AIDS Vaccine Development in Japan: Challenges and Opportunities

The world needs an AIDS vaccine

In the 20 years since HIV was identified as the cause of AIDS, the AIDS epidemic has grown to be the greatest public health crisis facing the world today. Currently, it is estimated that more than 40 million people are living with HIV, with close to 5 million new infections in 2005[1], mostly in developing countries.

In recent years, the international community has taken significant steps to scale up HIV prevention and to lay the groundwork for universal access to treatment. In 2005, an unprecedented US $8.3 billion was spent on low- and middle-income countries for programs in response to AIDS, up from an estimated US $6.1 billion spent in 2004[2]. This remains far short of what is estimated to be necessary to fully implement an effective AIDS response in poor countries. UNAIDS estimates the global resource requirement to be 15 billion US dollars in 2006; 18 billion in 2007 and 22 billion in 2008, including 5.3 billion for anti-retroviral treatment to cover 75% of people in the most urgent need[3].

While the world continues to move towards universal access for prevention and care, there is an urgent need to develop new preventive technologies. A preventive AIDS vaccine remains the best long-term solution to the epidemic and the massive toll it inflicts on individuals and communities.

The global context on AIDS vaccine development

Public sector investment

According to the most current estimate, the world invested[4] about 682 million US dollars on AIDS vaccine research and development (R&D) in 2004, which is almost double the amount invested in 2000[5]. Today, more than 30 vaccine candidates are in clinical trials, a significant increase from 7 in 1993.

Public sector contributions accounted for close to 90% of the total investment in 2004 (Figure 1). The US government contributed 526 million, or 86% of public spending and 76% of the global total[6]. The United States Government disburses most of its funding through the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health, which itself operates the world's largest AIDS vaccine R&D program. NIAID currently has 14 experimental vaccine candidates in clinical trials around the world, mostly through its HIV Vaccine Trials Network (HVTN)[7].

Europe as a whole, including the European Commission, accounted for just over 9% of public sector spending, or about 57 million US dollars. This includes efforts by individual countries such as France and Italy, which are also part of the European Vaccine Effort against HIV/AIDS (EuroVacc), a region-wide initiative. There are currently 7 European-developed candidates in the pipeline[8].

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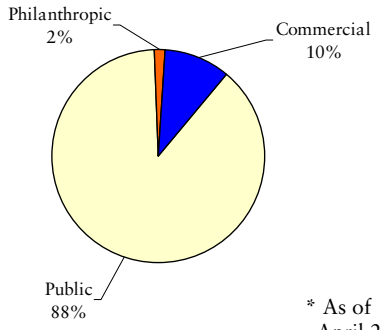
The multilateral organizations – WHO, UNAIDS, and the World Bank – contribute around 2 million US dollars annually. No clinical trials are conducted under the sponsorship of these international organizations.

Figure 1. Sources of funding for preventive HIV vaccine R&D (2004)



Total= US$ 682 mn

Industry and philanthropic initiatives

The relatively low investment by the private sector in AIDS vaccine development – 68 million US dollars or about 10% of global spending – is due to weak financial incentives for companies to embark on AIDS vaccine development. Much of the anticipated potential market for an AIDS vaccine is in developing countries where there is limited ability to pay for a product. As a result, companies view AIDS vaccine R&D as a high-cost and high-risk investment with low profitability.

The lack of industry involvement in AIDS vaccine R&D inspired the establishment of the International AIDS Vaccine Initiative (IAVI), a public-private partnership (PPP). As an NGO, IAVI works in partnership with public research entities as well as private companies, while undertaking its own R&D efforts. In 2005 IAVI spent approximately $45 million on R&D activities related to advancing and testing the 6 products within IAVI's current product pipeline. Most of IAVI's funds come from donor governments in North America and Europe.

Among the private foundations, the Bill and Melinda Gates Foundation has contributed by far the most to AIDS vaccine development, with total investment of 135 million US dollars by 2005. In addition, the Gates Foundation has pledged up to 360 million US dollars over the next five years to fund proposals from a wide range of research institutes around the world.

The Global HIV Vaccine Enterprise

The recent establishment of the Global HIV Vaccine Enterprise[9] is expected to facilitate better coordination of R&D efforts and accelerate progress in AIDS vaccine development. The Enterprise is an alliance of independent research entities, such as NIAID and IAVI, which aims to promote better collaboration and coordination based on a shared scientific plan.

More is needed

While it is encouraging that AIDS vaccine R&D investment has increased in recent years, this amount still falls short of the annual target of 1.2 billion US dollars necessary to fully implement AIDS vaccine development at the global scale[10]. Many governments, including Japan's, are currently spending relatively little in this area and have room to increase investment to help close the funding gap of 450-500 million US dollars a year.

The current state of AIDS vaccine R&D in Japan

General vaccine R&D

It is useful to assess the current resources available in Japan for vaccine development and manufacturing as a basis for Japan's potential contribution to the global search for an AIDS vaccine. There is no question that Japan has a high level of capacity for general vaccine development. Currently, there are 8 private companies and public institutions[11] in Japan producing 27 vaccines altogether, including MMR and BCG and vaccines for such diseases as influenza,

Japanese meningitis, Hepatitis B, cholera, and polio – and meeting excellent quality control standards[12]. Among these, the BCG vaccine produced by Japan BCG is a United Nations pre-qualified vaccine.

In response to bio-terror threats, a smallpox vaccine produced by Kaketsuken in Japan is currently being tested jointly with VaxGen for use in the United States. Another example that indicates the capacity of Japanese manufacturers is the current effort to develop a vaccine against avian influenza. Four Japanese vaccine manufacturers, under the leadership of the National Institute for Infectious Diseases, are joining forces to accelerate clinical trials in Japan for a new vaccine[13].

The current capacity of the Japanese vaccine industry may be an indication of its potential to contribute to process development or manufacturing of an AIDS vaccine, once a promising vaccine candidate is advanced beyond clinical trials. Kaketsuken, for example, is poised to manufacture doses of recombinant vector of a Japanese AIDS vaccine candidate developed by the National Institute of Infectious Diseases for future small-scale clinical trials.

AIDS vaccine R&D

Overall the field of AIDS vaccine development is much less active in Japan. Only a few AIDS vaccine candidates have advanced to the pre-clinical stage. The most advanced of these candidates is a product based on recombinant BCG and recombinant vaccine DIs as vectors[14], which was jointly developed by the National Institute for Infectious Diseases in Japan and the National Institute of Health of Thailand, with major funding of 700 million yen (roughly 6.2 million US dollars) from the Japan Science and Technology Corporation, a funding arm of the Ministry of Education, Culture, Sports, Science and Technology.

In the spring of 2004, the AIDS Vaccine Development Association (AVDA) was established with the initial goal of advancing this candidate into clinical trials. Aspiring to be the first PPP model in Japan, AVDA works to advocate for further involvement from the government and industry, serve as the link to other global efforts, and ultimately strengthen the long-term environment for AIDS vaccine development in Japan.

Another candidate that is poised to advance to the clinical trial stage is based on a sendai virus vector, developed by Tokyo University Medical Research School in partnership with a small bio-tech company, DNAVEC. In addition, there are 5 to 10 AIDS vaccine research programs – still in early stages of laboratory research – that are ongoing in Japan, all being undertaken by public universities or research institutes.

The informal estimate of government's allocation for domestic AIDS vaccine R&D in the 2005 budget is roughly 276 million yen (2.4 million US dollars), of the aggregate of 1.82 billion yen (15 million US dollars) for all HIV/AIDS-related research[15]. Japan's spending for AIDS vaccine R&D is less than one hundredth of what the United States spends for this purpose, even when these figures are adjusted for the relative size of the two countries' economies[16]. In relation to many other countries, Japan ranks among those devoting the smallest share of their national wealth to AIDS vaccine research, and is well behind countries such as Canada, the Netherlands, and South Africa (Table 1).

Policy environment to encourage product development

It is worth noting that Japan does have tax incentives in place that are beneficial to those companies interested in joining the AIDS vaccine R&D effort. For example, the so-called Industry Revitalization Law includes tax reduction for capital investment. Under this measure, the cost of a production line that is coupled with scientific R&D receives special deductions[17]. In addition, the tax credit for scientific research and development

Table 1. Public sector investment in preventive HIV vaccine R&D in 2004 by country as a percentage of GDP.* Within each category countries are listed alphabetically.

Less than 0.0005	0.0005 to 0.001	0.001 to 0.002	0.002 to 0.003	0.003 to 0.004	0.004 to 0.005
-Australia -Brazil -China -Finland -France -Germany -India -Italy -Japan -Norway -Russia -Thailand	-Denmark -Netherlands -Sweden -United Kingdom	-Canada	(none)	-South Africa	-Ireland -United States

*GDP estimates are for the year 2003. Source: 2005 World Development Indicators. The World Bank. Washington, DC.
Note: no GDP data were available for Cuba for 2003.

has expanded over time, most recently in 2003[18]. Along with the existing deduction for capital investment, there are now tax credits for the entire process, from research to product development.

Similarly, with the intention of strengthening the traditionally weak interaction between industry, university, and public research centers in Japan, the government in 1998 passed a set of regulations for what are called "technology licensing organizations (TLOs)". TLOs are expected to serve as a bridge between industry and public research institutes (including universities), to coordinate patent and other legal issues – in essence, to be the facilitator to bring technologies born in laboratories into the market as products.

Although these changes may have gradually benefited other research efforts, these measures alone have not had a positive impact on increasing industry's involvement in AIDS vaccine development.

Challenges in engaging Japan in AIDS vaccine development

Disconnect in public perception

Although public understanding of HIV/AIDS as a global issue has increased in recent years – as reflected in the support for Japan's leadership in the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)[19] – there is a remarkable lack of interest when it comes to addressing HIV/AIDS in Japan. Japan has a low number of reported infections: in 2005, the total number of newly reported cases of HIV infection was 778, and new AIDS patients totaled 346, making the total number of people living with HIV/AIDS in Japan just over 12,000[20]. However, the number of new infections is increasing every year, and many experts suspect that the reported numbers do not accurately reflect the reality in Japan. The alarming situation in Japan should prompt the government to consider policies and measures beyond the provision of information and education mostly targeted to the general public.

Strong stigma is still associated with the disease, giving way to hostile discrimination and prejudice in Japan for those infected with HIV. This makes it difficult for those who are HIV-positive to speak up and bring the government's inadequate policies and programs on prevention to the public's attention. Unless more urgent need to halt the infections is felt at home, public support for Japan's more active engagement in AIDS vaccine development will not grow.

Perceived risk in providing international assistance

In spite of its status as the second largest international donor[21] and one of the leading donors to the GFATM, Japan has spent almost nothing in AIDS vaccine R&D from its Overseas Development Assistance (ODA) funds. The underlying reason for such inaction seems to be the perceived risk of conducting clinical trials in developing countries. There is really no precedent, and hence established mechanism, for providing large-scale support for new product development, such as an AIDS vaccine. Government officials are wary of unanswered questions on issues ranging from intellectual property, product liability, and general accountability in the course of clinical trials.

Yet another challenge is the short timeframe in which results are expected. Like other donor countries, Japan has embraced a results-oriented approach to ODA spending. There is ever-increasing pressure to demonstrate the tangible benefits of ODA-financed projects within a given timeframe to a well-defined recipient community. Global AIDS vaccine R&D, at its current stage, is too open-ended to invest current taxpayers' yen. Hence, there is no political will to put AIDS vaccines on the priority list at the moment.

Structural obstacles still remain to Japan providing its ODA to the global effort on AIDS vaccine R&D even if such perception of risk is overcome. First, grants from the Japanese government – one of three mechanisms of aid, the others being loans and technical assistance (TA) – can only go to developing country governments, multilaterals like the UN, Japanese NGOs, and local grassroots NGOs in developing countries. Since the majority of direct R&D work is undertaken by research institutes in industrialized countries or international NGOs such as IAVI, this may limit programs and recipients of the Japanese assistance to non-scientific activities of small scale.

Limitations also exist in the area of TA. Under the TA scheme, Japanese experts are sent to developing countries to collaborate with counterparts, often in research centers, to transfer established technology. However, AIDS vaccine R&D is not considered "established" technology in Japan, and therefore, there are no current policy grounds for funding AIDS vaccine research activities in developing countries.

Considerable advocacy is required to make the case for the overwhelming benefit of developing an AIDS vaccine in the future against the current perceived risk of investing in clinical trials. Similarly, a new mechanism that enables ODA funds to be channeled to AIDS vaccine research and development is needed.

Recommendations

As one of the most advanced countries in medical and scientific research, and as a leader in the global effort to fight infectious diseases such as HIV/AIDS, there are increasing expectations for Japan to make significant contributions to the global search for an HIV/AIDS vaccine, the best hope to control the epidemic.

The following are some concrete actions that can pave the way for more engagement by Japan in AIDS vaccine R&D:

- Stronger and better-coordinated advocacy on HIV/AIDS in Japan. In the wake of the regional AIDS conference held in Japan[22] in 2005, the HIV/AIDS NGO community in Japan has a unique opportunity to come together to coordinate and strengthen general advocacy on HIV/AIDS. Raising awareness among the general public about the necessity to develop new preventive technologies, including an AIDS vaccine, should be part of the general advocacy goal.

- Take gradual steps towards building consensus and political will, which can serve as a solid foundation for mobilizing additional Japanese funding and scientific effort for AIDS vaccines. The Japanese government can take gradual steps towards full involvement in vaccine R&D. They can begin by working with multilaterals such as WHO or UNAIDS. Furthermore, they can support local NGOs which provide information and education on safe and ethical clinical trials, or other non-scientific, supporting services such as testing and counseling on the ground. Simultaneously, the government should explore new mechanisms for funding clinical trials for AIDS vaccines.

  To this end, governments committed to AIDS vaccine research and development should encourage their Japanese counterparts to increase their involvement, as agreed at recent G8 meetings[23]. Other stakeholders, such as developing country governments and international NGOs like IAVI and AVDA, should similarly keep the pressure on policy makers and politicians in Japan.

- Better communication on on-going AIDS vaccine R&D in Japan. Media in Japan should give more attention to Japanese scientists who are working to develop an HIV/AIDS vaccine, and tell the story of what many consider to be one of the most important medical research efforts of our time. This will potentially lead to more public support and incentives for more Japanese researchers, and possibly companies, to enter this field.

Notes and References

[1] UNAIDS/WHO. *UNAIDS/WHO AIDS Epidemic Update: December 2005*. Geneva.

[2] UNAIDS. *Resource needs for an expanded response to AIDS in low- and middle-income countries*. Geneva. August 2005.

[3] Ibid.

[4] In this context, "invested" means annual funding provided in a year as opposed to the funds that were actually spent ("expenditure") on R&D in that year.

[5] Unless otherwise cited, all investment and expenditure figures are taken from the HIV Vaccines and Microbicides Resource Tracking Working Group (AIDS Vaccine Advocacy Coalition, Alliance for Microbicide Development, International AIDS Vaccine Initiative, UNAIDS). *Tracking Funding for Preventive HIV Vaccine Research & Development: Estimates of Annual Investments and Expenditures 2000 to 2005*. New York. June, 2005.

[6] *Doing Their Part? Public, Private and Philanthropic Sector Investments in AIDS Vaccine Research and Development*, IAVI Policy Brief. New York. May 2005.

[7] www.hvtn.org/about/faqs.html

[8] *AIDS Vaccines at the Crossroads.* AIDS Vaccine Advocacy Coalition Report. New York. September 2005. pp 10-11.

[9] Originally proposed in June 2003 in an article published in the journal *Science* by 24 leaders in HIV vaccine research. www.hivvaccineenterprise.org

[10] Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise. *The Global HIV/AIDS Vaccine Enterprise Scientific Strategic Plan,* PLoS Med 2:e25, 2005.

[11] They are: *Kitasato Kenkyujo* (The Kitasato Institute Research Center for Biologicals), Takeda, *Kaketsuken* (The Chemo-Sero-Therapeutic Research Institute), *Biken* (The Research Foundation for Microbial Diseases of Osaka University), Denka Seiken, Japan BCG, *Nihon Polio Kenkyujo* (Japan Polio Research Institute), Meiji Diaries Corporation. Takeda, Denka Seiken and Meiji are private companies, and the rest are public entities.

[12] www.wakutin.or.jp/

[13] Asahi Shimbun. December 7, 2005.

[14] A vector is a delivery vehicle designed to transport foreign genetic material. For an HIV vaccine, the vector delivers a functional HIV gene or gene fragment.

[15] Informal estimate given by the Ministry of Health, Labour and Welfare.
[16] HIV Vaccines and Microbicides Resource Tracking Working Group.
[17] There is an accelerated depreciation of 24% for capital investment.
[18] There is a 12% deduction across the board for inter-sectoral collaboration and commissioned research.
[19] Initially conceived at the Kyushu/Okinawa G8 Summit in 2000, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) was created in February 2002 to provide financing for programs to fight the three major infectious diseases in developing countries. Japan has been on the Board of the Global Fund since its inception, and was the Vice Chair of the Board for the first year of Fund's existence. Japan has contributed about 350 million USD to the Global Fund to date.
www.mofa.go.jp/mofaj/press/release/18/rls_0315b.html
[20] Report of the AIDS Surveillance Committee. www.api-net.jfap.or.jp
[21] Japanese ODA for FY2004 totaled 8.96 billion USD. www.oecd.org
[22] The 7th International Congress of AIDS in Asia and the Pacific (ICAAP) was held in Kobe from July 1-5, 2005, attended by about 3,000 people from more than 20 countries in the region.
[23] At Summit meetings in 2004 and 2005, G8 countries pledged to continue their support for AIDS vaccine R&D efforts, and to consider innovative financing mechanisms, such as Advance Market Commitments (AMC). www.mofa.go.jp/mofaj/gaiko/summit/seaisland04/hiv_z.html

The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 23 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI's financial and in-kind supporters include the Alfred P. Sloan Foundation, the Bill & Melinda Gates Foundation, The New York Community Trust, The Rockefeller Foundation, The Starr Foundation; the Governments of the Basque Country, Canada, Denmark, European Union, Ireland, The Netherlands, Norway, Sweden, United Kingdom, and United States; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Continental Airlines, DHL and Pfizer; leading AIDS charities such as Broadway Cares/Equity Fights AIDS, Crusaid, Deutsche AIDS-Stiftung, and Until There's A Cure Foundation; other private donors such as the Haas Charitable Trusts; and many generous individuals from around the world. For more information, see www.iavi.org.

The **AIDS Vaccine Development Association (AVDA)** is a non-profit organization in Japan established in 2004. Its mission is to promote the Japanese development of an AIDS vaccine, along with its production and access, to end the HIV/AIDS epidemic worldwide. For more information, see www.avda.jp.

Imagine a World without AIDS.