MAJOR ARTICLE

Decreased HIV Transmission after a Policy of Providing Free Access to Highly Active Antiretroviral Therapy in Taiwan

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Background. Taiwan established a nationwide surveillance system for human immunodeficiency virus (HIV) infection in 1989 and adopted a policy to provide all HIV-infected citizens with free access to highly active antiretroviral therapy (HAART) beginning in April 1997. This provided an opportunity to determine the effect of the widespread use of HAART on the evolution of the HIV epidemic.

Methods. We analyzed national HIV surveillance data. The HIV transmission rate was estimated by use of an exponential model of HIV epidemic evolution, with statistical projection over the interval between infection and detection to fit the surveillance data.

Results. By the end of 2002, the cumulative number of HIV-infected citizens in Taiwan had reached 4390 (0.019% of the total population). After free access to HAART was established, the estimated HIV transmission rate decreased by 53% (0.391 vs. 0.184 new cases/prevalent case-year [95% confidence interval, 31%–65%]). There was no statistically significant change in the incidence of syphilis, in the general population or among HIV-positive patients, during the same period.

Conclusion. Providing free HAART to all HIV-infected citizens was associated with a 53% decrease in the HIV transmission rate and contributed to the control of the HIV epidemic in Taiwan.

A higher HIV load is one of the major determinants of the risk of HIV transmission [1–3]. Highly active antiretroviral therapy (HAART) [4, 5], which profoundly suppresses HIV-RNA levels in body fluids [6–8], not only remarkably prolongs the survival of treated patients [9, 10] but also reduces rates of mother-to-child perinatal transmission [11, 12] and heterosexual transmission [13], according to the results of clinical studies. In theory, the widespread use of HAART could lead to a reduction in the rate of HIV transmission in the entire population and contribute to the control of the HIV pandemic [14–18]. Nevertheless, there is a lack of empirical data to verify this argument, because of the expense of HAART, which is simply not affordable to the majority of people with HIV, except those in affluent countries [19, 20]. Furthermore, most countries lack an effective surveillance system for tracking the incidence of asymptomatic HIV infection [19, 21, 22]. A possible negative consequence of the widespread use of HAART is the potential increase in unsafe sexual behavior due to optimism about treatment [23, 24]. Mathematical simulations have suggested that a modest increase in unsafe sexual behavior can offset the effect of a large decrease in infectiousness by the widespread use of HAART [25, 26]. Thus, the effect of widespread use of HAART on the evolution of an HIV epidemic remains uncertain.

Similar to other countries, Taiwan has been affected by the HIV epidemic since the mid-1980s [27]. To counteract the threat of the HIV epidemic, the Department of Health of Taiwan established a nationwide active surveillance system for HIV infection in 1989.

Received 31 May 2003; accepted 30 January 2004; electronically published 22 July 2004.

Financial support: Department of Health, Executive Yuan, Taiwan (grants DOH92-DC-1032); National Health Research Institutes, Taiwan (integrated grant NHRI-EX92-9204PP).

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The Journal of Infectious Diseases 2004;190:879–85

0022-1899/2004/19005-0002$15.00

Unlike the majority of other countries, Taiwan adopted a policy to provide all HIV-infected citizens with free access to HAART through the National Health Insurance program, beginning in April 1997. The combination of an effective surveillance system and a policy to provide free HAART to all HIV-infected citizens made it possible to study the effect of widespread use of HAART on the evolution of the HIV epidemic in Taiwan. We analyzed HIV surveillance data through statistical modeling, to estimate the HIV transmission probability ratio in the Taiwanese population, before and after the implementation of the free-HAART policy. To differentiate the effect of HAART from that of behavioral changes, the incidence of syphilis in the general population and among HIV-positive patients was also analyzed, for comparison.

MATERIALS AND METHODS

Surveillance of HIV infection and AIDS. Both HIV infection and AIDS became reportable diseases in Taiwan in 1984. All identified cases must be reported to the Center for Disease Control (CDC; Taipei, Taiwan). To protect the rights of these patients, all personal information was kept confidential. Cases of HIV infection detected by ELISA must be confirmed by Western blot. For each case of HIV, the date of first detection, age, sex, HIV risk factors, date of development of AIDS, and date of death are registered. AIDS was defined according to Centers for Disease Control and Prevention (Atlanta, GA) criteria [28]. The identification of cases of AIDS depended on reports from physicians. The identification of cases of asymptomatic HIV infection depended on active screening. As both a moral obligation and an incentive for voluntary testing, the government offered free antiretroviral therapy (ART) to all identified HIV-infected citizens. Nationwide routine screening of blood donors was started in 1988. High-risk populations—such as patients with syphilis, gonorrhea, or other sexually transmitted diseases; prostitutes; male homosexuals; patients with hemophilia; injection drug users; prisoners; and individuals having multiple sex partners—were encouraged or persuaded to receive voluntary testing. Pre- and posttest counseling about safer sex and ART were routinely offered. Among the general population, young couples were encouraged to undergo HIV testing before marriage. Pregnant women were also encouraged to undergo HIV testing as part of obstetric care. To further improve the detection rate of asymptomatic HIV infection, compulsory HIV testing was also enacted among enlisted servicemen (military service is mandatory for all men at 20 years of age in Taiwan) in 1989. The performance of the active surveillance system was measured by the proportion of AIDS among newly identified cases. A lower proportion of AIDS among newly identified cases indicates a shorter median interval between infection and detection.

Policy of providing free access to ART. At the beginning of the HIV epidemic, the government decided to ensure that all HIV-infected citizens would have free access to ART and medical care. Initially, a special government fund, which was subject to annual review by the legislature, was raised to purchase the needed antiretroviral agents. After 1 January 1998, the antiretroviral agents were purchased through the National Health Insurance system. Under this policy, zidovudine was introduced in 1987, followed by didanosine (in 1992) and deoxycytidine (in 1995). To maximize the benefits of ART, special clinics were created where antiretroviral agents were prescribed and their use monitored by qualified physicians. In 1997, the government decided to provide free access to HAART to all HIV-infected citizens, despite the high cost. On 7 April 1997, saquinavir, indinavir, ritonavir, lamivudine, and stavudine were simultaneously introduced. The timing of the initiation of HAART and the regimens were based on guidelines recommended in the United States [4, 5]. Early intensive treatment was encouraged, except for patients with blood HIV-RNA levels <5000 copies/mL and peripheral CD4 cell counts in the normal range. Regular monitoring of adverse effects of drugs, blood cell counts, blood chemistry, and CD4 cell counts was also provided free of charge. To improve drug compliance, newer agents that were more convenient to use, including efavirenz (since 2000), nevirapine (since 2000), lopinavir/ritonavir (since 2001), and abacavir (since 2001), were added to the therapeutic armamentarium.

Estimating the rate of HIV transmission. Under the assumption of a stable interval distribution between infection and detection, we can use a modified back-calculation method [29–31] to predict surveillance results from theoretical incidence curves. If the HIV prevalence is low and the incidence curve therefore follows an exponential model [17, 32], then the predicted surveillance data will also follow an exponential model, which allows us to estimate the average HIV transmission rate (new cases/prevalent case-year), R, by regressing the natural logarithm of numbers of newly detected cases against time t. R will be equal to the slope of the regression line plus the average risk of mortality, m. Because the magnitudes of R and m during the HAART era might be different from that during the pre-HAART era, the regression should be conducted separately. Linear regression alone can give an unbiased estimate of R during the pre-HAART era but will slightly overestimate R during the HAART era, because the interval distribution between infection and detection caused a convex theoretical surveillance curve after the implementation of the HAART policy. To obtain an exact estimate of R during the HAART era, we can estimate the parameters of this interval distribution from the proportion of those with AIDS among newly identified cases, calculate the predicted surveillance curve, and then conduct a nonlinear regression procedure to adjust for the effect of this nonlinearity.

Estimation of the total number of HIV-infected patients in Taiwan. If all identified cases of HIV and AIDS are reported, as in Taiwan, we can estimate the total number of HIV-infected patients from the reduction in the transmission rate after the implementation of the HAART policy. Because new patients with HIV acquired their infection from either identified patients (x% of the total) or from unidentified patients, the reduction in R in Taiwan (denoted ΔR) is the weighted mean of the reduction in R of identified patients (denoted $\Delta R'$) and that of unidentified patients (0, by definition). Therefore, $\Delta R = (x\%)(\Delta R')$ and $(x\%) = \Delta R/\Delta R'$. Because the maximal possible value of $\Delta R'$ is 100%, the minimal value of x% would be ΔR.

Incidence of syphilis and gonorrhea. The incidence of syphilis and gonorrhea in the general population was studied using nationwide surveillance data. Syphilis and gonorrhea are also reportable diseases in Taiwan. To be registered, patients with syphilis must have compatible clinical symptoms or signs and positive Venereal Disease Research Laboratory (VDRL) test results or *Treponema pallidum* hemagglutination assay (TPHA) titers; patients with gonorrhea must have compatible clinical symptoms or signs and positive urethral-culture results. The incidence of syphilis among HIV-positive patients was directly measured in the 1152 HIV-positive patients who were treated and monitored at the Taipei Municipal Venereal Disease Control Institute (TMVDC; Taipei, Taiwan), where regular VDRL titer monitoring has been part of the treatment of HIV-positive patients since 1989. To be counted as a case of newly acquired syphilis after a diagnosis of HIV infection, there must be compatible clinical symptoms or signs, positive TPHA titers, and a 4-fold increase in VDRL titer, compared with the baseline titers at the time of diagnosis of HIV infection.

Statistical analysis. Linear regression was used for model fitting in estimating R. The slopes of linear regression lines during the pre-HAART and HAART eras were compared by a linear model:

$$Y_t = \beta_0 + \beta_1 X + \beta_2 t + \beta_3 tX + \varepsilon_t .$$

X is a dummy variable that is used to describe the era ($X = 0$ for the pre-HAART era and $X = 1$ for the HAART era). Y_t is the natural logarithm of the number of cases at time t. Here, we assume that infections occur at discrete points in time, such as the beginning of each 4-month period. Thus, β_2 and $\beta_2 + \beta_3$ are the slopes of the regression lines during the pre-HAART era ($X = 0$) and during the HAART era ($X = 1$), respectively. β_3, the coefficient of the slope dummy variable tX, is the difference in slopes between the regression lines during the pre-HAART and HAART eras. Our test of slope change is therefore based on the significance of the β_3 estimate. With the results of linear regression used as the initial guess values, a nonlinear regression curve was also fitted, by use of the least-squares method, for surveillance data from the HAART era. The risk of mortality was calculated as the number of deaths of HIV-infected individuals during the 4-month interval, divided by the mean number of prevalent cases at the beginning and end of the interval; this was compared by use of the Wilcoxon rank-sum test. The incidence of syphilis during the pre-HAART and HAART eras was compared using the large-sample method for person-time data. The software programs used for computation and illustration were SAS (version 8.0; SAS Institute), S-PLUS 2000 (MathSoft), and Excel 2002 (Microsoft). Two-tailed $P < .05$ was considered to be statistically significant.

RESULTS

Surveillance of HIV and AIDS, 1984–2002. From January 1984 to the end of December 2002, a total of 29,429,255 ELISA tests for HIV were performed in Taiwan, including 20,635,116 tests for blood donors, 2,357,235 compulsory HIV tests for enlisted servicemen, and 896,200 tests for prisoners. The number of newly detected HIV infections and cases of AIDS (imported cases were not included) every 4 months is shown in figure 1*A*. The proportion of AIDS among newly identified cases remained stable before 2001 (0.25 ± 0.05), but this rate decreased (to 0.16 ± 0.01) in 2001 and 2002 ($P = .0003$; Wilcoxon rank-sum test). Up to the end of December 2002, the cumulative number of confirmed HIV-infected citizens in Taiwan reached 4390, or 0.019% of the total population (22,520,776 persons) in Taiwan. Among these 4390 patients, 3541 were still alive at the end of 2002. The prevalence of HIV among people 15–64 years old ($n = 15{,}890{,}584$) was 0.021%. In 2001, the HIV seroprevalence rates were 0.009% (6 cases/67,443 population) among enlisted servicemen, 0.014% (6 cases/41,379 population) among pregnant women, and 0.1% among patients with other sexually transmitted diseases.

Among the 4390 HIV-positive patients, the majority were men (92.9%). The most common age at diagnosis was 20–29 years (36.5%), followed by 30–39 (33.5%) and 40–49 (13.2%) years. Sexual contact (96.4%) was the predominant risk factor, followed by injection drug use (1.9%), hemophilia (1.2%), transfusion (0.3%), and mother-to-child transmission (0.2%). The percentage of injection drug users (IDUs) decreased from 3.8% during the pre-HAART era (January 1990–April 1997, $n = 1149$) to 0.8% during the HAART era (May 1997–December 2002, $n = 3094$) ($P < .01$; χ^2 test). Among sexually acquired cases, 54.5% of patients reported they were men having sex with men (MSM), but the actual percentage of MSM was probably much higher, because male homosexuality remained a social taboo in Taiwan, and patients were reluctant to disclose their true sexual orientation. Because disposable needles can be easily purchased from any drugstore at a price as low as US$0.03/needle, IDUs in Taiwan usually did not share needles. Many HIV-positive IDUs in Taiwan actually acquired HIV through sexual contact.

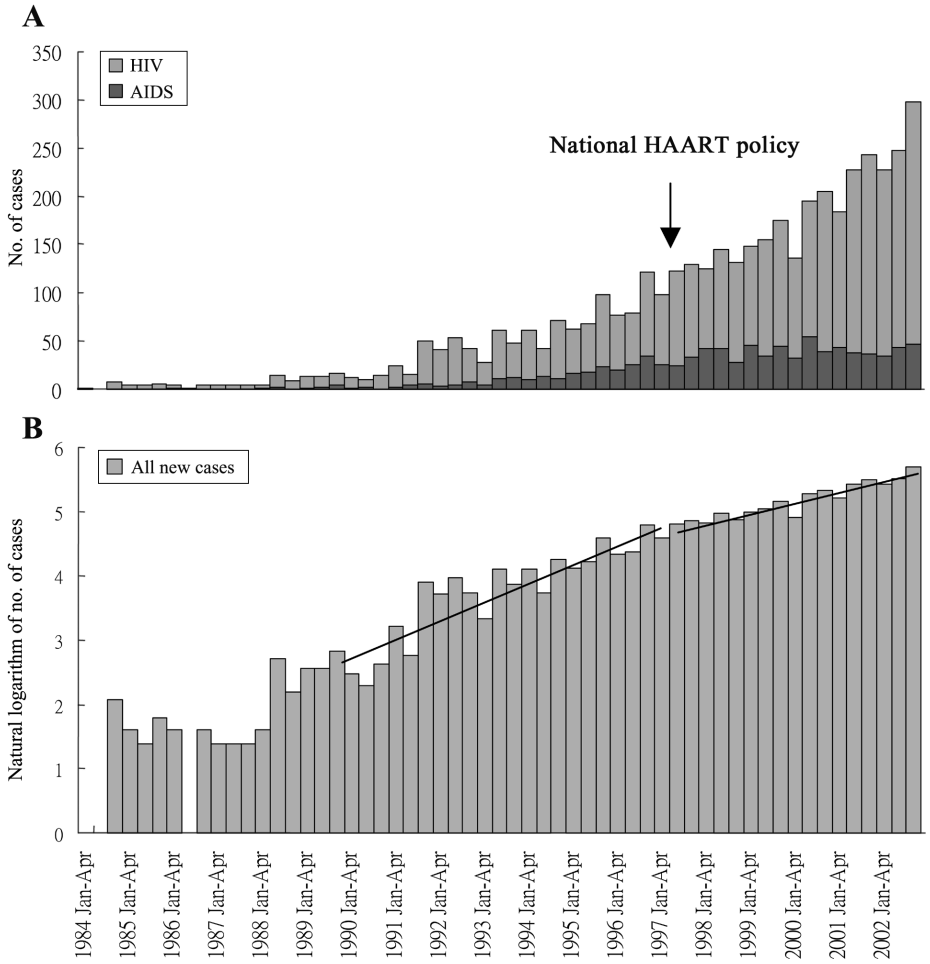

Figure 1. *A,* Nos. of newly detected cases, including asymptomatic HIV infection and AIDS, every 4 months in Taiwan, January 1984–December 2002. The national policy of providing free access to highly active antiretroviral therapy (HAART) was started 7 April 1997. *B,* Natural logarithm of the nos. of all newly detected cases every 4 months in Taiwan, January 1984–December 2002. Regression lines are shown.

Reduction of HIV transmission during the HAART era. The natural logarithm of the numbers of newly detected cases every 4 months is shown in figure 1*B*. The slopes of the linear regression line during the pre-HAART (January 1990–April 1997) and HAART (May 1997–December 2002) eras were 0.292 ± 0.033 ($R^2 = 0.80$; $P < .0001$) and 0.156 ± 0.014 ($R^2 = 0.90$; $P < .0001$), respectively, for each prevalent case-year. The slope decreased significantly during the HAART era, compared with that during the pre-HAART era ($P = .005$). Residual analysis showed that the residuals had no autocorrelation over time during either time period. On the basis of the average proportion of AIDS (among newly identified cases) of 0.25, the interval distribution between infection and detection was simulated by use of a Weibull model $F(t) = 1 - \exp(-0.0982t^{2.286})$, with a median time from infection to detection of 2.35 years (figure 2). Using 0.156 as the initial value, nonlinear regression was conducted and converged on the slope value of 0.138/prevalent case-year during the HAART era.

The Kaplan-Meier survival curves of HIV-infected patients during the pre-HAART and HAART eras are shown in figure 3. The average risk of mortality, m, which was calculated by averaging the number of deaths per number of prevalent cases every 4 months during 1991–1996, was 0.099 ± 0.031 cases/prevalent case-year, which was significantly reduced to (0.046 ± 0.019) cases/prevalent case-year during 1998–2002 ($P = .0002$; Wilcoxon rank-sum test).

Thus, the estimated R during the pre-HAART era was $0.292 + 0.099 = 0.391$ new cases/prevalent case-year. After implementing the policy to provide free access to HAART, R was reduced to $0.138 + 0.046 = 0.184$ new cases/prevalent case-year. The reduction in the average HIV transmission rate in Taiwan was thus $(0.391 - 0.184)/0.391 \times 100\% = 53\%$ (95% confidence interval [CI], 31%–65%).

Estimation of the total number of HIV-infected patients in Taiwan. Because $\Delta R = 53\%$, the minimal value of $x\%$ would be 53%. This implies that the upper limit of the total num-

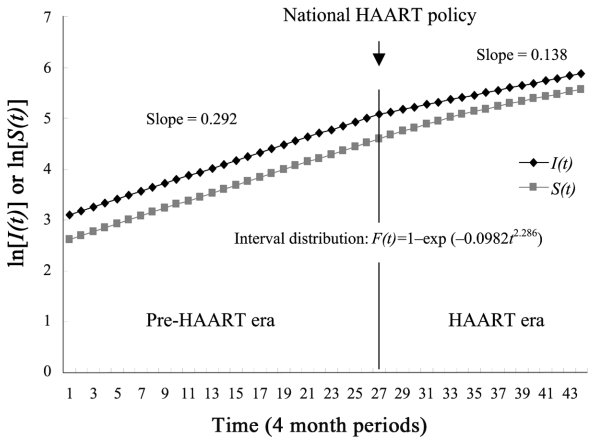

Figure 2. Incidence curve *(It)* (simple exponential model) and the predicted surveillance curve *(St)* during the pre–highly active antiretroviral therapy (HAART) era and after the introduction of HAART. The interval distribution *(Ft)* between infection and detection caused a convex surveillance curve after the implementation of the free-HAART policy.

ber of HIV-infected patients in Taiwan at the end of 2002 is 4390/53% = 8283 (95% CI, 6754–14,161). The 8283 patients would account for 0.036% of the total population, which does not violate the low prevalence assumption.

Incidence of syphilis and gonorrhea. The nationwide annually reported numbers of cases of syphilis and gonorrhea were 3200 and 520 during 1993, 3240 and 263 during 1994, 3054 and 175 during 1995, 3172 and 121 during 1996, 3050 and 95 during 1997, 2407 and 91 during 1998, 3037 and 163 during 1999, 3854 and 367 during 2000, 3694 and 397 during 2001, and 4182 and 838 during 2002. There was no statistically significant change in the reported numbers of cases of syphilis and gonorrhea during this period. Among the 1152 HIV-positive patients who were treated and monitored at TMVDC, the incidence of newly acquired cases of syphilis after the diagnosis of HIV infection was 60 episodes/11,048 person-months during the pre-HAART era (1 January 1990–31 March 1997) and 158 episodes/32,023 person-months during the HAART era (7 April 1997–31 December 2002). There was no significant difference in incidence between the 2 periods ($P = .53$), with an incidence ratio of 0.91 (95% CI, 0.67–1.22).

DISCUSSION

Our research shows that, after implementing a policy of providing free access to HAART to all HIV-infected citizens, the HIV transmission rate decreased by 53% in Taiwan. This result makes a strong case for the more widespread use of HAART as a major control measure against the HIV and AIDS epidemics in countries with low prevalence. It should be emphasized that the Taiwan government also provided free access to zidovudine, didanosine, and deoxycytidine to all HIV-infected citizens during the pre-HAART era. Thus, the reduction in the HIV transmission rate would probably be >53% if there had been no ART in the baseline situation. This reduction in HIV transmission contributed greatly to the control of the HIV epidemic. The extremely low prevalence of HIV in Taiwan is a testament to the success of the policy of providing free access to HAART.

Study of the evolution of HIV epidemics has been hampered by the asymptomatic nature of early HIV infection, which makes the direct measurement of the incidence of HIV in large populations, such as the entire Taiwanese population, very difficult. Before the HAART era, data on the evolution of HIV epidemics were mainly obtained by backward projection from AIDS surveillance data [30, 31]. The usefulness of this approach has diminished since the introduction of HAART, which can delay or even prevent the development of AIDS in HIV-infected patients [5, 10, 22]. In the present study, R was estimated by use of an exponential model of HIV surveillance results, which had been predicted by a modified back-calculation projection from a theoretical exponential incidence curve to fit the observed surveillance data. The validity of our model depends on 2 assumptions: a low prevalence of HIV, which is the prerequirement of the simple exponential incidence curve used in the present study, and a stable interval distribution, for use in the projection. In Taiwan, >29 million screening ELISA tests were conducted during 1984–2002 among the population of 22 million persons, and the screening activity has been constantly focused on persons who are at an increased risk of HIV infection, with the incentive of free ART and medical care. Even if the actual total number of cases of HIV and AIDS was 10-fold higher than the detected 4390, it would still account for a prevalence rate as low as 0.19% of the total population. For the second assumption, the Department of Health of Taiwan

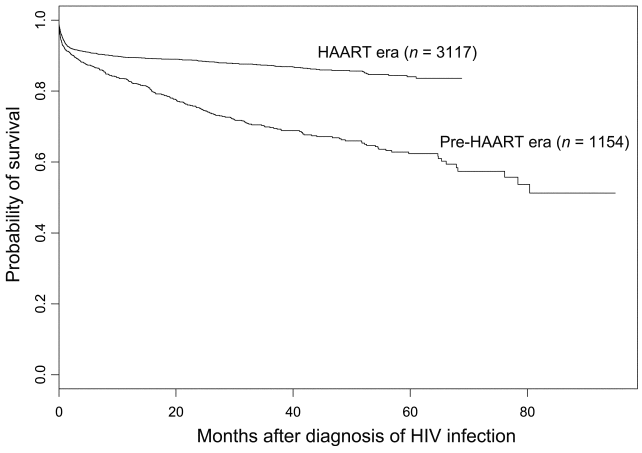

Figure 3. Kaplan-Meier survival curve of 1154 HIV-infected patients diagnosed between 1 January 1990 and 7 April 1997 (monitored until 7 April 1997) and 3117 HIV-infected patients diagnosed after 7 April 1997 (monitored until 31 December 2002). HAART, highly active antiretroviral therapy.

made an extraordinary effort in establishing a nationwide active surveillance system beginning in the late 1980s. Since 1990, the active HIV screening and reporting system has functioned well. This notion was supported by the high R^2 values of the linear-regression model used to explain the surveillance data in the 2 studied time periods (0.80 for 1990–1997 and 0.90 for 1997–2002) and the stable proportion of the development of AIDS among newly identified cases before 2001. The decreased proportion of cases of AIDS in 2001 and 2002, which was probably due to the improved performance of HIV surveillance among an increasing number of asymptomatic people who voluntarily received testing, will yield a biased slope estimate higher than it should be during the HAART era. Thus, the actual effect of HAART on reducing the HIV transmission might be higher than the 53% estimated in the present study.

For an observational study, any conclusion about a causal link must be carefully examined to exclude the influence of potential confounding factors. The present study is also an ecological study and might be subject to ecological fallacy. However, the major confounding factor (patterns of behavior) probably cannot explain the decrease in the average transmission rate of HIV after April 1997 in Taiwan. Although we had no reliable way of obtaining an accurate estimation of trends of risky sexual behavior, which was a private matter, the surveillance data on syphilis can be used as the surrogate marker. If there indeed had been a decrease in the rate of unprotected sex, there should have been a corresponding decrease in the incidence of syphilis. Our results showed that there was no such trend, either in the general population or among HIV-positive patients. This indicates that the decreased rate of HIV transmission was unlikely to be caused by a decrease in risky sexual behaviors among the general population and HIV-positive patients in Taiwan after 1997.

No specific intervention program, such as needle exchange or methadone maintenance programs, has been put in place for injection drug–related HIV infection in Taiwan. Because disposable needle can be easily purchased from any drugstore at a very low price (~$0.03/needle), IDUs in Taiwan have not usually shared needles during the past 2 decades. The most likely explanation for the significantly lower proportion of IDUs during the HAART era is that HIV-positive IDUs in Taiwan did not transmit HIV to other IDUs. In fact, most HIV-positive IDUs in Taiwan acquired HIV through sexual contact.

Antiretroviral drug resistance among patients recently infected with HIV has become a disturbing problem in the United States [33, 34]. Widespread drug resistance will certainly diminish, or even nullify, any effect of the free-HAART policy on HIV transmission. Thus, a well-functioning medical, nursing, and laboratory infrastructure is essential to ensure the long-term success of HAART and to avoid the rapid emergence of drug resistance. To conserve resources, the Taiwan CDC has facilitated the establishment of special clinics that are capable of delivering qualified medical care, including appropriate prescription and the monitoring of CD4 cell counts, plasma HIV load, and adverse effects of drugs. This has contributed to an extremely low rate of treatment failure caused by primary drug resistance for patients recently infected with HIV in Taiwan [35]. Further monitoring of the prevalence of drug resistance remains mandatory.

Although our results support that the policy of providing free access to HAART can significantly decrease the rate of HIV transmission among a population, one must be aware that such a policy alone cannot eradicate the HIV epidemic. The number of newly detected cases of HIV is still slowly increasing in Taiwan, which indicates a basic reproductive number >1 [32]. Because the HIV epidemic runs an exponential course during its early phases [17, 21], a reduction in HIV transmission by 53% means that the evolution of the epidemic was slowed down by 53%. However, the epidemic will eventually catch up if we cannot further reduce the transmission rate of HIV by additional preventive action. Although public education about safer sex and condom use has been widely distributed in Taiwan since the mid-1980s, more effort is needed. There are still thousands of new cases of syphilis each year, which indicates that unsafe sexual practices are still common. To further reduce the rate of HIV transmission, the ongoing challenge is how to make condom use a social standard for sexually active young persons.

Our results of a significant reduction in the transmission rate of HIV may not be directly extrapolated to countries with a high prevalence of HIV. For countries with low prevalence, such as Taiwan, an early adoption of a universal HAART policy will result in a slower increase in the incidence and prevalence rates when the epidemic is still in its early exponential phase. To the contrary, for countries with a high prevalence, with a mature epidemic and stable incidence rate, the provision of universal access to HAART may result in a decrease in incidence rate of HIV, but the prevalence of HIV and AIDS might not significantly change for a relatively long period of time, because the decrease in the number of new cases is offset by the longer survival of existing patients [36]. Providing free access to HAART in countries with a high prevalence of HIV will also have financial constraints. Further studies are needed to determine the best preventive and therapeutic strategies for HIV infection and AIDS under these conditions.

In conclusion, after implementing a nationwide policy of providing free access to HAART to all HIV-infected citizens, the average transmission rate of HIV decreased by 53% in Taiwan. The widespread use of HAART can be an effective measure to control HIV epidemics in countries with a low prevalence.

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