Journal of the Operational Research Society (2005) 56, 222–233

www.palgrave-journals.com/jors

Use of discrete-event simulation to evaluate strategies for the prevention of mother-to-child transmission of HIV in developing countries

MS Rauner[1]*, SC Brailsford[2] and S Flessa[3]

[1]*University of Vienna, Vienna, Austria;* [2]*University of Southampton, Southampton, UK; and* [3]*University of Heidelberg, Heidelberg, Germany*

HIV/AIDS affects over 40 million people worldwide, and more than 70% of these people live in Africa. Mother-to-child transmission of HIV accounts for over 90% of all HIV infections in children under the age of 15 years. However, implementing HIV prevention policies in Africa is extremely difficult because of the poor medical and socio-economic infrastructure. In this paper, we present a discrete-event simulation model that evaluates the relative benefits of two potentially affordable interventions aimed at preventing mother-to-child transmission of HIV, namely anti-retroviral treatment at childbirth and/or bottlefeeding strategies. The model uses rural Tanzanian data and compares different treatment policies. Our results demonstrate that strategic guidelines about breastfeeding are highly dependent on the assumed increase in infant mortality due to bottlefeeding, the efficacy of anti-retroviral treatment at childbirth, and the maternal health stage. The cost of averted infections, though low by Western standards, may represent significant obstacles to policy implementation in developing countries.

Journal of the Operational Research Society (2005) **56,** 222–233. doi:10.1057/palgrave.jors.2601884
Published online 24 November 2004

Keywords: vertical HIV/AIDS transmission; discrete event simulation; cost-effectiveness analysis; epidemic policy model; decision-support-system

Introduction

Operational Research models have long been established as an effective tool for tackling a wide range of health-care problems. Discrete-event simulation (DES) has been widely used as a modelling approach, especially for modelling disease processes in order to evaluate treatments and other interventions. DES offers great benefits because of its flexibility, its ability to deal with variability and uncertainty, and its use of animation and graphics to facilitate communication with health-care professionals and decision-makers. DES deals with individual patients, and this makes it ideal for modelling situations where this level of resolution is necessary in order to make the model realistic.

In this paper, we present a DES model designed to evaluate HIV interventions targeted at HIV-positive mothers and their babies. HIV/AIDS affects more than 40 million people worldwide, and over 70% of HIV-infected people live in Africa. Mother-to-child ('vertical') transmission of HIV, during childbirth and subsequently via breastfeeding, accounts for nearly all HIV infections in children under the age of 15 years, and has a devastating socio-economic impact. More than 2 million children under 15 years lived with HIV/AIDS in Africa at the end of 2003, while about half a million children under 15 years died due to the pandemic and about 620 000 acquired HIV in Africa during 2003.[1] Our aim was to determine whether bottlefeeding strategies, in combination with HIV treatment at childbirth, are a blessing or a curse for low-income countries. On the one hand, bottlefeeding might inhibit HIV transmission, but on the other hand bottlefed babies are likely to have a higher background mortality risk compared with breastfed babies.[2–4] In the model we used rural data from Tanzania to evaluate several different treatment policies. In Africa a very large proportion of working-age adults are infected with HIV.[5] Developing and implementing cost-effective and affordable interventions in developing countries is a key problem for policy-makers, made very difficult by low levels of primary medical care, high poverty rates and the social stigma associated with HIV infection. We found that under certain circumstances bottlefeeding strategies are actually counterproductive and should be avoided.

One of the authors of this paper has worked for more than 5 years in Tanzania. For part of this time, he was a consultant to several AIDS control projects. He saw millions of US$ of foreign aid invested in programmes that ultimately had little effect on the incidence or prevalence of HIV in Tanzania.[6]

*Correspondence: MS Rauner, Department of Innovation and Technology Management, Institute of Business Studies, University of Vienna, Bruenner Str. 72, A-1210 Vienna, Austria.
E-mail: marion.rauner@univie.ac.at

The first 'wave' of donations reached Eastern Africa in 1988 and was spent on ELISA readers (HIV-test equipment) or AIDS health education programmes. Much enthusiasm was lost in the early 1990s when decision-makers were forced to admit that the disease was spreading exponentially and that most control programmes were unsuccessful, or had at best very limited success. Around 1994, a second wave of donations reached Tanzania and this was mainly spent on the treatment of AIDS patients. Most money was absorbed by big institutions and had no major impact on the lives of people directly affected by AIDS. Currently, the third wave of AIDS-related donations is flooding Tanzania. An effective, efficient and equitable investment of billions of US$ in the fight against AIDS is urgently needed. This investment must be based on professional forecasts—estimates that can only be provided by comprehensive decision-support models such as our DES model.

Choice of modelling methodology

Simple decision tree models have been used to investigate the cost-effectiveness of cheap short-course HIV treatment programmes (with drugs such as zidovudine, lamivudine or nevirapine) at childbirth for developing countries, mainly in Africa.[7–10] As the costs of these drugs have decreased in recent years, such interventions have become affordable for developing countries.[11] Skordis and Nattrass[12] found that nevirapine treatment in South Africa would actually be a cost-*saving* intervention in terms of health and welfare expenses. Stringer *et al*[13] reported that HIV treatment programmes at childbirth should combine targeted strategies (HIV testing before treatment) and universal strategies (provision of the drug without HIV testing) to prevent the maximum number of vertical HIV infections. However, this type of model does not allow a realistic description of the time spent in the different health states, and it is not easy to incorporate individual risk characteristics or to modify the model assumptions. Using a more sophisticated Monte-Carlo simulation model, Wood *et al*[14] showed that cheap short course anti-retroviral treatment would not only prevent vertical HIV transmissions but would also have a positive impact on life expectancy in sub-Saharan Africa. However, the effect of the mother's infection state on infectiousness[15] was not incorporated in these simple models.

Several models have investigated vertical HIV treatment strategies in combination with bottlefeeding strategies. Using a simple decision tree model, Wilkinson *et al*[16] calculated that a short course of treatment with zidovudine, combined with bottlefeeding for 4 months, would be a cost-effective and affordable intervention strategy for South Africa, but they did not consider the possible negative impact of bottlefeeding on infant mortality. Söderlund *et al*[17] applied a discrete-time Markov chain simulation to this problem, incorporating increased mortality due to bottlefeeding. However, they did not include different HIV severity stages of mothers at birth, and furthermore babies were not linked to their mothers. Vieira *et al*[18] used a DES model to analyse mother-to-child transmission, incorporating many interventions, examining the period of pregnancy and delivery in detail. However, they did not consider different durations of breastfeeding or any of the trade-offs in infant mortality and its consequences on population size, and they did not present a cost-effectiveness analysis based on realistic cost data.

Dynamic compartmental epidemic models based on the system dynamics (SD) approach have been widely used as the basis of AIDS policy models.[19,20] This technique is appropriate for populations in which the main routes of HIV transmission are homosexual contacts or intravenous-drug-using contacts, since the implicit assumption of homogeneous mixing within each compartment or risk group is valid for these transmission routes. However, in developing countries the main transmission routes are heterosexual contacts and vertical transmission. To model vertical transmission in a compartmental model in order to evaluate prevention strategies targeted at mothers and their babies, one would essentially need a separate compartment for each mother–baby pair, since it is necessary to be able to link each mother with her baby for the entire period of breastfeeding and even later. The consequent vast number of compartments is not feasible in an SD model and suggests the need for an approach in which individuals can be easily tracked. The obvious choice is DES, which has the additional advantage of being able to incorporate individual variability.

DES considers individual entities and traces their progress through a system represented as a network of queues and activities. Disease progression can be modelled as a virtual queuing system by regarding the disease state dwelling times as activity durations, where the 'activities' are assumed to be unconstrained (ie no servers are required, and hence there are no actual queues). At the same time, however, patient entities may also be taking part in a genuine, resource-constrained, queuing system, for example waiting for hospital admission, medical treatment, or a screening test. Thus, in a realistic model of a health-care system, patient entities may be participating in several concurrent activities or queues. Moreover, these activities and queues are interdependent: if patients change disease state, their treatment may need to be changed, they may no longer require a screening test, and hospital appointments may need to be rescheduled.

Most DES software assumes that at any given time each entity is either participating in a unique activity, or is queuing in a unique queue. Davies *et al*[21] developed a flexible structure that allows an entity to engage in an unlimited number of simultaneous activities or wait in any number of queues. Activities can be de-scheduled, interrupted or delayed. The advantages of this approach in the health context have been described by Davies and Davies[22] and it is now referred to as the patient-oriented simulation

technique (POST). This approach has been used in many application areas, for example models for the evaluation of screening policies for diabetic retinopathy[23] and models for the treatment and secondary prevention of coronary heart disease.[24]

Our HIV vertical transmission model was coded in Borland Delphi, using the POST library of procedures and functions.[21] POST uses a system of two-way pointers to connect entities, queues and activities,[23] which is particularly well suited to connecting a woman entity to her babies, and conversely linking a baby back to its mother. This is shown schematically in Figure 1, where the woman entity in the centre of the diagram is linked 'upwards' to her own mother, and 'downwards' to her children—and *vice versa*. Every entity has the same structure, so female babies are born with links to their own future children! These links enable the relevant entities to be rapidly found, and the necessary operations performed, during the simulation run.

The decision support system

To support policy-makers in a comprehensive analysis of appropriate prevention strategies, we developed a decision support system consisting of three linked components; an Excel front-end for data input, the simulation model itself, and an Excel output analysis model.

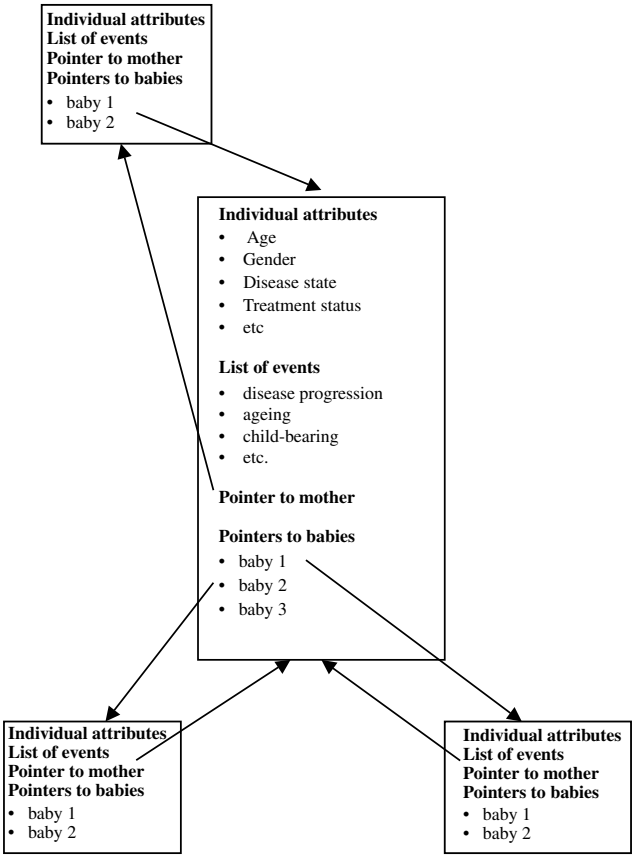

Figure 1 Schematic diagram showing the mother–baby pointers in the entity structure.

The data input component

The data input component is an Excel spreadsheet that allows the user to view and modify any of the model parameters in an explicit, transparent way. The spreadsheet consists of 27 individual worksheets containing tables of data, often with the source referenced, which can either be used as default or edited as the policy-maker chooses. Epidemiological and demographic data were derived from the literature (see Data section). Scenarios representing different testing and treatment strategies are user-input and can easily be created by editing the corresponding table. The data arrays are converted by an Excel macro into a single text file, which is read into the simulation model at the beginning of each set of runs.

The simulation model

The DES model initially creates an entire population of individuals, each with their own personal characteristics: age, gender, maternal stage (pregnant or breastfeeding), breastfeeding status, and all the maternal links as shown in Figure 1. The 'life histories' of these individuals are then simulated as time progresses. They grow older; the females conceive, give birth to, and breastfeed children; people die; children grow up and in turn bear children themselves who begin the whole process again. Moreover, individuals acquire HIV, and then progress through the stages of HIV infection, possibly also transmitting the virus to other people.

Policy-makers can then use this 'natural history' model of the demographic and epidemiological processes within a population to superimpose a number of intervention strategies—for example HIV testing and treatment programmes, education campaigns to modify sexual behaviour, and the provision of bottlefeeding to substitute for breastfeeding. In the output analyser, the costs of these interventions can be calculated and the benefits determined, in terms of HIV/AIDS prevalence and incidence, and deaths averted.

Women of childbearing age (12–45 years) are assigned a 'maternal stage', as follows:

1: Not pregnant and with no child under 2

2–4: The three trimesters of pregnancy (0–3, 3–6 and 6–9 months)

5–9: Age of baby (0–3, 3–6, 6–12, 12–18 and 18–24 months)

To resolve ambiguity, the maternal stage always refers to the most recent pregnancy, since a woman might become pregnant while she has a child aged less than 2 years.

Breastfeeding can potentially continue for up to 2 years. Each person has a breastfeeding status (never breastfed,

currently breastfeeding, formerly breastfed). It is assumed that babies under the age of 12 months will either be breastfed or bottlefed on formula milk. However, babies over the age of 12 months are either breastfed, or fed on solid food, such as maize porridge.

HIV can be transmitted in four ways. Sexual transmission is not modelled explicitly in the simulation, but annual infection rates were derived from Flessa's SD model.[25,26] All sexually active non-HIV-infected adults (ie all people aged between 12 and 45 years) are assumed to be at risk. The probability of infection depends on their age, gender and in the case of females their maternal stage. Infection is also possible via other causes (eg blood transfusions). The other two transmission routes represent, of course, the vertical routes of childbirth and breastfeeding.

Six HIV/AIDS disease stages are used in the model, as follows: HIV negative, HIV+ acute, HIV+ asymptomatic, HIV+ symptomatic, AIDS and Death. Reverse transitions are not possible. The transition times in the stages from HIV+ asymptomatic through to Death are modelled by a Weibull distribution, whose parameters were estimated from two percentile points using Dubey's[27] method. The transition from HIV+ acute to HIV+ asymptomatic was modelled by a uniform distribution, which gave a good fit to Auger *et al*'s[28] data for this transition in children, and Hethcote and Van Ark's[29] data for adults. Children are assumed to progress either quickly or slowly, following Hethcote and Van Ark's model[29] in which one-third progressed quickly and two-thirds progressed slowly.

Individuals therefore take part in many simultaneous 'activities', for which the POST software is ideally suited. These activities comprise the ageing process, the processes of acquiring HIV infection (by each of the four possible routes), the disease progression process, the process of mortality from causes other than AIDS, the processes of conception, childbirth and breast/bottle feeding, and (potentially) the processes of HIV testing and treatment. In order to obtain an initial population in which all children under 12 years are linked to their mothers, the simulation was run with a 12-year warm-up, starting in 1990, using initial data derived from Flessa's SD model[25,26] for the spread of the HIV/AIDS epidemic in Tanzania up to 1990. During the warm-up, no screening or treatment is assumed to take place. This warm-up was necessary as no sufficiently detailed data linking the HIV/AIDS status of mothers and their offspring were available. The main simulation itself is then run for 12 years, from 2002 to 2013. A longer time horizon is unrealistic since better treatment or even a vaccine is very likely to become available within the next decade. Clinical trials of some vaccines are already in stage three.[30] Furthermore, a longer duration would underestimate the reduction in the sexual infection rates caused by increasing numbers of HIV-negative children reaching sexual maturity. With a 12-year time horizon, this problem does not arise, but it would have to be taken account of in a longer simulation.

Treatment can be given either at delivery (to mother and baby) or routinely, and routine treatment can continue for a user-specified length of time. The chances of receiving treatment depend on age, gender, test status, disease stage, maternal stage (in the case of women) and breastfeeding stage (in the case of babies). Moreover for babies, the likelihood of receiving treatment also depends on the disease stage, test status and treatment status of their mother. Both types of treatment can affect three things: the rate of disease progression, the probability of HIV transmission via delivery and the probability of transmission via breastfeeding. It is assumed that routine treatment remains effective as long as it is given, and that when treatment ceases, all the above rates return to their 'untreated' values. On the other hand, treatment at delivery can remain effective for a chosen length of time. For each simulated year, policy-makers can specify whether a programme of delivery or routine testing will take place (and at what interval), and whether a programme of delivery or routine treatment will take place (and for how long), for men, women, children and babies.

The simulation model is stochastic and multiple iterations must be performed in order to draw statistically valid conclusions. The necessary number of iterations can be found by requiring that the 95% confidence interval containing the true value of some key output be smaller than a chosen percentage of the estimated mean of this output. The chosen number of iterations is a trade-off between the level of accuracy achievable and the necessary runtime. On our fastest machine, a Pentium-4 PC with about 2 GH processor and 1 GB memory, a run of 1000 iterations with a 12-year simulation horizon took over 30 h. We decided that 500 iterations was a satisfactory compromise, as this gave results for the 95% confidence interval within 2% of the estimated mean for the individual runs, and within 4% for the difference between the means of two runs (where the baseline scenario, that is, no screening or treatment, was compared with a prevention policy).

The output analyser

The results from the simulation are then read into the Excel output analyser, a tool originally developed by Rauner for her AIDS policy model in Vienna.[31–33] This tool can present the results of the simulation model for every simulated year graphically, either aggregated (eg the annual HIV incidence for all children under 12 years) or broken down into user-specified subgroups (eg the annual HIV incidence for previously breastfed baby boys aged 18–24 months).

Moreover, the output analyser allows policy-makers to specify the fixed and variable costs of testing, treatment and bottlefeeding as well as educational campaigns. It is also possible to use our outcome tool for cost–utility or cost–benefit analysis by assigning multipliers for the life years gained/lost or cost-values per life years gained/lost, respectively.[34] The total costs can then be calculated for any

scenario of interest and can also be discounted at varying discount rates over the simulation horizon.

Data

We used input data from a variety of sources. Demographic data, such as the age-specific fertility and mortality rates, were derived from the literature.[35,36] If the census data were not sufficiently detailed, primary data were sampled in Tanzania.[37] We used Flessa's[38] multicompartment SD model to calibrate the population structure and social and spatial mobility. In rural districts in Tanzania, most women breastfeed for 2 years. For example, 90% of mothers are still breastfeeding at 17 months.[39]

In our pattern population, which corresponds to Tanzanian data, HIV/AIDS prevalence at the end of 2002 was about 30% in adults and 20% in adults and children.[40–44] Progression data for HIV/AIDS were derived from Flessa,[40] Marseille *et al*[10] as well as Hethcote and Van Ark.[29]

Test sensitivities, specificities and costs were based on UNICEF *et al.*[11] The purchase cost of a test kit suitable for a developing country is $1.20. Treatment efficacy was derived from UNICEF *et al.*[11] Based on Guay *et al*[45] and De Cock *et al*,[46] we assumed that a single course of nevirapine treatment reduced the HIV transmission risk by 50% at delivery and by 50% during breastfeeding. In a recent South African study with an investigation period of 8 weeks, Moodley *et al*[47] confirmed these findings. These studies suggested a range of possible values for the *duration* of effectiveness and so we performed sensitivity analyses for this factor (see Results section).

In developing countries, nevirapine is frequently supplied free of charge. Normally, nevirapine would cost $0.27 and $0.01 for adults and babies, respectively.[11] We assumed a cost of $67.35 for the expected annual treatment of opportunistic infections in individuals with AIDS, as calculated by Flessa.[40]

In industrialized countries, HIV-positive mothers would be advised not to breastfeed their babies. The costs of bottlefeeding would not be a burden on their household budgets. On the other hand, women in developing countries cannot afford to buy the necessary pots, bottles, teats and powder milk, and so these costs would have to be covered by intervention programmes. In Northern Tanzania, we found that a suitable aluminium pot would cost about $2 The initial costs for bottles and teats would amount approximately to an additional $6. Therefore, we assumed that the fixed costs of bottlefeeding were $8.[6] Babies over 6 months can tolerate some solid food, while babies aged 12 months and older can be fed solely with solid food such as maize porridge.[6] Using this information, we calculated the weekly costs of bottlefeeding for babies aged 0–3, 3–6 and 6–12 months to be $1.27, $1.56 and $0.97, respectively, by assuming costs of $1.5 per kg of powder milk.[6] We assumed that babies whose mothers died while they were still breastfeeding continued to be breastfed free of charge by another mother from the extended tribal family.

However, bottlefeeding has many drawbacks in developing countries. Lack of money, combined with poor levels of education, within a family household might lead to negligence in sterilization practice—with fatal consequences for the baby. The infrastructure required to supply clean water is often lacking, and the infections obtained from unsterilized teats and unboiled water might be more rapidly fatal than HIV-infection. The majority of sub-Saharan Africans have no access to safe drinking water. The WHO[4] reported that mortality rates are many times higher in bottlefed children compared with breastfed children in less developed countries. Thus, when implementing bottlefeeding strategies in developing countries one has to consider the possibility of increased mortality rates due to bottlefeeding. As the multipliers published by the WHO[4] excluded deaths in the first week of life, we used the multiplier of 3.6 for 2–3 months also for 0–1 months so as not to overestimate the mortality risk due to bottlefeeding in our study (Table 1).

Furthermore, educational campaign costs such as staff costs, vehicle costs (fixed and variable), office rent, information materials (eg posters) and the training of local personnel have to be incurred in order to implement these interventions at delivery and during breastfeeding. We calculated annual costs of $15 000 for a population of 100 000, based on pricing knowledge by Flessa,[40] amounting to about $1050 for our pattern population.

Validation of the model was carried out as far as possible in the standard way. A wide range of internal consistency checks, such as extreme-value tests, were performed to verify that the computer model was logically correct. For example, if no mothers breastfed, then the model should show that no HIV transmission should occur via this route, and if treatment at delivery were 100% effective no transmission should take place at birth. The disease progression parameters were consistent with Brailsford's previous calculations.[48] The health status of the population at the end of the warm-up period was consistent with the results from Flessa's[25] previously validated compartmental model.

Table 1 Increase in infant mortality risk caused by bottlefeeding for babies in developing countries

Pooled age-group (months)	*Mortality multiplier due to bottlefeeding*
0–1	4.2
2–3	3.6
4–5	2.5
6–8	1.7
9–11	1.4
12–15	1.6
16–19	2.1
20–23	1.7

Model assumptions

Our initial population in 1990 was 4578 adults and children plus about 415 babies (about 5000 people in total). We assumed all women who gave birth were tested for HIV at the time of delivery, and all women who tested positive were treated and/or advised to bottlefeed, according to the policy being investigated. We assumed the test sensitivity and specificity were both 100% and that all women were 100% compliant with bottlefeeding instructions. These assumptions are, of course, unrealistic but they enable clearer comparisons to be made since they show the maximum benefit achievable from a given policy. In all our scenarios, all individuals with AIDS symptoms were tested and treated for opportunistic infections. Our aim was to evaluate whether strategies to prevent vertical transmission of HIV, combining bottlefeeding and treatment with nevirapine at delivery, are cost-effective, affordable and politically enforceable in developing countries.

The key outcome measure we chose was the additional number of HIV-negative children aged under 12 years who were alive at the end of the simulation time horizon of 12 years, compared with a baseline scenario with no intervention. The number of HIV infections averted was not a suitable outcome measure, since this would include cases where vertical transmission was prevented by an intervention, but the child subsequently died as a result of the increased mortality risk due to bottlefeeding. This negative effect would not have been captured by counting averted infections. Moreover, savings in Quality Adjusted Life Years (or, more appropriately for developing countries, Disability Adjusted Life Years) were unsuitable as an outcome measure because of the short simulation horizon.[49] Our chosen outcome measure reflected the extent to which the potential future workforce would be increased as a result of intervention programmes, and therefore we did not discount costs or benefits.[5]

Results

Nevirapine-only policy

We first analysed the growth of the total population with HIV/AIDS in our Tanzanian pattern region from 2002 to 2013, and compared the baseline no-intervention scenario with a policy in which nevirapine is given at delivery but there was no bottlefeeding. The duration of efficacy of nevirapine is currently uncertain[45,46] and therefore we considered three plausible assumptions. In scenario A0, nevirapine is assumed only to be effective at delivery, and in scenarios B0 and C0 it remains effective for 3 and 6 months, respectively. The results are shown in Table 2. In the absence of HIV/AIDS, the population would more than double from about 5000 to 10 242 between 2002 and 2013, an annual increase of about 7%. Although the HIV/AIDS epidemic slows down this population explosion, the differences between the baseline scenario and the intervention scenarios A0, B0 and C0 are negligible.

Combined policies—nevirapine plus bottlefeeding

We then investigated three additional policies combining nevirapine treatment with bottlefeeding. The policies we considered were:

(a) starting bottlefeeding at delivery (scenarios A1–A9);
(b) starting bottlefeeding at three months (scenarios B1–B9);
(c) starting bottlefeeding at six months (scenarios C1–C9).

Because the increase in infant mortality due to bottlefeeding varies according to the infrastructure and setting (urban/rural), we assumed either a 0, 50 or 100% increase in the mortality risk to that reported by the WHO,[4] giving nine cases in total. Because of the uncertainty in the duration of nevirapine efficacy, we carried out a sensitivity analysis for each of these nine cases by assuming three plausible values

Table 2 Population trajectories in breastfeeding-only scenarios in which nevirapine is effective at delivery only (A0), for 3 months (B0), and for 6 months (C0), compared with no intervention

Year	*Baseline scenario (no intervention)*	*Scenario A0 (breastfeeding; nevirapine effective at delivery only)*	*Scenario B0 (breastfeeding; nevirapine effective for 3 months)*	*Scenario C0 (breastfeeding; nevirapine effective for 6 months)*
2002	6759	6759	6758	6758
2003	6861	6859	6860	6860
2004	6947	6946	6947	6947
2005	7029	7029	7032	7032
2006	7107	7106	7113	7111
2007	7176	7178	7186	7183
2008	7237	7244	7253	7252
2009	7289	7300	7313	7312
2010	7343	7355	7374	7375
2011	7397	7414	7435	7438
2012	7447	7471	7497	7499
2013	7500	7528	7560	7564

Table 3 Features of the nevirapine scenarios (A0, B0 and C0) and combined bottlefeeding-plus-nevirapine scenarios (A1-A9, B1-B9 and C1-C9) investigated

Nevirapine efficacy	*Start of bottlefeeding*	*No additional mortality*	*50% increase in mortality*	*100% increase in mortality*
Delivery	Never		A0	
	Delivery	A1	A2	A3
	Third month	A4	A5	A6
	Sixth month	A7	A8	A9
3 months	Never		B0	
	Delivery	B1 (similar to A1)	B2 (similar to A2)	B3 (similar to A3)
	Third month	B4	B5	B6
	Sixth month	B7	B8	B9
6 months	Never		C0	
	Delivery	C1 (similar to A1)	C2 (similar to A2)	C3 (similar to A3)
	Third month	C4 (similar to B4)	C5 (similar to B5)	C6 (similar to B6)
	Sixth month	C7	C8	C9

for the efficacy: for delivery alone, for delivery plus 3 months of breastfeeding or for delivery plus 6 months of breastfeeding. This gave a total of 27 combined scenarios, shown in Table 3. Some of our scenarios were similar and thus gave the same results. For example, scenarios A1, B1 and C1 are identical, since in all three bottlefeeding starts at delivery and therefore the duration of effectiveness of nevirapine is irrelevant. However, they are all required, since we need to contrast A1 with A0, B1 with B0 and C1 with C0. We then compared all these results with a baseline scenario in which there were no interventions.

In all 27 combined scenarios, the population size only varied between about -2.3 and $+2.1\%$, compared with the nevirapine-only scenarios A0, B0 and C0. The results showed that if the mortality due to bottlefeeding were high, then bottlefeeding could have a counterproductive effect. Also, if nevirapine proved to be more effective and longer lasting, then we would see larger differences in population size. Furthermore, by using a longer evaluation period, the differences among the HIV/AIDS scenarios would become more evident, since averted HIV infections in children would result in a larger number of fertile adults, giving birth in due course to more children.

In all the combined scenarios, HIV and AIDS prevalence in adults rose from about 27 to 32% and from about 2 to 4%, respectively, between 2002 and 2013. In the absence of vertical HIV prevention, HIV/AIDS prevalence in children would rise from 4.1 to 7.1% for the baseline scenario over the same period. The nevirapine-only policy would reduce total HIV/AIDS prevalence by between 20.7% (scenario A0) and 37.8% (scenario C0) after 12 years, compared with the no-intervention baseline scenario. However, our results show that combined nevirapine-plus-bottlefeeding policies could, in certain circumstances, actually *increase* HIV/AIDS prevalence in children by reducing the total number of healthy children.

Table 4 shows the minimum and maximum cost-effectiveness-ratios (CERs) and the absolute numbers of additional live HIV-negative children for each nevirapine-plus-bottlefeeding scenario, and each nevirapine-only scenario, compared with the no-intervention baseline scenario. The minimum cost version assumes nevirapine is free of charge and testing costs are low (no shipment costs) and the maximum cost version assumes high nevirapine and testing costs (trifold costs due to shipping costs). The CERs were calculated by dividing the additional costs over the whole run of the intervention (C_{BF}) compared with the baseline scenario (C_B) by the number of additional live HIV-negative children at the end of the simulation due to the intervention (P_{BF}) compared with the baseline scenario (P_B):

$$\mathrm{CER} = \frac{C_{BF} - C_B}{P_{BF} - P_B} \tag{1}$$

The costs were not discounted. The CERs can be interpreted as the additional costs per additional HIV-negative child alive for a prevention programme compared to the no-intervention baseline. In Table 4, for each of the nine combinations of infant mortality and nevirapine efficacy, the four policies are ranked in decreasing order of cost-effectiveness, and the most cost-effective combined policy is shaded. If a policy is not ranked (eg scenario A5, shown as '—') this means that in this case, bottlefeeding *reduces* the number of live HIV-negative children, compared to the nevirapine-only policy, and therefore it would never be recommended. In the worst case, scenario A6, there are actually fewer live HIV-negative children than in the no-intervention scenario, that is, it is better to do nothing at all, and so the CER is negative.

By comparing the outcomes of the combined scenarios with the corresponding nevirapine-only scenario, policy-

Table 4 Cost-effectiveness of nevirapine strategies (A0, B0 and C0) and combined bottlefeeding-plus-nevirapine strategies (A1–A9, B1–B9 and C1–C9), not discounted

		No additional mortality					*50% increase in mortality*					*100% increase in mortality*				
Nevirapine efficacy	*Start of bottle-feeding*	*Scenario*	*CER in US$**		*Number of additional HIV-children alive*	*CER rank*	*Scenario*	*CER in US$*		*Number of additional HIV-children alive*	*CER rank*	*Scenario*	*CER in US$*		*Number of additional HIV-children alive*	*CER rank*
			Min	*Max*				*Min*	*Max*				*Min*	*Max*		
At delivery only	Never	A0	242	488	73	1	A0	242	488	73	1	A0	242	488	73	1
	Delivery	A1	326	913	287	2	A2	436	1709	205	2	A3	705	1970	121	2
	3rd month	A4	996	2598	92	4	A5	1883	4910	47	—	A6	Negative	Negative	−1	—
	6th month	A7	785	1951	88	3	A8	951	2361	72	—	A9	1273	3168	53	—
Up to 3 months	Never	B0	109	242	136	1	B0	109	242	136	1	B0	109	242	136	1
	Delivery	B1	326	913	287	2	B2	436	1709	205	2	B3	705	1970	121	—
	3rd month	B4	476	1279	184	4	B5	626	1683	135	—	B6	949	2554	86	—
	6th month	B7	455	1161	146	3	B8	524	1336	126	—	B9	581	1484	112	—
Up to 6 months	Never	C0	97	222	145	1	C0	97	222	145	1	C0	97	222	145	1
	Delivery	C1	326	913	287	2	C2	436	1709	205	3	C3	705	1970	121	—
	3rd month	C4	476	1279	184	4	C5	626	1683	135	—	C6	949	2554	86	—
	6th month	C7	348	901	186	3	C8	385	1000	166	2	C9	421	1088	152	2

*Range of CER based on minimum and maximum cost assumptions.
Nevirapine strategies (A0, B0 and C0) and combined bottlefeeding-plus-nevirapine (A1–A9, B1–B9 and C1–C9) were compared with the no-intervention baseline strategy.

makers can evaluate whether or not bottlefeeding should be recommended in addition to treatment with nevirapine at delivery. For example, consider the case when the increase in infant mortality is 100% of the WHO estimate and nevirapine is effective for 3 months after delivery. From Table 4 we see that there would be about 136 additional live HIV-negative children in the nevirapine-only scenario B0, compared with the no-intervention scenario. Since the CER is higher and the number of additional HIV-negative children alive is lower in every one of the combined scenarios B3, B6 and B9, compared with the corresponding scenario B0, policy-makers would never recommend bottlefeeding in these circumstances, since it produces worse outcomes than nevirapine treatment alone. However, if bottlefeeding were assumed (optimistically) to have no effect on infant mortality, the number of live HIV-negative children would increase from 136 (scenario B0) to 287, 184 and 146 for scenarios B1, B4 and B7, respectively. In this case nevirapine-only is still the most cost-effective policy, but bottlefeeding will always be recommended if there is enough money. The advice would be to start bottlefeeding at delivery, since B1 is ranked second after B0. Furthermore, this policy would yield more than twice the number of live HIV-negative children, compared with the nevirapine-only policy B0.

Table 4 shows that, irrespective of the mortality risk, the costs per additional live HIV-negative child are always higher for a campaign which includes bottlefeeding, compared with the costs of a nevirapine-only campaign. Depending on the efficacy of nevirapine, worst-case costs of up to about \$1709 (scenario C2) have to be invested per additional healthy child. This CER is about seven times higher than for the nevirapine-only programmes (scenarios B0 and C0) in which the drug is effective up to several months after birth.

If bottlefeeding increased infant mortality to the extent reported by the WHO,[4] bottlefeeding would actually make matters worse in many of the scenarios we investigated (ranked with '—' in Table 4). In particular, for the most realistic scenarios, in which nevirapine is assumed to be effective up to 3 months after birth, bottlefeeding should be avoided (scenarios B3, B6 and B9). However, if the additional mortality risk was half or less that reported by the WHO,[4] then bottlefeeding from birth would be most cost-effective and also more children would be alive and healthy (scenarios B1 and B2).

If nevirapine was effective for 6 months after birth and the increase in infant mortality due to bottlefeeding is 50% of the WHO estimate,[4] then bottlefeeding from birth would save most lives (scenario C2), but the most cost-effective strategy would be breastfeeding until 6 months (scenario C8). However, if the mortality risk turns out to be higher than the WHO numbers,[4] then bottlefeeding should be avoided in our rural sample population for Tanzania.

Policy implications for developing countries

Since in most cases combined nevirapine-plus-bottlefeeding strategies would save more lives compared with nevirapine-only strategies, as shown in Table 4, the costs of these programmes, ranging from \$326 to \$1970 per additional healthy child, would place a heavy burden on the slender health-care budgets of developing countries. Since the annual per capita health-care expenditure of developing countries is often less than \$10 and the general domestic product per capita is below \$1000,[50] this scale of bottlefeeding programme might not be affordable without the help of sponsor organizations such as the World Bank or church organizations.

If we take into account the future production loss due to the HIV-infected workforce in developing countries,[5] bottlefeeding strategies become more affordable options. Given that breastfeeding has a negative impact on the health of HIV-positive mothers in developing countries, as suggested by Nduati *et al*[51] and discussed by Newell,[52] then bottlefeeding strategies become even more attractive.

Moreover, policy-makers have to decide whether or not investment in intervention programmes targeted at vertical HIV transmission would be the best option among possible HIV intervention programmes—let alone among all other health-care programmes.[53] For example, programmes targeted at sex workers have been found to be more than eight times as effective as other HIV prevention programmes.[53] The decision about how to share the available health-care budget among cost-effective prevention programmes is also always a political and ethical one.[54] In comparison, in industrialized countries both mother and baby would receive the best available treatment, such as costly HAART, including nucleoside regimens, protease inhibitor regimens, non-nucleoside reverse transcriptase inhibitor regimens and multidrug salvage regimens.[1] In addition to being a therapeutic treatment, HAART almost totally prevents vertical transmission, but it is not affordable for developing countries.

Furthermore, many practical problems arise when undertaking bottlefeeding programmes in developing countries. It is difficult to guarantee that the pot used to heat the water has not been contaminated by laundry or animals—dogs, chickens and sheep frequently share living space with families in rural locations. Powdered milk might be given to older children or even to animals instead of the baby, a risk that does not exist with breastfeeding. In addition, the high prevalence of rats and mice and many other vermin in African towns and villages calls for high logistical efforts, such as packaging powdered milk in small quantities in waterproof, rat-resistant material, increasing the costs yet again. Finally, bottlefeeding mothers might be assumed to have HIV and might therefore be stigmatized and even abandoned by their husbands. Decision-makers must be culturally aware and highly sensitive in order to avoid a

social marketing campaign for bottlefeeding, which could ultimately lead to the deaths of millions of babies in developing countries.

In April 2001, the UN Secretary General issued a call to action for the creation of a fund to fight HIV/AIDS, malaria and tuberculosis.[6] With a targeted annual budget of $10 billion, the Global Fund to Fight AIDS, Tuberculosis and Malaria is now funding a number of vertical intervention programmes. At the same time, the World Health Organization, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and several agencies for development aid, such as the United States Agency of International Development (USAID) and the German Institute of Medical Mission (DIFÄM) are increasing their AIDS work. If this joint and intensified effort is not to suffer the same fate as all previous efforts, policy-makers need help for evidence-based prevention decisions by models such as ours.

Discussion

We have shown that discrete event simulation is a very powerful and flexible technique for modelling mother-to-child transmission of HIV, and the use of the POST methodology results in a very realistic model of the spread of the epidemic within a population. We plan to develop the model in a number of ways. First, we will include the effects of vaccination, since this is now a distinct possibility.[30] Another improvement will be to model HIV transmission during delivery more accurately, as in Vieira *et al*,[18] to account for differences in the probability of transmission due to duration of labour and parity (number of previous births). This will be straightforward to implement since these factors are already included in the current version of the model, but are not used at present. Interventions targeted at 'high-risk' mothers during delivery to reduce the probability of transmission could therefore be evaluated. An interesting but far more challenging possibility is to incorporate sexual transmission of HIV by the use of detailed mixing patterns instead of fixed yearly transmission rates. This would allow the simulation to be run for much longer time periods, taking account of changes in HIV prevalence and incidence in the sexually active population. Clearly, the model could be applied to other countries for which data were available, and a vast range of potential scenarios could be studied, even with the existing data, to enable the scarce resources of developing countries to be used in the most efficient and effective way. We are actively pursuing ways in which this can be done.

Lack of financial resources and basic infrastructure (clean water, electricity, transport) are defining features of the economies of developing countries. Operational Research models such as this, when publicized sufficiently, can raise the awareness of politicians, international welfare, religious and charitable organizations and pharmaceutical companies by showing what can be practicably achieved in such circumstances for different levels of financial outlay. Developing the model is just a first step towards bringing about change; the next, challenging step is to persuade people to use the results. We have already begun to disseminate our results through conferences and intend to use the current model and results as a basis for further research in partnership with health-care organizations.

The model is not intended to be used in the field by health-care workers and thus 'user-friendliness' is less important than the accuracy of the results and the reliability of the recommendations. However, the aim of the Excel-based DSS is to provide a framework for policy analysis; for instance, to show drug companies that providing a drug like nevirapine at cost to developing countries would make a genuine, significant difference to the health of the population. The model has not yet been tested with practitioners, but the next planned steps in this research will hopefully involve working more closely with health policy-makers.

The only lasting solution for delivering developing countries from the devastating burden of the HIV epidemic would be the widespread administration of an effective vaccine as soon as possible.[30] Several simulation models mainly investigated this effect[55–58] for heterosexual, homosexual and intravenous-drug using communities in the past. A modified version of our model could provide insight into the long-term effects of vaccination on both the heterosexual and vertical transmission dynamics of HIV in developing countries.

Acknowledgements—The first investigation on this project was started during Marion Rauner's Erwin-Schroedinger Visting Scholarship, funded by the Austrian Science Fund, at the Department of Industrial Engineering and Engineering Management, Stanford University. We are grateful to Helmut Dier for his help in the development of the evaluation tool and to David Crabbe for his support in programming parts of the input and simulation tool. Thanks are also due to Ruth Davies and Margaret Brandeau for valuable comments on this work. We also thank our colleagues for providing us with the necessary computer power for the simulation runs. We are very grateful to Ruth Davies for allowing us to use the POST software and to Keith Cooper for his assistance in speeding up the simulation run times. We also thank the Evangelical Lutheran Church in Tanzania, the Christian Social Services Commission, the Gesellschaft fuer technische Zusammenarbeit (GtZ), the Institute of Medical Mission (DIFÄM) and the Evangelical Lutheran Church of Bavaria for enabling and funding the field work which was necessary to provide sufficient data for this work. We are also grateful to the Editor Ruth Davies and the anonymous reviewers for their most valuable comments on this paper.

References

1 Joint United Nations Programme on HIV/AIDS (2003). *AIDS Epidemic Update: December 2003*. World Health Organization: Geneva.

2 Dop MC (2002). Breastfeeding in Africa: will positive trends be challenged by the AIDS epidemic? *Sante* **12**: 64–72.

3 Coutsoudis A, Goga AE, Rollins N and Coovadia HM (2002). Free formula milk for infants of HIV-infected women: blessing or curse? *Health Policy Plan* **17**: 154–160.
4 WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality (2000). Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. *Lancet* **355**: 451–455.
5 Rosen S *et al* (2003). AIDS is your business. *Harvard Bus Rev* **81**: 80–87.
6 Flessa S (2002). *Gesundheitsreformen in Entwicklungslaendern: eine kritische Analyse aus Sicht der kirchlichen Entwicklungshilfe*. Lembeck: Frankfurt am Main.
7 Mansergh G *et al* (1996). Cost-effectiveness of short-course zidovudine to prevent perinatal HIV type 1 infection in a sub-Saharan African developing country setting. *JAMA* **276**: 139–145.
8 Wilkinson D, Floyd K and Gilks CF (1998). Antiretroviral drugs as a public health intervention for pregnant HIV-infected women in rural South Africa: an issue of cost-effectiveness and capacity. *AIDS* **12**: 1675–1682.
9 Marseille E, Kahn JG and Saba J (1998). Cost-effectiveness of antiviral drug therapy to reduce mother-to-child HIV transmission in sub-Saharan Africa. *AIDS* **12**: 939–948.
10 Marseille E *et al* (1999). Cost effectiveness of single-dose nevirapine regimen for mothers and babies to decrease vertical HIV-1 transmission in sub-Saharan Africa. *Lancet* **354**: 803–809.
11 UNICEF, UNAIDS, WHO/HTP and MSF (2001). *Sources and Prices of Selected Drugs and Diagnostics for People Living with HIV/AIDS*. WHO: Geneva, Switzerland.
12 Skordis J and Nattrass N (2002). Paying to waste lives: the affordability of reducing mother-to-child transmission of HIV in South Africa. *J Health Econ* **21**: 405–421.
13 Stringer JS *et al* (2003). Comparison of two strategies for administering nevirapine to prevent perinatal HIV transmission in high-prevalence, resource-poor settings. *J Acquir Immune Defic Syndr* **32**: 506–513.
14 Wood E *et al* (2000). Extent to which low-level use of antiretroviral treatment could curb the AIDS epidemic in sub-Saharan Africa. *Lancet* **355**: 2095–2100.
15 Jacquez JA (1997). Mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr Hum Retrovirol* **16**: 284–292.
16 Wilkinson D, Floyd K and Gilks CF (2000). National and provincial estimated costs and cost effectiveness of a programme to reduce mother-to-child HIV transmission in South Africa. *S Afr Med J* **90**: 794–798.
17 Söderlund N, Zwi K, Kinghorn A and Gray G (1999). Prevention of vertical transmission of HIV: analysis of cost effectiveness of options available in South Africa. *BMJ* **318**: 1650–1656.
18 Vieira I, Harper P, Shahani A and de Senna V (2003). Mother-to-child transmission of HIV: a simulation-based approach for the evaluation of intervention strategies. *J Opl Res Soc* **54**: 713–722.
19 Rauner MS and Brandeau ML (2001). AIDS policy modeling for the 21st century: an overview of key issues. *Health Care Mngt Sci* **4**: 165–180.
20 Heidenberger K and Roth M (1998). Taxonomies in the strategic management of health technologies: the case of multiperiod compartmental HIV/AIDS policy models. *Int J Techn Mngt* **15**: 336–358.
21 Davies R, O'Keefe RM and Davies HTO (1993). Simplifying the modeling of multiple activities, multiple queuing and interruptions: a new low-level data structure. *ACM T Model Comput Sim* **3**: 332–346.
22 Davies R and Davies HTO (1994). Modelling patients flows and resource provision in health systems. *Omega* **22**: 123–131.
23 Davies R *et al* (2000). Using simulation modeling for evaluating screening services for diabetic retinopathy. *J Opl Res Soc* **51**: 476–484.
24 Cooper K *et al* (2002). The development of a simulation model of the treatment of coronary heart disease. *Health Care Mngt Sci* **5**: 259–267.
25 Flessa S (2003). Decision support for AIDS control programmes in Eastern Africa. *OR-Spectrum* **25**: 265–291.
26 Heidenberger K and Flessa S (1993). A system dynamics model for AIDS policy support in Tanzania. *Eur J Opl Res* **70**: 167–176.
27 Dubey SF (1967). Some percentile estimators for Weibull parameters. *Technometrics* **9**: 119–129.
28 Auger I *et al* (1988). Incubation periods for paediatric AIDS patients. *Nature* **336**: 575–577.
29 Hethcote HW and Van Ark JW (1992). *Modeling HIV Transmission and AIDS in the United States*. Springer: Berlin, Germany.
30 Mwau M and McMichael AJ (2003). A review of vaccines for HIV prevention. *J Gene Med* **5**: 3–10.
31 Rauner MS (2002). Resource allocation for HIV/AIDS control programs: a model-based policy analysis. *OR-Spectrum* **24**: 99–124.
32 Rauner MS (2002). Using simulation for AIDS policy modeling: benefits for HIV/AIDS prevention policy makers in Vienna, Austria. *Health Care Mngt Sci* **5**: 121–134.
33 Rauner MS (1999). *Strategisches Management von Praeventiv-programmen, Ein umfassendes Entscheidungsunterstuetzungs-system fuer die AIDS-Epidemie*. Peter Lang: Frankfurt am Main, Germany.
34 Gold MR, Siegel JE, Russell LB and Weinstein MC (eds) (1996). *Cost-effectiveness in Health and Medicine*. Oxford University Press: New York, NY.
35 United Republic of Tanzania (1988). *1988 Population Census: Preliminary Report*. Ministry of Home Affairs: Dar-es-Salaam, Tanzania.
36 United Republic of Tanzania (1992). *Women and Men in Tanzania*. Ministry of Community Development, Women and Children: Dar-es-Salaam, Tanzania.
37 Flessa S (1997). *Costing of Health Services of the Evangelical-Lutheran Church in Tanzania*. Evangelical-Lutheran Church in Tanzania: Arusha, Tanzania.
38 Flessa S (1998). Many world of health: a simulation of the determinants of the epidemiological transition. *Z Bevoelker-ungswiss* **23**: 459–494.
39 Staewen C (1991). *Kulturelle und psychologische Bedingungen der Zusammenarbeit mit Afrikanern*. Weltforum Verlag: Muenchen, Cologne, London.
40 Flessa S (2002). *Malaria und AIDS. Gesundheitsoekonomische Analysen auf Grundlage von Disease Dynamics Modellen*. Hans Jacobs: Lage, Germany.
41 Flessa S (1999). Decision support for malaria-control programmes—a system dynamics model. *Health Care Mngt Sci* **2**: 181–191.
42 United Republic of Tanzania (1999). *Health Statistics Abstract 1999*. Ministry of Health: Dar-es-Salaam, Tanzania.
43 United Republic of Tanzania (1997). *National AIDS Control Programme, HIV/AIDS/STD Surveillance. Surveillance Report No. 12*. Ministry of Health: Dar-es-Salaam, Tanzania.
44 World Bank (1992). *Tanzania: AIDS Assessment and Planning Study*. World Bank: Washington, DC.
45 Guay LA *et al* (1999). Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-

to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* **354**: 795–802.
46 De Cock KM *et al* (2000). Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* **283**: 1175–1182.
47 Moodley D *et al* (2003). A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* **187**: 725–735.
48 Brailsford SC, Shahani AK, Basu R and Sivapalan S (1996). Practical models for the care of HIV and AIDS patients. *Int J STD AIDS* **7**: 91–97.
49 Graham JD *et al* (1998). Evaluating the cost-effectiveness of clinical and public health measures. *Annu Rev Public Health* **19**: 125–152.
50 UP/UNDP (2003). *Human Development Report 2003. Millenium Development Goals*. Geneva: Oxford.
51 Nduati R *et al* (2001). Effect of breastfeeding on mortality among HIV-1 infected women: a randomised trial. *Lancet* **357**: 1651–1655.
52 Newell M (2001). Does breastfeeding really affect mortality among HIV-1 infected women? *Lancet* **357**: 1634–1635.
53 Marseille E, Hofmann PB and Kahn JG (2002). HIV prevention before HAART in sub-Saharan Africa. *Lancet* **359**: 1851–1856.
54 Owens DK (1998). Interpretation of cost-effectiveness analyses. *J Gen Intern Med* **13**: 716–717.
55 Longini Jr IM, Hudgens MG, Halloran ME and Sagatelian K (1999). A Markov model for measuring vaccine efficacy for both susceptibility to infection and reduction in infectiousness for prophylactic HIV vaccines. *Stat Med* **18**: 53–68.
56 Edwards DM, Shachter RD and Owens DK (1998). A dynamic HIV-transmission model for evaluating the costs and benefits of vaccine programs. *Interfaces* **28**(3): 144–166.
57 Bogard E and Kuntz KM (2002). The impact of a partially effective HIV vaccine on a population of intravenous drug users in Bangkok, Thailand: a dynamic model. *J Acquir Immune Defic Syndr* **29**: 132–141.
58 Porco TC and Blower SM (1998). Designing HIV vaccination policies: subtypes and cross-immunity. *Interfaces* **28**(3): 167–190.

Received August 2003;
accepted July 2004 after four revisions