large number of scenarios encompassing several alternative comparator therapy regimens of varying cost. The authors’ conclusions reflected the scope of the analysis. In particular, in their recognition that the design of the model meant that the cost of alternative regimens was a key influence on the results. The authors reported further limitations to their study. First, they looked at only one gene locus as a predisposing factor (there may be others). Second, because they chose a disease-specific outcome, comparisons of cost-effectiveness with other health technologies would be difficult.

Implications of the study
The authors noted that a recent policy document suggested stringent criteria for establishing the usefulness of a pharmacogenetic test, including analytic validity, clinical validity and clinical utility. They suggested that testing for HLA B*5701 appears to fulfil some of these criteria, but that clinical utility would require prospective studies. Whether implemented or not, clinicians should still use the abacavir risk management programme, which has been developed to reduce the likelihood of fatalities from this serious adverse reaction. The authors also noted that of critical importance in clinician prescribing is the diminished choice of therapies following the development of resistance to non-abacavir regimens. Finally, there is a need for a full economic model of HIV treatments as the authors considered it out of their scope.

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Other publications of related interest


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