Potential cost-effectiveness of maternal and infant antiretroviral interventions to prevent mother-to-child transmission during breast-feeding

Maclean C C, Stringer J S

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
Several prophylactic treatments for the prevention of mother-to-child human immunodeficiency virus (HIV) transmission during breastfeeding (BF) were examined:

BF for 6 months with daily infant nevirapine (NVP) prophylaxis;
maternal 3-drug combination antiretroviral therapy (ART) during pregnancy and for 6 months of BF; and
maternal combination ART during pregnancy only for women who meet CD4 criteria (CD4+ count =/≤ 200 cells/mL).

Each of the three interventions was compared with three alternative strategies:

BF for 12 months;
BF for 6 months; and
formula feeding for 12 months.

All strategies were evaluated in the context of available voluntary counselling and testing (VCT), and intrapartum and neonatal single-dose NVP prophylaxis.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 40,000 pregnant women presenting for antenatal care.

Setting
The setting was primary care. The economic study was carried out in Zambia.

Dates to which data relate
The clinical data and some resource use estimates were derived from studies published between 1999 and 2003. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

**Modelling**
A Markov model was constructed to assess the natural history of vertical HIV transmission in a hypothetical cohort of 40,000 pregnant women presenting for antenatal care in Lusaka, Zambia. The model also assessed the impact of each of the interventions examined on the costs and benefits. Infants were assumed to progress through the health states uninfected, HIV-infected, acquired immune deficiency syndrome (AIDS) and dead. All women were offered VCT and those who tested positive were offered one of the interventions. The time horizon appears to have been lifetime. The cycle length was unclear.

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

- HIV prevalence;
- women with a CD4+ count =/< 200 cells/mL;
- counselling and testing uptake;
- adherence to peripartum ART;
- the proportion of stillbirths;
- the monthly risk of mortality due to NVP toxicity;
- the efficacy of each of the interventions (risk of HIV transmission);
- survival data; and
- utility weights.

**Study designs and other criteria for inclusion in the review**
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. Inclusion criteria for the primary studies were not reported. The evidence came from clinical trials, as well as prospective/retrospective studies and meta-analyses. Limited information on the design of the primary studies and the patients' characteristics was provided. The majority of the studies were performed in sub-Saharan Africa, but some were data derived from studies conducted in the USA.

**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**
Sixteen primary studies provided clinical data.
Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates. When multiple estimates were available for a model input, the authors justified the choice of the value they used in the model.

Investigation of differences between primary studies
Not stated.

Results of the review
HIV prevalence was 0.15 (range: 0.005 - 0.45).

The rate of women with a CD4+ count < 200 cells/mL was 0.20 (range: 0.05 - 0.40).

The rate of counselling uptake was 1 (range: 0.50 - 1) and that of test uptake was 0.64 (range: 0.30 - 1).

The adherence rate to peripartum ART was 0.74 (range: 0.5 - 1).

The proportion of stillbirths was 0.10 (range: 0.05 - 0.25).

The monthly risk of mortality due to NVP toxicity was 0 (range: 0.001 - 0.1).

The risk of HIV transmission in the peripartum was:
0.251 with no intervention,
0.549 with no intervention and a CD4+ count < 200 cells/mL, and
0.198 with no intervention and a CD4+ count =/> 200 cells/mL.

The relative efficacy in reducing the risk of maternal-to-child HIV was:
47% (range: 20 - 64) with NVP,
34.8% (range: 15 - 55) with NVP and a CD4+ count =/> 200 cells/mL,
82% (range: 65 - 100) with ART,
91% (range: 65 - 100) with ART and a CD4+ count < 200 cells/mL,
4.4 to 6.6% (varied by age) with BP and no intervention, and
37% (range: 0 - 100) with BF and infant NVP.

The cumulative risk of death in HIV-infected children was 0.26 at 1 year, 0.45 at 2 years and 0.62 at 5 years.

The cumulative risk of progressing to AIDS was 0.17 at 1 year, 0.28 at 2 years and 0.35 at 5 years.

The median duration of survival after developing AIDS was 9 months (range: 4 - 21).

The monthly risk of mortality due to no BF was between 0.00094 and 0.0078 (varied by age).

The life expectancy of HIV-negative infants was 35.3 years (range: 45 - 65).

The utility weights were 0.877 for infants who were HIV-infected and 0.495 for those with AIDS.
Methods used to derive estimates of effectiveness
The authors made some assumptions to derive estimates of effectiveness that were not available from the literature.

Estimates of effectiveness and key assumptions
Adherence to both BF NVP and to combination ART was 0.74 (range: 0 - 1). The relative efficacy in reducing the risk of HIV transmission was 82% (range: 50 - 100) with BF and ART, and 91% (range: 50 - 100) with BF and ART CD4+ count < 200 cells/mL.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were obtained by combining data on mortality and quality of life derived from the literature. Few details of the utility weights used to calculate the QALYs were reported. An annual discount rate of 5% was applied.

Direct costs
The costs were evaluated from the perspective of the government health district. The health services included in the economic evaluation were counselling, HIV testing, CD4+ testing, NVP, NVP during BF, combination ART, formula, and additional public health expenditure of an HIV-positive child. The unit costs were presented, but the information on the quantities of resources used was less clear. The unit costs were estimated from local sources, as well as from published studies and average wholesale prices. The authors justified the choice of the cost estimates among those available from the literature or the market. Resource consumption was, in general, derived from the literature. Discounting was relevant, owing to the long timeframe of the decision model, and an annual rate of 5% was used. The price year was 2003.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
The robustness of the model results (cost-utility ratios) to wide variations in all model inputs was examined. The ranges of values used were either derived from the literature (95% confidence intervals from clinical trials) or were set by the authors. One-way sensitivity analyses were used.

Estimated benefits used in the economic analysis
All results refer to a cohort of 40,000 women.

The estimated QALYs were:
- 446,208 with BF for 6 months,
- 445,922 with BF for 12 months,
- 447,391 with BF for 6 months with NVP.
446,187 with formula for 12 months,
446,689 with combination ART based on CD4+ count, and
451,250 with combination ART to all HIV-infected women.

Cost results
The estimated costs were:

$806,995 with BF for 6 months,
$816,858 with BF for 12 months,
$900,633 with BF for 6 months with NVP,
$1,483,935 with formula for 12 months,
$1,016,630 with combination ART based on CD4+ count, and
$1,244,421 with combination ART to all HIV-infected women.

Synthesis of costs and benefits
Average and incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative prophylactic strategies. The authors stated that, by World Bank measures, the decision-makers’ willingness to pay for a QALY gained in developing countries was set at $64, which represented the threshold for the cost-effectiveness of an intervention.

The average cost per QALY was:

$1.81 with BF for 6 months,
$1.83 with BF for 12 months,
$2.01 with BF for 6 months with NVP,
$3.33 with formula for 12 months,
$2.28 with combination ART based on CD4+ count, and
$2.76 with combination ART to all HIV-infected women.

In the evaluation of infant NVP prophylaxis, the incremental analysis showed that BF was the reference strategy, BF for 12 months and formula for 12 months were dominated, and the incremental cost per QALY gained with BF for 6 months with NVP was $79.13.

In the evaluation of combination ART based on CD4+ count, the incremental analysis showed that BF was the reference strategy, BF for 12 months and formula for 12 months were dominated, and the incremental cost per QALY gained with BF for 6 months with combination ART based on CD4+ count was $317.16.

In the evaluation of combination ART to all HIV-infected women, the incremental analysis showed that BF was the reference strategy, BF for 12 months and formula for 12 months were dominated, and the incremental cost per QALY gained with BF for 6 months with combination ART to all HIV-infected women was $86.75.

The sensitivity analysis showed interesting results. For BF with daily infant NVP to be cost-effective, NVP should be at least 44% effective (it was 37% in the base-case analysis), or cost no more than $5 per month ($6 in the base-case...
analysis). It would also be cost-effective if adherence was at least 87% (74% in the base-case), or the cost of caring for an infected infant exceeded $575. If NVP was donated, it would only have to be minimally effective to be the preferred option.

The results for ART to all HIV-infected women were sensitive to estimates of adherence and the cost of ART. ART was the preferred strategy if adherence exceeded 83% (keeping efficacy at 82%), if efficacy exceeded 95%, or if the cost of ART was less than $34.50 per month.

The strategy of combination ART based on CD4+ count was the optimal strategy only if the cost of the CD4 test was very low and the proportion of women having a CD4 count ≤ 200 cells/mL was very low.

Authors’ conclusions
Breastfeeding (BF) for 6 months was the most cost-effective strategy to avoid vertical transmission of the human immunodeficiency virus (HIV) in pregnant women living in developing countries. The sensitivity analysis showed scenarios where both infant nevirapine (NVP) prophylaxis and antiretroviral therapy (ART) were cost-effective, for example, if infant NVP was donated or if ART cost less than $34.50 per month.

CRD COMMENTARY - Selection of comparators
The authors discussed extensively the choice of the comparators under examination, focusing on the context of developing countries. In general, the comparators selected reflected the preventive options available for resource-poor areas. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data came from published evidence. However, it would appear that the primary studies providing the clinical data were identified selectively and a systematic review of the literature might not have been performed. Limited information on the design and characteristics of the primary studies was provided, although some of them were clinical trials performed in sub-Saharan Africa. Further, the methods used to extract the data from each study and to combine the primary estimates were not reported clearly. Thus, it was not possible to assess the quality and robustness of the primary sources and to evaluate the approach used to pool clinical data in the decision model. Some assumptions were also made. The issue of uncertainty was extensively addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
QALYs were used as the summary benefit measure. This was appropriate because QALYs capture the impact of survival and quality of life in a single measure. Discounting was applied. Utility adjustments were derived from the literature, but limited information on the source of the data was reported. QALYs are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The costs included were consistent with the perspective adopted in the study, thus indirect costs were not included in the economic evaluation. Extensive information on the unit costs was provided and some details of the quantities of resources used were also given. A detailed breakdown of the cost items was reported, which enhances the possibility of replicating the results of the study in other settings. The source of the cost data was reported. The costs were treated deterministically in the base-case, but the cost estimates were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods. Discounting was relevant and was appropriately carried out.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. However, extensive sensitivity analyses
were carried out, which not only examined the robustness of the base-case results but also enhanced the external validity of the analysis. The study referred to pregnant women attending antenatal care in a developing country and this was reflected in the authors’ conclusions. The authors noted some limitations of their study. For example, some benefits (i.e. improved maternal health due to ART) were not taken into consideration, and the uncertainty surrounding some model inputs.

**Implications of the study**
The study results supported the current policy of recommending BF for 6 months to avoid vertical transmission of HIV in a resource-poor setting. However, under some conditions, either infant NVP or ART might be cost-effective. Also, it should be noticed that BF for 6 months with NVP was the most effective strategy, and a small reduction in NVP would make it cost-effective also from the perspective of developing countries.

**Source of funding**
Supported in part by the US National Institutes of Health and the Elizabeth Glaser Pediatric AIDS Foundation.

**Bibliographic details**

**PubMedID**
15793368

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-HIV Agents /adverse effects /economics /therapeutic use; Breast Feeding /adverse effects; Costs and Cost Analysis; Female; HIV Infections /epidemiology /mortality /prevention & control; HIV Seroprevalence; Humans; Infant, Newborn; Infectious Disease Transmission, Vertical /prevention & control; Markov Chains; Nevirapine /adverse effects /economics /therapeutic use; Pregnancy; Pregnancy Complications, Infectious /prevention & control /virology; Risk Factors; Rwanda; United States /epidemiology

**AccessionNumber**
22005000771

**Date bibliographic record published**
31/12/2005

**Date abstract record published**
31/12/2005