HIV Vaccines for Developing Countries: Advancing Research and Access

-Background Paper-

May 2002

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For further information, contact:

Canadian HIV/AIDS Legal Network - Réseau juridique canadien VIH/sida
417, rue Saint-Pierre, suite 408, Montréal (Québec) Canada H2Y 2M4
Telephone/Téléphone : 514-397-6828 Fax/Télécopieur : 514-397-8570
E-mail/Courriel : info@aidslaw.ca; Web : http://www.aidslaw.ca

May 2002

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Acknowledgments

Funding for this project was provided by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the WHO-UNAIDS HIV Vaccine Initiative (HVI), the Canadian International Development Agency (CIDA), Health Canada (International Affairs Directorate), and The POLICY Project, a five-year project funded by the United States Agency for International Development and implemented by The Futures Group International in collaboration with Research Triangle Institute (RTI) and The Centre for Development and Population Activities (CEDPA).

This background paper was written by Sam Avrett. The views expressed in this paper are offered by the author to facilitate dialogue and action, and do not necessarily reflect the views of UNAIDS, the WHO-UNAIDS HIV Vaccine Initiative, CIDA, Health Canada, the Canadian HIV/AIDS Legal Network, or The POLICY Project.

Canadian HIV/AIDS Legal Network

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Table of Contents

1. Foreword

The mission of the Canadian HIV/AIDS Legal Network is to provide education, legal and ethical analysis, and policy development related to HIV/AIDS in Canada and internationally. This paper on HIV vaccine development arises from our strong belief that greater funding and commitments are needed to ensure successful vaccine development for developing countries, an ethical vaccine research process, and global access to HIV vaccines once they are developed.

This background paper is written and distributed with two goals:

- To increase support for the development of HIV vaccines suitable for use in developing countries; and
- To facilitate support for the widest possible access to such vaccines.

This document is part of a larger project led by the Canadian HIV/AIDS Legal Network to facilitate dialogue among researchers, funders, affected communities, national governments, and the international community about legal, ethical and human rights aspects of HIV vaccines, and to enhance the policy foundations for global community mobilization and advocacy. This document is intended to complement and build on prior documents produced by the Canadian HIV/AIDS Legal Network related to human rights and HIV vaccine development.[1, 2]
This project has produced four outputs:

- this background paper, noting the imperatives for funding HIV vaccine research for developing countries; the inadequacy of current approaches and the obstacles to more rapid research and development; and potential action steps to quickly mobilize substantially greater support for such research, including greater funding from governments and other donors and the private sector, and greater political commitment to research in developing countries.[3]
- An international expert meeting, held in April 2002 in Montreal, to review the current situation and obstacles to greater funding and commitment to HIV vaccine research and development, identify opportunities for advocacy over 2002-2004, and review and amend an action plan and advocacy tool.
- an advocacy tool, in English, French, and Spanish, which can be put to use quickly by community-based organizations and other advocates, setting out in user-friendly fashion the ethical, legal, and human rights imperatives for allocating more resources at international, national, and community levels for development of HIV vaccines suitable for use in developing countries;
- a summary report, in English, French, and Spanish, including a summary of the background paper, the meeting report, and a plan of action for mobilization and advocacy at all levels for global HIV vaccine funding and access initiatives.

The groundwork for this paper's recommendations has been established at more than 20 international meetings and conferences during 2000-2002 that have successively stated and restated commitments to accelerating the HIV vaccine effort. Now more than ever, the foundation is set for action.

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[1] Patterson, D. *Resolving Legal, Ethical and Human Rights Challenges in HIV Vaccine Research.* Montreal: Canadian HIV/AIDS Legal Network, 2000. www.aidslaw.ca

[2] A new paper from the Canadian HIV/AIDS Legal Network by David Thompson is forthcoming on ethical issues related to HIV vaccine clinical trials at www.aidslaw.ca

[3] This background paper is not intended as a review of the science and scientific issues of HIV vaccine development; such scientific overviews can be found at www.iavi.org or www.niaid.nih.gov/vaccine

2. HIV vaccine development in a human rights framework

2.1 Developing HIV vaccines and other new technologies is a global health obligation

HIV vaccine development is a global public health obligation, based on global health need, public health potential, and emerging scientific feasibility. Global health needs are admittedly vast, but one clear priority is to focus attention on improving public health in the world's poorest countries. More of the world's resources can and should be dedicated to core determinants of public health in resource-limited countries, including control of major infectious diseases, improvement of basic health environmental factors such as clean air and water, assurance of basic nutrition, shelter, and education, resolution of political conflict, and alleviation of the most egregious social and economic inequities.

Control of the HIV/AIDS epidemic is integrally linked with this global health picture. HIV is the fastest spreading lethal infectious disease in the world today, and is, by itself, a major global health catastrophe.[4] At an estimated current rate of 14,000 new HIV infections per day around the world, the HIV epidemic has already claimed the lives of approximately 20 million people and has infected an additional 40 million. HIV/AIDS is now the leading cause of death in sub-Saharan Africa and is the fourth biggest killer worldwide. The human and economic cost of the existing AIDS epidemic is already enormous.

Furthermore, the global AIDS crisis is still beginning. The current human and economic costs are vastly outweighed by the cost of the coming epidemic, especially if the world takes insufficient action. The impending loss from HIV and AIDS can be measured in loss of economic activity, loss of workers and leaders, or loss of human lives, but the sum of any such measurement points to the need for further action. By any scale, the current overall effort against AIDS, including research on new treatments, vaccines, and microbicides, is not yet sufficient.

Vaccines are a proven health promotion strategy

Effective HIV vaccines, if delivered in combination with basic health care and other HIV prevention and treatment, could assist millions of people to avoid HIV infection or AIDS. In the two hundred years since Edward Jenner released his study on the first vaccine against smallpox, vaccination[5] has succeeded in dramatically reducing or controlling many infectious diseases, including diphtheria, plague, rabies, tetanus, typhoid fever, whooping cough, and yellow fever. Smallpox has been eradicated as a public health threat through vaccination campaigns. During the coming decade, vaccination campaigns might soon eliminate the scourge of polio. Newer vaccines, such as those developed against Hepatitis B and *Haemophilus influenzae* type B (Hib), are beginning to have a global impact on those diseases. One imperative for HIV vaccines, therefore, stems from the powerful impact of other vaccines on arresting other global epidemics.

Given the relative cost and potential benefit, vaccine development is an ethical issue of global benefit and justice. HIV vaccines could potentially help to halt the global economic devastation of HIV and AIDS at a relatively low cost of development. Safe, effective, inexpensive, and

[4] UNAIDS. *AIDS Epidemic Update.* December 2001. www.unaids.org

[5] In common usage, 'vaccination' and 'immunisation' are often used interchangeably, although 'immunisation' is arguably the scientifically preferable term. However, for clarity and consistency, this paper will use the term 'vaccine' to refer to products that seek to create immune responses to prevent infection and disease, and 'vaccination' to refer to the use of vaccines.

widely accessible HIV vaccines could also have the highest comparative benefits in countries and communities with the least resources and the highest HIV infection rates. In their potential to address the disproportionate burden of HIV around the world, HIV vaccines represent a possible tool for a fairer and more just distribution of response to the epidemic. As with low-cost HIV treatments, diagnostics, and potentially effective vaginal microbicides, it is unethical not to invest in development of, and wider access to, potential HIV vaccines.

Sufficient scientific feasibility has been shown for HIV vaccine development

The feasibility of developing effective HIV vaccines is rooted in scientific data: several experimental HIV vaccines have been shown to protect monkeys against HIV infection and to generate immune responses in people. To build on this scientific potential, leading HIV vaccine designs must now be evaluated in Phase III efficacy trials to see what immune responses they elicit and what protection they provide, and then to use that information to construct new generations of improved HIV vaccines. Rigorous research efforts must also be maintained to learn more about basic immunology, virology, and the dynamics of potential immune protection against HIV, and to continue improving HIV vaccine designs. But certainly the evidence of potential feasibility of HIV vaccine development is equal to or greater than the immunologic and empiric evidence that existed for the feasibility of vaccines against Lyme disease, rotavirus, and pertussis (whooping cough) before those vaccines entered into large-scale clinical trials. The scientific case for moving forward is clear.

As the scientific possibility increases of having an effective HIV vaccine, the ethical imperative of realizing this benefit also increases. The scientific potential for an HIV vaccine may even be increasing more rapidly than the pace of global vaccine development funding, widening the gap of relative underinvestment. In short, investment in HIV vaccine development efforts must accelerate not only because HIV vaccines are needed, but also because HIV vaccines are becoming increasingly possible.

2.2 HIV vaccine development is a human rights obligation

A human rights framework can advance global health and science

Individual health and public health are considered to be basic human rights, and have been defined as such at least since the 1948 Universal Declaration of Human Rights.[6] The onset of the HIV/AIDS epidemic has provided a strong catalyst for explicit inclusion of human rights into public health strategies. In 1987, for example, a call for human rights and solidarity with people living with HIV/AIDS was included by the World Health Organization

[6] Patterson, 2000. http://www.aidslaw.ca/durban2000/e-durban2000.htm#cf

(WHO) as an essential part of its global response to HIV and AIDS.[7] Since then, many organizations and advocates have worked to further define the link between health and human rights, and to develop language that anchors public health obligations and responsibilities into the framework of international ethics and law.[8]

Specific obligations by States, through national laws and constitutions, international treaties, or other norms or declarations, in turn provide a framework for ensuring action and accountability. A human rights framework may therefore be useful in defining obligations and potential action for HIV vaccine development.

A human rights framework can advance HIV vaccine advocacy

In international law, the obligation for States to invest in the development of HIV vaccines and other technology for health derives primarily from international treaties, such as the 1945 Charter of the United Nations,[9] and what has become accepted as the basis for customary international law, such as the 1948 Universal Declaration of Human Rights.[10, 11, 12] In the 1945 Charter of the United Nations, Member States of the UN adopted an obligation by force of treaty in Chapter IX, Articles 55 and 56, to promote "solutions of international economic, social, health, and related problems…" and to "take joint and separate action" toward this end. Further legal imperatives for the just access and distribution of the benefits of new technologies for health can be found in Article 27(1) of the Universal Declaration of Human Rights (UDHR), adopted by the UN General Assembly several months after the 1946 WHO Constitution came into force, stating in Article 27 (1) a fundamental human right to "share in scientific advancement and its benefits."

The legal intention and obligation of governments to cooperate internationally to realize economic, social, and cultural rights, including promoting the advancement of, and access to, technological advances has since been reinforced and restated in many key international documents. These include the 1966 International Covenant on Economic, Social & Cultural Rights (ICESCR),[13] the 1975 Charter of Economic Rights and Duties of States,[14] the 1975 Declaration on the Use of Scientific and Technological Progress in the Interests of Peace and for the Benefit of Mankind,[15] the 1978 WHO/UNICEF Alma-Ata Declaration,[16] and the 1998 World Health Declaration.[17]

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[7] World Health Assembly Resolution 40.26. *Global Strategy for the Prevention and Control of AIDS*. Geneva: WHO. May 1987.

[8] Gruskin, S. and Tarantola, D. *Health and Human Rights.* Cambridge: FXB Center for Health and Human Rights, Working Paper #10. 2000. www.hsph.harvard.edu/fxbcenter/working_papers.htm

[9] *Charter of the United Nations*, 26 June 1945 (entered into force 24 October 1945), TS 67 (1946).

[10] Patterson, D. 2000.

[11] UN General Assembly Resolution 217(III), UN GAOR, 3d Sess., Supp. No. 13, UN Doc. A/810 (1948).

[12] Elliot, R. *TRIPS and Rights*. Toronto, Canadian HIV/AIDS Legal Network, November 2001. In this paper prepared by Richard Elliot, a detailed analysis is included noting precedents in which states, through their statements and actions, have recognized their obligations to realize human rights under the Universal Declaration of Human Rights as legally binding, thereby constituting it as such. Elliot's paper can be accessed online at www.aidslaw.ca/Maincontent/issues/cts/TRIPS-brief.htm

[13] *International Covenant on Economic, Social and Cultural Rights*, 993 UNTS 3. See Patterson 2000 for discussion about the interpretation of Article 12 by the Committee on Economic, Social & Cultural Rights.

[14] UN General Assembly. *Charter of Economic Rights and Duties of States* 1975. Chapter II, Article 13.

[15] UN General Assembly, Resolution 3384 of 10 November 1975, Articles 1, 3, 5, 6 and 7. Note that these declared obligations of states complement the obligations set out in Articles 15(4) and 2 of the *International Covenant on Economic, Social and Cultural Rights* regarding States' legal obligations to cooperate internationally to realize economic, social, and cultural rights, including the right to the benefit of technological advances.

The 1966 ICESCR, in particular, states the requirement of governments to respect, protect and fulfill the rights to the basic necessities of life, such as food, housing, education, and work. Article 12 of the ICESCR proclaims a human right to "the highest attainable standard of physical and mental health", requiring governments, among other steps, to prevent, treat, and control disease. Article 15 of the ICESCR further outlines a human right to benefit from technological advances, and the obligation of States to cooperate internationally to realize this right. The ICESCR was adopted by the UN General Assembly in 1966, and as of September 2001, the ICESCR had been ratified or acceded to by 152 UN Member States, and another 7 States have signed it, signalling their intent to become legally bound.

In June 2001, the 189 Member States of the United Nations reaffirmed their recognition of the need for a stronger global response to the AIDS epidemic and, as part of this response, the need for HIV vaccine research, development, and access, [18] and committed to:

> "Encourage increased investment in HIV/AIDS-related research, nationally, regionally and internationally, in particular for the development of sustainable and affordable prevention technologies, such as vaccines and microbicides, and encourage the proactive preparation of financial and logistic plans to facilitate rapid access to vaccines when they become available."

The June 2001 Special Session on HIV/AIDS was preceded by at least three previous United Nations declarations in 2000 and 2001 that included national commitments to respond to HIV/AIDS, [19] and at least seven regional declarations related to national commitments to respond to HIV/AIDS.[20]

These international public health, ethical, and legal commitments compel States to act. These commitments also set a clear mandate for agencies affiliated with the United Nations system, such as the World Health Organization (WHO), the World Bank, and the World Intellectual Property Organization (WIPO) to address HIV vaccine research, development, and access as an integral part of their on-going work.

HIV vaccine development is interdependent with other global health efforts

HIV vaccine development has a central goal of adding a safe, effective, inexpensive, and widely accessible tool to these global HIV prevention and treatment efforts. As such, the efforts to

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[16] World Health Assembly Resolution 32.30. *International Conference on Primary Health Care.* WHO with UNICEF (1979)

[17] World Health Assembly Resolution 51.5. *World Health Declaration.* WHO (1998)

[18] UN General Assembly Special Session on HIV/AIDS (UNGASS). *Declaration of Commitment on HIV/AIDS*, June 2001, para 70. Paragraphs 23 and 89 also include commitments for HIV vaccine development and access.

[19] The United Nations Millennium Declaration (September 2000); the Political Declaration and Further Actions and Initiatives to Implement the Commitments made at the World Summit for Social Development (July 2000); and the Political Declaration and Further Action and Initiatives to Implement the Beijing Declaration and Platform for Action (June 2000).

[20] Further regional commitments by countries on HIV/AIDS were made through the Call for Action to Fight HIV/AIDS in Asia and the Pacific (April 2001); the Abuja Declaration and Framework for Action for the Fight Against HIV/ AIDS, Tuberculosis and other Related Infectious Diseases in Africa (April 2001); the Panama Declaration of the Ibero-America Summit (November 2000); the Declaration of the Caribbean Partnership Against HIV/AIDS (14 February, 2001); the European Union Programme for Action on HIV/ AIDS, Malaria and Tuberculosis (May 2001); the Baltic Sea Declaration on HIV/AIDS Prevention (May 2000); and the Central Asian Declaration on HIV/AIDS (May 2001).

research, develop, and ensure eventual access to HIV vaccines are interwoven into broader agendas for public health. Much can and should be done now to control HIV and AIDS around the world in parallel to long-term development of HIV vaccines. For example, a range of interventions can support prevention of HIV infection, even in resource-limited settings. Although sustained behavioral HIV risk-reduction and condom use have clear limitations, particularly for women who have little power to negotiate sexual relationships that put them at risk, a great deal can be done now to prevent HIV infection.[21] Potential interventions include:

- interventions to ensure safety of blood supplies,
- access to antiretroviral therapy for prevention of mother-to-child transmission,
- information and access to sterilized injection equipment, and
- an increased level of health and socio-economic power of women.

HIV prevention campaigns have had success in countries such as Australia, Senegal, Thailand, and Uganda, where strong public awareness, provision of condoms, education about and access to clean injection equipment, multiple one-to-one patient centered counseling, and access to STD treatment and general health care have contributed to lower HIV and STD infection rates. Furthermore, success of HIV prevention and HIV treatment efforts are linked. Access to antiviral treatments to prevent AIDS among those who are already HIV-infected provides additional incentive for people to learn their HIV status; this treatment access can be extended to many more people than now have access, particularly in light of price reductions in 2000-2002 for many of these drugs.[22]

As much as global health might benefit from successful development of HIV vaccines, HIV vaccine development and access also depends on the success of global public health efforts. As with all vaccines, HIV vaccines will only have a major impact where there is public access to health information and health care. Many individuals and communities will only use and benefit from HIV vaccines when they have some access to and trust in health officials who would administer those vaccines.

The human right to HIV vaccine development is interdependentwith all human rights

The obligation for HIV vaccine development is interdependent with other fundamental human rights related to research, including the the right to protection against harm through research or research-related discrimination, and the right to individual voluntary informed consent to participation in biomedical research.

Promotion of individual human rights is essential to progress in HIV vaccine development and access. Understanding, access to, and use of HIV vaccines will be supported by increased capacity of individuals to understand and act to protect their health. Rights-based efforts to reduce poverty, harm from drug use, and lack of access to medical care could augment the impact of HIV vaccines in preventing HIV and AIDS. Reductions in social stigma associated with HIV infection, drug use, and homosexual and heterosexual sex could reduce individual delay in seeking HIV testing, HIV treatment, and counseling about HIV risk-reduction, also enhancing the impact of HIV vaccines.

Human rights advocates should support HIV vaccine development and access

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[21] Global AIDS Program, US Centers for Disease Control (CDC). *The Global HIV and AIDS Epidemic 2001*. MMWR 2001; 50: 434-439. at http://jama.ama-assn.org/issues/v285n24/ffull/jwr0627-1.html

[22] Medecins Sans Frontieres. *Campaign for Access to Essential Medicines*. www.accessmed-msf.org.

Human rights advocacy related to HIV vaccine development has already yielded important successes related to individual rights and clinical research. These successes include

- government and clinical trial site commitments and protocols to ensure individual autonomy and informed consent in the course of clinical trials,
- commitments, protocols, and structures to protect clinical trial participants against social harms due to potential discrimination or breaches of confidentiality, and
- commitments, protocols, and structures to ensure proper ethical review of clinical trial implementation.

However, human rights work can and should expand its focus onto broader areas of HIV vaccine development and access, and onto larger policy issues. With defined obligations under international law to support biomedical research and development of new technologies against AIDS, TB, malaria, and other global killers, governments and advocates have a responsibility to translate these obligations into clear commitments and plans with timelines and outcomes that can be monitored and enforced. Commitments can take many forms, including international plans and collaborations, national plans and timelines, contractual agreements underlying public-private partnerships, best-practice guidelines for public information and education, legislation supporting biomedical research and development, and must apply to all areas of HIV vaccine research, development, and access in order to advance global health and human rights.

4. Key HIV vaccine-related meetings in 2000-2002

This background paper draws upon a wealth of global effort and dialogue. Increased funding, primarily from national governments and the Gates Foundation, has accelerated attention and work on HIV vaccine development. This is reflected in more than twenty meetings and conferences held in 2000 and 2001 covering issues related to HIV vaccine development. The following is a listing of some of these meetings.

- In May 2000, UNAIDS released annotated guidance points on the ethical considerations of HIV vaccine research. [23] These guidance points were the product of two years of consultation and debate around the world, and provided new groundwork for legal and ethical discussions in the field.
- In March 2000 in Pretoria, the WHO-UNAIDS HIV Vaccine Initiative and the African Council of AIDS Service Organizations (AfriCASO) held a meeting on the community role in the development and evaluation of candidate HIV vaccines in Africa. Recommendations for NGOs were made addressing situation assessment, collaboration, information sharing and coordination.
- In June 2000 in Nairobi, the WHO-UNAIDS HIV Vaccine Initiative, Southern African Development Community (SADC), and the Society on AIDS in Africa (SAA) met to discuss ways to accelerate the development and future availability of HIV vaccines for Africa. A 'Nairobi Declaration' was adopted and a draft African strategy for an HIV vaccine outlined.[24]
- In July 2000 in Durban, UNAIDS co-hosted an official satellite conference at the 13th International AIDS Conference on critical legal issues and HIV/AIDS. The meeting was a joint project of the Canadian HIV/AIDS Legal Network and the AIDS Law Project of South Africa. One focus of this meeting was resolving legal and ethical obstacles to HIV vaccine development and access. A background paper (subsequently updated to include the Durban satellite proceedings[25]) was circulated before the meeting to be discussed in a working group, and recommendations made for addressing some of the issues raised. The meeting was opened by Dr Peter Piot, Executive Director of UNAIDS and attended by UNAIDS Human Rights Adviser Miriam Maluwa, and WHO-UNAIDS HIV Vaccine Initiative Team Leader José Esparza. It was significant that for the first time in such a community setting, attention was focused more on the problems of funding and access than on narrow issues relating to the medical treatment of persons infected during a vaccine trial.
- In July 2000, also at the Durban conference, the International Council of AIDS Service Organizations (ICASO) released a primer on HIV vaccine development targeted to community organizations, and covering basic scientific, ethical and policy issues.[26] This project was funded by both IAVI and the WHO-UNAIDS HIV Vaccine Initiative.
- In September 2000, the WHO-UNAIDS HIV Vaccine Initiative sponsored a meeting in Geneva to develop a plan of action for an African Strategy for an HIV vaccine. Key thematic areas identified at the meeting included advocacy and resource mobilization.

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[23] UNAIDS. *Ethical Considerations in HIV Preventive Vaccine Research: UNAIDS Guidance Document.* Geneva: UNAIDS, May 2000. hereinafter 'UNAIDS Guidance Document' www.unaids.org.

[24] The Nairobi Declaration: An African Appeal for an AIDS Vaccine. Printed and distributed by WHO-UNAIDS in collaboration with AfriCASO, SAA, and SADC. www.unaids.org/publications/documents/vaccines/vaccines/ JC469-NairobiDeclar-E.pdf

[25] Patterson, 2000. www.aidslaw.ca

[26] Avrett, S, Link, D. Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups. International Council of AIDS Service Organizations (ICASO), June 2000. www.icaso.org

- In October 2000 WHO-UNAIDS HIV Vaccine Initiative hosted a meeting to consider the potential policy and scientific issues if an HIV vaccine trial were to show a candidate HIV vaccine to be only partly effective.

- In February 2001, the European Commission approved a 2002-2006 Program of Action, reaffirming financial support for research and development, committing to more funding for research and clinical trials infrastructure in the EU and in developing countries, further development of new industry incentives, regulatory issues, research financing mechanisms, further funding of the World Bank economic research and policy efforts, and further funding of the European Commission AIDS Vaccine Task Team and collaborations with GAVI, IAVI, UNAIDS, and WHO.
- In April 2001, the US National Bioethics Advisory Commission released an extensive report on ethics and international clinical trials.[27]
- Also in April 2001, the Society of Women with AIDS in Africa (SWAA) held a large conference in Kampala, Uganda, where HIV vaccine and microbicide development was discussed.
- Also in April 2001, the Organization of African States held an African Summit on HIV/AIDS in Abuja, Nigeria, producing a declaration that included an endorsement of international HIV vaccine development, commitment to the Africa AIDS Vaccine Program, and demonstrations of political leadership on AIDS that could accelerate African efforts for HIV vaccine development.
- Also in April 2001, the World Health Organization, World Trade Organization (WTO), and the Global Health Council held a meeting in Høsbjør, Norway focused on issues of differential pricing and financing of essential drugs, tangentially covering issues of importance to HIV vaccine deployment.
- In June 2001, the United Nations General Assembly held the first-ever Special Session focused on HIV/AIDS, resulting in a Declaration of Commitment with specific references to the need for HIV vaccine development.
- In July 2001 in Genoa, the countries of the G-8 met, reviewing commitments made by Member States of the United Nations, and formally launching a Global Fund Against AIDS, Tuberculosis and Malaria (GFATM). The GFATM will not fund vaccine research, but it may well fund the national health programs reaching adolescents and young adults with public health vaccines, STD screening and education, and credible HIV prevention, treatment, and care strategies, that will provide an important basis for future delivery and access to HIV vaccines.
- In September 2001, an international vaccine meeting, AIDS Vaccine 2001, was held in Philadelphia, where the science of HIV vaccine development was reviewed and political commitments were restated by government officials and leading researchers of Rwanda, Thailand, South Africa, Uganda, and the United States.
- In October 2001, the regional Asia-Pacific conference on AIDS, the International Conference on AIDS in Asia and the Pacific (ICAAP) was held, with a plenary, several workshops, and a WHO-UNAIDS HIV Vaccine Initiative sponsored satellite meeting on HIV vaccine development.
- Also in October 2001 in Sao Paulo, a Latin American conference on HIV vaccines was sponsored by the Brazilian National AIDS Program, the State AIDS Program of Sao Paulo, Grupo Pela Vidda, and GIV, with funding from IAVI and UNAIDS, to further the commitment by Latin American government officials, pharmaceutical company

[27] National Bioethics Advisory Commission. Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. NBAC, April 2001. http://bioethics.georgetown.edu/nbac/pubs.html

representatives, academic researchers, international agency representatives and community activists from a range of AIDS organizations.

- In December 2001, the International Conference on AIDS and STDs in Africa (ICASA) was held in Burkina Faso, where HIV vaccine presentations and a skills-building workshop allowed participants to meet with policy and science experts from Kenya, Senegal, South Africa, Uganda and a range of international organizations.
- Finally, in December 2001, the WHO Commission on Macroeconomics and Health released its groundbreaking report on global health needs and opportunities, including a recommendation for global funding of $1.5 billion for research and development of drugs and vaccines for AIDS, TB, malaria, and other diseases affecting poor countries.[28]

These international meetings were complemented by a range of national level efforts, beyond the scope of this paper to describe in detail. In Nigeria, for example, a national plan on HIV vaccine development was drafted and finalized during 2001,[29] and the Nigerian group Journalists Against AIDS hosted an international discussion on their nigeria-aids listserve to increase the awareness and information of journalists and community at large.[30]

[28] This report can be obtained on the internet at www.who.int/cmhreport

[29] A workshop was convened by the Nigerian National Action Committee on AIDS (NACA) to develop an National HIV Vaccine Plan on 15-17 January 2001, and then a follow-up meeting was held one year later on 22-23 January 2002 to finalise this plan.

[30] Nigeria journalist e-mail forum on vaccines in late December on the listserve www.nigeria-aids.org

4. Ensure commitment to HIV vaccine development

In 1998, the late Jonathan Mann called for greater specific commitment to the HIV vaccine effort:

> "What is needed is to develop AIDS vaccine candidates according to procedures and milestone-driven strategies which have produced highly successful vaccines which save millions of lives from diseases like polio, whooping cough, and measles... Science is an instrument of public health. The larger responsibility, central to the moral authority and legitimacy of our governments, is protection of public health."[31]

Commitment is needed at all levels - local, national, and international, and from governments, private sector, and civil society - to ensure globally consistent and coordinated HIV vaccine effort over time. International commitments are especially required due to the global scale of the HIV epidemic, the corresponding scale of the required scientific effort for HIV vaccines, and the need for HIV vaccine strategies relevant to combating the epidemic in every country. Commitment at the highest level is needed in many countries. Leadership and commitment are instrumental in building partnerships and coalitions that transcend national boundaries. Leadership and commitment are also essential in achieving adequate sustained funding for HIV vaccine development in the context of an adequately funding AIDS and public health effort.

A long-term commitment and long-range vision are important for all stages of HIV vaccine research, development, and access. Ensuring public health delivery infrastructure and incentives to allow eventual rapid production and deployment of HIV vaccines requires advance planning as well as responsiveness to immediate public health needs for care, prevention, and other vaccines. Approving and funding large Phase III vaccine efficacy trials requires major commitments of funding and program efforts for multiple years, even in the face of uncertainty and debate about the unknown efficacy of the candidate HIV vaccines to be tested.

4.1 Ensure accountability through plans and timelines

Despite the clear mandates by international law for advancement of economic and social rights, and the enormous costs of not doing so, rights-based arguments have been slow to mobilize governments and other institutions. One factor has been that relevant international treaties and declarations have permitted diffusely defined responsibilities, vague timeframes for implementation, and few mechanisms for monitoring and enforcement. By contrast to some of the economic sanctions permitted within the European Union or World Trade Organization to force government action on matters such as deficit spending or trade policy, mechanisms for national accountability for respecting, protecting and fulfilling rights such as public health, literacy, or housing are cumbersome and limited.

The HIV/AIDS epidemic shines a stark light on this lack of accountability. Although the world's governments and international institutions have repeatedly pledged themselves to action against the epidemic, the response by many countries has been too little and too slow.

In a July 2000 speech at the International AIDS Conference in Durban, South Africa, Kenneth Roth of Human Rights Watch suggested that national government plans were key to ensuring accountability and progress.[32] In his speech, Roth recommended public transparent plans and

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[31] Mann, J. *Paralysis in AIDS Vaccine Development Violates Ethical Principles and Human Rights*. IAPAC Newsletter, May 1998.

[32] Roth, K. Human Rights and the AIDS Crisis: The Debate Over Resources. Human Rights Watch. July 2000. www.hrw.org/editorials/2000/aids-print.htm

timelines for addressing all human rights aspects of HIV and AIDS as a way to provide leadership, begin discussions about public priorities related to HIV/AIDS in the context of other health, economic, and social needs, and track resource allocation and progress toward specific milestones over defined periods of time.

Governments of all countries should devise and publicly adopt country-specific plans and timetables for HIV vaccine development. These plans and timelines should be reinforced by mechanisms for monitoring and enforcement. Development of national plans for HIV vaccine development is supported by documents such as the 'International Guidelines on HIV/AIDS and Human Rights':

> "States should establish effective national frameworks for their response to HIV/AIDS which ensure a coordinated, participatory, transparent and accountable approach, integrating HIV/AIDS policy and program responsibilities across all branches of government."[33]

National plans should also be supported by mechanisms to ensure international cooperation in technology development and transfer. This responsibility for cooperation has been outlined in several international documents, including for example, the 1975 Charter of Economic Rights and Duties of States, which states:

> "All States have the responsibility to cooperate in the economic, social, cultural, scientific, and technological fields for the promotion of economic and social progress throughout the world, especially that of the developing countries. ...All States should promote international scientific and technological cooperation and the transfer of technology, with proper regard for all legitimate interests including, inter alia, the rights and duties of holders, suppliers, and recipients of technology. In particular, all States should facilitate the access of developing countries to the achievements of modern science and technology, the transfer of technology, and the creation of indigenous technology for the benefit of the developing countries in forms and in accordance with procedures which are suited to their economies and needs. … Accordingly, developed countries should cooperate with the developing countries in the establishment, strengthening, and development of their scientific and technological infrastructures and their scientific research and technological activities so as to help to expand and transform the economies of developing countries."[34]

4.2 Support explicit national plans for HIV vaccine development

The development of national HIV vaccine plans, including national commitments to clinical trials, regulatory and ethical review capacity, and vaccine delivery infrastructure, can help to spur progress in vaccine development through public dialogue and oversight. National HIV vaccine plans have already been developed in some, but not all of the countries now supporting HIV vaccine development. These countries include high-income countries, such as Australia, Canada, Japan, the United States, and, in Europe, Denmark, France, Germany, Ireland, Italy, Netherlands, Norway, Sweden, and the United Kingdom. They also include at least a dozen middle and low-income countries, in the Caribbean (Cuba, Haiti, and Trinidad), South America (Brazil and Peru), Africa (Kenya, South Africa, and Uganda), and Asia (China, India, and Thailand).

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[33] Office of the UN High Commissioner for Human Rights and UNAIDS. *HIV/AIDS and Human Rights: International Guidelines*. 1997, Guideline #1. www.unaids.org

[34] UN General Assembly, *Charter of Economic Rights and Duties of States*, 1975. Chapter II, Article 13.

As one model of public national planning for HIV vaccine development, Brazil developed its first National HIV Vaccine Development Plan in 1992, and supported the creation of a national vaccine advisory committee in the same year to regularly review and oversee government-funded HIV vaccine development efforts. Since 1992, the national vaccine plan has been updated at regular intervals, and in 2000, the Brazilian government updated its National Guidelines for Research in Human Subjects. In 1994, the Brazilian government lent its political and financial support to a Phase I HIV vaccine trial, and in 2001 supported the start of a Phase II HIV vaccine trial in Rio de Janeiro. In a recent example of multisectoral dialogue about national vaccine efforts, in October 2001, the Brazilian National AIDS Program and the State AIDS Program of Sao Paulo collaborated with the community organizations Grupo Pela Vidda and GIV to organize a Latin American conference on HIV vaccines. Convening government officials, pharmaceutical company representatives, academic researchers, international agency representatives and community activists from a range of AIDS organizations, this meeting concluded with a commitment by all parties to further integrate HIV vaccine issues into the broader agenda of the Brazilian government and the participating international health organizations.

In a second example of national planning for HIV vaccine development, the Ugandan government was the first African government to develop a national plan focused on HIV vaccines and the first to sponsor an HIV vaccine trial in the early 1990s. In 1997, Uganda led a process through a National Consensus Conference to develop Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda. The Ugandan government has helped to support the international success of local research institutions such as the Joint Clinical Research Center (JCRC), Makerere University, the Uganda Cancer Research Institute, and the Uganda Virus Research Institute. In the late 1990s, Uganda was the site for a Phase I HIV vaccine trial, and in 2001 facilitated new collaborations with the US Department of Defense and with IAVI.

In Asia, the Thai National AIDS Prevention and Control Commission began drafting the first Thai national HIV vaccine plan in 1993, and has regularly updated this plan to include procedures for scientific and ethical review of all proposed HIV vaccine research. The Thai government sponsored its first Phase I HIV vaccine trial in 1994. Since then, the Thai Ministry of Public Health, the Royal Thai Army, and universities such as Mahidol, Chulalongkorn, and Chiang Mai have been actively supportive of HIV vaccine trials. In total, more than half of all HIV vaccine trials conducted in developing countries have been conducted in Thailand. The Thai government has worked to maximize the benefit of this research for their country and region. HIV vaccines have been developed based on Thai strains of HIV. Thai scientists lead every clinical trial as principal investigators or co-investigators. The Thai government leads negotiations with foreign companies and governments involved in Thai HIV vaccine development to obtain capacity-building assistance for Thai laboratories, research clinics, data management centers and universities, and vaccine production facilities. The Thai government has also taken the lead in seeking to increase access to intellectual property rights to vaccine technologies through international collaborations, early preclinical work, and arrangements for joint manufacturing of vaccines.

Several other examples of national HIV vaccine plans exist, such as a recent planning process conducted in Nigeria. Among the two dozen countries supporting HIV vaccine development, not all are perfect in all aspects of their response to HIV/AIDS, public health, economic justice, and human rights. Yet the development of national plans for HIV vaccine development, as one aspect of a response to AIDS and public health, is an important contribution to providing leadership in this area and permitting public dialogue about relative priorities and resource allocations. HIV vaccine development plans can create sufficient consensus to move forward with HIV vaccine

efforts in a steady, predictable way, even as debates continue regarding overall health, economic, and social priorities.

4.3 Support increased national funding for HIV vaccine development

National commitment also includes explicit commitment to funding for HIV vaccine development in the context of increased global health research for diseases of resource-limited countries, such as tuberculosis and malaria. Many global leaders, including members of the international Commission on Macroeconomics and Health (CMH), have recognized the need to increase investment. As stated in the CMH December 2001 report,

> "There is an urgent need for investments in new and improved technologies to fight leading killer diseases. New advances in genomics bring us much closer to the long-sought vaccines for malaria and HIV/AIDS, and lifetime protection against TB. The evidence suggests high social returns to investments far beyond current levels. The Commission therefore calls for a significant scaling up of financing for global R&D on the heavy disease burden of the poor."[35]

The 2001 UN General Assembly Declaration of Commitment on HIV/AIDS recently supported increased funding of HIV vaccine development, in the context of other funding increases:

> "Increase investment and accelerate research on the development of HIV vaccines, while building national research capacity especially in developing countries, and especially for viral strains prevalent in highly affected regions; in addition, support and encourage increased national and international investment in HIV/AIDS-related research and development"[36]

> "Encourage increased investment in HIV/AIDS-related research, nationally, regionally and internationally, in particular for the development of sustainable and affordable prevention technologies, such as vaccines and microbicides, and encourage the proactive preparation of financial and logistic plans to facilitate rapid access to vaccines when they become available"[37]

Updated economic analyses can support increases to global funding for HIV vaccines

Analyses of overall global investment in HIV vaccine development by several leading HIV vaccine policy groups placed the world's effort in 2000 for HIV vaccines at approximately $470 million per year.[38, 39] This number may have doubled by 2003. Even with recent increases, this is a small investment relative to total world spending on health, education, and research. In the late 1990s, the world's combined gross national product (GNP) was valued at approximately $30 trillion. Approximately $1,750 billion of this was spent for health each year, another $1,750 billion for education, and $71 billion for health research and development.[40, 41]

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[35] Commission on Macroeconomics and Health (CMH). December 2001 Report. Executive Summary, pp 9 and 14 and Action Agenda, Recommendation 4. www.who.int/cmhreport
[36] UNGASS. Paragraph 70.
[37] UNGASS. Paragraph 89.
[38] IAVI, *Accelerating the Development of an AIDS Vaccine for the World: An Opportunity for G-8 Leadership*, July 2001. www.iavi.org.
[39] Avrett, S, Cappiello, D, Collins, C, et al. *Six Years and Counting: Can a Shifting Landscape Accelerate an AIDS Vaccine?* Washington, DC: AVAC, 2001. www.avac.org
[40] World Bank *World Development Report 2000/2001: Attacking Poverty* Washington DC: World Bank, 2001, at Tables 6 and 7.

The small amount spent on HIV vaccine research and development reflects an overall underinvestment in development of drugs and vaccines for diseases affecting poor countries. In total, less than $3 billion is spent worldwide on health research and development on HIV, malaria, tuberculosis, and other tropical diseases. High-income countries spend less than $500 million on health research targeted specifically to health in poor countries, and middle and low-income countries, with 85% of the world's population, spend only about $2.2 billion on health research, about 3% of the world expenditures. In the late 1990s, international development assistance contributed only about $350 million annually for health research and development.[42] As stated by Bernard Pecoul in a 1999 article, "The result [of this funding imbalance] is predictable: only 13 of 1233 new drugs that reached the market between 1975 and 1997 were approved specifically for tropical diseases."[43]

These types of analyses of relative investment, reviewing the sources, destination, and use of HIV vaccine development funding, are useful in supporting a framework for increased investment. Experts in the field continue to claim that further rapid increases in global funding could be absorbed and effectively used toward the HIV vaccine effort for developing countries. Major funding can especially be channeled toward common health research efforts, such as quality clinical trial infrastructure and design capacity in developing countries, regulatory expertise and private-sector manufacturing capacity in developing countries, and basic research areas such as immunology and virology. Further economic analyses can form the basis for ensuring maximal use of current investments in HIV vaccine research, development, and access, and further investment toward potential gaps and needs.

New funding should be channelled to public-private partnerships and clinical trial capacity

Increased global investment should especially be placed into replication and expansion of public-private partnerships for HIV vaccine development. Globally, only about twenty major public-private partnerships involving the for-profit vaccine companies exist for HIV vaccine development. Most of these partnerships are sponsored by IAVI and the US NIH, through contracts averaging about $5 to $7 million per vaccine development team. These development partnerships represent important efforts not only toward moving HIV vaccines into clinical evaluation, but also toward building the manufacturing capacity and intellectual property arrangements necessary for large-scale trials and eventual global access. New expenditures by the national governments of high-income countries, either through direct contracting or through IAVI, could dramatically increase the number of HIV vaccines being developed through public-private collaborations.

Clinical trial infrastructure in middle and low-income countries could also absorb increased funding. More than ten countries in the Caribbean, South America, Africa, and Asia are conducting or planning HIV vaccine trials. Clinical trial infrastructure requires funding for health clinics, laboratories, storage facilities, trained medical personnel and technicians, support of long-term volunteer cohorts, and investment in an environment of health promotion, treatment, and care that includes capacity for quality primary health care and perinatal care. Clinical trial infrastructure also includes national regulatory and ethical review capacity to ensure the highest

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[41] Neufeld, V, MacLeod, S, Tugwell, P, Zakus, D, and Zarowsky, C. *The rich-poor gap in global health research: challenges for Canada*. CMAJ, 27 April 2001, 164 (8), pp. 1158-1159.
[42] OECD Development Assistance Committee *Recent Trends in Official Development Assistance to Health* Geneva: OECD, November 2000.
[43] Pecoul, B et al, JAMA 281, 361 (1999), cited in Reich, M: *The global drug gap*, Science, 287, March 2000.

quality of clinical trial design in promoting both scientific advancement and human rights. National governments of high-income countries could increase their support for this infrastructure development, either through direct bilateral aid to the Caribbean, South America, Africa, and Asia, or indirectly through the World Bank, IAVI, or the WHO.

Increased funding should come from all countries, but especially from five.

Aside from the Gates Foundation and private investment in five vaccine companies, nearly all of current HIV vaccine development funding, including funding at WHO, UNAIDS, the World Bank, and IAVI, ultimately comes from national government spending. Only five private sector vaccine companies annually invest more than $5 million of privately raised funds: Merck, VaxGen, Aventis-Pasteur, Wyeth, and Chiron. The additional ten to fifteen private-sector companies, mostly biotechnology ventures, develop candidate HIV vaccines primarily with funding contracts from IAVI and the US National Institutes of Health (NIH). In total, the private for-profit sector now invests only about $50-$70 million per year in private investment dollars, supplemented by approximately $25 million annually from the US, French and other national governments.

The largest national government HIV vaccine programs are those of Canada (Health Canada), France (ANRS), the Netherlands (Health Ministry), Sweden (Karolinska), the United Kingdom (MRC), and the United States. The largest single source of funding for HIV vaccine research and development, by far, is the US government, primarily through the US National Institutes of Health (NIH) and the US Agency for International Development (USAID). In total, the US government invests approximately $350 million annually, accounting for more than three-quarters of all government spending and probably two-thirds of the total worldwide funding investment.

In most cases, national government spending on HIV vaccine research and development is focused primarily on domestic research and development efforts, with only a few countries, such as Ireland, Denmark, and Norway, devoting a significant portion of national government funding to international efforts, such as to IAVI. One result of this pattern is that most HIV vaccine research and development to date has occurred in the US, Canada, and Western Europe. During the past five years, this has begun to change. Wealthy countries are beginning to invest increased amounts into international clinical trial networks and are contributing more to IAVI, meaning that HIV vaccine trials are underway or planned in the Caribbean (Cuba, Haiti, and Trinidad), South America (Brazil and Peru), Africa (Kenya, South Africa, and Uganda), Asia (China, India, and Thailand), and Australia.

Given the constraints of what philanthropy, private investors, and for-profit companies can and will provide, most of the additional annual funding for HIV vaccine research will have to come from the national governments of high-income countries. National leaders of all countries should work to increase current funding levels for HIV vaccine development. Most of the increased spending could come from the five governments of the largest OECD countries: France, Germany, Japan, the United Kingdom, and the United States.

National leaders can target increased national funding in several ways, including:

- increased national research agency funding to researchers and companies through grants and contracts,
- increased international development funding to multilateral agencies such as the European Commission, the World Bank IDA and DGF program, and the WHO-UNAIDS HIV Vaccine Initiative,

- increased funding for public-private partnerships such as IAVI, and
- increased direct bilateral aid to low-income and middle-income country governments to support HIV vaccine clinical trial infrastructure and vaccine delivery systems.

For example, increased funding by the United States government can be directed in two major directions:

- to the US National Institutes of Health (NIH) for funding of intramural and extramural research and development, and for contracts to public-private partnerships,
- to USAID for vaccine-related appropriations to IAVI, GAVI, the World Bank, and the WHO-UNAIDS HIV Vaccine Initiative.

This increased investment is politically realistic in the United States. The current Bush administration has shown a clear interest in funding increases for both the US NIH and for the World Bank IDA Program, and has proposed $27.3 billion in funding for the US NIH in 2003.

Among multilateral agencies, the World Bank might be an especially powerful vehicle for increased global investment in all aspects of HIV vaccine research, development, and access. Having established an AIDS Vaccine Task Force in 1998, the World Bank has explicitly recognized the need for new funding for HIV vaccine development for several years.[44] In 2001-2003, the Bank is expected to lend more than $800 million from its International Development Association (IDA) program for Multi-Country HIV/AIDS Program (MAP) loans throughout the world. In June 2000, the World Bank also established $1 billion in IDA credits for national efforts in low-income countries for the prevention of HIV/AIDS, malaria and tuberculosis. The World Bank could accelerate their HIV vaccine efforts by creating and awarding direct Development Grant Facility (DGF) funding and by doubling current IDA lending levels for vaccine research and development efforts and for clinical trial infrastructure and effective health care and vaccine delivery systems in low-income countries.

[44] For example, in a June 1999 World Bank Africa Region report *Intensifying Action Against HIV/AIDS in Africa*, "The Bank should identify new ways of financing the development of affordable vaccines and other prevention options, such as microbicides, and support research efforts to provide decision makers with the data and tools they need to intensify their efforts against the epidemic."

5. Expand public involvement in HIV vaccine development

HIV/AIDS is increasing its human and economic cost at every level of society throughout the world. The global scale and deep entrenchment of the HIV epidemic, due partly to behaviors, values, and social structures of every society, requires a response to the epidemic from all quarters. This response must be dynamic and inclusive, being renewed and recreated for, and from, every new generation until the epidemic is ultimately controlled.

From a human rights perspective, broad public involvement is also needed in responding to HIV to ensure that strategies to address the HIV/AIDS epidemic consider a full range of individual and societal obligations. In the case of HIV vaccine development, public involvement is needed to support the societal obligation to develop new technologies for public health, while also promoting other fundamental human rights related to biomedical research, such as the right to individual freedom and security, and the right to individual voluntary informed consent to participation in research. An inclusive and dynamic public ownership of the HIV vaccine development effort can mobilize new energy and expertise for HIV vaccines in the context of broader public health goals.The imperative to involve 'community' in biomedical research is acknowledged in several documents, including reports by UNAIDS and by the US National Bioethics Advisory Commission:

> "To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research."[45]

> "Researchers and sponsors should involve representatives of the community of potential participants throughout the design and implementation of research projects…." US National Bioethics Advisory Commission, recommendation 2.3 [46]

Public involvement must be broadly based and focused on the entire effort

Useful input, involvement, and advocacy can come from public and private-sector researchers, leaders of pharmaceutical and biotechnology companies, national government leaders, research trial participants, people living with HIV, local political leaders, religious leaders, business and labor union leaders, journalists, legal advocates, youth advocates, civil rights advocates, community educators, and local philanthropists,foundations and other sources.[47]

Large Phase III clinical trials of HIV vaccines are worth special attention in discussion about public mobilization, since they are a central effort and hub where researchers, companies, government agencies, and community advocates often find common cause and issues of concern. Coalition-building and community education are particularly important in the context of large clinical trials simply because public mobilization can be prevented or slowed by controversy or concerns generated by clinical research. Research participants and the communities where they

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[45] UNAIDS Guidance Document, at 19. www.unaids.org

[46] National Bioethics Advisory Commission, 2001, at 14. http://bioethics.georgetown.edu/nbac/pubs.html

[47] For an analysis of the definitional factors of 'community', including location, social ties and common action, see MacQueen, K, McLellan, E, Metzger, D, et al. What is Community? An Evidence-Based Definition for Participatory Public Health. *American Journal of Public Health* December 2001; vol.91, no.12: 1929-1938.

live are therefore a particularly important part of public mobilization. As new Phase III efficacy trials begin around the world, the largest group of people involved in, and affected by, global HIV vaccine development will be research participants. Aside from being indispensable to successful clinical trial recruitment and retention, research participants and their communities have a fundamental stake in the ethical conduct, success, and urgency of the global HIV vaccine effort. Research participants and communities have unique local knowledge about the potential impact and acceptability of planned clinical research. Partnership with these communities is therefore essential to any scaled-up global HIV vaccine development effort.

Public mobilization is not simply about clinical trial implementation, but about the broader process of vaccine development and access. Ultimately, to mobilize the public, build new coalitions, and lead advocacy efforts, core stakeholders and community leaders must be familiar with the entire process of vaccine research, development, and access. This means that support and partnerships for public involvement must come not only from clinical trial sites but also from government agencies and institutions engaged in preclinical research and public health delivery of vaccines.

Public involvement requires increased understanding, support, and participation

Public involvement in HIV vaccine development is a matter not just of disseminating information about science, but also of incorporating concepts of law, ethics, human rights, sociology, political organizing, communications, and marketing. Three indicators of successful public involvement might be defined[48] as:

- Increased public understanding about basic concepts of HIV, public health, HIV prevention, vaccines, biomedical research, and human rights.
- Increased public support for HIV vaccine research, development, and access, particularly through coalitions and partnerships that allow participation, information exchange, and on-going communication, training, and support.
- Increased public participation as measured by the inclusivity, diversity, and dynamism of multisectoral involvement in HIV vaccine development collaborations and partnerships.

These efforts toward broad public ownership of the HIV vaccine development effort have just begun, and yet they are a cornerstone to building increased political commitment and governmental resources.

5.1 Increase public understanding about HIV vaccine development

The public in many countries is largely unaware or unconcerned about the imperatives of HIV prevention, vaccine deployment and access, and biomedical research for new health technologies. Simply advancing basic, clear, and broad understanding about these concepts could vastly accelerate the global effort for HIV vaccine research, development, and access.

To build public understanding, governments, international agencies, the private sector, and other institutions can incorporate several strategies and intended outcomes into HIV vaccine planning. These include:

- development of user-appropriate materials about basic concepts of HIV, public health, HIV prevention, vaccines, biomedical research, and human rights,

[48] These three indicators were defined by a working group at the international expert consultation held in Montreal by the Canadian HIV/AIDS Legal Network in April 2002.

- train, fund, and partner with experienced opinion leaders such as political leaders, journalists, community advocates, research trial participants, researchers, government officials, and company representatives to support their efforts in communicating accurate information and in mobilizing positive public attention and support,
- support the capacity of potential and new opinion leaders to disseminate information and education about HIV vaccine development and broader issues of public health, and
- integrate basic HIV vaccine information into all AIDS and public health messages.[49]

Examples of vaccine education and advocacy materials includes important written material from Africa such as materials distributed by the WHO-UNAIDS HIV Vaccine Initiative from community meetings held in Pretoria and Nairobi in 2000[50], a African communications and media handbook contracted by UNAIDS,[51] a primer on vaccines published by ICASO and distributed through AfriCASO[52], the IAVI Report distributed directly in Africa by IAVI[53], and news articles produced through outreach and education among journalist networks in Nigeria[54] and Kenya[55]. In the United States, national community educational materials include regular publications by community groups such as the AIDS Vaccine Advocacy Coalition[56], recruitment materials published by VaxGen, and web site information and bulletins published by the US NIH and HVTN trials network.[57] In most of these publications, the content includes news about the planning and start of vaccine trials, basic trial protocol details, recruitment and retention updates, local and national meeting announcements, and written perspectives of trial site community educators, trial participants, and community members.

Stakeholders around the world continue to need educational materials and training about the entire continuum of HIV vaccine development and access. One source for relevant models for materials development and training might be found in training programs for ethical review committees, which could be adapted entirely or modified to include an HIV vaccine component. One model for training members of ethical review institutions comes from Australia, where in 2001 the Australian Health Ethics Committee completed a National Workshop Series in eight cities for 1055 participants, all clinical researchers and members of health research ethics committees. With presentations about ethical issues and case studies to facilitate dialogue, these trainings allowed ethicists, governmental research agency staff, academic researchers, regulatory agency staff, pharmaceutical company staff and members of ethics committees to enhance individual and organizational capacity for research review.[58]

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[49] This last item was labeled by one vaccine advocate at the April 2002 Network meeting as an "A, B, C plus D" approach to HIV prevention, where "D" represents development of vaccines, microbicides, and other new technologies.
[50] UNAIDS reports at www.unaids.org/publications/documents/vaccines/vaccines/JC615-AAVP-E.pdf
[51] African Media Handbook by Yinka Adeyemi. www.unaids.org/publications/documents/vaccines/ vaccines/ JC475-MediaHandb-E.pdf
[52] ICASO Primer. www.icaso.org/vaccines/vaccineprimer.htm
[53] IAVI Report. www.iavi.org
[54] Nigeria-aids listserve archives of the Journalists Against AIDS in Nigeria. www.nigeria-aids.org/eforum.cfm
[55] For example, a journalist workshop was held in Kenya on HIV vaccines on 2-4 December 2001. The East African Standard (www.eastandard.net) in particular has covered news related to HIV vaccine trials.
[56] AVAC web site. www.avac.org
[57] HVTN *HIV Vaccines and the Community: The Community Advisory Board Bulletin* November 2001; vol 2, issue 10
[58] See summary report of 2001 workshop series at www.health.gov.au/nhmrc/issues/ahecrep.htm

One model of training is offered by the HIV Vaccine Trials Network (HVTN) and the AIDS Vaccine Advocacy Coalition (AVAC) in the United States, where coalition-building has been attempted through use of a core group of community educators who have visited local community organizations and networks to offer information, elicit community questions and concerns, and to try to engage larger numbers of community leaders into dialogue about HIV vaccines. In the clinical trial sites of the HVTN, full-time community educators at every site have been hired since 1997 to do this work. In the case of AVAC, part-time community education consultants were hired in 2001 to design and conduct a series of community outreach presentations in more than six US cities to build community involvement in HIV vaccine advocacy. Targeted community networks for both HVTN and AVAC included HIV prevention planning groups, injection drug use harm reduction advocates, African-American and Latino/a community leaders, and AIDS service organizations. These efforts will be expanded in 2002 and 2003.

5.2 Increase public support for HIV vaccine development

One core challenge and irony of public support for HIV vaccines, and all HIV prevention and public health, relates to the vulnerability of many of the communities that most need HIV vaccines. Individual risk for HIV infection and AIDS often corresponds to a lack of individual social and economic power over one's health, and an absence or fragmentation of strong legal, political and social networks to address community health concerns. This vulnerability is combined with the political history of AIDS and of biomedical research in many countries and communities, the abstract and complex nature of HIV prevention, vaccine science and clinical research, and the fact that potential coalition partners - government officials, pharmaceutical company leaders, clinical trial site researchers and staff, research trial participants, political leaders, journalists, and community advocates - often come from multiple social and economic strata and perspectives.

This has meant that large-scale public support for HIV vaccine development has not been automatic, and that civil society leaders, including political leaders, people living with HIV, legal and civil rights advocates, and religious leaders, have often not been very willing to step forward and embrace biomedical research. Active organizing and outreach to involve new stakeholders must be a concerted effort by those leading vaccine advocacy coalitions, including governments, industry, clinical trial sites, and community organizations.

Coalitions and partnerships are essential

Public support for HIV vaccine development depends on the creation of coalitions and partnerships that facilitate stakeholder participation, information exchange, and on-going communication, training, and support. In turn, the success of coalitions, partnerships, networks and alliances related to HIV vaccines depend on:

- the extent, diversity, dynamism of their membership,
- the degree to which they are inclusive, participatory, and supportive in their activities and decision-making,
- their links with government officials, pharmaceutical company leaders, clinical trial site researchers and staff, and independent public opinion leaders such as research trial participants, political leaders, journalists, and community advocates,
- their clear and publicly available plans and timelines for providing information, training and support.

Coalitions can usefully inform, train, and support their allies and partners to relay accurate information and skills related to:

- HIV vaccine development history, funding, products, research and trials, and access efforts
- aspects of clinical trial design including research recruitment and retention, informed consent protocols, risk-reduction protocols, and strategies to prevent social harms
- models and strategies for integrating clinical trial plans and activities into ongoing community-based care settings, public health education efforts and HIV prevention efforts.
- information and dialogue about experimental vaccine products, proposed trial designs, and decision-making processes to license and deploy partially effective or fully effective vaccines.
- community organizing strategies and skills
- national policy and advocacy lobbying strategies and skills
- media and communications strategies and skills

For the purposes of broad public mobilization, the coalition must have an adequate number and range of committed, credible, informed, and honest voices. Many of these voices must be seen as working toward the broader, long-term public interest of an HIV vaccine for the world, as well as for their more narrow individual or institutional interests. Coalitions cannot be owned by, or closed to, only one organization, and must continually recruit new allies to maintain force and momentum. This requires investment in a dynamic partnership and capacity building.

Successful coalitions are already being developed

The past fourteen years of HIV vaccine development offer numerous examples of success in overcoming these barriers and engaging a range of diverse partners in coalition for HIV vaccines. These examples include both short-term meetings and opportunities for dialogue as well as long-term structures for coalition work. Current international examples of both include:

- on-going work by the HVTN to support international working groups and community consultations related to clinical trials of HIV vaccines,
- on-going work by ICASO to create and support an international coalition of vaccine advocates to raise and address concerns about HIV vaccine development,
- on-going work by AVAC to build a US-based coalition in support of the global HIV vaccine effort,
- recent community workshops on HIV vaccines sponsored by the WHO-UNAIDS HIV Vaccine Initiative at regional AIDS meetings, including workshops at the ICAAP meeting in Melbourne in October 2001 and a vaccine workshop at the ICASA conference in Burkina Faso in December 2001,
- meetings of the African AIDS Vaccine Programme in April and June 2002.

The African AIDS Vaccine Programme (AAVP) may offer a particularly useful model for coalition-building and community outreach. Originally convening approximately thirty community advocates from around Africa in Pretoria in March 2000, the first AAVP meeting sought to facilitate a conversation among community actors about the role of community in the development and evaluation of HIV vaccines in Africa. Brief presentations were made about the science of HIV vaccine development and aspects of clinical trial research. Community participants then discussed and created plans for building their own knowledge base about planned HIV vaccine research, working in coalition with other community advocates for information sharing and policy development, and coordinating future advocacy through AfriCASO and other networks. Follow-up meetings of this African network have since been held in Nairobi (June 2000), Geneva (September 2000), Ouagadougou (December 2001) and will be convened in Nairobi (April 2002) and Cape Town (June 2002). This model of outreach has worked to convene the stakeholders on a regular basis, aiming for sustained engagement of

community leaders in many countries, and supporting information, dialogue, and skills-building for participants in the coalition.

5.3 Increase public participation in HIV vaccine development

Broadly positive public perceptions about HIV vaccine development will be enhanced where government officials, political leaders, researchers, research trial participants, journalists, community advocates, and other leaders are publicly seated at the research table and clearly owning the process, while also maintaining their integrity as voices independent from the institutional interests and motivations of their governments, research organizations, pharmaceutical companies, or community organizations.

This public participation in vaccine development is driven by three factors:

- the capacity of a broad range of people to participate in an informed way
- existence of structures and rules for whereby new people can become involved in a meaningful way, such as membership guidelines and opportunities in vaccine development partnerships, clinical trial planning committees, and regulatory and ethical structures
- Existence of adequate incentives and support for sustained participation.

Models exist for public participation

One model for public participation in HIV vaccine development has been the Australian HIV Vaccine Consortium, which is unique in that it explicitly included a community organization from the beginning.[59] Formed in 2000 with funding from the US NIH, the Australian HIV Vaccine Consortium was formed around a programme to develop and test a prime-boost HIV vaccine, with Phase I safety studies planned to begin in Sydney in mid-2002. Made up of seven institutions and led by the academic partner, the Consortium included the Australian Federation of AIDS Organisations (AFAO) as one of the seven central partners. AFAO is a national community AIDS education and advocacy organization, which includes the AIDS councils from every Australian state and territory and the national advocacy organizations relating to injection drug users, sex workers and people with HIV/AIDS. AFAO was included as a co-investigator, and shared fully in decision-making processes about all aspects of the program. This allowed for early inclusion of social research issues and community perspectives even while the vaccine product was in pre-clinical phase.

Trinidad and Tobago offers an additional model for public participation in standing national committees of a HIV vaccine ethics committee and a trial site community advisory board.[60, 61] Both structures include trial participants, representatives of local AIDS service providers and AIDS clinicians, and other members of the communities from which trial participants are being recruited. Both provide structures by which community members, researchers, government officials, and company representatives can communicate with each other about HIV vaccine development efforts.

Public understanding, support, and participation is a broad human rights concern

[59] Presented by Robin Gorna of AFAO at the October 2001 ICAAP in Melbourne, Australia.
[60] Trinidad and Tobago 1998 HIV Vaccine Ethics Committee terms of reference and background document. www.healthsectorreform.gov.tt/whitepapers/hivethics.htm
[61] Trinidad and Tobago, 1998 CAB operating guidelines and membership list.

HIV vaccine research and development is happening now in approximately 25 countries. Broad public involvement is essential to support this effort as a human rights obligation. Broad involvement is also needed to ensure adequate debate about the relative balance of all human rights inherent in biomedical research. Public involvement can ultimately maximize what communities understand, and what each potential research participant understands, about:

- HIV vaccine research goals, potential benefits and potential harms of the research,
- the potential effects of decisions not to proceed or participate in research on overall public health and individual health in the community
- Needs for access outside of research studies to health services such as behavioural HIV risk-reduction counseling, provision of female and male condoms and clean drug injection equipment, drug overdose prevention counseling, drug treatment, methadone maintenance, drug detoxification interventions, primary health care, perinatal care, perinatal treatment with nevirapine and other antiviral drugs, other antiviral treatment in the case of HIV infection, suicide prevention counseling, case management, direct financial assistance, housing and other referrals, legal counseling, and crisis counseling.

6. Ensure HIV vaccine development

The human rights obligation to research and develop new technologies such as HIV vaccines has been outlined in chapter 2 of this paper, and is reflected in the June 2001 UN General Assembly Declaration of Commitment on HIV/AIDS, in which 189 countries committed to:

> "Encourage increased investment in HIV/AIDS-related research, nationally, regionally and internationally, in particular for the development of sustainable and affordable prevention technologies, such as vaccines and microbicides, and encourage the proactive preparation of financial and logistic plans to facilitate rapid access to vaccines when they become available." [62]

The for-profit private sector is an essential partner in HIV vaccine development

As described in chapter 4 of this paper, overall investment in HIV research and development can be increased. Some of this increased investment can come from government funding and improved coordination of public-sector research efforts based in government and academic research centers. However, private industry investment, in combination with public sector commitment and funding, is central to ensure development of HIV vaccines and other technologies for improved health in the world's poorest countries. The private for-profit sector companies are indispensable particularly because they have the mission, structure, and potential resources to bring new products to market as quickly and efficiently as possible.

However, for HIV vaccine development, the private, for-profit sector is dissuaded by a combination of economic disincentives and opportunity costs, collectively (and dismally) called 'market failure'. Few pharmaceutical companies are willing to risk hundreds of millions of dollars of investment in HIV vaccine research. In fact, given low profit margins, high volume production requirements, and liability concerns related to vaccines, only a few large companies engage in any vaccine development and manufacturing. Hence, a laissez-faire approach to private sector research and development will not result in the development of HIV vaccines suitable and accessible for use in the developing world in a reasonable timeframe.[63]

Public-private partnerships and incentives are needed to ensure private sector involvement. These partnerships and incentives work to address several factors that motivate private sector investment in HIV vaccine development, including:

- **anticipated cost of research and development**, which is likely to cost, from lab bench to market, a sum of $250 million or more per product.[64]

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[62] UN General Assembly Special Session on HIV/AIDS. *Declaration of Commitment on HIV/AIDS*, June 2001, para 70. Paragraphs 23 and 89 also include commitments for HIV vaccine development and access.
[63] Ainsworth, M. et al. "Accelerating an AIDS vaccine for developing countries: Recommendations for the World Bank." World Bank AIDS Vaccine Task Force, 2000. www.iacn.org
[64] According to a November 2001 report from the Tufts Center for the Study of Drug Development, the average cost of private sector development of a new prescription drug is $802 million. The US consumer organization Public Citizen challenged this report, arguing that the true average cash expenditure on the prescription drugs chosen by the Tufts study was about $240 million, and that for all drug development, even including the cost of dead-end research and drug failures, the average cost is about $110 million per drug developed. The cost of HIV vaccine development can probably be disputed in the same way, but will doubtless be in a higher range because of the complexity of the product design, manufacture and evaluation.

- **anticipated cost of vaccine production**, which could be significant relative to anticipated revenue and profit, depending on global demand and price.
- **anticipated demand for an HIV vaccine**. The global reach of HIV ensures some demand, but demand by governments, health care providers and individuals might be reduced by a simple lack of awareness about the need for HIV vaccination, stigma of acknowledging risk, acceptability of a partially effective vaccine, acceptability of the cost or complexity of administering the vaccine, and trust about vaccine efficacy and long-term safety.
- **expectations about pricing.** The market price of what governments and individuals can and will pay for an HIV vaccine will probably be far below the public health value of an HIV vaccine in terms of lives saved, but must be higher than the development and production cost of the vaccine for the company to get a return on its investment.
- **opportunity costs** of researching and developing an HIV vaccine. As profit-driven entities, pharmaceutical and biotechnology companies do compare the expected long-term cost and revenue of all potential product development options, leading many to opt for work toward more potentially lucrative gene therapies and other immune-based therapies and diagnostics.

The total annual global investment by all companies in HIV vaccine development is probably less than $150 million. Incentives can and should be used to increase this investment.

Incentives for HIV vaccine development are often divided into 'push' incentives that significantly offset starting costs of research, development and production (also labeled in this paper as 'vaccine development incentives'), and 'pull' incentives that seek to increase the chance of adequately priced demand for vaccines once those vaccines are produced (labeled here as 'vaccine access incentives'). Many recommendations on both sets of incentives have been presented by industry,[65] and by the International AIDS Vaccine Initiative (IAVI),[66] [67] the AIDS Policy Research Center of the University of California San Francisco (UCSF),[68] and the AIDS Vaccine Advocacy Coalition (AVAC)[69].

It should be noted that most of the work so far in creating and advancing industry incentives has been in the European and North American legislatures and governments. This is a strategic choice: most of the major vaccine companies (Aventis-Pasteur, Chiron, GlaxoSmithKline, Merck, and Wyeth) base their operations in those countries and the wealth of those countries increases the potential impact of direct governmental subsidy, tax legislation, regulatory change, and changes in demand and pricing tolerance.

Development and access strategies

To catalyze greater investment in HIV vaccine development and access, government agencies and legislatures have a range of policy and program tools at their disposal. These are briefly

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[65] See November 2000 presentations by representatives of Aventis and SmithKline at First GAVI Partners' Meeting, in Noordwijk, the Netherlands, 20-21 November 2000 www.vaccinealliance.org/download/noordsummary.doc , and the January 2001 IFPMA testimony to European Commission. http://europa.eu.int/comm/trade/pdf/med_c01.pdf

[66] Widdus, R. *AIDS vaccines for the world: preparing now to assure access*. Report for the Durban International AIDS Conference, IAVI, July 2000. www.iavi.org

[67] Madrid, Y. *A new access paradigm: public sector actions to assure swift, global access to AIDS vaccines*. New York: IAVI, June 2001. www.iavi.org

[68] Collins, C and Morin, S. *The policy of AIDS vaccines: exploring legislative options for advancing AIDS vaccine research and delivery*. San Francisco: UCSF, April 2001. http://hivinsite.ucsf.edu

[69] AVAC e-mail calls to action on legislative incentives, 1999-2001.

categorized and described below, and then discussed more fully in the remainder of Chapter 6, and Chapter 7.

IVaccine development strategies include:

Vaccine Development Strategy 1: direct government funding of private sector vaccine development, including contracts with pharmaceutical and biotechnology companies and also funding for public-private partnerships such as IAVI.

Vaccine Development Strategy 2: government-directed tax credits for the private sector to support industry research and development efforts.

Vaccine Development Strategy 3: collaboration between the public and private sector, involving funding or sharing of other resources.

Vaccine Development Strategy 4: direct government sponsorship of research and development, including global public funding for basic and targeted research, funding for initial vaccine design and development, strong ethical and regulatory capacity to ensure rapid review and approval of clinical trials, and strong clinical trials infrastructure, including capacity for Phase IV field evaluation of HIV vaccines.

Vaccine access strategies include:

Vaccine Access Strategy 1: efforts to improve international intellectual property law to improve the international environment for vaccine invention, ownership and licensing, import, and manufacture, providing more consistent, clear and conducive pathways for rapid deployment of new HIV vaccines.

Vaccine Access Strategy 2: systems to ensure global demand and delivery of existing vaccines, such as funding the direct purchase and delivery of vaccines for 74 low and middle-income countries through the Global Alliance for Vaccines and Immunizations (GAVI).

Vaccine Access Strategy 3: national policies to improve private sector cost/return equations, including tax credits, differential pricing, and liability protection and compensation related to the manufacture and sale of HIV vaccines.

Vaccine Access Strategy 4: infrastructure to ensure that HIV vaccines can be delivered appropriately, including establishment of new vaccine delivery systems aimed at adolescents and young adults, and development of sound HIV prevention, treatment and care strategies as a context for HIV vaccine delivery.

In this arena, policy has often preceded action. Although many private sector incentive strategies have now been defined for HIV vaccines, their implementation is still at an initial and often fragmented stage. Much more can be done to achieve a strong, concerted global effort.

6.1 Increase direct government funding of private sector vaccine development

In 2002, about a dozen pharmaceutical and biotechnology companies are involved in HIV vaccine development. Only about half of these use their own funds, from other product revenue or private investors, toward their HIV vaccine programs. Only two - Merck and GlaxoSmithKline - conduct HIV vaccine development without some government funding. Many biotechnology firms, such

as Advanced Bioscience Labs, Progenics, and Therion, depend almost entirely on government funding for their programs. More of the combined vaccine research and development capacity of these companies could be applied to HIV vaccine development. Furthermore, the combined vaccine manufacturing capacity of these companies could be increased.

The United States government has acknowledged direct contracting as an important strategy, and is the now the world's most significant direct funder of private-sector vaccine development. The effort of the US NIH to partner with private sector HIV vaccine development efforts has accelerated during the past five years. In 2000, two NIH programs in particular - the HIV Vaccine Development Resource Program contracts (VDRPs) and HIV Vaccine Design and Development Teams (HVDDT) program – provided twelve contracts valued at more than $85 million to vaccine developers to advance promising vaccine candidates into testable products.[70]

IAVI is itself a mechanism to channel government funding for vaccine development involving industry. The United States, as well as the national governments of the United Kingdom, Netherlands, Canada, Denmark, Ireland, and Norway, now fund efforts in the private sector indirectly through IAVI, at a total amount of approximately $25 million per year, half of which is passed on through contracts to industry partners such as AlphaVax, Therion, and Virax.[71]

Government and IAVI funding of private companies offer important models for advancing public health priorities using the for-profit sector. Both the NIH and IAVI link their funding to pricing or intellectual property provisions to maximize the sharing of technological innovation and progress, and are able to do this while allowing company enough ownership of products and technologies to allow a prospect of reasonable return on its own investment.

To accelerate private sector involvement in HIV vaccine development, national research agencies, particularly in high-income countries with major research budgets such as the French ANRS, Japanese NIH, and the UK MRC, should create new direct contracting mechanisms with industry for HIV vaccine development, modeled after existing contracts of IAVI or the US NIH.

6.2 Enact research tax credits for private sector vaccine development

Compared to other research and development efforts, where the scientific prospects are clearer and the market more certain, an HIV vaccine effort can seem an undesirable investment within a large pharmaceutical company. Research tax credits are an incentive aimed at enhancing the attractiveness of HIV vaccine research as an investment option. Research tax credits are a familiar legislative option and policy tool. Research tax credits also have a track record of success, with at least one study showing that a 10% decrease in the cost of research and development leads to more than a 10% increase in private sector research and development in the long run.[72] [73]

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[70] NIAID Vaccine web site at www.niaid.nih.gov/vaccine and summarized in the May 2001 AVAC report *Six Years and Counting* at www.avac.org. NIH contracts have been awarded to major vaccine companies such as Wyeth and Chiron.

[71] IAVI web site. www.iavi.org

[72] Bloom, N, Griffith, R, van Reenan, J *Do R&D tax credits work? Evidence from an international panel of countries 1979 - 1994* London: Institute for Fiscal Studies, 1998, IFS Working Paper Number W99/08.

[73] Warda, J. Measuring the Value of R&D Tax Treatments in OECD Countries. *STI Review* 2002; 27: 184-206. A good overview of R&D tax credits in 24 OECD countries.

HIV vaccine research tax credits are an incentive primarily to companies that have substantial revenues and profit, and a potential or on-going interest and expertise in HIV vaccine development, namely Aventis-Pasteur, Chiron, GlaxoSmithKline, Merck, and Wyeth. HIV vaccine research tax credits also have the most leverage in countries where these five companies base most of their operations, primarily the US, Canada, and the countries of the European Union.

Proposed tax credits for HIV vaccine research and development are modeled on, and built on top of, general tax credits for research and development, such as the Canadian Scientific Research and Experimental Development (SR&ED) tax incentive or the US 1981 Research and Experimentation (R&E) Tax Credit and tax credits within the 1983 Orphan Drug Act.[74] The strategy of modifying or supplementing these general R&D tax credits with additional tax credits specific to HIV and other diseases was recognized in December 2001 by the Commission on Macroeconomics and Health:

> "To support private sector incentives for late-stage drug development, existing orphan drug legislation in the high-income countries should be modified to cover diseases of the poor such as the tropical vector-borne diseases." Recommendation 6, CMH Action Agenda

The longest-running effort to introduce HIV vaccine tax credit legislation has been in the United States, where legislation was introduced successively in 1999, 2000 and 2001[75], proposing a 30% tax credit on all research and development of vaccines for malaria, TB, HIV and other diseases that kill more than one million people annually, above and beyond the existing R&E Tax Credit. This legislation also proposed that smaller biotechnology firms could opt to pass through a 20-25% tax credit to equity investors who provide new financing for this research and development. This legislation is likely to be introduced again in 2002.

In the UK last year, the Chancellor of the Exchequer announced consultations on the design of a new vaccines tax credit, with legislation to be contained in the Finance Bill 2002, whereby companies carrying out research on vaccines and drugs to prevent and treat malaria, TB and strains of HIV most prevalent among the world's poor would be eligible for a further 50% relief on qualifying expenditure, on top of any existing R&D expenditure relief.[76] However, the UK Treasury then announced a general 50% tax credit for all research and development by UK industry, deflating momentum for a more specific tax credit.

So far, these tax incentives have not successfully passed, due largely to an anemic community lobbying effort, a strong pharmaceutical lobby which is resistant to tax legislation shifting research priorities to only marginally profitable ventures such as HIV vaccines, and a tendency for these small specific tax incentives to get lost in power struggles over larger tax and spend issues.

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[74] Country-specific analyses of these general tax credits can be found for Canada in a 1996 evaluation at www.fin.gc.ca/resdev/fedsys_e.html and for the US R&E Tax Credit in a 1999 Congressional Research Service memorandum at www.house.gov/berry/prescriptiondrugs/resources/crs_pharm_tax_memo.pdf

[75] The three years of legislative proposals were: the *Lifesaving Vaccine Technology Act* introduced in March 1999, sponsored by Senator John Kerry (S.1718) and Representative Nancy Pelosi (HR 1274); the *Vaccines for the New Millennium Act* of 2000 sponsored by Senator John Kerry (S.2132) and Representative Nancy Pelosi (HR 3812); and the *Vaccines for the New Millennium Act* of 2001 sponsored by Representative Nancy Pelosi and Jennifer Dunn (HR 5219), text of which can be found at www.avac.org See also summary of 107th Congress initiatives in 2001 by Chris Collins on that site.

[76] See announcement at www.inlandrevenue.gov.uk/budget2001/revbn16.htm

However, research tax incentives remain a potentially effective policy tool for increasing industry investment, and thus should remain on the global advocacy agenda. Legislatures in the high-income countries where major vaccine companies are based, particularly France, Germany, the UK, and the US, but also countries such as Australia, Belgium, Canada, and Switzerland, should enact tax incentives to facilitate industry research and development for HIV vaccines.

6.3 Promote collaborations between the public and private sector

Public-private partnerships are an attractive avenue for encouraging otherwise neglected health research, and should be expanded and replicated in the field of HIV vaccine development. Partnerships have the potential to combine government funding and public health priorities with private sector efficiency. Well-constructed public-private partnerships can have a flexible, innovative focus on product development that also addresses a global health need.

The primary challenge to establishing and managing these collaborations is the different missions, operating culture and strategies of government and industry. Companies are reluctant to work with government research agencies if too much control is lost over timelines, technical strategies, intellectual property, and manufacturing facilities.[77]

Despite these challenges, both the US NIH and IAVI have created and demonstrated successful models for public-private partnerships in HIV vaccine development.

IAVI offers a model of product-specific partnerships, linking private sector vaccine developers with academic research facilities and clinical trial sites, aimed at rapidly developing HIV vaccines for clinical evaluation in both high-income and low-income countries. IAVI has now established five vaccine development partnerships:[78]

- a Kenya/Oxford partnership, linking the UK Medical Research Council and the University of Nairobi with vaccine manufacturing firms Cobra Pharmaceuticals (UK) and IDT (Germany).
- a South Africa/AlphaVax partnership, linking South Africa's University of Cape Town, National Institute of Virology and Medical Research Council with the US-based biotechnology company AlphaVax.
- a South Africa/Targeted Genetics partnership, linking the US Children's Research Institute and several clinical trial sites in South Africa and East Africa with US-based biotechnology company Targeted Genetics Corporation.
- a Uganda/IHV partnership, linking the Ugandan Virus Research Center, the Institute of Human Virology at the University of Maryland, and the University of Oxford, with the Swiss biotechnology company Berna Biotech.
- an India/Therion partnership, linking India's Ministry of Health and Family Welfare and the Indian Council for Medical Research with the US biotechnology company Therion.

In each of these IAVI-sponsored partnerships, intellectual property and technology transfer agreements have been negotiated with all partners such that if a vaccine is determined to be effective and licensable and the patent-owning partners decide not to license and produce that vaccine for use in particular countries or markets, the license for the vaccine can be made available to other manufacturers for those countries and markets, subject to a chance of first and last approval of this proposed arrangement by the original patent owners.

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[77] Reich, MR. Public-Private Partnerships for Public Health. Nature Medicine, vol. 6, no. 6, June 2000.
[78] E-mail announcements by IAVI, archived at www.iavi.org

The US NIH has also increased its emphasis and efforts for public-private partnerships to develop HIV vaccines. These include NIH / NIAID contracts with the companies of Chiron and Wyeth, as well as NIH Vaccine Research Center (VRC) contracts with companies Vical and GenVec. In an NIH - Merck collaboration announced in December 2001, the US government agreed to provide Merck with the use of its large international clinical trial network, the HVTN, and Merck agreed to share certain proprietary scientific tools and methodologies that could be adopted for use in the evaluation of other, competing vaccines. More intensive partnerships involving direct government funding and negotiated agreements on development timelines, use of manufacturing facilities, and intellectual property rights also exist between the US NIH and companies including Wyeth and Chiron.[79]

The types of public-private partnerships described above can and should be replicated. National research agencies and nationally-funded research institutions and universities in every country, particularly those where HIV vaccines are produced and/or tested, should seek to engage in public-private partnerships such as those modeled by IAVI

6.4 Increase direct government sponsorship of research and development

Public funding for basic research, initial vaccine design and development, and clinical trials infrastructure provides a useful balance to private sector efforts, and can act as an incentive for the private sector in producing inventions and innovations that industry can use. Unlike industry, which is generally focused on time-limited, cost-limited outcomes related to profit, government research agencies can afford to be responsive to public health interest and to less focused goals related to the advancement of scientific knowledge.

Government research agencies have demonstrated capacity to develop vaccines. One example of publicly-funded vaccine development is the work within the US NIH, led by researchers John Robbins and Rachel Schneerson, to successfully develop conjugate vaccines against *Hemophilus influenzae* type b (Hib), a leading cause of infant meningitis, and *Staphylococcus aureus*, a major cause of infection and death among hospital patients.[80] In the case of the Hib vaccine, it was government and academic researchers who first conceived of, designed, and tested this vaccine in the 1970's. This provided incentive for subsequent work by industry to produce and improve this vaccine, including combining the Hib vaccine into combinations with vaccines against diphtheria, tetanus, pertussis and hepatitis B. All four vaccine manufacturing giants - Aventis-Pasteur, GlaxoSmithKline, Merck, and Wyeth - subsequently entered into the business of manufacturing and selling Hib vaccines.[81]

National government investment in global research capacity and clinical trials infrastructure also plays an important role in facilitating vaccine development by industry. This is certainly the case in high-income countries such as the United States, where the US NIH continues to fund basic and targeted HIV vaccine research at more than 135 academic centers in the US and around the world, and funds an international HIV Vaccine Trials Network (HVTN) of more than two dozen clinical sites worldwide. It is also the case in middle-income countries, such as Brazil, South Africa and Thailand, and low-income countries such as Kenya and Uganda. For example, IAVI's current partners in Africa - the Uganda Virus Research Center, University of Cape Town, and University of Nairobi - have built their research capacity over time with resources from their own

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[79] NIH press release, 20 December 2001. www.nih.gov/news/pr/dec2001/niaid-20.htm

[80] More information can be found on the US NIH web site at www.nichd.nih.gov/new/releases/cviawar2.cfm and www.nih.gov/news/pr/feb2002/nichd-13.htm

[81] These companies in turn sell Hib vaccine for a profit in high-income markets and work with WHO and GAVI for low-cost sales and, in some cases, donations of Hib vaccine for use in low-income countries.

governments and from Europe and North America. Similarly in Thailand, the clinical trial capacity of the Bangkok Municipal Authority and Mahidol University, conducting a Phase III trial in 1999-2002 of an experimental VaxGen HIV vaccine, has been supported and developed for more than ten years by the Thai government in collaboration with WHO, UNAIDS and US and European government research agencies.

Governments can do more to support research and development capacity that eases the burden and cost of industry vaccine development efforts. In Africa, Kenya, South Africa, Uganda have all made some national government investment in clinical trial infrastructure for HIV vaccine development, but these efforts could be expanded. In Europe, the European Union is now considering the creation of a European Clinical Trials Platform with the stated intention of collaborating with industry to develop at least one HIV vaccine, but this effort needs encouragement.

National research agencies in every country should evaluate the opportunity to build their national biomedical research capacity, through funding of local research institutions and clinical trial infrastructure, in the context of global efforts for an HIV vaccine.

7. Ensure HIV vaccine access

Ensuring future access to HIV vaccines is a human rights issue

A fundamental human obligation to "share in scientific advancement and its benefits" has been stated in the 1946 Universal Declaration of Human Rights (UDHR) and amplified in several international rights documents since, such as the 1975 Charter of Economic Rights and Duties of States:

> "All States should facilitate the access of developing countries to the achievements of modern science and technology, the transfer of technology, and the creation of indigenous technology for the benefit of the developing countries in forms and in accordance with procedures which are suited to their economies and needs."[82]

Ensuring future access to potential HIV vaccines and its underlying technologies is therefore a matter of international treaty and joint national declaration, and a matter of potential national commitment and law. Ensuring future access to potential HIV vaccines is also a matter of justice and global benefit. Widely accessible HIV vaccines could have the highest comparative benefits in countries and communities with the least resources and the highest HIV infection rates. As with low-cost HIV treatments, diagnostics, and potentially effective vaginal microbicides, it would be unethical not to invest in mechanisms to ensure global access to potential HIV vaccines.

Future access to HIV vaccines is tied to current access to vaccines and public health

Legal and policy work on HIV vaccine access necessarily embraces promotion of existing vaccines and other HIV prevention and treatment technologies. Future access to HIV vaccines will depend heavily on current systems to manufacture, deliver, and provide access to other vaccines. Future access to HIV vaccines is also tied to the success of other efforts for HIV awareness, prevention, and care, and global public health.

Current access to vaccines continues to be a global challenge. Although vaccination programs continue to successfully reach into war-torn and remote communities to eliminate diseases such as polio, international health agencies still struggle to support high rates of vaccination against most diseases throughout the world. Even in the case of the extremely safe triple vaccine for measles, mumps, and rubella (MMR), introduced more than 25 years ago, although 500 million doses have now been administered around the world, hundreds of millions of people remain unprotected against these three diseases.

Access to HIV prevention and treatment interventions will also continue to be a challenge. Access to antiretroviral therapy for prevention of mother-to-child transmission, access to sterilized injection equipment, access to AIDS diagnostics and treatments, and access to health care and STD treatment remain elusive. This is relevant to the future accessibility and potential impact of HIV vaccines. Many individuals and communities will only use and benefit from HIV vaccines when they have some access to and trust of health officials who would administer those vaccines. As with all vaccines, HIV vaccines will best prevent disease in combination with public access to health information and health care.

[82] UN General Assembly, Charter of Economic Rights and Duties of States, 1975. Chapter II, Article 13.

The successes and experiences of AIDS treatment advocacy and HIV vaccine advocacy are linked. HIV treatment advocates continue to create new models for policy work on issues such as public involvement in biomedical research, access to experimental products, and national and international regulatory review and licensure of new products. AIDS treatment advocates are now demonstrating success in using law to compel international and national use and expansion of mechanisms for delivery, demand, and access to essential medicines and health technologies. Current policy work, including legal analysis and advocacy, to make AIDS drugs and other treatments accessible to the world's poorest countries, while allowing companies to recoup their costs and satisfy their shareholders, will clearly pave the way for future pricing and distribution of vaccines and microbicides.

Four categories of HIV vaccine access strategies

As defined in many publications during the past two years[83] [84] [85], HIV vaccine access strategies can be described in four broad categories:

Vaccine Access Strategy 1:
Improve the international environment for vaccine invention, ownership and licensing, manufacture, export and import, and deployment. Globally consistent, clear and conducive pathways for rapid deployment of new HIV vaccines can be supported through:

- clarification of international intellectual property laws and arrangements related to HIV vaccine technology development and technology transfer. This includes examination of international WTO standards, analysis of bilateral and multilateral agreements developed in regional blocs such as the EU, and analysis and promotion of more specific product-by-product agreements to facilitate future access to HIV vaccines, vaccine-related technologies, and on-going research data, such as agreements created by IAVI in the context of its public-private partnerships.
- clarification of trade law and reduction of trade barriers related to vaccines, including reduction of national taxes, tariffs, and storage fees for vaccines that exist in many countries, and
- improvement of national and regional capacity for regulatory review of new vaccines.

Vaccine Access Strategy 2:
Ensure global demand and delivery of existing vaccines. This includes:

- funding the direct purchase and delivery of vaccines for 74 low and middle-income countries through the Global Alliance for Vaccines and Immunizations (GAVI),
- working with other middle-income and high-income countries to ensure high national demand and purchase of future HIV vaccines, and
- broad NGO-led community education to ensure sustained retail demand for HIV vaccines where such private market demand is possible.

Vaccine Access Strategy 3:
Improve private sector balance of cost and return, including:

- national sales-based tax credits for vaccines, especially in high-income countries,

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[83] Widdus, R. *AIDS vaccines for the world: preparing now to assure access*. Report for the Durban International AIDS Conference, IAVI, July 2000. www.iavi.org
[84] Madrid, Y. *A new access paradigm: public sector actions to assure swift, global access to AIDS vaccines*. New York: IAVI, June 2001. www.iavi.org
[85] Collins, C and Morin, S. *The policy of AIDS vaccines: exploring legislative options for advancing AIDS vaccine research and delivery*. San Francisco: UCSF, April 2001. http://hivinsite.ucsf.edu

- international commitment to global differential pricing for vaccines and essential medicines to maximize global access while preserving private-sector incentives, and
- liability protection and compensation related to the manufacture and sale of HIV vaccines.

Vaccine Access Strategy 4:
Ensure that HIV vaccines can be delivered appropriately, including establishment of new vaccine delivery systems aimed at adolescents and young adults, and development of sound HIV prevention, treatment and care strategies as a context for HIV vaccine delivery.

7.1 Improve the international environment for HIV vaccine access

The environment for vaccine invention, ownership and licensing, manufacture, export and import, and deployment can be improved through

- clarification of international intellectual property laws and arrangements related to HIV vaccine technology development and technology transfer. This includes examination of international WTO standards, analysis of bilateral and multilateral agreements developed in regional blocs such as the EU, and analysis and promotion of more specific product-by-product agreements to facilitate future access to HIV vaccines, vaccine-related technologies, and on-going research data, such as agreements created by IAVI in the context of its public-private partnerships.
- clarification of trade law and reduction of trade barriers related to vaccines, including reduction of national taxes, tariffs, and storage fees for vaccines that exist in many countries, and
- improvement of national and regional capacity for regulatory review of new vaccines.

Intellectual property and HIV vaccines

Patents and intellectual property laws, which allow inventors to own and profit from their inventions, are a powerful incentive for development of new technology, public dissemination of innovation, technology transfer, and investment. Laws regarding patents and intellectual property generally try to facilitate both ownership of inventions for profit and public dissemination of those inventions so that innovation is shared and applied. Legal frameworks for intellectual property are generally successful in promoting eventual public access to innovation; where intellectual property is not clearly protected, new technology and innovation risk being hidden as trade secrets.

This principle is stated in the World Trade Organization *Agreement on Trade-Related Aspects of Intellectual Property Rights* (the "TRIPS Agreement"), Article 7:

> "The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations."

and further reinforced by the UN General Assembly in July 2000, where the Member States of the United Nations committed themselves to:

> "…acknowledge the contribution of intellectual property rights to promote further research, development, and distribution of drugs, and the fact that these intellectual property rights

should contribute to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare."[86]

As potential suppliers of life-saving products, companies that develop, or hold the rights to, experimental HIV vaccines that show efficacy in a Phase III trial will have to address more than just the challenges of immediate scale-up of manufacturing facilities and delivery systems. Potential HIV vaccine producers face inconsistent licensing processes and patent protections from country to country, shifting rules about importing and sale of vaccines, inconsistent national guidelines for vaccine deployment, and uncertain patent and collaboration disputes with other companies if more than one vaccine technology is involved. Clear, consistent global frameworks for licensing, intellectual property law, and trade law related to vaccines are needed for rapid HIV vaccine deployment.[87]

Current international standards for intellectual property protection are set out through the joint agreements of the Member States of the World Trade Organization (WTO).[88] [89] These standards remain general because of their wide-ranging scope and because country concerns about national sovereignty block specificity. For example, proposals for international licensing standards of new biotechnology products cover not only vaccines, but other pharmaceutical products and products in the agriculture, chemical and food industries - fierce battle grounds for economic and political interests.

The issue of national sovereignty is an important one in discussion of international standards for HIV vaccine deployment. Passage and enforcement of global standards for deployment of new biotechnology (such as agricultural or food products) have often been opposed by European countries and the United States on grounds of national economic interests. Global accords on biotechnology access have also been opposed by human rights and public health activists based on national public health priorities (such as arguments for invoking national sovereignty and national health crises in Southern African to challenge restricted intellectual property rights over HIV/AIDS drugs in those countries) or public health fears (as in the case of genetically-modified crops). This presents a formidable challenge in developing consistent international rules for HIV vaccine regulatory review, licensing, importation, and sale.

'Globalization' of vaccine regulatory approval, licensure, manufacturing and supply is necessary, and is perhaps inevitable, given the world's public health need for widely produced, inexpensive vaccines and other health technologies. In countries such as Brazil, China, and India, local pharmaceutical industries are gaining capacity for the invention and manufacture of new vaccine technologies. As clinical research expands in all countries, national government regulatory

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[86] UN General Assembly, Resolution S-24/2, *Further Initiatives for Social Development.* July 2000: Part III, Articles 12, 101.

[87] Intellectual property related to HIV vaccines is complex. A September 2001 AVAC analysis found that just the dozen leading HIV vaccine products involved more than 1000 patents covering technologies, compounds, methods, and processes, owned by several hundred government, industry, and academic institutions.

[88] These agreements are negotiated on a regular basis. At the fourth WTO Ministerial Conference in Doha, Qatar, on 9-14 November 2001, trade ministers representing more than 140 countries agreed on the next round of negotiations for a global trade agreement, to be concluded by 2005.

[89] One such agreement drawing considerable attention in HIV and public health circles has been the Agreement on Trade-Related Aspects of Intellectual Property Rights (the "TRIPS Agreement"). For more analysis of the TRIPS agreement with regard to health and human rights, please see Elliot, R. *TRIPS and Rights*. Toronto, Canadian HIV/AIDS Legal Network, November 2001, at www.aidslaw.ca/Maincontent/issues/cts/TRIPS-brief.htm

bodies are developing new procedures for review and approval of products. Whether this capacity is gained quickly or slowly, by formal or informal technology transfer, and by coordinated or fragmented approach, will in turn depend on the establishment of globally-acceptable guidelines and application of intellectual property protection.[90] The world's need for inexpensive, globally produced HIV vaccines also demands that high-income countries must accept global trade accords and lower barriers to importation of vaccines produced elsewhere, even at threat to domestic industry and political pride.[91]

As noted above, advocacy organizations such as IAVI and AVAC set out important guideline documents in 2000-2001 to suggest improvements in the international legal and regulatory environment related to vaccine deployment and access. In addition to promoting and defending proper, fair application of existing international WTO standards on intellectual property protections, two general and incremental advocacy pathways are suggested;

- a product-by-product approach to establishing intellectual property agreements that ensure eventual global access to specific HIV vaccines, and
- a country-by-country approach that harmonizes and supports improvements to trade law, regulatory review, and intellectual property rights protection on a multilateral basis (such as within the EU) or on a bilateral basis (such as between India and the United States).[92]

As advocacy clears these pathways to markets, vaccine companies are likely to take advantage of the opportunities, research reliable estimates of demand in those markets, develop adequate private sector and public sector production capacity, and develop explicit delivery plans and systems.[93]

7.2 Ensure global demand and delivery of existing vaccines.

Global need for an HIV vaccine is already high and increasing with every passing year. However, HIV vaccine delivery and access depends largely on demand, which is the translation of need into decisions and ability by governments, public health institutions, and individuals to pay for and use HIV vaccines.

Global demand for HIV vaccines should be assured in four broad categories: multilateral agencies such as GAVI, governments of middle-income countries, governments of high-income countries,

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[90] Although industry in countries such as Brazil and India already have capacity to manufacture most pediatric vaccines for national use and for export, they still generally do not have the capacity to develop or produce the newest and most promising types of HIV vaccines. Each of these vaccines has dozens of associated product and process patents with multiple owners. It is to the ultimate advantage of those intellectual property owners to establish consistent international legal frameworks for the ownership and use of these technologies.

[91] This recommendation supporting global trade accords, such as WTO agreements, and lower barriers to vaccine importation, should not be confused as contradictory to later recommendations for tiered pricing. A country such as the United States could set a high domestic price for national and private retail purchase of HIV vaccines while also opening its markets to all potential global suppliers.

[92] As one example of potential action, in March 2002, US legislation was drafted to provide the US Food and Drug Administration (FDA) with $2 million to begin new technical assistance and partnerships with regulatory agencies in resource-limited countries to build regulatory capacity related to research on life-saving biomedical technologies.

[93] Companies do already aggressively prepare for markets even in a fragmented environment. For example, VaxGen has already developed production plans and has contracted with South Korean vaccine production facilities to produce gp120 vaccine in case efficacy is demonstrated in Phase III trials in late 2002.

and a private retail market. National legislatures in high-income countries should strongly endorse several measures to ensure global demand from all four of these categories.

Multilateral agency demand

The largest volume of demand (i.e. tens of millions of doses) will come from GAVI and its partners of WHO, UNICEF, UNFPA, and other large multilateral aid agencies. This demand will probably be at the lowest possible price and at practically no profit for industry suppliers. However, given the extent of the HIV epidemic and the need for HIV vaccines in the poorest countries of the world, global delivery and access will rely primarily on demand and purchase by these international institutions. This is certainly the case for drugs aimed at diseases prevalent in the world's poorest countries. As stated at the April 2001 WHO-WTO Workshop on Differential Pricing and Financing of Essential Drugs,

> "Getting drugs, whether patented or generic, to the people who need them will require a major financing effort, both to buy the drugs and to reinforce health care supply systems, and for these countries most of the additional financing will have to come from the international community."[94]

WHO and UNICEF have a long history of direct purchase of vaccines, arranging multi-year, large volume (i.e. 3 million doses per month) purchases of traditional pediatric vaccines through the Global Alliance for Vaccines and Immunizations (GAVI) and its predecessor Children's Vaccine Initiative (CVI). GAVI is now funded for direct purchase and delivery of vaccines for 74 low and middle-income countries, and for example, annually purchases more than 20 million doses of two combination vaccines - diphtheria, tetanus and pertussis plus hepatitis B (DTPHepB) and a five-antigen (pentavalent) combination that also includes *Haemophilus influenzae* Type B (DTPHepBHib) from GlaxoSmithKline.[95]

The success of this type of GAVI effort will have a major bearing on the degree to which major vaccine companies invest in HIV vaccines for the world. While companies are unlikely to make any profit from large-scale GAVI purchases of HIV vaccines, the promise of even a minimal cost-return on the production of millions of doses will allow companies to plan to provide this amount and thus produce vaccines for the world. National legislatures in high-income countries should strongly endorse direct funding for GAVI to ensure its success.

Middle-income country demand

Additional bulk demand for HIV vaccines (i.e. millions of doses) will come from governments of middle-income countries, at very low prices but still slightly higher than those negotiated with GAVI and other agencies. Government demand is determined by public health recommendations by the ministries of health, such as by the Brazilian National Advisory Committee on Immunizations or the Medical Council of India. These recommendation will be affected by the opinion of public health professionals about the scientific data on HIV vaccine efficacy, their views of the importance of addressing AIDS in their countries, and the likely impact of HIV vaccination strategies. Recommendations will also be influenced by public opinion and the potential cost of adding an HIV vaccine into existing vaccine delivery systems.

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[94] Proceedings of the WHO-WTO meeting at Hosbjor. www.who.int/medicines/library/edm_general/who-wto-hosbjor/who-wto-hosbjor.html

[95] GAVI December 2001 newsletter. www.vaccinealliance.org/newsletter/dec2001/report.html

One example from 2001 for the need to ensure vaccine demand by middle and low-income governments is the case study of the vaccine deployment against Hib (*haemophilus influenzae* type B). Hib causes an estimated 3 million cases of serious disease every year, including perhaps 20% of all cases of severe childhood pneumonia, killing an estimated 400,000-500,000 children each year. Safe effective vaccines have existed for more than a decade,[96] and have been recommended by WHO for routine infant vaccination since mid-1990s[97]. The current cost of a three-dose schedule is about $6, and the cost of global delivery of that vaccine to children in poor countries is an estimated cost of $21-22 per year of healthy life gained.[98] Beginning in 1999, the Global Alliance for Vaccines and Immunizations (GAVI) began offering direct funding and supply of vaccine for national Hib vaccination programs around the world, but as of the end of last year, only Kenya, Malawi and Rwanda have requested this support from GAVI.[99] This lack of demand is attributed mostly to the lack of awareness or acknowledgement by national public health authorities about the extent of Hib in their countries, but also to hesitance by those authorities to adding the cost of adding one more vaccine into heavily burdened distribution systems.

The lesson from this is that future national demand for HIV vaccines should be supported by ample information provided by the WHO-UNAIDS HIV Vaccine Initiative, and by multilateral and bilateral funding subsidies from agencies such as the World Bank, DFID and USAID. National legislatures in high-income countries should endorse and fund additional effort by WHO and UNAIDS in working with the governments of major middle-income countries such as Brazil, China, India, Indonesia, Mexico, Nigeria, Russia, South African and Taiwan, to define the probable need for HIV vaccines, prepare for evidence-based HIV vaccination guidelines, and initiate training programs for health professionals about potential HIV vaccines.

High-income country demand

Bulk purchase (again, millions of doses) from governments of high-income countries is a third source of demand, and perhaps the most important in terms of industry hopes for a profitable market for HIV vaccines. The price and volume negotiated by these governments will be an important factor in company revenues, and thus in industry capacity to supply the world. These governments' demand for HIV vaccines will be largely influenced by:

- public health recommendations by committees advising the health ministries, such as the National Advisory Committee on Immunization (NACI) in Canada, the Technical Committee of Vaccination (CTV) in France, the Joint Committee on Vaccines and Immunisation in the UK, and the Advisory Committee on Immunization Practices (ACIP) in the US,
- opinions of public health professionals about the scientific data on HIV vaccine efficacy,
- the perceived impact of vaccination strategies on HIV infection and disease,
- safety and moral concerns related to infant and adolescent vaccination against AIDS,
- officials' views of the importance of addressing AIDS in their countries,
- general public opinion and politics related to AIDS,
- nationalism related to the vaccine design, manufacture, research data, and approval,

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[96] Conjugate Hib vaccines were first licensed and introduced in the US in 1987 and in other countries soon after.

[97] WHO position paper on Haemophilus influenzae type B conjugate vaccines, www.who.int/vaccines and WHO updated fact sheet. www.who.int/vaccines-documents/DoxGen/H4-Inno.htm

[98] Miller M. and McCann L. Policy analysis of the use of hepatitis B, Haemophilus influenzae type B, streptococcus pneumoniae conjugate and Rotavirus vaccines in national immunization schedules. Health Economics, January 2000.

[99] GAVI website. www.vaccinealliance.org

- political expediency in relation to all of the above.

As learned in the case of hepatitis B vaccine, recommendations by governments and private insurers for universal coverage of all infants and adolescents, rather than vaccination only of targeted high risk individuals, can be controversial even when the scientific data are clear. National governments are also under great pressure to contract with local industry and to negotiate low prices from manufacturers. A striking example comes from the United States in its October 2001 negotiations with industry for supply of smallpox vaccine and ciprofloxacin. Even in the case of national emergency, the US government negotiated strong price discounts. For smallpox vaccine, the final price was $2 per dose for 250 million doses, even though 40 million doses had been purchased from the same company at $8.50 per dose a year earlier.[100] For ciprofloxacin, the US drove Bayer from a pre-11 September price of $1.89 per tablet to a price of $.85 per tablet, even using threat of a patent withdrawal to achieve this. Interestingly, the US government chose Bayer even when an Indian company, Ranbaxy Pharmaceuticals, was able to offer an even more competitive offer.[101]

The lesson from this experience is that national legislatures, such as the US Congress, can do more to support strong messages on global health and high-volume, high-priced demand in high-income countries, tying this as an incentive to industry to supply developing countries with affordable drugs and vaccines.

Individual retail demand

The final source of demand for HIV vaccines, and the source of highest marginal profit for industry, will be the private, retail market wherever national licenses can be obtained and where individuals and local health care providers are able and willing to pay. The willingness and ability of individuals, providers and health care systems to pay will be influenced by the same politics related to vaccine safety and infant and adolescent vaccination that has continued to plague vaccination campaigns throughout Western Europe and North America.[102] Individual retail demand for HIV vaccines might also be different because of the specific populations at greatest risk for HIV and the political history of HIV in many countries. Unlike diseases such as Lyme disease, hepatitis B, or hepatitis A, risk for HIV infection remains stigmatized and connected to issues of morality. Political mistrust of public health authorities and institutions might seriously dampen demand for an HIV vaccine. And uninformed AIDS advocates and media have the potential to generate controversy and contradictory messages about new HIV vaccines that would likely confuse the public health recommendations.

Even in the case of a widely publicized non-stigmatized disease such as Lyme disease, a lack of individual retail demand has been an important factor in vaccine production and access. In February 2002, GlaxoSmithKline announced that it was withdrawing its vaccine against Lyme disease from the market, citing insufficient demand despite the wide attention and awareness about the vaccine in high-income markets in the United States, and initial demand for the vaccine in 2000 by hundreds of thousands of people and $40 million in revenue.[103] A stronger public relations and education effort, particularly by NGOs, might have been able to extend a positive popular perception of this vaccine, resulting in stronger demand for this Lyme vaccine beyond merely eighteen months.

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[100] AP Wire, 26 October 2001, *Smallpox Vaccine Makers Watch Feds*
[101] Reuters, 17 October 2001, *Feds Nudging Bayer on Anthrax Drug Patent.*
[102] Immunization Action Coalition. www.immunize.org/genr.d/vaxsafe.htm
[103] Reuters news release, 26 February 2002. http://biz.yahoo.com/rf/020226/n26120004_1.html

7.3 Improve private sector balance of cost and return

Three major strategies - tax credits, differential pricing, and liability protection and compensation - are usually discussed as vaccine access incentives for private sector manufacture and supply of HIV vaccines once they are developed and licensed. Particularly in high-income countries where there is a private retail market for vaccines, legislatures should introduce and pass sales-based tax credits as part of overall HIV vaccine tax incentive efforts. Legislatures and politicians should also state their explicit national commitment for global differential pricing as a way to ensure HIV vaccine access to poor countries, and order inclusion of HIV vaccines into existing childhood vaccine liability compensation fund guidelines.

Tax credits for the sale of HIV vaccines

Tax credits on HIV vaccine sales have been consistently included in the recurring tax legislation efforts for vaccine research and development. These proposed tax credits have covered future sales of vaccines for malaria, tuberculosis, and HIV/AIDS or any infectious disease killing more than one million people annually, to accelerate the invention and production of these vaccines for distribution in low-income countries. The proposed tax credits would be 100%, providing an incentive of a dollar of tax credit for every dollar's worth of qualifying vaccine sold to a qualifying organization, representing up to $1 billion of additional funding for future vaccine purchases.

As with research tax credits, sales tax credits are an incentive primarily to companies that have substantial overall revenues and the intention of large-scale manufacture and sale of HIV vaccines, which are the five major vaccine companies of Aventis-Pasteur, Chiron, GlaxoSmithKline, Merck, and Wyeth. HIV vaccine sales tax credits will also have the most leverage in countries where these five companies base most of their operations, primarily the US, Canada, and the countries of the European Union.

Sales tax credits for HIV vaccines have been proposed so far only in the United States, and have not yet been adopted despite introduction in 1999, 2000, and 2001, and with explicit White House support in 2000 as a part of its March 2000 Millenium Vaccine Initiative.[104] Sales tax credit legislation is likely to be introduced again in the US in 2002 and deserves support in the US and elsewhere.

Differential pricing

Differential pricing, also referred to as 'tiered pricing', 'equity pricing', or 'preferential pricing', refers to the concept that prices of essential drugs and vaccines should in some way reflect global ability to pay as measured by level of income. The goal of differential pricing is to offer very low vaccine prices for poor countries to ensure access for their populations, while keeping vaccine prices high enough elsewhere for companies to have a return on their investment.

Two basic definitions are used for the division of the world's countries into 'tiers' or 'bands' for vaccine pricing. In 1994, UNICEF and WHO developed a four-tiered system to target vaccine assistance to countries according to total GNP, per-capita income level, and population size.[105]

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[104] US White House March 2000 press release. http://usinfo.state.gov/regional/af/usafr/t0030202.htm

[105] DeRoeck D and Levin A. Review of financing of immunization programs in developing and transitional countries. *Special Initiatives Report* 1998; No. 12. Partners for Health Reform. Bethesda, Maryland: ABT Associates Inc.

The World Bank has since proposed an alternate two-tier system to define eligibility for International Development Assistance (IDA). This latter two-tiered system is used more often in discussions about ensuring differential pricing.

Differential pricing for vaccines already exists. Prices for pediatric vaccines for low-income countries can be as low as only 1% to 5% of the prices for the same vaccines in high-income countries. GAVI and UNICEF succeed in getting these low prices from vaccine manufacturers through large volume (tens of millions of doses), bundled purchases of combination vaccines, and multi-year purchase guarantees.[106] Given that the same systems for negotiating and purchasing vaccines will be used for HIV vaccines, it is likely that the global pricing structure for HIV vaccines could be the same.

The challenge for differential pricing is to create advocacy and tolerance in high-income countries for higher vaccine prices, to support rigid market segmentation to prevent resale of low-priced vaccines from one country to another, and possibly to create mechanisms to make price differences less apparent, such as sale-donation combinations.[107] Organizing legislative and other public expressions of endorsement for differential pricing in high-income countries should be a primary advocacy strategy. In the United States for example, explicit commitments to differential pricing from politicians, health insurers, ADAP and Medicaid advocates, and fair pricing coalitions would go far as a positive signal for HIV vaccine development.

Liability

Tort liability is a clear disincentive for HIV vaccine development in the major markets of the North America and Western Europe. Legal battles are generally initiated under product liability and consumer protection laws. Examples of vaccine liability as a disincentive since 1990 include a 1992 decision by the UK Department of Health to stop using a SmithKline Beecham measles-mumps-rubella (MMR) vaccine after escalation of lawsuits; a January 2002 UK class action lawsuit initiated over possible side effects from similar MMR vaccines produced by Aventis Pasteur, GlaxoSmithKline, and Merck; and a February 2002 decision by GlaxoSmithKline to end production of Lyme disease vaccine amid sagging demand and hundreds of lawsuits from people alleging vaccine side effects. In the last case, the Lyme disease vaccine, given in three doses and provided to hundreds of thousands of people, had undergone additional safety review by the US Centers for Disease Control, which reported in January 2002 that a review of 905 reports of side effects showed no unusual or unexpected problems.

Vaccine liability has been addressed in these countries largely through legislated compensation funds, such as funds established through the 1979 UK Vaccine Damage Payments Act and the 1986 US National Childhood Vaccine Injury Act. These funds are paid for through an excise tax on vaccines, and provide a no-fault alternative to the tort system to compensate claims of adverse vaccine reactions, thus shielding vaccine companies from liability and litigation as an incentive to ensure supply. In 2002 in both the UK and the US, debates have already begun in Parliament and Congress over the vaccine compensation funds to revisit compensation amounts, threshold requirements for proof of harm, and other eligibility criteria.[108] Work should be undertaken to

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[106] Children's Vaccine Initiative. *CVI Forum: Special Vaccine Industry Issue*. 1996; Number 11.
[107] Vaccine sale-donation combinations are already used to support low-cost vaccine access by poor countries; one example is an Wyeth donation of 10 million doses of Hib conjugate vaccine to GAVI, announced in 2000. http://usinfo.state.gov/regional/af/usafr/t0030202.htm
[108] For the UK, see www.cabinet-office.gov.uk/regulation/act/proposals.htm . In the US, the debate is centered in the House Energy and Commerce Committee among Reps. Burton, Weldon, and Waxman.

include HIV vaccines into the list of currently covered vaccines in the existing compensation funds.

7.4 Ensure infrastructure for vaccine delivery

As companies become able and willing to manufacture and supply HIV vaccines for the world, a key factor in global access will be the capacity of national delivery systems to reach people at risk for HIV and AIDS.[109] To ensure delivery of HIV vaccines, all countries should develop experienced national health programs that can reach adolescents and young adults with public health vaccines (such as hepatitis A and B vaccines), STD screening and education, and credible HIV prevention, treatment, and care strategies.

Experience with other vaccines suggests a range of strategies and incentives for boosting delivery and access. These strategies include:

- Establishing systems to administer vaccines, STD education and screening, and credible HIV prevention, treatment, and care through existing institutions, including not only through public and private health care systems but also through schools, military, workplace, churches and missions, and/or NGOs. Establishment of these programs should include education and training of personnel, payment, and quality assurance monitoring to create vaccination programs with a surrounding context of health education and health care.
- Creating vaccination and public health education and screening requirements linked to school enrollment, military service, employment, food assistance or maternity and childcare assistance.
- Supporting vaccination and other public health campaigns with communications efforts and data collection to build popular and political commitment, such as implementation of national vaccination days or national campaigns with set targets for numbers and percentages of people vaccinated. In the case of HIV vaccines, broad communications efforts to build positive political perceptions will be essential. The case of Hepatitis B vaccine in France, where the French Ministry of Health suspended Hepatitis B vaccinations in French schools in 1999 because of the public misinformation about potential long-term side effects, provides a clear advance warning.

Specific delivery systems cannot be developed for HIV vaccines until the major parameters of those vaccines are known, such as their protective effect against infection and disease, their level of efficacy, the number of required doses, the duration of protection, the route of administration, cold-chain requirements, and cost. However, work by GAVI and its multilateral partners of WHO, UNICEF, UNFPA and the World Bank with national public health systems should help to create new national health programs reaching adolescents and young adults with sound HIV prevention, treatment and care strategies, into which an HIV vaccine strategy can be added later.

Awareness and support for potential HIV vaccine campaigns are also needed within national public health systems and at a broader political level. Given that Phase III efficacy data on one HIV vaccine is due at the end of 2002, national public health systems should be challenged to increase their efforts to inform public health officials and the public about the future.

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[109] Brugha, Lancet 2 February, 2002. In this February 2002 article in Lancet, researchers from the London School of Hygiene and Tropical Medicine suggest the success of GAVI's vaccine distribution in 52 countries correlated strongly to the strength of pre-existing capacity and health infrastructure in those countries.

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9. Web Sites

AIDS Vaccine Advocacy Coalition
Contains useful resources, including the HIV Vaccine Handbook and an annual advocacy report.
www.avac.org

Canadian HIV/AIDS Legal Network
Contains several publications related to HIV vaccine policy.
www.aidslaw.ca

Global Alliance for Vaccines and Immunizations
Contains updated information and articles about access and use of vaccines around the world.
www.vaccinealliance.org

HIV InSite
Contains useful references on HIV vaccines, including a 2001 monograph on access.
http://hivinsite.ucsf.edu

Immunization Action Coalition
An US-based advocacy site with materials supporting vaccination programs
www.immunize.org

International AIDS Economics Network
Information on the economic aspects of vaccine development
www.iaen.org

International AIDS Vaccine Initiative
A major resource on HIV vaccine development
www.iavi.org

International Council of AIDS Service Organizations
Contains a community primer on HIV vaccines
www.icaso.org

National AIDS Manual
A central source of HIV/AIDS information on the internet.
www.nam.org.uk

United States National Institutes of Health
Contains a wealth of background information about the science of HIV vaccine development
www.niaid.nih.gov/vaccine

UNAIDS
Contains documents including 2000 ethics guidelines and the 2000 Nairobi Declaration
www.unaids.org

World Health Organization
Contains useful information about vaccine development and deployment
www.who.int/vaccines

World Medical Association
Contains the revised version of the Declaration of Helsinki
www.wma.net