Prediction of Cost-effectiveness for Human Immunodeficiency Virus (HIV) Screening Program in Japan

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We predicted the cost-effectiveness of undertaking human immunodeficiency virus screening programs in Japan. Effectiveness of antiviral drug, zidovudine as prophylactic treatment for asymptomatic HIV infected persons brought the concept of widespread screening programs. The cost-effectiveness of two strategies: 1) screening and prophylactic treatment for asymptomatic HIV positive person whose T4 cells fall below 500/cubic millimeter and 2) no screening, were compared in different groups of populations (blood donors, homosexuals, and Thai females). The key data such as the life years gained by prophylactic treatment, the prevalence of HIV among different groups, the initial T4 cell count, the time to develop AIDS, and the efficacy of aerosolized pentamidine were obtained from published literatures. The costs were estimated according to the cost book of health care published by Ministry of Health and Welfare of Japan. In the population with prevalence of 1-4%, which includes homosexuals of Tokyo and Thai females, the incremental cost-effectiveness ratio is US $12,836-$13,333 per life year gained. In the population with very low prevalence such as average blood donors, the incremental cost-effectiveness ratio rises to $1,444,092 per life year gained. Comparing with other medical intervention it is found that the HIV screening program for the population with prevalence over 0.1% is cost-effective. Sensitivity analyses which alter each of the variables in the analysis indicate that if the effectiveness of zidovudine is 50% and 25% of the published rate, then the program remains cost-effective at the prevalence rate of 0.5% and 3% respectively. J Epidemiol, 1995; 5: 35-41.

HIV/AIDS has turned as the devastating pandemic in the world. Although the total number of HIV infected persons (2,914) and AIDS (685) in Japan is fewer than other developed countries but it is increasing sharply warning to intervene¹. WHO estimated that there may actually exist 20,000 HIV infected persons in Japan². The prevalence of HIV infection (Table-1) is 0.000472% in averages among blood donors although in Tokyo it is 0.001346%³, 1.3% among homosexuals in Tokyo area and 0.5% among homosexuals of other areas⁴. In a small district of Tokyo metropolitan area, where the foreign prostitutes are relatively concentrated, a study among 1,000 foreigners of whom majority were Thai, revealed that the HIV prevalence was around 4% and particularly high infection rate (14%) was noted in the <20 age groups⁵. In another study, it is found that the infection rate among Thai females, suspected to be engaged in sex business, were 2.3% in Nagano Prefecture and 4.2% in Ibaraki Prefecture⁶. Now-a-days zidovudine and prophylaxis for Pneumocystis Carinii Pneumonia (PCP) have been shown to be effective prophylactic medication for asymptomatic HIV infected person⁷,⁸ which increases the interest to undertake massive screening programs. But who should be tested for HIV⁹-Thai females engaged in sex business, homosexuals, prostitutes, intravenous drug users (IVDU), STD clinic patients or blood donors. Policies regarding HIV testing are heavily dependent on the prevalence of HIV seropositivity, the sensitivity and specificity of HIV blood tests, and public policy¹⁰. Also the cost of screening programs and the subsequent treatments with prophylaxis for

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asymptomatic HIV infected person is so high that the socioeconomic evaluation may affect the policy making. The analysis of the cost-effectiveness for HIV screening program according to prevalence has not yet conducted in Japan. This paper aims to outline the cost-effectiveness of undertaking HIV screening program among different groups of population. It is also hoped that it will help the policy makers for their decision making.

**METHODS**

**Strategy and Analytic Model**

We did cost-effectiveness analysis by comparing two alternative strategies: (a) screening for HIV and prescribe as per recommendation\textsuperscript{10,11} zidovudine prophylaxis for the asymptomatic HIV positive person whose T4 cell count fall below 500 per cubic millimeter and zidovudine plus aerosolized pentamidine prophylaxis for PCP whose T4 cell count fall below 200 per cubic millimeter (b) no screening. In screening strategy we considered a hypothetical number of population is screened and those identified as HIV positive will get periodic medical follow-up and receive zidovudine when their T cell count fall below 500 cells per cubic millimeter. They will also receive zidovudine plus prophylaxis for PCP when their T4 cell count fall below 200 cells per cubic millimeter. The prophylaxis will delay the progression towards PCP and AIDS, and thereby increase life expectancy. In this strategy the incurring cost(Cs) will be cost for screening, cost for medical follow-up, cost for prophylactic treatment and cost for treating AIDS. Life years gained by prophylaxis was based on the data by Schulman et al.\textsuperscript{12}. In 'no screening' strategy identical hypothetical number, like that of screening strategy, is not screened and they will develop AIDS according to the prevalence and it is assumed that they will get treatment only after becoming symptomatic. Incurring cost in this strategy will be the cost for the treatment of PCP and AIDS (CNS). The calculated life expectancy of 'screening strategy' (Es) minus the calculated life expectancy of 'no screening strategy' (ENS) will equal the total life years gained (E) of the infected persons modified by prophylactic treatment. The additional cost of screening strategy C=(Cs-CNS) includes the cost of screening, the cost of medical follow-up, and the cost of prophylactic treatment, assuming the survival rate after developing AIDS and the cost of treating AIDS will be same in both screened and non-screened population.

The cost-effectiveness of 'screening' strategy relative to 'no screening' strategy can be expressed algebraically as $CE=Cs-CNS/Es-ENS$, where CE represents cost-effectiveness, Cs-CNS the additional cost of screening, and Es-ENS the additional effectiveness of screening (additional life years gained)\textsuperscript{13}.

**Data Acquisition and Assumptions**

The model which sometimes relies on data adapted from studies in other countries, as not all the relevant data are available from the Japanese population, assumed that the initial T4 cell count of the screened population will be similar to the feature found among 1665 asymptomatic persons in the Multicenter Cohort Study: 4.6% with a T4 cell <200 cells per cubic millimeter, 36.4% with a T4 cell between 201-500 per cubic millimeter, and 59% with a T4 cell >500 cells per cubic millimeter\textsuperscript{14}. We also assumed that the mean time to develop AIDS will be similar to the median time to develop AIDS, found in the study of MacCarthy et al.\textsuperscript{15}: 10.75 years for T4 cell >500 per cubic millimeter, 9 years for T4 cell count between 201-500, and 2 years for T4 count <200 per cubic millimeter and the persons receiving zidovudine will gain additional 3.29 years\textsuperscript{16}. It is also assumed that the T4 count >500 cell group will lose T4 cell gradually and take zidovudine roughly after (10.75-9)=1.75 years and take zidovudine continuously and take aerosolized pentamidine when their T4 cell count decline to 200 per cubic millimeter; T4 cell 201-500 group will continuously take zidovudine and take aerosolized pentamidine for PCP prophylaxis when their T4 cell count decline to 200 per cubic millimeter; and T4 <200 group will take zidovudine and aerosolized pentamidine. In 60% of the HIV infected person PCP is the initial opportunistic infection\textsuperscript{17} and aerosolized pentamidine will reduce the PCP episodes 60% to 70%\textsuperscript{16} although we assumed 60% effective. It is also assumed that the sensitivity and the specificity of combined ELISA and western blot test is 100% although specificity was 0.9999927\textsuperscript{18} and sensitivity of ELISA and western blot was 99.7% and 97.8% respectively\textsuperscript{19}.

**Cost Estimates**

In this model only direct costs are estimated. The procedure of HIV testing, initial evaluation of the HIV positive individuals, frequency and contents of follow-up, and drug schedule has been adapted from several sources\textsuperscript{12,15,20}. For 'screening strategy' estimated cost comprises the costs for physician visit, the costs for screening test (ELISA x 1 for all screened population and ELISA x 2 plus Western blot for seropositive person), the costs for initial investigation of the seropositive persons and the costs for follow-up of the seropositive persons. The estimated cost of the initial investigation includes the costs of comprehensive physical examination, the costs of complete blood cell count, the costs of T-cell subsets, the costs of blood chemistry, and the costs of chest X-ray. The costs of follow-up for 'non-zidovudine taking group' (T cell >500) are the sum of quarterly physician visit costs, quarterly complete blood cell count costs and quarterly T-cell subsets determination costs. The costs of follow-up for 'zidovudine taking group' (T cell=201-500) includes...
the costs of zidovudine, 400 mg/day which is recommended for Japanese\textsuperscript{20}, the costs of monthly physician visit, the costs of monthly complete blood count, the costs of quarterly blood chemistry to assess kidney and liver function and the costs of quarterly T cell subsets determination. In addition to above mentioned for T4 cell > 500/cubic millimeter group, T4 cell 201-500/cubic millimeter group and T4 cell < 200/cubic millimeter would be $523, $6,426, and $8,487 respectively.

**Effectiveness Estimates**

Zidovudine blocks replication of HIV by inhibiting viral enzyme reverse transcriptase production and in vitro it also block the infectivity and cytopathic effect of HIV where immune functions of normal T cells remain intact\textsuperscript{22}). The full effect of zidovudine therapy on the progression of HIV infection in asymptomatic patients, including survival benefit, will not be known for several years so that all the data of survival benefit using in different literatures are derived from short term studies. Schulman et al.\textsuperscript{12}) developed two models to examine the potential range of effects of long-term zidovudine therapy. In one-time effect model survival benefit by the zidovudine therapy is considered only in the first year and in other years remains unaffected. In the continuous-treatment model patients will show reduced rate of disease progression during each year of zidovudine therapy. Following this continuous-treatment model Schulman et al. found that total discounted survival benefit would be 3.29 years. Continuous survival benefits have been noted in patients with AIDS or advanced AIDS related complex who are receiving long term zidovudine therapy\textsuperscript{23}). So we assumed continuous survival benefit in our study. In a controlled trial among 1338 persons with fewer than 500 CD4-positive cells per cubic millimeter, followed for two years, 33 cases of AIDS were diagnosed in the placebo group, as compared with 11 in the 500-mg/day zidovudine group\textsuperscript{7}). It was also noticed that there were no significant differences between the placebo and the 500-mg zidovudine groups with respect to severe hematological abnormalities; severe hepatotoxicity was uncommon; severe subjective symptoms were infrequent except nausea (incidence of severe nausea among zidovudine group was 3.3%); and severe myalgia was reported by three patients (0.7%), and 1 patient (0.2%) in the zidovudine group, and placebo group respectively\textsuperscript{7}). Zidovudine also increase survival of the AIDS patients, the median survival of the zidovudine users was 690 days against 280 days for the control patients\textsuperscript{24}).

The efficacy of aerosolized pentamidine is 60% to 70% and 75% to 80% of patient with HIV infection will eventually develop one or more episodes of PCP unless given prophylaxis and the reported mortality for a first episodes of PCP is 5% to 20%\textsuperscript{16}).

**RESULTS**

The major component of the cost of screening programs is the costs of prevention (to delay in the progression towards PCP and AIDS) which includes cost for follow-up and costs for zidovudine and pentamidine (Table 1). The costs for screening only is almost same among the different

| Reference Population with Prevalence (%) | Cost of Program Till AIDS Develop (US$) | Life Years Gained |
|----------------------------------------|----------------------------------------|-------------------|
|                                        | Cost for Screening | Cost for Prevention * Cost for Follow-up | * Cost for Zidovudine & Pentamidine | |
| Blood Donors (average)                 | 0.000472            | 4,130,031           | 2,719                               | 16,810               | 1.55 |
| Blood Donors (Tokyo)                   | 0.00134             | 4,130,087           | 6,572                               | 47,724               | 4.41 |
| Homosexuals (average)                  | 0.5                 | 4,162,000           | 2,550,568                           | 18,049,343           | 1,645 |
| Homosexuals (Tokyo)                    | 1.3                 | 4,195,000-4,325,000 | 5,101,136-15,303,409                | 36,098,686-108,296,058 | 3,290-9,870 |
| Thai Females (Nagano)                  | 2.3                 | 4,279,500           | 11,732,614                          | 83,026,978           | 7,567 |
| Thai Females (Tokyo)                   | 4.0                 | 4,390,000           | 20,404,546                          | 144,394,744          | 13,160 |
| Thai Females (Ibaraki)                 | 4.2                 | 4,403,000           | 21,424,773                          | 151,614,481          | 13,818 |

* Discounted at the annual rate of 5%
groups. Table-2 presents incremental cost-effectiveness ratio and cost per HIV positive case found in different group of population for HIV screening program. The incremental cost-effectiveness of high risk group such as homosexuals and Thai females ranges from US $12,828 to $14,340 per life year gained. On the other hand cost-effectiveness of the blood donors is $507,666 to $1,444,092 per life year gained. Population group with a prevalence of 0.1%, the incremental cost-effectiveness ratio is $19,646 per life year gained. We compared the results with other medical intervention in Japan (Table 3) and found that the screening program above the prevalence of 0.1% is cost-effective.

**Sensitivity Analyses**

Unfortunately, estimates of the benefits of health practices, in terms of mortality and morbidity probabilities, are rarely known with certainty. So we did sensitivity analyses (Table-4) by assuming that efficacy of zidovudine is only 50% and 25% of the original calculated value, found that screening program is also cost-effective at the prevalence rate of 0.5% and 3% respectively. The costs of medical service is also variable, we assumed that all the medical services other than drug price doubled, still then

| Reference population | Prevalence estimates (%) | Incremental cost-effectiveness ratio per life year gained (in US$)* | Cost per HIV case found (in US$) |
|----------------------|--------------------------|-------------------------------------------------------------|---------------------------------|
| Blood Donors (in average) | 0.000472 | 1,444,092 | 8,750,065 |
| Blood Donors (in Tokyo) | 0.00134 | 507,666 | 3,082,155 |
| Homosexuals (in average) | 0.5 | 14,340 | 8,325 |
| Homosexuals (in Tokyo) | 1-3 | 12,891-13,333 | 1,441-4,195 |
| Thai Females (in Nagano) | 2.3 | 12,959 | 1,861 |
| Thai Females (in Tokyo) | 4 | 12,836 | 1,098 |
| Thai Females (in Ibaraki) | 4.2 | 12,828 | 1,048 |

* Discounted at the annual rate of 5% Considering exchange rate 100 yen = 1 US$

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**Table 3. Cost-effectiveness of other medical interventions**

| Strategy | Cost Per Life Year Saved (US$) |
|----------|--------------------------------|
| * FOBT Two day method for colorectal cancer screening in male | 40,771 |
| * FOBT two day method for colorectal screening in female | 50,621 |
| * TCF only for colorectal cancer screening in male | 33,085 |
| * TCF only for colorectal cancer screening in female | 41,303 |
| * Screening for gastric cancer in male | 6,063 |
| * Screening for gastric cancer in female | 15,425 |
| # Renal dialysis | 46,249 |
| + Coronary artery bypass surgery | 113,087 |
| = High dose chemotherapy with autologous bone marrow transplantation in metastatic breast cancer | 115,800 |

* * Study in Japan for Japanese population during 1991[36,37], considering yen value of 1991 and exchange rate 100 yen = 1 US$.
# Social cost for incenter dialysis for men[2] in 1989 US dollar.
+ Study of a 55 year-old man with three vessel disease[12]. In 1989 US$
= Data for hypothetical 45 year-old woman with metastatic (stage IV) breast cancer who had no bone marrow involvement and no comorbid illness. In 1991 US$[36]
FOBT = Fecal Occult Blood Test,
TCF = Total Colonoscopy
the screening program is cost-effective at the prevalence rate of 0.1%.

### DISCUSSION

The most important part of the cost is the cost of zidovudine and pentamidine (80% at the prevalence of 1%) and the efficacy of the zidovudine has been proved in short term study. The success of the program is heavily dependent on the life years gained by the zidovudine. The limitation of the study is that there is uncertainty about the long term effectiveness of zidovudine due to the emergence of their resistant viral strains of HIV or loss of cells or cell function that mediates efficacy. It is observed that sequential therapy (zidovudine→dideoxynosine) is better than continued zidovudine monotherapy and a clinical trial being conducted in Japan in which clinical effects and emergence of drug resistant HIV by combination therapy (zidovudine→dideoxynosine) is compared with those by zidovudine monotherapy. Upto this time zidovudine, dideoxynosine and zalcitabine already licensed for use against HIV, and others ( stavudine, alovudine, and 3-TC) are still under clinical evaluation. But in future if dideoxynosine or other drugs proved to be effective combining with zidovudine to avoid viral resistance like that of tuberculosis, the screening program might be cost-effective.

Only direct cost, from the cost book of the hospital, is estimated in our study. Indirect cost, which includes mainly wages that would have been paid for the time lost in work place because of morbidity and mortality, is not accounted because of difficulty in acquisition of age-specific mortality and morbidity of the HIV infected patient.

False positive outcome in HIV testing is a tremendous psychological burden which is unbearable for the affected persons. But one false positive case can be found among 135,187 persons without HIV infection and with adequate attention to program design and quality control, the false positive rate can be kept at an acceptably low level. At the prevalence rate of 0.1%, if 1,000,000 persons undergo into screening program 1,000 person will be HIV positive and among them 7 person will be false positive which is tolerable and does not affect the benefits of the screening program.

There are several uncertain assumptions in our study. We assumed that the initial T4 cell distribution will be similar to that of Phair et al. If we assume that the T4 cell distribution in our predicted screening program will be like that of Luby et al. having T4 cell > 500 is 42%, T4 cell 200-500 is 46%, and T4 cell < 200 per cubic millimeter is in 12% of screening population, then the incremental cost-effectiveness ratio only slightly change. At 0.1% prevalence rate the incremental cost-effectiveness ratio changes from $19,646 to $19,995 which does not affect the overall cost-effectiveness.

Another assumption is the mean time to develop AIDS. If it is assumed that the ratio of the mean to median will be 1.36 like the survival time calculation of the AIDS patient, at the 0.1% prevalence rate the incremental cost-effectiveness changes from $19,646 to $24,052 which is also within acceptable range.

Other benefits of screening is that the screening itself has a negative effect in risky behaviours. In the study of McCusker et al. who assessed the effects of HIV antibody testing on subsequent sexual behaviour found that, except for the number of the steady partners, the levels of all sexual activities of study participants declined overtime. Seropositive persons after knowing that they are HIV-
growth to $101 million in 1993 from $21.3 million in 1992. The expenses regarding HIV/AIDS will increase in the future, estimated to be $6.53 million considering lifetime medical care cost of each AIDS patient among the Japanese tourist traveling high HIV prevalence countries, IVDU or local commercial sex workers whose prevalence of infection is 0.1% or more. The objectives of HIV screening program should not only prolong the life expectancy of the infected individuals but also to prevent HIV transmission by reducing high risk behaviors and possibly by partner notification.

Data regarding the quality of life of the asymptomatic HIV infected person, taking zidovudine, is not available. Although in a randomized double-blinded trial for two years, the subjects in the zidovudine (500 mg/day) groups had significant increases in the number of T4 cell, significant declines in p24 antigen levels. Nausea was the only toxicity that was significantly more frequent than in the placebo group.

Prevalence of the disease among the population is the key factor for the success of a screening program. In Japan the seroprevalence study of all high risk groups such as IVDU, health care workers, prostitutes, and STD clinic patients has not been performed widely. It is very important to identify the target group to be screened for HIV. This may be done by mass media publicity about HIV/AIDS, featuring the consequence of high risk behaviors and thereby encouraging HIV testing for them; voluntary screening and counseling of the persons who practice high risk behaviors; and eliciting sexual and drug abuse histories by general practitioners. STD clinic patients should be also encouraged to do HIV testing. Japanese tourists traveling high HIV prevalence countries should also be included in the HIV testing program as 690 HIV positive cases were predicted from the 230,000 male tourist visiting Thailand during 1990.

The expenses regarding HIV/AIDS is increasing worldwide. About $7.8 billion has been spent in USA to treat the AIDS patients during 1993 although in Japan it is estimated to be $6.53 million [considering lifetime medical care cost of each AIDS patient $75,000 as that of USA]. But in Japan the coverage rate of the reports of HIV infection was estimated to be 11.5% and the total number of HIV and AIDS patient at the end of 1997 are predicted to be 23,200 and 2,700 respectively. So in near future the expenses regarding HIV/AIDS will increase many folds. The MOHW budget for 'Stop AIDS Plan' grew to $101 million in 1993 from $21.3 million in 1992 excluding the expenses covered by state health insurance and social security. To undertake HIV screening program among 1 million population at the prevalence of 0.1%, along with follow-up and prophylaxis cost upto 1 year, $45.17 million is required which is bearable by existing budget. This one million population might be consisting of different high risk groups. To prevent HIV epidemic, it is necessary to identify the source of HIV transmission and according to the source, the screening population should be elicited. It may be foreign prostitutes residing in Japan, homosexuals, Japanese tourists visiting high HIV prevalent countries, IVDU or local commercial sex workers whose prevalence of infection is 0.1% or more. The objectives of HIV screening program should not only prolong the life expectancy of the infected individuals but also to prevent HIV transmission by reducing high risk behaviors and possibly by partner notification.

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