ORIGINAL ARTICLE

Cost-effectiveness of Highly Active Antiretroviral Therapy for HIV Infection in Taiwan

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Background/Purpose: Since the late 1980s, the Taiwanese government has provided all HIV-infected citizens with free access to antiretroviral therapy. Recently, there is controversy as to whether or not free access to expensive highly active antiretroviral therapy (HAART) should be continued for HIV-infected patients. This study aimed to evaluate the cost-effectiveness of HAART therapy.

Methods: HAART-associated improvement in survival was obtained by analyzing the follow-up data of all HIV-positive patients identified during April 1984 to March 1997 (pre-HAART era) and May 1997 to April 2003 (HAART era) in Taiwan. Data on quality of life in HIV-positive patients was obtained from a cross-sectional survey of 224 patients using standard gamble method and World Health Organization Quality of Life-BREF instrument. Information regarding the cost of HAART was obtained from the National Health Insurance (NHI).

Results: In 2000, the average annual NHI expenditure on HAART per HIV-positive patient receiving HAART was NT$210,018 (US$6177, at an exchange rate of 34.0 NT$/US$). In the AIDS group, the cost was NT$176,441 (US$5189) per life year gained and NT$241,700 (US$7109) per quality-adjusted life year gained. For non-AIDS patients, the corresponding costs were NT$226,156 (US$6652) and NT$332,582 (US$9782), respectively. These estimates have not yet included the additional cost savings from HAART-associated reduction in hospitalization and use of antimicrobial agents for opportunistic infections, and the additional life years gained from the reduction in HIV transmission under the universal availability of HAART.

Conclusion: HAART for HIV infection is cost-effective, especially when the societal and epidemiologic factors are considered. We recommend that the policy of providing free HAART to all HIV-infected citizens be continued. [*J Formos Med Assoc* 2007;106(8):631–640]

Key Words: cost-effectiveness, HAART, health policy, highly active antiretroviral therapy, HIV infection

From the beginning of the human immunodeficiency virus (HIV) epidemic in Taiwan in 1986, the Taiwanese government decided to ensure that all HIV-infected citizens had free access to antiretroviral therapy.[1] The introduction of highly active antiretroviral therapy (HAART) in April 1997 dramatically improved the survival of patients with HIV infection.[1–3] These antiretroviral agents, however, are expensive and must be used in combination.[4–6] The wholesale prices in the United States ranged from approximately US$2500 per patient per year for the nucleoside analogs to

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US$8000 per patient per year for one of the protease inhibitors in 1998.[7,8] Furthermore, the combination therapy must be continued throughout the patient's life.[4–6]

In Taiwan, when the number of HIV-infected patients was small, the National Health Insurance (NHI) could cover the cost and provide all HIV-infected citizens with free access to such therapy.[1] Since 2003, however, a new wave of HIV epidemic of CRF07_BC subtype was introduced from southwest China via heroin-trafficking routes into Taiwan.[9] Up till the end of 2006, at least 5034 intravenous heroin abusers have already been infected.[10] With the anticipated huge financial burden on the NHI due to the explosive growth in the number of new HIV cases, controversy has emerged with regard to whether the policy of providing free HAART should be continued.

Several studies have suggested that HAART is cost-effective,[8,11–13] with the incremental cost per life year (LY) gained estimated at US$12,000–21,000 in the United States,[8] US$22,110 in Swizerland,[11] US$12,813–14,587 in Canada,[12] and US$675–1622 in South Africa.[13] These studies, nevertheless, were either based on hypothetical computer simulations[8,11] or on databases from only a few hospitals.[12,13] The present study aimed to evaluate the cost-effectiveness of HAART in HIV-infected patients through analyzing nationwide databases in Taiwan.

Methods

Study design

This was an intervention study comparing treatment effectiveness before versus after the introduction of HAART in Taiwan in April 1997. We calculated the incremental cost-effectiveness ratio[14] based on the average cost and the quality-adjusted life expectancy (estimated mean quality-adjusted lifetime survival) after the diagnosis of HIV infection. Comparisons were made between the pre-HAART era (April 1, 1984 to March 31, 1997) (as the baseline scenario) and the HAART era (May 1, 1997 to April 30, 2003).

Survival data of HIV-infected patients

Both HIV infection and acquired immunodeficiency syndrome (AIDS) are reportable diseases in Taiwan.[15] All identified cases must be confirmed by Western blot and reported to the Centers for Disease Control (Taipei, Taiwan). For each case confirmed by Western blot, the Centers for Disease Control maintains a periodically updated data profile, including the date of diagnosis, age, gender, date of development of AIDS,[3] and date of death. The survival status of each patient is further verified by cross-checking with the national death certification database maintained by the Department of Health and Ministry of the Interior, Taiwan.[16]

Survival analysis and extrapolation

The follow-up data were analyzed by the Kaplan–Meier method[17] to yield the estimated survival function of HIV-infected patients in the two eras. A constant excess hazard model was used to project long-term survival of HIV-infected patients, with linear extrapolation of a logit-transformed curve of survival ratio between HIV-infected patients and an age- and gender-matched reference population.[3] The survival function of this reference population was generated by a Monte Carlo method[18] from the life table of the general population of Taiwan. At the end of 2006, Taiwan had a population of 22,876,527, of whom 16,443,867 (71.2%) were aged 15–64 years, and a life expectancy at birth of 77.5 years. The statistics and life tables for the general population were obtained from vital statistics published by the Department of Statistics, Ministry of the Interior, Executive Yuan, Taiwan (available online at http://www.moi.gov.tw/W3/stat/). The methodologic details have been described elsewhere.[3,18–22] To facilitate the computation, we developed a software program MC-QAS, which was built in the R and S-PLUS 2000 (MathSoft Inc., Cambridge, MA, USA) environment; it can be freely downloaded from http://www.stat.sinica.edu.tw/jshwang (released in December 2004). The standard error of the survival estimate was obtained using a bootstrap method.[23] Life expectancy was estimated by

extrapolating the survival curves to 50 years after the diagnosis of HIV infection.[3]

Quality of life data

Quality of life data from HIV-positive patients during the HAART era in Taiwan was obtained from a cross-sectional survey of 224 patients in 2000–2001. Health profiles were measured using the abbreviated version of the World Health Organization Quality of Life Instrument (WHOQOL-BREF),[24,25] and health utility was assessed using standard gamble method.[26] Part of the results using WHOQOL-BREF have been reviewed and published.[25] The domain scores were expressed as a percentage of the highest possible scores. To analyze the temporal trend in the quality of life after the diagnosis of HIV infection, the scores were plotted against the interval between the diagnosis of HIV infection and the time of the survey. The kernel type smoother with a bandwidth of 0.1 was used to estimate the mean quality of life over time. As there were no data on the quality of life in HIV-infected patients in the pre-HAART era in Taiwan, we used a conservative best-case analysis and assumed it to be the same as that of the HAART era.

Quality-adjusted survival

Quality-adjusted survival was defined by the integration of survival and quality of life using the following formula:[18,19]

$$E(QAS_{\lceil} x_i) = \int_0^{\infty} E(q(t_{\lceil} x_i)) S(t_{\lceil} x_i) dt$$

where $E(QAS_{\lceil} x_i)$ is the expected value of quality-adjusted survival of patient population x_i, $E(q(t_{\lceil} x_i))$ is the expected health utility of patient population x_i, $S(t_{\lceil} x_i)$ is the survival function of patient population x_i, and x_i is the patient population either during the pre-HAART era or the HAART era.

The unit of $E(QAS_{\lceil} x_i)$ is the quality-adjusted life year (QALY). The quality-adjusted life expectancy (QALE) after the diagnosis of HIV infection was calculated by the integration of life expectancy and temporal trend of health utility.

Cost of antiretroviral therapy

The medication cost of HAART per patient per year was calculated by dividing the total national expenditure on HAART with the number of HAART users in the year 2000. Because no data were available for the cost of antiretroviral therapy in the pre-HAART era in Taiwan, we assumed that the cost of single nucleotide reverse transcription inhibitor (NRTI) therapy commonly used in the pre-HAART era in Taiwan was 1/6 that of a HAART regimen using 2 NRTIs +1 protease inhibitor, according to the reported ratio of wholesale drug prices in the United States (US$2500 per patient per year for the nucleoside analogs; US$8000 per patient per year for one of the protease inhibitors).[7,8]

Because the above-stated HAART cost data from the NHI was cross-sectional, we reconstructed the longitudinal average cumulative cost by the following method. The average medication cost per patient in the n^{th} year after the diagnosis was estimated by multiplying unit medication cost per patient per year with the average of probabilities of survival at the beginning and at the end of the n^{th} year. Since 2002, the practice of initiating HAART in asymptomatic HIV-infected patients has changed to the new criteria of CD4 count < 350/μL or peripheral blood HIV-RNA level > 55,000 copies/mL.[4,5] We therefore assumed that, on average, no HAART was needed in the first 2 years after diagnosis for HIV-positive patients without initial presentation of AIDS-defining illnesses.[3] The cumulative cost was adjusted by a 3% annual discount rate.

Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio of HAART was calculated by the following formula:

Incremental cost per LY or QALY gained = (Estimated lifetime cost of antiretroviral drugs per patient in the HAART era – Estimated lifetime cost of antiretroviral drugs per patient during the pre-HAART era)/(Estimated mean lifetime survival or mean quality-adjusted survival in the HAART era – Estimated mean lifetime survival or mean quality-adjusted survival during the pre-HAART era).

Sensitivity analysis

Due to uncertainties in the estimation of long-term survival time after diagnosis of HIV-infected patients in the HAART era, we conducted sensitivity analysis on survival estimates to see whether the length of survival time had a significant effect on the incremental cost-effectiveness ratio.

Results

HAART-associated survival improvements

A dramatic improvement in patients' survival was observed during the HAART era compared with the pre-HAART era. The Kaplan–Meier survival curves of patients presenting with AIDS (AIDS group) during the pre-HAART era ($n=259$) and the HAART era ($n=718$) are shown in Figure 1A, and those of patients initially without AIDS-defining illness (non-AIDS group) during the pre-HAART era ($n=997$) and the HAART era ($n=2633$) are shown in Figure 1B. The estimated lifetime survival curves are shown in Figure 2. In the AIDS group, the life expectancy (mean survival time) after the diagnosis of HIV infection increased from 1.47 ± 1.70 years (mean ± standard error) during the pre-HAART era to 10.61 ± 3.15 years during the HAART era; in the non-AIDS group, the corresponding increase was from 10.45 ± 2.16 years to 21.53 ± 5.72 years during the HAART era (Table).

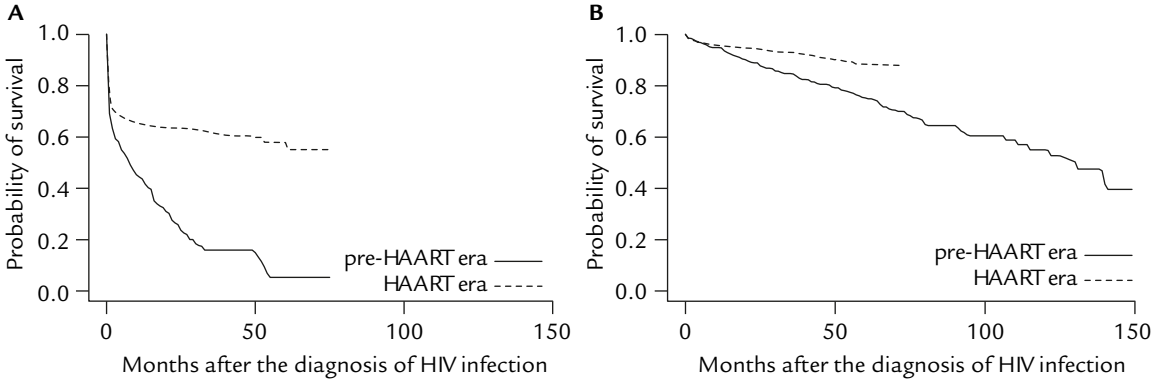

Figure 1. Observed survival curves for HIV-positive patients during the pre-HAART era (April 1, 1984 to March 31, 1997) and the HAART era (May 1, 1997 to April 30, 2003): (A) AIDS group ($n=259$ *vs.* 718); (B) non-AIDS group ($n=997$ *vs.* 2633).

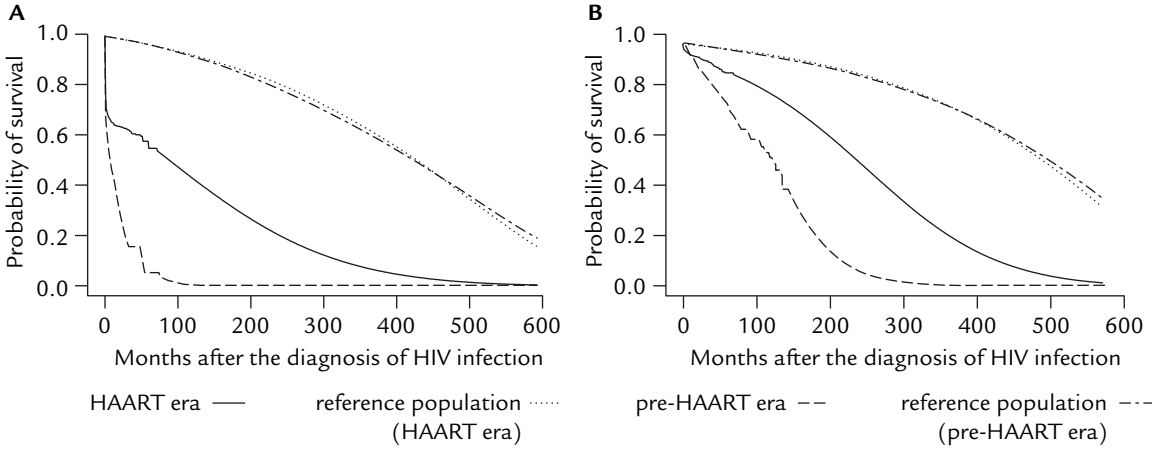

Figure 2. Projected lifetime survival curves for HIV-positive patients during the pre-HAART and HAART eras: (A) AIDS group; (B) non-AIDS group.

Estimation of QALE gained after HAART

Figure 3 shows the temporal trend in health profiles and health utility after the diagnosis of HIV infection, calculated from cross-sectional data from a total of 224 patients including 63 AIDS patients (22 diagnosed during the pre-HAART era) and 161 non-AIDS patients (58 diagnosed during the pre-HAART era). The longest follow-up

Table. Cost and cost-effectiveness of highly active antiretroviral therapy (HAART)

	HAART era		Pre-HAART era	
	AIDS group	Non-AIDS group	AIDS group	Non-AIDS group
Estimated mean ± SEM survival time, year	10.61 ± 3.15	21.53 ± 5.72	1.47 ± 1.70	10.45 ± 2.16
Estimated mean ± SEM QALE, QALY	7.75 ± 2.30	14.64 ± 3.89	1.07 ± 1.24	7.11 ± 1.47
Mean lifetime cost of ART per patient (NT$)	1,658,913	2,744,176	46,246	238,370
Incremental cost per LY gained (NT$)	176,441	226,156	–	–
Incremental cost per QALY gained (NT$)	241,700	332,582	–	–

SEM = standard error of the mean; QALE = quality-adjusted life expectancy; QALY = quality-adjusted life-year; ART = antiretroviral therapy; LY = life-year.

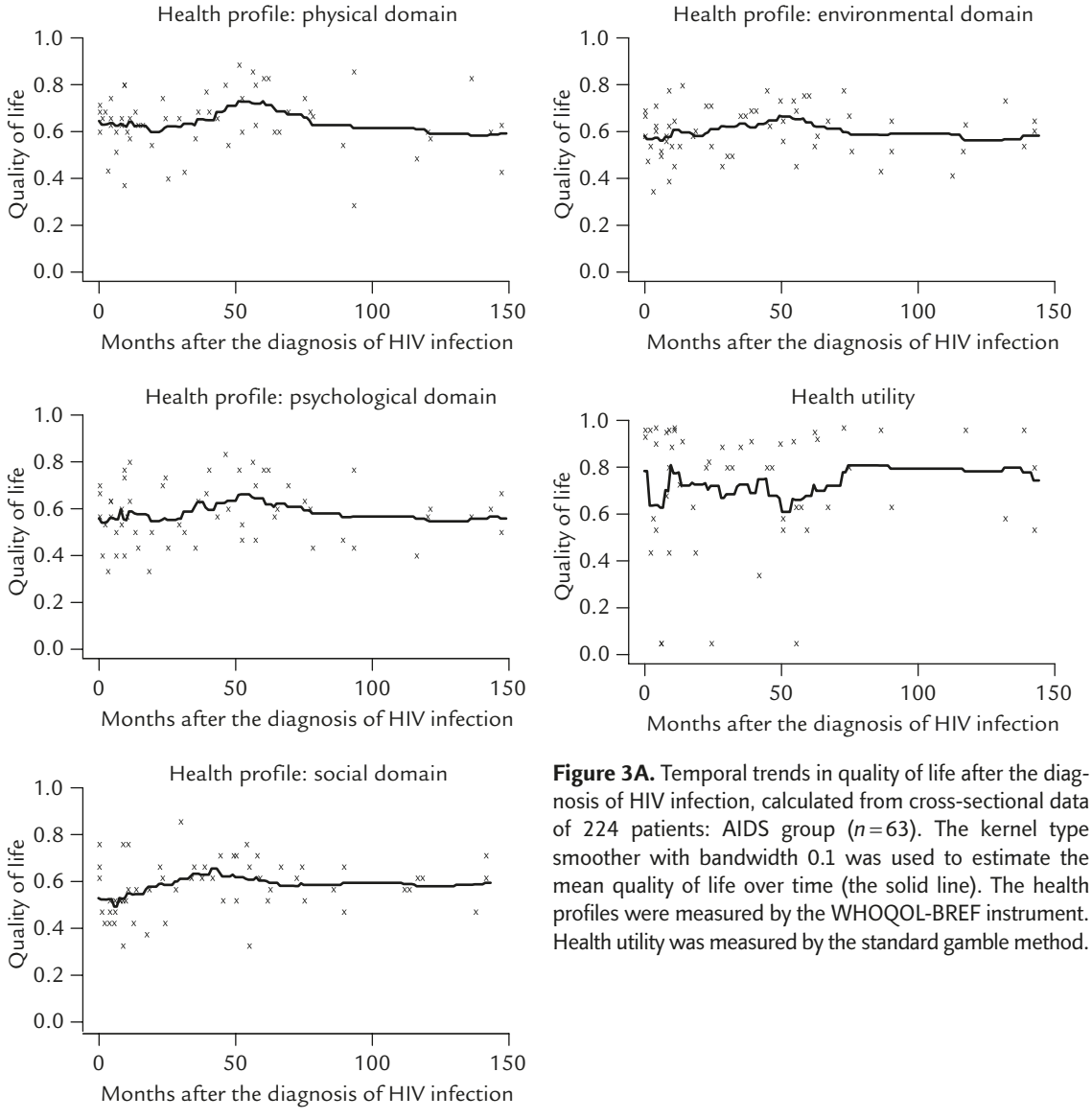

Figure 3A. Temporal trends in quality of life after the diagnosis of HIV infection, calculated from cross-sectional data of 224 patients: AIDS group ($n = 63$). The kernel type smoother with bandwidth 0.1 was used to estimate the mean quality of life over time (the solid line). The health profiles were measured by the WHOQOL-BREF instrument. Health utility was measured by the standard gamble method.

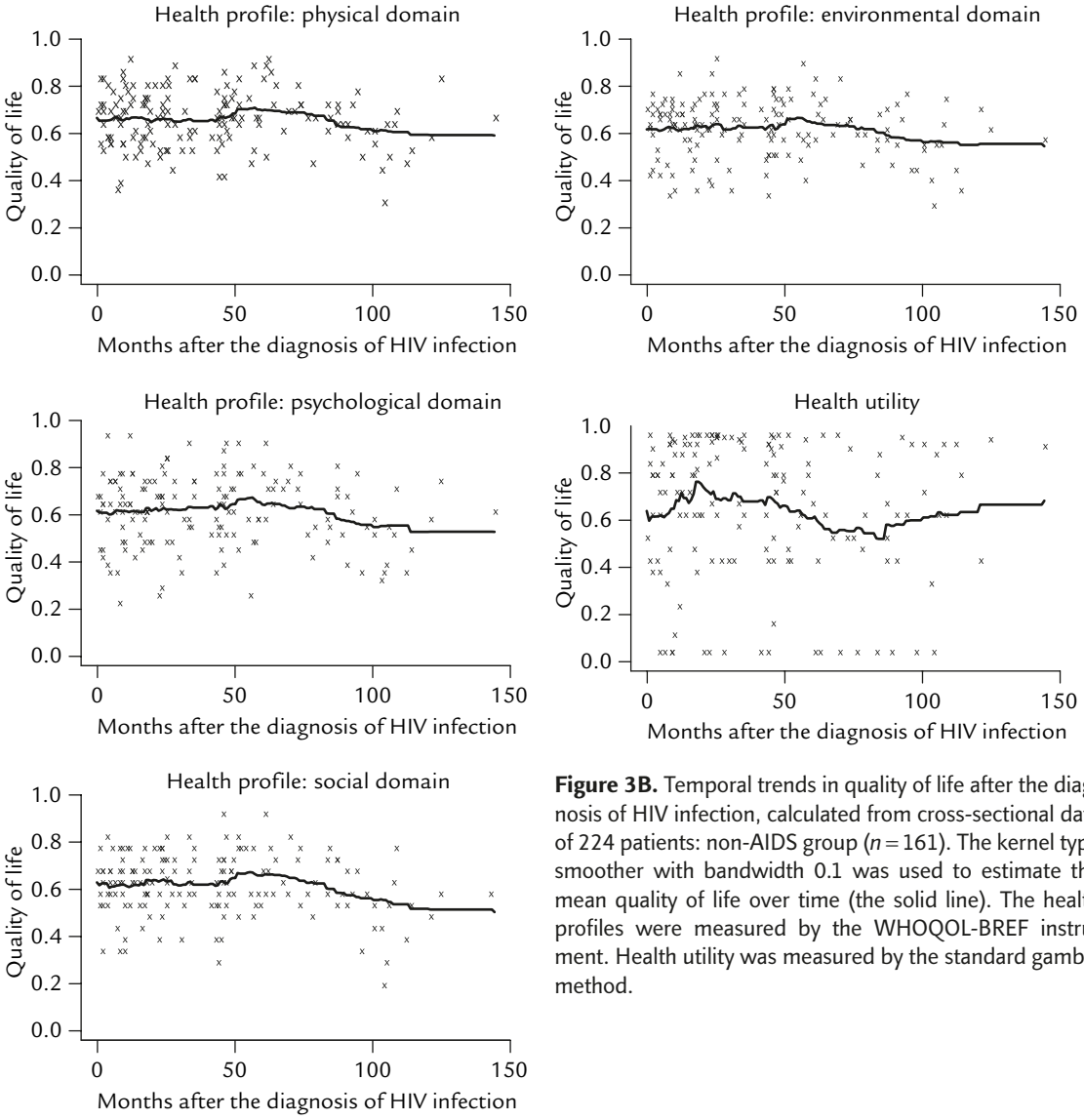

Figure 3B. Temporal trends in quality of life after the diagnosis of HIV infection, calculated from cross-sectional data of 224 patients: non-AIDS group ($n = 161$). The kernel type smoother with bandwidth 0.1 was used to estimate the mean quality of life over time (the solid line). The health profiles were measured by the WHOQOL-BREF instrument. Health utility was measured by the standard gamble method.

time after diagnosis among these 224 patients was 12.25 years. Both the AIDS and non-AIDS groups showed no temporal trend of decrease in either health utility or any health profile over the follow-up period (Figure 3). We therefore applied a constant value for health utility in the QALE estimation. The QALE of AIDS patients after diagnosis increased from 1.07 ± 1.2 QALY to 7.75 ± 2.30 QALY, while that of non-AIDS patients increased from 7.11 ± 1.47 QALY to 14.6 ± 3.89 QALY (Table).

Cost of antiretroviral therapy

In 2000 in Taiwan, the average annual NHI expenditure on HAART per HIV-positive patient receiving HAART was NT$210,018 (US$6177 at an exchange rate of 34.0 NT$/US$). There was no change in the price of HAART from 2000 to 2004. Based on the assumptions of a stable price for HAART afterwards, and an annual discount rate of 3%, the cumulative cost of lifetime HAART was estimated to be NT$1,658,913 per patient in the AIDS group, and NT$2,744,176 per patient in the non-AIDS group. The annual cost of antiretroviral therapy during the pre-HAART era was estimated to be NT$35,003 per patient. The cumulative cost of lifetime antiretroviral therapy during the pre-HAART era was estimated to be NT$46,246 and NT$238,370 in the AIDS and non-AIDS groups, respectively.

Incremental cost for each LY and QALY gained

The incremental costs are shown in the Table. For the AIDS group, the cost was NT$176,441 (US$5189) per LY gained and NT$241,700 (US$7109) per QALY gained. For the non-AIDS group, the corresponding costs were NT$226,156 (US$6652) and NT$332,582 (US$9782), respectively.

Sensitivity analysis

Uncertainty in estimated survival time in the HAART era has a minimal effect on the incremental cost-effectiveness ratio. A variation within one standard error of the mean in estimated survival time in the HAART era resulted in a range of incremental cost-effectiveness ratio from NT$159,747 (US$4698) to NT$210,691 (US$6197) per LY gained for the AIDS group. Similarly, a variation within one standard error of the mean in estimated survival time in the HAART era resulted in a range of incremental cost-effectiveness ratio from NT$187,053 (US$5502) to NT$348,716 (US$10,256) per LY gained for the non-AIDS group.

Discussion

Our analyses showed that the incremental cost-effectiveness ratio of HAART for HIV infection was NT$176,441–226,156 (US$5189–6652) per LY gained and NT$241,700–332,582 (US$7109–9782) per QALY gained, depending on the stage of HIV diseases. Although there has been no objective cut-off value in the interpretation of the results of cost-effectiveness, most authorities have agreed that the threshold for cost-effectiveness is somewhere between US$20,000/QALY and US$100,000/QALY, with thresholds of US$50,000–60,000/QALY frequently proposed in other developed countries.[27–31] An incremental cost-effectiveness ratio of NT$241,700–332,582 (US$7109–9782, at 34.0 NT$/US$) per QALY gained in Taiwan seems well below the lower cut-off value of US$20,000/QALY, or, is much better than those reported from the United States (US$13,000–23,000/QALY)[8] or Canada (US$12,913–14,587/LY).[12]

A major determinant of the cost-effectiveness ratio, of course, is the drug price. We found that the unit cost of HAART per patient per year (NT$210,018 or US$6177 in 2000) in Taiwan was significantly lower than those anticipated from the wholesale price in the United States (US$2500 per patient per year for the nucleoside analogs to US$8000 per patient per year for one of the protease inhibitors in 1998).[7,8] It appeared that Taiwan obtained a reasonable discount during price negotiations. In many parts of the world, however, concerns about access to HAART and market competition have resulted in mass production of less expensive generic drugs and reduction in the prices of many brand-name products.[32–34] Generic antiretroviral drugs may cost only one-tenth of the brand-name products.[33] As a result, South Africa can reach an incremental cost-effectiveness ratio of as low as US$675–1622 per LY gained.[13] In Taiwan, there was no change in the price of HAART from 2000 to 2004 because the efficacy of generic drugs remained uncertain during this period and brand-name products were therefore used to ensure the quality and effectiveness of antiretroviral agents. If the quality of generic drugs can be demonstrated, introduction of these less expensive products to replace brand-name ones may significantly reduce the financial burden of providing HAART. The cost reduction of antiretroviral agents would likely further improve the cost-effectiveness profile of HAART in the future.

There are several limitations and underestimations in the present assessment of the cost-effectiveness of HAART. First, since quality of life data were unavailable during the pre-HAART era, we used a conservative best-case analysis, assuming that the quality of life in HIV-infected patients was the same between the pre-HAART and HAART eras. Several studies, however, have shown that treatment with HAART actually improved the overall quality of life.[35,36] Therefore, the actual QALY gain during the HAART era might have been better than our estimates. Second, in

the present study, we did not consider the costs of medical care other than HAART, the intangible cost of fear and suffering, and the indirect cost to patients and their families. Because the medical costs other than HAART included at least the use of ventilator for pneumonia and various expensive antimicrobial agents for opportunistic infections, which depended on the standard of clinical care and have been rapidly evolving, it is difficult to objectively model a longitudinal trend in cost by analyzing available cross-sectional data. It is also difficult to quantify the intangible cost and indirect cost longitudinally. Since many studies consistently showed that HAART decreased the risks of opportunistic infections and associated hospitalization,[2,4–6,37] we would anticipate an adjustment in a favorable direction if we consider the cost of medical care other than HAART. In addition, HAART also provides renewed health, more employment[38] and hope for the future[39] for HIV-infected patients. Therefore, there will be a further favorable adjustment.

From an epidemiologic viewpoint, the universal availability of HAART also greatly benefit people who are not yet infected. HAART profoundly suppresses HIV-RNA levels in blood and other body fluids and therefore decreases the infectiousness of HIV-infected patients,[1,2] which probably slowed down the spread of the HIV epidemic in Taiwan during 1997–2002 and was demonstrated in our previous study.[1] Thus, a universal HAART policy will contribute additional LY gain through averting new HIV cases. Although HAART alone cannot eradicate the HIV epidemic and must be accompanied by effective HIV-related risk-reduction intervention,[40] the ethical acceptability and the willingness to participate in voluntary screening and counseling programs actually depend on the availability of HAART.[41,42] If these factors are also considered, the cost-effectiveness ratio of HAART would be even better than the current estimates.

In conclusion, our analyses show that HAART for HIV infection is cost-effective, with an incremental cost-effectiveness ratio of NT$176,441–226,156 (US$5189–6652) per LY gained and NT$241,700–332,582 (US$7109–9782) per QALY gained. If we consider the cost of medical care other than HAART, the intangible cost, the indirect cost to patients and their families, the reduction of HIV transmission, and the facilitation of HIV screening and risk reduction programs, the cost-effectiveness ratio would be even better. We therefore recommend that providing free access to HAART to all HIV-infected citizens should be continued.

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