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Original Article

Cost-Effectiveness Analysis of Antiretroviral Drug Treatment and HIV-1 Vaccination in Thailand

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SUMMARY: The prevalence of adult HIV/AIDS in Thailand is declining due to intense prevention strategies, but it still continues to be a critical health problem with a prevalence of 1.5%. Several HIV vaccine candidates for the prevention of HIV infection or progress to AIDS were examined in clinical trials. We evaluated the cost-effectiveness of a vaccination regimen (rBCG prime-rDIs boost) currently in its pre-clinical phase. The cost-effectiveness of three interventions (vaccination, highly active antiretroviral treatment [HAART], and the combination of the two) through an existing vaccination program was assessed in a Markov model. The disability-adjusted life year (DALY) was the main effectiveness measure. In the base case the efficacy of the vaccine for preventing HIV infection was assumed to be 30%. The cost of the vaccine was estimated on the basis of its predicted production capacities in Thailand. The incremental cost-effectiveness ratios of vaccination, HAART, and the combination were about $US 75, $US 610, and $US 267 per DALY averted compared with the do-nothing strategy in the base case. The HAART-only strategy seemed to be less cost-effective than the other options under the current assumptions. Sensitivity analyses indicated that the new HIV infection rate and the vaccine efficacy could affect the results.

INTRODUCTION

Although HIV infection and AIDS have been given high priority as international health issues since the early 1980s, the situation worldwide does not show the expected improvement (1). Since the numbers of newly infected people are very high in the developing countries, the economic impact as well as the health consequences of the epidemic should be considered seriously (2,3).

In Thailand, the first HIV infection was reported in 1984, and the number of infections peaked in the mid-1990s. The efforts of the Thai government in the early 90s to improve the situation, including extensive and intensive campaigns to promote condom use and HIV education in susceptible populations, succeeded in preventing a further explosion of new HIV infections (4). As a consequence, HIV prevalence is currently falling, but the estimated number of HIV/AIDS cases was still 570,000 as of the end of 2003 (1).

The introduction of highly active antiretroviral treatment (HAART) has dramatically reduced the number of deaths and AIDS-related opportunistic infections in developed countries. However, even though the WHO estimates that more than 1 million Asian patients are in need of HAART, only 6-7% have access to this expensive therapeutic regimen (5). In Thailand and in other Asian countries hit hard by the epidemic, the availability of antiretroviral therapies for HIV-infected patients is still limited (4). However, since the production of generic antiretroviral products by the Thai Government Pharmaceutical Organization started in 2001, these drugs are now available at much lower prices (4,6,7). The government planned to provide them to 50,000 people in 2004 (4).

The possibility of using vaccination strategies to mitigate the HIV/AIDS epidemic has been pursued in the past several decades, and dozens of vaccine candidates have been and are being examined in clinical trials (3,4,8,9). The first two large phase 3 randomized controlled clinical trials of recombinant gp 120 vaccines were conducted in North America/Netherlands and Thailand, but they did not show the expected efficacy (10-12). In spite of these negative outcomes, substantial effort and funds are being invested in vaccine research to find candidates with sufficient potency (13,14).

In Asia, international efforts have been made to develop vaccines that would meet local needs. Many clinical trials of vaccines have already been conducted through international development programs in Thailand. An international collaboration project between Japan and Thailand was started in 1998 to develop vaccine candidates for Thai HIV patients (3,15). As a result of this bilateral research project, a prime-boost regimen of recombinant Bacillus Calmette-Guerin (rBCG) vaccine and recombinant vaccinia virus DIs (rDIs) vaccine has been proposed. This prime-boost regimen was shown to induce high levels of protective cellular immune response in animals (16). While efforts to obtain further data on safety and immunogenicity and to establish a foundation for clinical development are being made, it is critical to discuss and estimate the societal value of such a new intervention, because the clinical development of HIV vaccines requires substantial R&D resources, and the justification for resource consumption must always be based on quantitative discus-

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sions.

We evaluated the cost-effectiveness of the proposed vaccination regimen using information on local medical services and on the production facilities of the vaccine candidates currently planned in Thailand. To clarify the economic profile and to compare our results with previous studies we compared the vaccine regimen with the HAART strategy as well as the combination of the two treatments.

METHODS

Model structure: A Markov model with annual cycles to simulate the progression of HIV infection and estimate the costs, effects, and cost-effectiveness of the prime-boost vaccine regimen was developed. At the beginning of the cycles a cohort consisting of 10-year-old uninfected children was assumed to occupy one of five health states: uninfected, early-HIV, late-HIV, AIDS, or deceased. The transition from one state to another occurred with pre-specified probabilities. The same model structure was applied to all of the interventions, but the added costs and reduced HIV risks corresponding to each intervention strategy were assigned in the simulation. The model began at age 10 and continued through HIV infection, AIDS, or death due to any cause. Life table data to estimate annual age-adjusted all-cause mortality in Thailand were obtained from the WHO website.

New HIV infections in the follow-up period were estimated based on a projection prepared by the Thai experts (17). The projection assumed that 50% of new male infections and 66% of new female infections occur between the ages of 15 and 24, and that women tend to become infected earlier than men because of social and biological susceptibility to HIV infections. Although infection rates would be affected by various factors including implementation of the vaccination policy itself and thus should be handled as an endogenous variable in a dynamic model with interactions of different populations, they were assumed to be constant during the estimation process because of the uncertainty in the real-world impact of the implementation of the vaccine administration strategy in Thailand and the limitations of the basic Markov model. Possible changes in infection rates over time were not calculated based on a model, but a sensitivity analysis in which applying a sufficient range of infection rates was applied could provide an estimate of the range of cost and effectiveness ratios in this hypothetical setting. Cost and effectiveness for men and women were calculated separately because of the significant gender differences in the predicted infection patterns and mortality. The annual probability to proceed from HIV to the AIDS stage (0.0878) was calculated as the ratio between the number of new AIDS patients and the number of total people infected with HIV in 2000 (17). The annual mortality among AIDS patients (0.795) was estimated from the new AIDS patients' deaths in 2000 (17). It was assumed that risk behaviors were not affected by the choice of the interventions, because several analyses showed that high-risk behaviors did not increase, at least in clinical trial settings in Thailand as well as in other countries (10,18-21). However, it is still unclear how people would behave under specific vaccination schemes where vaccines with established effectiveness and safety are available. Our model is not appropriate for discussing the impact of behavioral changes, and a dynamic model with different scenarios in terms of risk behaviors would be necessary for the purpose. Vaccine program implementation rates were not incorporated as an endogenous parameter in the model. We discounted the costs and health benefits at a rate of 3% in the base case. DATA Professional (TreeAge Software, Inc., Williamstown, Mass., USA) was used as a statistical tool.

HIV vaccines and HAART: We assumed in the base case that the vaccines prevent 30% of HIV infections (scenario 1), because this magnitude of efficacy was required as a goal for marketing approval in the previous vaccine trials (10,12, 14,18). Since there is significant uncertainty in the ways that vaccine candidates might work, scenario 2, in which the vaccines do not prevent infection but slow progression by reducing transition rates from HIV to AIDS by 30%, was examined. Loss of immunity was not assumed. It was assumed that the prime-boost regimen would be implemented in the existing framework of national vaccination programs such as measles, mumps and rubella (MMR) vaccination in grade 1 school children with minimum incremental costs excluding the vaccine costs (2,9). Although estimated vaccination costs may differ conspicuously from one social group to another (9), this diversity was not considered in our model, but left to sensitivity analyses.

A consensus on the treatment recommendation for when the therapy should be initiated for asymptomatic HIV disease was not reached (19). In our model, two HIV stages to reflect the impact of HAART as a treatment option were included. HAART was assumed to be initiated at the latter stage of HIV prior to the AIDS stage. The average effect of HAART was assumed to be a prolongation of the late-HIV stage for 5 years (20). We did not include the costs associated with adverse effects and drug resistance. This simplification was likely to make cost-effectiveness ratios look favorable for HAART (22).

Costs related to immunization and treatments: Base-case cost parameters are shown in Table 1. We obtained data on medical spending, expected environments for vaccine programs and general parameters for healthcare provisions from the Thai Ministry of Public Health and other health institutions in Thailand. Several parameters in Table 1 were estimated from interviews with medical and health experts. Our analysis was from the standpoint of the medical service decision-maker who cares about both public and private costs. Productivity loss was not considered explicitly in the analysis since this study was conducted as a cost-effectiveness analysis, and thus labor productivity may be included as a loss of quality of life.

Cost estimates for HIV/AIDS immunization and/or treatment regimens varied largely depending on the types of healthcare schemes and scopes of the estimators (23-26). In our base-case estimates we generally adopted values similar to previous publications (4,23-25). Because the costs of antiretroviral drugs decreased rapidly due to generic production, we used the current cost ($US 360/person/year) converted to the year 2000 level in the base case (4,6,7,25). All costs were adjusted to year 2000 levels using the Consumer Price Index.

Effectiveness: Life-years (LYs) and disability-adjusted life years (DALYs) were used as effectiveness measures to compare our results with previous ones (27-29). Since DALYs are based on health status, duration of status, and age of onset, we undertook Monte Carlo simulations with 1,000,000 trials to obtain estimates of DALYs (30). Approximate 95% confidence limits for incremental cost effectiveness ratios (ICERs) were estimated based on the confidence box in the cost-effectiveness plane (30).

Sensitivity analysis: The robustness of an ICER to the

Table 1. Cost parameters used in the model

Parameter	Base case value in $US (2000)	Reference
Direct medical cost for a HIV infection patient (per year)[1)]	210	Reference (23); based on Thai experts' opinions.
Direct medical cost for an AIDS patient (per year)[1)]	830	Reference (23)
Medical cost (general; per visit)	4.5	Reference (24)
Indirect medical costs (travel, accommodation)		Reference (25)
AIDS patient (per visit)	4	
HIV patient/family members (per visit)	1.5	
Average cost of HAART regimens (per year)	340	Reference (4)
Cost of rBCG vaccine (per dose)	0.14	Based on Thai and Japanese experts' interviews; reference (9)
Cost of rDIs vaccine (per dose)	1.4	Based on Thai and Japanese experts' opinions; reference (9)

[1)]: Direct medical cost includes treatment costs including doctor and hospital fees, clinical tests and medications for opportunistic infections.
HAART, highly active antiretroviral treatment.

variation of important parameters was assessed using one-way sensitivity analysis. The ranges of parameter values were set by previous cost-effectiveness analysis and recent reports on HIV/AIDS worldwide (1). The upper limit of cost related to HAART reflected the public price in the past (25). For new HIV infection rates, the lower (one-tenths of the base case) and upper (10-fold) values corresponded roughly to the rates of many developed countries and sub-Saharan African countries suffering seriously from HIV/AIDS, respectively (1).

RESULTS

The ICERs in comparison with the do-nothing strategy under the base-case assumptions are presented in Table 2. Assuming that vaccination prevents 30% of HIV infections (scenario 1), the ICER was $US 99 per LY gained. The second assumption that vaccination reduces progression rates to AIDS by 30% (scenario 2) provided an ICER of $US 802 per LY. The HAART treatment only yielded an ICER of $US 707 per LY. When the vaccination and HAART were used in combination, the ICER ($US 315 per LY) improved compared with the HAART-only strategy, but it was still worse than the ICER of scenario 1.

Similar cost-effectiveness profiles were obtained when effectiveness was measured in DALYs (Table 2). HIV vaccination resulted in $US 75 and $US 825 per DALY averted under the assumptions of the protection against HIV infection and the prevention of progress to AIDS by 30%, respectively. The HAART-only strategy had an ICER of $US 610 per DALY averted. The combination of vaccine and HAART led to an ICER of $US 267 per DALY averted. The assumption of scenario 1 had the best ICER, even when the vaccine efficacy was as low as 30%.

Sensitivity analyses: The robustness of the findings was explored in one-way sensitivity analyses by varying the uncertain input parameters within reasonable bounds (Table 3). The results were most sensitive to the changes in new HIV infection rates in the cohort. If the new Thai HIV infection rate was one-tenths of the base case values predicted in a Thai expert report (17), the ICER from the vaccine preventing HIV infection would reach more than $US 2,000 per DALY. A 10-fold increase in the new infection rate reduced costs to less than the cost of the do-nothing strategy, resulting in cost-saving. Changes in the HIV infection rate had a similar impact on the strategies with HAART, but relative changes in the ICERs were smaller in the strategies with HAART than in the vaccine-only strategies.

Variations in the vaccine costs did not have a significant impact on the predicted ICERs. A 10-fold increase in the vaccine prices increased ICERs by threefold in the vaccine strategy (scenario 1), whereas the reduction in vaccine prices

Table 2. Incremental cost-effectiveness ratios in life-years (LYs) and disability-adjusted life-years (DALYs) among treatment strategies

Strategy	Incremental cost[1)] ($US)	ICER[2)] ($US/LY)	ICER[2)] ($US/DALY)	95% CI[3)] ($US/DALY)
Vaccine (scenario 1)[4)]	6.9	99	75	[56; 102]
Vaccine (scenario 2)[5)]	20.0	802	825	[526; 1,744]
HAART	48.9	707	610	[466; 856]
Vaccine[3)] and HAART	131.4	315	267	[228; 317]

[1)]: Incremental cost compared with no-treatment.
[2)]: Incremental cost-effectiveness ratios compared with no-treatment.
[3)]: 95% confidence interval using confidence interval box.
[4)]: In scenario 1 it is assumed that the vaccination reduces HIV infection rates by 30%.
[5)]: In scenario 2 it is assumed that the vaccination reduces progression rates to AIDS by 30%.
CI, confidence interval; HAART, highly active antiretroviral treatment; ICER, incremental cost-effectiveness ratio.
Note:
ICER = {(cost of each strategy) − (cost of "no treatment")}/{(effectiveness of each strategy) − (effectiveness of "no treatment")}.

Table 3. One way sensitivity analysis: impact on the incremental cost effectiveness ratios ($US/DALY) of varying key parameters

	Vaccine (scenario 1)[1)]	Vaccine (scenario 2)[2)]	HAART	Vaccine[1)] +HAART
Base case	75	825	610	267
Vaccine costs (base case: $US 1.68) ($US 0.84; $US 16.8)	(66; 240)	(799; 1,288)	–	(205; 331)
HAART (base case: $US 340) ($US 34; $US 3,400)	–	–	(215; 4,110)	(130; 1,535)
HIV infection rate (compared with the base case assumption) (1/10; 10-fold)	(2,312; <0)	(6,660; 243)	(1,284 ;606)	(1,891; 143)
Vaccine efficacy (base case: 30%) (15%; 60%)	(271; <0)	(1,128; 322)	–	(452; 44)
HAART efficacy (base case: 5-year extension of life on average) (3-year; 10-year)	–	–	(651; 539)	(220; 301)
Discount rate (base case: 3%) (0%; 6%)	(<0; 328)	(407; 1,066)	(660; 471)	(181; 422)

[1)]: See Table 2, footnote[4)].
[2)]: See Table 2, footnote[5)].
Abbreviations are in Table 2.
In parentheses ICERs correspond with the minimum and the maximum values of parameters in the same row.

by half did not affect the base case ICERs. The assumption of the cost of HAART was directly associated with the overall desirability of the HAART strategy. If the annual HAART price was assumed to be one-tenths of the base-case assumption ($US 34), the ICER would be closer to the level of the expected vaccine strategy (4).

There is significant uncertainty about the expected level of efficacy of successfully developed vaccines. Our model showed that vaccines preventing HIV infection (scenario 1) with higher efficacy than the base case would reduce costs (i.e., cost-saving). Vaccines that slow down the process to AIDS (scenario 2), on the other hand, still had an ICER of $US 322 per DALY under the 60% efficacy assumption. The ICER level of HAART in its base case could be achieved even when vaccine efficacy decreased to 9.5% in scenario 1.

The efficacy of HAART depends on several factors including virus types, target populations, timing of initiation (i.e., CD4 cell level and viral load), and the adherence and emergence of drug resistance (19). The ICER under the base case assumption of the average 5-year extension of the HIV stage did not fluctuate substantially in the range of the sensitivity analysis. Discount rates did not lead to significant changes in the interpretations of results.

DISCUSSION

In spite of both clinical and financial difficulties, dozens of HIV vaccines are being developed throughout the world (8,31). Although no vaccine has so far been proven to be clinically effective in a large randomized controlled clinical trial, vaccine development programs are given high priority because, once a vaccine's distribution is established, it is expected that it will become a reasonably affordable, accessible, and long-term solution to the HIV/AIDS pandemic (3,9,32). The vaccine candidates developed under the international program are expected to enter clinical phases as soon as a foundation for clinical development is established. The effectiveness and safety of the proposed regimen consisting of rBCG priming followed by rDIs boost will be tested in Thailand. Our analyses were primarily aimed at evaluating the economic aspects of the regimen with the rBCG-rDIs vaccines, but they could easily be extended to other prevention and treatment schemes thanks to the model's simplicity.

When considering the adoption of HIV intervention programs in a specific country or region, it is necessary for the decision-makers to determine whether the cost-effectiveness ratios of the programs are acceptable, with a ceiling cost-effectiveness ratio of the best alternative intervention in mind. Although a number of reports have examined the cost-effectiveness of various interventions in Africa or sub-Saharan areas, there are only a limited number of publications on HIV interventions that have been implemented (or will be implemented) in Thailand (29,33,34). The use of zidovudine to prevent mother-to-child HIV transmission represented a $US 35 - 40 per DALY in the context of routine health care in northern Thailand (35). For the prevention of mother-to-child HIV transmission, a cost-effectiveness ratio (CER) of $US 73.4 per quality-adjusted life years was reported in another estimation (33). Economic evaluations of HIV vaccines appeared in some publications, but they were not performed in the Thai settings. For example, a break-even cost per dose for a hypothetical AIDS vaccine was estimated to be in the range of $US 320 to $US 2,908 in sub-Saharan Africa (36). Another study reported a CER of $US 3.4 per DALY for a hypothetical infant vaccination in sub-Saharan Africa through the Expanded Program on Immunization (2). However, those figures entailed significant uncertainty, especially in terms of the effectiveness of the vaccines, as the recent negative results of phase 3 trials have shown (10-12).

We obtained an ICER of $US 50 - 100 per DALY for the rBCG-rDIs vaccine regimen under the assumption of 30% infection prevention. The ICER of HAART was estimated to be about $US 610 per DALY. This estimation was lower than the previous results of $US 1,100 - $US 1,800 for antiretroviral therapies for adults in Africa (29). However, it was suggested that the ICER of HAART varies depending on the assumption of prevailing prices. If the price of HAART was $US 3,400, which was about the same as the price level of branded antiretroviral products in the 1990s, an ICER of as high as $US 4,110 per DALY was obtained in the sensitivity analyses (Table 3). According to the WHO guideline (2001), the international experience of accepted cost-utility ratios

suggested that the threshold of cost per LY or QALY is about three times per capita gross domestic product (GDP). If this ratio is applied to the situation of interest, the calculated threshold ($US 21,000) was above the level of our estimations and thus, along with the CERs in recent publications (33-35), seemed to the support the possible acceptability of our estimations in Thailand.

To judge the vaccines' efficacy, two different scenarios were used in our analyses. In scenario 1 (Tables 2 and 3), vaccines were assumed to prevent HIV infection at a certain rate (base case: 30%), and in scenario 2 the vaccines did not prevent infection but slowed down the progress to AIDS at a certain rate (base case: 30%). The ICERs in scenario 2 were less favorable than those in scenario 1. These results, together with the generally high ICERs of HAART, may indicate that strategies for treating HIV-infected patients at a later stage of the disease are a relatively expensive approach compared with infection-prevention strategies. The excellent CERs reported for strategies such as condom distribution, blood safety testing and voluntary counseling and testing were consistent with our conjecture (29,33). An additional analysis showed that a vaccine efficacy of larger than 9.5% in scenario 1 would achieve a better ICER than the base case HAART. This finding supports the high expectation for preventive vaccines from an economic standpoint, although clinical investigators do not generally think that this level of efficacy is sufficient for candidate HIV vaccines (12,18). Practically, it is almost impossible to establish this level of efficacy (9.5%) in current clinical trial settings because of the constraints in achievable sample sizes and study lengths.

The estimated ICERs were most affected by the assumption of new infection rates (Table 3). Under the lower infection rate assumption, both vaccine scenarios as well as HAART had much worse ICERs than the base cases. On the other hand, the vaccines yielded low ICERs and cost-saving in scenario 1 under the assumption of the most-afflicted countries. These results were also in agreement with previous publications (2,29).

It is not only the ratio of cost-effectiveness but also the size of a budget that determines the feasibility of a program. If it is assumed that all the 10-year-old children in the country are to be vaccinated, the annual expenditure would be about $US 4 million for the vaccine cost alone. The cost for the program implementation would add to this amount. Considering the fact that the recent national HIV/AIDS budget was about $US 35 million per year, this size of expenditure for a single project might be burdensome but not infeasible in the short term. When it comes to the long-term impact of a national immunization program on Thai society as a whole, the short-term budgetary restriction might not be regarded as a serious obstacle to program implementation.

Finally, the limitations of this analysis should be acknowledged when the present results are generalized. The first limitation is that the target population was not specified sufficiently for the implementation of real-world programs. As a previous report suggested, program implementation costs could vary significantly depending on the chosen target populations (9). Secondly, our Markov model was created to be as simple as possible because of the current inevitable uncertainty about the actual vaccine programs and a lack of information about them. Recent economic analyses on antiviral drugs almost always adopted several disease steps characterized by CD4 cell counts or other test results related to the progress of the disease (20,35). We set only three HIV/AIDS stages and estimated the transition probabilities using population data and clinical trial results, and did not use information on the clinical conditions of each patient. Thirdly, the scope of our model did not cover the effects on people outside the cohort or the target population. The societal impact of the HIV/AIDS epidemic depends on many external factors in the society. From this perspective, the consideration of productivity loss is very important, but we did not consider it explicitly in our model.

In conclusion, the proposed vaccination regimen had ICERs of $US 99 per LY or $US 75 per DALY. It is likely that the vaccination regimen may be more cost-effective than the antiretroviral drug therapies. The values of ICERs were sensitive, however, to epidemiological conditions (e.g., new infection rates) and to the magnitude of vaccine efficacy. To interpret these results with less uncertainty, it is necessary to perform further analyses of the cost-effectiveness profiles of feasible HIV/AIDS interventions that meet the specific needs in Thailand.

Note

DALY = $-[D*0.16*e^{-0.04*a}/(0.04 + r)^2*\{e^{-(0.04 + r)*L}*(1 + (0.04 + r)*(L + a)) - (1 + (0.04 + r)*a)\}]$ where D is the disability weight (health, 0; HIV infected, 0.136; AIDS, 0.505; death, 1), r is the discount rate (0.03), L is the duration of disability or time lost due to premature mortality, and a is the age of onset. For technical details see References 27 and 28.

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