The cost effectiveness of antiretroviral regimens for the treatment of HIV/AIDS

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
Three alternative antiretroviral therapy (ART) regimens for the treatment of human immunodeficiency virus or acquired immune deficiency syndrome (HIV/AIDS) were studied. The three regimens were:

- zidovudine plus either didanosine or zalcitabine (ERA-I);
- stavudine plus (didanosine or zalcitabine) or lamivudine plus (zidovudine or didanosine or zalcitabine or stavudine) (ERA-II); and
- two nucleoside reverse transcriptase inhibitors plus either one protease inhibitor or one non-nucleoside reverse transcriptase inhibitor (ERA-III).

The three alternative regimens were selected to represent the evolution in the use of ART over time, from dual combination therapy to triple drug combination therapy. The triple drug combination represents the strategy also known as highly active ART (HAART).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult HIV-positive men and women with CD4+ counts of at least 350 cells/microL.

Setting
The setting was not stated. The economic study was carried out in the province of British Columbia in Canada.

Dates to which data relate
The effectiveness and resource use data were mainly gathered from October 1992 to June 1996. The price year was 1997.

Source of effectiveness data
The effectiveness evidence was derived mainly from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the analysis of the effectiveness.
Study sample
Power calculations to determine the sample size were not performed. Eligible patients who participated in the British Columbia Drug Distribution Program between October 1992 and June 1996 were included in the study. They were divided into three groups depending on the treatment received. The overall group comprised 815 patients. There were 463 individuals in the ERA-I group, 231 in the ERA-II group and 121 in the ERA-III group. In the ERA-I group, the median age was 36 years (interquartile age range: 31 - 43) and 93.1% of the participants were men. In the ERA-II group, the median age was 37 years (interquartile age range: 33 - 43) and 88.3% were men. In the ERA-III group, the median age was 38 years (interquartile age range: 32 - 45) and 93.4% were men. It was not stated whether some patients were excluded from the initial study sample for any reason.

Study design
This was a retrospective cohort study that included three groups of patients. The patients were assigned to each group on the basis of the treatment received. The maximum follow-up period for the survival data was 15 months. There were comparable follow-up data for this period.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis, as the patients were retained in their initial treatment group irrespective of subsequent switches. The primary health outcome used in the analysis was survival, which was estimated using the Kaplan-Meier approach. The study groups were comparable at baseline in their demographic characteristics, CD4+ cell counts, and prophylaxis.

Effectiveness results
Survival at 12 months was 89.6% in the ERA-I group, 91% in the ERA-II group and 97.6% in the ERA-III group. The difference between ERA-I and ERA-II survival was not statistically significant.

Clinical conclusions
The effectiveness analysis showed that survival improved significantly with the ERA-III treatment in comparison with both the ERA-I and ERA-II strategies.

Modelling
A modelling approach was used to calculate survival, using data from 220 VLAS participants that showed a 70% crude mortality rate for all causes. It was assumed that the treatment effect decreased exponentially over time.

Measure of benefits used in the economic analysis
The summary benefit measure used in the analysis was the life-years gained (LYG). These were obtained by combining the observational data with the information reported in the "reference cohort". A modelling approach was used and the benefits were discounted at a rate of 5%.

Direct costs
A 5% discount rate, as suggested by the Canadian Coordinating Office for Health Technology Assessment, was used to calculate the present values of lifetime costs. The unit costs and the quantities of resources used were not presented separately. The health services in the economic evaluation were drugs and treatment of opportunistic diseases (e.g. oesophageal candidiasis, cryptococcosis, cytomegalovirus, HIV dementia, Kaposi's sarcoma, lymphoma). The cost/resource boundary of the third-party payer was adopted. Resource use was estimated using actual data coming from the sample of patients included in the effectiveness study. The cost of drugs was estimated from the province-wide treatment programme. The cost of treating opportunistic diseases (including inpatient resources, procedures, investigations and physicians) came from St. Paul's Hospital, the largest HIV/AIDS tertiary care hospital in Canada.
the costs were deflated to 1997 values using the Price Index for medicinal and pharmaceutical products.

**Statistical analysis of costs**
The costs were not treated stochastically and were presented as point estimates. However, a regression analysis was performed to model the monthly cumulative costs.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
Canadian dollars (Can$). The conversion rate from Canadian to US dollars ($) was $1 = Can$1.5.

**Sensitivity analysis**
One-, two- and three-way sensitivity analyses were carried out to estimate the robustness of the cost-effectiveness ratios to variations in the following factors:

- no discounting of survival;
- variation of the costs by 25%;
- variation of the costs by 25% and the use of CD4+ cell count-unadjusted mortality rate for the VLAS cohort;
- treatment effect was one time benefit only, ending after the first year (pessimistic scenario), or treatment effect was continuous and equal to that observed in the first year (optimistic scenario);
- use of the annual hypothetical acquisition cost rather than the actual acquisition cost of the study drugs.

A threshold analysis was performed to assess the survival benefit needed for the cost-effectiveness ratio to be at certain bounds.

**Estimated benefits used in the economic analysis**
The estimated number of LYG was 1.18 between ERA-III and ERA-I, 1.11 between ERA-III and ERA-II, and 0.07 between ERA-II and ERA-I. Survival between ERA-I and ERA-II was not statistically significant at 12 months.

**Cost results**
The total incremental costs at 12 months were Can$69,208 between ERA-III and ERA-I, Can$52,213 between ERA-III and ERA-II, and Can$1,723 between ERA-II and ERA-I (the incremental costs in Table IV appear to be errors).

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the three alternative strategies. The incremental cost per LYG was Can$58,806 between ERA-III and ERA-I, and Can$46,971 between ERA-III and ERA-II. A cost-minimisation analysis was carried out to assess the cost-difference between ERA-II and ERA-I as survival was comparable. The cost-difference was Can$1,723 in favour of ERA-I.

The results of the sensitivity analysis showed that, under the different scenarios considered, the incremental cost per LYG varied from Can$292,234 to Can$14,498. Therefore, the results of the analysis depended on the scenario considered. When a threshold of Can$50,000 per LYG was used, the survival difference between ERA-III and ERA-II was 1.05 years. When a threshold of Can$100,000 per LYG was used, the survival difference between ERA-III and ERA-II was 0.53 years.
Authors’ conclusions

Triple combination therapy (ERA-III regimen) for the treatment of HIV/AIDS proved to be a cost-effective strategy in the USA, with an incremental cost-effectiveness ratio comparable to that of other currently funded therapies for the treatment of chronic diseases.

CRD COMMENTARY - Selection of comparators

The rationale for the choice of the comparators was clear. The authors included all HIV/AIDS treatments available in order to reflect the evolution in the treatment of HIV over time. You should decide whether the drugs used in each era represent widely used therapies in your own setting.

Validity of estimate of measure of effectiveness

The basis of the analysis of effectiveness was a retrospective cohort study. Power calculations were not performed and no justification for the sample size was provided. Therefore, it was unclear whether the number of patients included in each group was appropriate for the study question. It appears that a randomised design would not have been feasible because the study groups were identified in different periods, during which not all treatments were available. The authors noted that the use of an intention to treat analysis is likely to lead to biased results, as patients in the earlier eras were likely to switch to newer options. This was a conservative bias that underestimated the survival advantage of ERA-III over the earlier treatments. Data from the observational study were then "adjusted", with the mortality rate coming from a longitudinal study by means of a modelling approach. Some of the estimates were then varied in the sensitivity analysis.

Validity of estimate of measure of benefit

The use of the LYG as a summary benefit measure appears to have been appropriate for estimating the impact of the study interventions on the patients' health. Moreover, the use of survival permits comparisons with the benefits of other health care interventions, as it represents a comparable measure.

Validity of estimate of costs

The authors explicitly stated the perspective adopted in the study. However, they acknowledged that not all the relevant categories of costs were included in the analysis, as not all the treatment costs of HIV/AIDS patients were considered. Further, the unit costs and the quantities of resources used were not reported separately. The price year was given, thus simplifying reflation exercises in other settings. The authors also noted that the real costs might be higher than those estimated in the analysis, as the analysis was based on intention to treat, but some patients may have switched to newer and more expensive strategies. Clearly, this applies only to the costs estimated in ERA-I and ERA-II. Therefore, the cost-effectiveness of ERA-III treatments might be even more favourable. Due to uncertainty in some cost estimates, sensitivity analyses were performed. These showed the economic values that had the greatest impact on the results of the analysis.

Other issues

The authors compared their findings with those from other studies that evaluated other chronic diseases, in order to show that the cost-effectiveness of the study intervention was within the ranges of other health care programmes. However, the issue of the generalisability of the study results to other settings was not addressed explicitly. The results of the sensitivity analysis were clearly reported, thus enhancing the external validity of the analysis. The authors discussed the reasons for their choice of the modelling approach used in the analysis, rather than the alternative approach based on Markov modelling. Some limitations of the analysis were also noted. For example, the three treatments considered in the study did not represent actual alternative strategies but, instead, reflected changes in treatment patterns in developed countries.

Implications of the study
The authors stressed that the estimated cost-effectiveness ratio represents a conservative estimate and that the cost-effectiveness ratio of ERA-III may be even lower in a real life setting. The main implication of the study is that those countries that are still using ERA-I regimens could safely and efficiently switch directly to ERA-III treatments, without passing through the phase of ERA-II therapies.

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