Use of genotypic resistance testing to guide HIV therapy: clinical impact and cost-effectiveness


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 genotypic antiretroviral resistance testing (GART) for drug-resistant strains of human immunodeficiency virus (HIV).

Type of intervention
Diagnosis.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of HIV-infected patients with baseline CD4 counts of 0.250 x10^9 cells/L.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2000. Resource use and cost data were derived mainly from 1994 data. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A state-transition model, based on a first-order Markov process, was used to estimate the lifetime costs and benefits of adding GART to clinical judgment for drug-resistant strains of HIV in a cohort of one million patients aged 33 years, 80% of which were male. The health states were defined by a patient's current and maximum HIV RNA level (or viral load), CD4 cell count, time receiving HAART, history of effective and ineffective HAART, and previous opportunistic infections. Patients could move across health states at monthly cycles. The patients could enter and exit temporary health states such as Pneumocystis carinii pneumonia, toxoplasmosis, disseminated Mycobacterium avium complex, fungal infections, cytomegalovirus, and a residual category consisting of "other" acquired immune deficiency syndrome (AIDS)-related complications. These "other" complications included bacterial infections, tuberculosis and lymphoma. From these temporary health states, patients could die or survive, allowing a transition to a new chronic state. The time horizon of the model was lifetime.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the monthly risk for opportunistic infections according to CD4 cell count;
- HIV RNA suppression in patients taking HAART with zidovudine/lamivudine/indinavir, taking HAART with zidovudine/lamivudine/efavirenz, taking HAART after initial failure with and without GART, taking HAART with late salvage therapy, and taking initial HAART with primary resistance testing;
- the monthly increase in CD4 cell count in patients receiving effective HAART (with initial HAART; with HAART after initial failure with and without GART);
- the monthly increase in HIV RNA level after HAART failure;
- the frequency of HIV RNA level after HAART failure;
- health-related quality of life scores (according to CD4 cell count); and
- other clinical inputs used in the model.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature had been carried out to identify all relevant primary studies. The results of two clinical trials, the Community Programs for Clinical Research on AIDS (CPCRA) and the AntiretroVIRal ADAPtation (VIRADAPT), which provided clinical evidence on GART, were the main sources for input parameters. Other information came from other trials or cohort studies.

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 15 primary studies provided evidence.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
Only some of the key literature-based model inputs are reported here.

HIV RNA suppression in patients taking HAART was:
60% at 24 weeks with zidovudine/lamivudine/indinavir;

70% at 48 weeks with zidovudine/lamivudine/efavirenz;

34% (alternative estimate: 32%) at 12 weeks for HAART after initial failure with GART, and 22% (alternative estimate: 14%) at 12 weeks for HAART after initial failure without GART;

11% at 12 weeks with late salvage therapy; and

60 to 70% at 24 weeks with initial HAART with primary resistance testing.

The monthly increase in CD4 cell count in patients receiving effective HAART was 0.0121 x 10^9 cells/L with initial HAART, 0.0083 x 10^9 cells/L for HAART after initial failure with GART, and 0.0060 x 10^9 cells/L for HAART after initial failure without GART.

The monthly increase in HIV RNA level after HAART failure was (log10 copies/mL) was 0.5. The frequency of HIV RNA level after HAART failure was every 3 months.

The health-related quality of life scores were 0.94 with a CD4 cell count greater than 0.2 x 10^9 cells/L, 0.87 with a CD4 cell count between 0.100 and 0.200 x 10^9 cells/L, and 0.81 with a CD4 cell count between 0.050 and 0.100 x 10^9 cells/L.

**Measure of benefits used in the economic analysis**

The summary benefit measure was the quality-adjusted life-years (QALYs). These were derived by combining utility weights and survival data in a modelling approach. Utilities for the chronic and acute health states were obtained by transforming quality of life data from ACTG Protocols. The long-term benefits were discounted at an annual rate of 3%.

**Direct costs**

An annual discount rate of 3% was applied since the lifetime costs were estimated. The unit costs were not presented separately from the quantities of resources used for all items. The health services included in the economic evaluation were GART, HIV-related medications, late salvage regimens, tests for CD4 cell count, and HIV RNA level. The cost/resource boundary of the study was not clear, but only the direct medical costs were included in the economic evaluation. Both the costs and resource use data were mainly estimated from the AIDS Cost and Services Utilization Survey. A cost-to-charge ratio was applied to convert charges into costs of services. Drug prices were obtained from the Red Book. The cost of GART was obtained from the Boston Medical Center. Some quantities of resources used were derived from authors' assumptions. All the costs were adjusted to 1998 values using the medical care component of the Consumer Price Index.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

The indirect costs were not included in the economic evaluation.

**Currency**

US dollars ($).

**Sensitivity analysis**

Several univariate sensitivity analyses were carried out to examine the robustness of the cost-effectiveness ratios to
variations in key model inputs. Inputs such as the relative effectiveness of GART, health-related quality of life, cost-to-charge ratio, discount rate, duration of HAART efficacy, cost of GART, and efficacy of second-line and late therapy, were varied. Alternative values were derived from the literature or based on authors' assumptions. The scenario in which GART was used for primary resistance testing was also estimated.

Estimated benefits used in the economic analysis
Using the data from the CPCRA 046 study, the discounted (undiscounted) quality-adjusted life-expectancy was 60.9 (78.3) months with clinical judgment alone and 63.1 (81.3) months with GART.

Using the data from the VIRADAPT study, the discounted quality-adjusted life-expectancy was 62.2 months with clinical judgment alone and 66.4 months with GART.

Cost results
Using the data from the CPCRA study, the estimated discounted costs were $90,360 with clinical judgment alone and $93,650 with GART.

Using the data from the VIRADAPT study, the estimated discounted costs were $91,980 with clinical judgment alone and $97,790 with GART.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of the alternative strategies. The incremental cost per QALY gained was $17,900 when using data from the CPCRA study and $16,300 when using data from the VIRADAPT study.

The sensitivity analysis showed that the base-case cost-utility ratios remained below the value of $25,000 when the relative effectiveness of GART, health-related quality of life, cost-to-charge ratio, discount rate, duration of HAART efficacy, cost of GART, and efficacy of second-line and late therapy were varied.

The cost-effectiveness of GART used for primary resistance testing was also estimated. Under base-case assumptions, the incremental cost per QALY ranged from $11,600 to $69,000. For example, if a sub-set of patients comprising 20% of the population was assumed to have some degree of primary drug resistance, and if resistance testing reduced the probability of failure in this sub-set by 25%, then a 5% overall reduction in failure in the population would be expected. Thus, at a testing cost of $400 per patient, the cost per QALY gained would be $22 300.

Authors' conclusions
Genotypic antiretroviral resistance testing (GART), used to guide the choice of highly active antiretroviral therapy (HAART), was a cost-effective strategy for patients with human immunodeficiency virus (HIV). This conclusion held under a wide range of assumptions investigated in the sensitivity analysis. The estimated cost-utility ratio was comparable with that of many generally recommended interventions for HIV-infected patients.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (clinical judgement alone) was appropriate as it reflected the standard approach to determine drug resistance. The authors stated that phenotypic resistance testing, as an alternative to GART, was not investigated because of the lack of available data. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies. It was not stated whether a systematic review of the literature had been undertaken and the primary studies appear to have been identified selectively. Information on the design of
the primary studies was briefly reported. The authors stated that some data were derived from clinical trials. The methods used to extract and combine the data were not described. Key model inputs were varied in the sensitivity analysis, which addressed the issue of uncertainty in some estimates.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate as it incorporates the impact of the interventions on survival and quality of life. The authors stated that although quality of life weights were not obtained directly from preference-based utility scales, they were similar to those obtained directly from HIV-patients using time trade-off or standard gamble approached. Discounting was applied, as recommended in US guidelines. QALYs are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The perspective adopted in the study was not clear and only the direct medical costs were considered. In general, the unit costs were not presented separately from the quantities of resources used and a detailed breakdown of the items was not reported. Statistical analyses of the costs were not carried out, but key cost items were varied in the sensitivity analysis. The price year was reported, which enhances the possibility of reflating the results of the analysis. The source of the data was provided for most items.

Other issues
The authors made limited comparisons of their findings with those of other interventions for HIV patients, such as prophylaxis and HAART strategies. The issue of generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were carried out. This enhanced the external validity of the study. The authors noted some limitations of their analysis. For example, the use of unproven assumptions about the mechanism of disease progression and the speculative analysis of primary resistance testing.

Implications of the study
The authors stated that their findings support recent national recommendations that GART should become routine for HIV-infected patients in whom initial HAART has failed.

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Other publications of related interest


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