The cost-effectiveness of expanded testing for primary HIV infection

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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
Three diagnostic tests for primary human immunodeficiency virus (HIV) infection were examined:

HIV-1 RNA assay (by polymerase chain reaction, branched-chain DNA, or transcription-mediated amplification);

p24 antigen enzyme immunoassay (EIA); and

third-generation HIV-1 EIA.

Type of intervention
Diagnosis.

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

Study population
The study population comprised a hypothetical cohort of patients with viral symptoms and at least one risk factor for HIV infection. Risk factors for HIV infection included fever, rash or sore throat.

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 1988 and 2005. Some resource use and cost data came from sources published from 2000 to 2004. The price year was 2002.

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

Modelling
A decision tree model was constructed to assess the clinical and economic impact of the alternative diagnostic strategies for the detection of primary HIV in a hypothetical cohort of 3,030,303 individuals. In each diagnostic branch of the tree, patients could have a positive or a negative test result. In the case of a positive test, individuals could change or not change their sexual behaviour. In the case of no change in sexual behaviour, the partner could get infected or could remain uninfected. The time horizon of the model was 39.9 years, which represents the life expectancy of the mean age (39.5 years) of the hypothetical cohort under examination. The test results could be true-positive, false-positive, true-negative or false-negative. Treatment of patients in each branch was described. Antiviral therapy was given to patients with a CD4 cell count lower than 350 per microL, as US guidelines recommended.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- test characteristics,
- prevalence factors,
- utility values, and
- discounted quality-adjusted life-years (QALYs) for different scenarios.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature had been undertaken to identify the primary studies. Limited information on the design and characteristics of the primary studies was provided. Survival data came from life tables. Some utility data were estimated from a national sample of HIV-infected adults.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Twelve primary studies provided the clinical data.

Methods of combining primary studies
Most of the primary estimates were not combined since each study provided a series of estimates.

Investigation of differences between primary studies
Not reported.

Results of the review
The sensitivity of the p24 antigen EIA was 0.887 (range: 0.770 - 0.957) and the specificity was 0.9996 (range: 0.9950 - 0.9999).

The sensitivity of the HIV-1 RNA test was 1 and the specificity was 0.980 (range: 0.950 - 0.999).

The sensitivity of the third-generation HIV-1 EIA was 0.790 (range: 0.600 - 0.920) and the specificity was 0.970 (range: 0.930 - 0.990).

With respect to prevalence factors:

the rate of patients lost to follow-up was 31% (range: 16 - 62),
the prevalence in the screened population was 0.66% (range: 0.53 - 0.92),

the rate of patients who changed behaviour to avoid infecting a sexual partner was 50% (range: 0 - 96),

the rate of patients that were sexually active was 50% (range: 0 - 30), and

the rate of infectivity (probability of sexual transmission during PHI period) was 15% (range: 0 - 30).

The utility values were 0.937 (range: 0.926 - 0.949) for asymptomatic HIV infection and 0.682 (range: 0.400 - 0.800) for anxiety while waiting for confirmatory test results for patients with a positive screen.

The discounted QALYs were:

24 for no primary HIV infection;

23.9735 (range: 23.950 - 23.983) for positive screening result but no primary HIV infection;

11.9 (range: 11.832 - 11.952) for primary HIV infection diagnosed at screening with follow-up care and antiretroviral treatment started at a CD4 cell count of 350 per microL; and

11 for primary HIV infection not diagnosed at screening, or lost to care with antiretroviral treatment started when HIV diagnosed.

Measure of benefits used in the economic analysis
The summary benefit measures used were the QALYs and cases identified. These were estimated using a modelling approach. QALYs associated with different pathways were calculated directly from the literature. The total QALYs associated with the different screening strategies were calculated by multiplying the number of individuals following a certain pathway by the discounted QALYs associated with that pathway. The primary HIV infection cases lost to care (31% of those diagnosed), the false-positive diagnoses, the false-negative diagnoses, and the cases avoided per behaviour change, were also reported as model outputs. An annual discount rate of 3% was applied.

Direct costs
The author stated that a societal perspective was adopted in the analysis of the costs, but transportation costs were not included. The health services considered were the HIV-testing programme, laboratory tests, visits, and the lifetime medical costs for those diagnosed or not diagnosed with primary HIV infection. The cost of the testing programme included HIV counsellors and intake nurses, who arranged for telephone follow-up, visits to homeless shelters and travel vouchers to bring positive patients into care. The unit costs were presented separately from the quantities of resources used for only some items, while lifetime medical costs were presented as macro-categories. The cost of the HIV-testing programme was obtained from a state-funded programme in Massachusetts that offered HIV counselling, testing and referral to more than 3,000 patients entering one of four hospital-associated urgent care centres. The costs of the laboratory tests came from the Medicare fee schedule. Visit costs were estimated from a national survey of physician's office charges. Lifetime medical costs were based on a published simulation model. The source of the resource use data was unclear, but the data seem to have been mainly derived from authors' assumptions and published studies. Discounting was relevant since the costs were incurred over a long timeframe, and an annual rate of 3% was applied. The price year was 2002, and cost estimates of different fiscal years were inflated to 2002 using the Consumer Price Index.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included because they were considered negligible in comparison with other direct costs.
Currency
US dollars ($).

Sensitivity analysis
A threshold analysis was carried out to assess the lowest primary HIV infection prevalence at which expanded testing was cost-effective (below a threshold of $50,000 per QALY) using alternative values of prevalence that were derived from the literature. Other univariate sensitivity analyses were carried out to determine the robustness of the base-case results to variations in clinical and economic model inputs. A multivariate sensitivity analysis was performed using Monte Carlo simulation (100,000 interactions).

Estimated benefits used in the economic analysis
In the whole cohort, the estimated QALYs (in thousands) were 69,710.0 with no testing, 69,720.8 with third-generation HIV-1 EIA, 69,726.1 with p24 antigen EIA and 69,725.8 with the HIV-1 RNA assay.

The primary HIV infection cases diagnosed were 15,803 with third-generation HIV-1 EIA, 17,054 with p24 antigen EIA and 20,000 with the HIV-1 RNA assay.

The primary HIV infection cases lost to care (31% of those diagnosed) were 20,000 with no testing, 4,899 with third-generation HIV-1 EIA, 5,287 with p24 antigen EIA and 6,200 with the HIV-1 RNA assay.

The false-positive diagnoses were 90,257 with third-generation HIV-1 EIA, 1,127 with p24 antigen EIA and 59,169 with the HIV-1 RNA assay.

The false-negative diagnoses were 2,924 with third-generation HIV-1 EIA, 3,012 with p24 antigen EIA and 0 with the HIV-1 RNA assay.

The cases avoided per behaviour change were 403 with third-generation HIV-1 EIA, 435 with p24 antigen EIA and 501 with the HIV-1 RNA assay.

Cost results
In the whole cohort, the estimated costs (in millions) were $1,762.1 with no testing, $2,233.6 with third-generation HIV-1 EIA, $2,258.2 with p24 antigen EIA and $2,561.8 with the HIV-1 RNA assay.

Synthesis of costs and benefits
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of the alternative diagnostic strategies.

The incremental cost per case identified over the next less effective strategy (from the third-party payer perspective) was $29,836 with third-generation HIV-1 EIA, $29,090 with p24 antigen EIA and $39,985 with the HIV-1 RNA assay.

The incremental cost per QALY saved was $30,800 with p24 antigen EIA in comparison with no testing, while the other two diagnostic techniques were dominated.

The sensitivity analysis showed that the threshold value for primary HIV prevalence at which the cost per QALY of p24 antigen EIA in comparison with no testing exceeded the threshold of $50,000 was 0.35. For example, at a prevalence of 1% (urban patients with risk factors) the costs were $23,000 per QALY, while at a prevalence of 0.56% (patients with rash and other viral symptoms) the costs were $35,000 per QALY.

The other sensitivity analyses suggested that p24 antigen EIA generally remained the most cost-effective strategy. The exceptions were when the costs of the expanded testing and counselling enrolment programme were doubled and when no benefit to sexual partners of patients with primary HIV infection was assumed.
The probabilistic sensitivity analysis showed that the p24 antigen EIA testing strategy had a 19% probability of being dominant, a 48% probability of having a cost per QALY of less than $50,000, and a 33% probability of having a cost per QALY of more than $50,000 compared with no testing. The probability that p24 antigen EIA testing is less effective was 0%.

The HIV-1 RNA assay, when compared with the p24 antigen EIA, had a 3% probability of being dominant or having a cost per QALY of less than $50,000, a 44% probability of having a cost per QALY of more than $50,000, and a 53% probability of being dominated.

**Authors’ conclusions**

Expanded testing for primary human immunodeficiency virus (HIV) infection with p24 antigen enzyme immunosorbent assay (EIA) might be a cost-effective intervention to curtail the HIV epidemic in the USA.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparators was appropriate as three different strategies for HIV-testing were compared with no testing, which is often the current strategy in the USA given the low HIV prevalence. Ora-Quick HIV rapid test, which became available in late 2002 in the USA, was not included in the analysis because of a lack of data. You should decide whether these comparisons are relevant in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence was estimated from published studies. It was not stated whether a systematic review of the literature had been undertaken to identify the primary studies, which appear to have been included selectively. There was limited information on the studies used to estimate clinical inputs. Similarly, the methods used to extract and then combine the primary estimates were not described. Sensitivity analyses were carried out to address the issue of uncertainty.

**Validity of estimate of measure of benefit**

Both generic and disease-specific benefit measures were used in the economic analysis. While 'HIV infection cases' is comparable only with the benefits of similar interventions, the use of QALYs enables comparisons with the results of other health care technologies. The QALYs were estimated from the literature using data from a national survey. As suggested in US recommendations for economic evaluations, an annual discount rate of 3% was applied.

**Validity of estimate of costs**

A broad perspective was adopted in the study. Some categories of costs, such as the indirect costs or transportation, costs were not included because the author stated that their impact was negligible in comparison with the direct medical costs. The unit costs were presented only for some items. Other costs were presented as macro-categories, which represents a typical approach for the assessment of lifetime costs. The source of the data was reported for all items. The price year was reported, which enhances the possibility of performing reflation exercises in other time periods. The cost estimates were specific to the study setting, but key cost items were varied in the sensitivity analysis. Further, probabilistic distributions were assigned to all economic inputs in the Monte Carlo simulation. The author noted that the lifetime medical costs came from a study that used 1998 cost estimates, which might have been too old to reflect the actual costs of antiretroviral treatment. However, the base-case results were robust to variations in such cost estimates.

**Other issues**

The results of a few published studies were reported, but the author stated that comparisons with their findings were difficult because of the differences in the assessment of screening costs and benefits. The issue of the generalisability of the study results to other settings was not explicitly stated, but extensive sensitivity analyses were carried out. These enhance the external validity of the study. A potential limitation of the analysis was the use of data on test accuracy derived from patients who were recruited when they were outside the symptomatic phase of primary HIV infection.
The study referred to patients with risk factors for primary HIV and this was reflected in the author's conclusions.

**Implications of the study**
The study results supported the implementation of expanded testing for primary HIV infection with p24 antigen EIA.

**Source of funding**
None stated.

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