Advanced HIV infection treated with zidovudine monotherapy: lifetime values of absolute cost-effectiveness as a pharmacoeconomic reference for future studies evaluating antiretroviral combination treatments

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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
Monotherapy and combination therapy using anti retroviral drugs in patients with the HIV infection.

Type of intervention
Treatment.

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

Study population
Patients over the age of 13 with the HIV infection whose CD4+ count fell below 200 per cubic millimetre.

Setting
Primary care and hospital. The economic analysis was conducted in Verona and Firenze, Italy.

Dates to which data relate
Effectiveness data on zidovudine were taken from a study carried out between April 1992 and June 1994 and resource data were taken from literature published in 1996. 1996 prices were used.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Costing was not undertaken on the same patient sample as that used in the clinical analysis.

Study sample
Data on zidovudine monotherapy were taken from a study comparing monotherapy with two agent combination therapy using didanosine or zalcitabine. Eligible patients were those with a CD4 cell count below 200 or those with an AIDS-related condition who enrolled in one of 21 units conducting clinical trials in the USA. Patients were excluded if they had a history or symptoms of pancreatitis or peripheral neuropathy, AIDS dementia complex of stage 2 or higher, if they were intolerant to medication, were pregnant or were receiving short term treatment for an AIDS-related condition. The sample size in the study was selected to give an 80% power to detect a 33% reduction in disease progression or death in one of the combination therapy groups compared with monotherapy alone.
1,113 patients were recruited to the study of whom 375 received zidovudine with or without placebo, 366 received zidovudine and didanosine, and 372 received zidovudine and zalcitabine. 11 patients (1%) were excluded from the study although the reasons for exclusion were not recorded. The mean age of patients in the monotherapy group was 37.9 years (+/- 7.8) and 7% were women.

**Study design**
The study was a 21 centre double blind randomised controlled trial. Patients were randomised between the groups using a stratified permuted block design. The median duration of follow up was 35 months (range: 1 - 44 months)

**Analysis of effectiveness**
The analysis of the clinical study was based on intention to treat. The primary health outcomes used in the analysis were incidence of disease progression, mortality and adverse events experienced. At the analysis there were no differences between groups as patients had been stratified according to their baseline characteristics.

**Effectiveness results**
The effectiveness results for monotherapy, zidovudine plus didanosine and zidovudine plus zalcitabine groups were:

- Death or disease progression rates per 100 person years, 39.6, 34.3 and 36.2, (p=0.24);
- Disease-free survival at 12 months, 71.9%, 74.8% and 74.7%;
- Disease-free survival at 24 months, 44.7%, 50.2% and 48.8%;
- Disease-free survival at 36 months, 27.6%, 35.7% and 31.3%;
- Survival rates at 12 months, 90.5%, 89.2% and 90.9%;
- Survival rates at 24 months, 65.4%, 67.5% and 67.7%;
- Survival rates at 36 months, 41.6%, 49.4% and 46.2%;
- Incidence of adverse events per 100 person years, 26.5, 32.9 and 32.6.

**Clinical conclusions**
The study concluded that combination therapy using zidovudine plus didanosine or zalcitabine was not superior to treatment with zidovudine alone, although combination therapy may be more effective in patients who previously have received little or no zidovudine treatment.

**Modelling**
Lifetime effectiveness estimates were made using the Gompertz method, whilst a combination of the Gompertz method and the quality adjusted time without symptoms or toxicity (Q-TWIST) method was used to calculate lifetime utility. The Q-TWIST method divides survival time into time without symptoms or toxicity (TWIST), survival with treatment induced toxicity (TOX) and survival after relapse or disease progression (PROGR).

**Measure of benefits used in the economic analysis**
The measures of benefits were life years gained and quality adjusted life years (QALYs) gained. Utility values were taken from a previous estimation using the Q-TWIST method where time spent in the TWIST state has a score of 1, and time in the TOX and PROGR states have a utility of 0.5.
Direct costs
Cost data for zidovudine were taken from an Australian study published in 1996. This study estimated the lifetime healthcare costs associated with HIV infection. Costs in the analysis included ambulatory care, hospital bed days, investigation, procedures and drugs. Costs of zalcitabine and saquinavir were taken from a US national publication. Both costs and benefits were discounted at a rate of 5% per annum and 1996 prices were used.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analysis was conducted in which utility values for the time spent in the PROGR phase was varied between 0.40 and 0.60 and similarly time in the TOX phase was varied between 0.50 and 0.80.

Estimated benefits used in the economic analysis
For cohorts of 100 patients, overall survival from the time of diagnosis using zidovudine monotherapy was 252.1 years and progression free survival was calculated to be 209.6 years. Based on a reported adverse event rate of 26.5 per 100 person years the time spent in the TOX state was estimated to be 66.8 years and time spent in the TWIST state was 142.7 patient years. Quality adjusted life years for the monotherapy cohort of 100 patients were then calculated to be 197.4 QALYs or 1.97 QALYs per patient.

Cost results
The discounted lifetime cost per patient were estimated to be $93,000. Additional costs of saquinavir and zalcitabine were $9,500 per patient per year.

Synthesis of costs and benefits
The cost per life year gained using zidovudine monotherapy was $36,890 and the cost per QALY was $47,112. Cost per QALY ranged from $42,770 to $48,152 in sensitivity analysis.

Authors' conclusions
The authors concluded that it was necessary to determine the cost-effectiveness of zidovudine as a reference for other newer regimens for the treatment of HIV such as triple combination therapy. Currently clinical trials are in progress to determine the efficacy of combination therapy. The authors calculated that if an average cost per life year of $30,000 was acceptable then patients would need to survive an additional 1.16 discounted years using triple combination therapy compared with zidovudine monotherapy.

CRD COMMENTARY - Selection of comparators
The authors did not make a direct comparison with any other intervention as zidovudine was assumed to be the cheapest and simplest antiretroviral treatment for patients with HIV, and there is as yet a lack of effectiveness information for the preferred and most expensive option of triple combination therapy including zidovudine. However, a comparison with dual combination therapy may have been appropriate as there may be evidence to suggest that this is more effective in patients with little previous use of zidovudine.

Validity of estimate of measure of benefit
Utility scores were not determined from patients in the clinical trial but from published values for Q-TWIST which may not therefore be appropriate. The estimate of effectiveness was taken from a randomised controlled trial comparing zidovudine with dual combination therapy.
Validity of estimate of costs
Costs were taken from one published economic study undertaken in Australia, which was different from the study used for clinical effectiveness. Although the authors claim that healthcare costs in the USA and Australia are similar, the cost estimate used in the analysis may be inappropriate and biased. The authors themselves noted that the dosages in the clinical study and the economic analysis were not exactly the same. Only direct health care costs were included in this study and it is necessary to include costs to others in society such as patients and caregivers and the authors noted that the costs of adverse effects and the influence of reduced morbidity had not been taken into consideration when determining the additional costs of combination therapy.

Other issues
The results of this study are not generalisable and very much limited at present by their reliance on effectiveness data taken from two different sources. Nevertheless the study highlights the need for well designed evaluations to be undertaken to compare the incremental costs and benefits of alternative treatments for patients with HIV with advanced disease staging.

Implications of the study
There is a need for well designed economic evaluations incorporating quality of life measurements to be conducted prospectively alongside clinical studies to compare different treatments for patients with HIV.

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None stated.

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Other publications of related interest

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