

Resolving Legal, Ethical, and Human Rights Challenges in HIV Vaccine Research

A Discussion Paper

November 2000



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**Resolving Legal, Ethical, and Human Rights Challenges
in HIV Vaccine Research
A Discussion Paper**

Prepared by David Patterson for
Putting Third First – Critical Legal Issues and HIV/AIDS
A satellite meeting organized by the Canadian HIV/AIDS Legal Network
and the AIDS Law Project, South Africa, and co-hosted by UNAIDS
Durban, South Africa, 7 July 2000

Acknowledgments

The comments of the following people on an early draft of this paper are gratefully acknowledged: José Esparza, Kitty Barrett Grant, Ashraf Grimwood, Dale Guenter, Ralf Jürgens, Kelly MacDonald, Craig McClure, David Thompson, Ann Strode, and Mary Ann Torres. Opinions expressed, however, are those of the author, who remains responsible for any errors or omissions.

Funding

Financial support for the satellite meeting at which this paper was presented was provided by: Canadian International Development Agency; Correctional Service Canada; Health Canada, HIV/AIDS Programs Policy & Coordination Division and the International Affairs Directorate; Joint United Nations Programme on HIV/AIDS, Liberty Life Foundation; National Institutes of Health, Office of AIDS Research; Open Society Initiative for Southern Africa, Swedish International Development Cooperation Agency; The United States Agency for International Development (USAID), through the POLICY Project, implemented by The Futures Group International in collaboration with Research Triangle Institute and The Centre for Development and Population Activities.

Une version abrégée de ce document est disponible en français.

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1. Foreword

This paper is a revised version of a paper prepared for *Putting Third First: Critical Legal Issues and HIV/AIDS*, an official satellite meeting of the XIII International AIDS Conference, Durban, South Africa, July 2000. The satellite meeting was held just prior to the Conference, on Friday, 7 July 2000, and was a joint project of the AIDS Law Project, South Africa and the Canadian HIV/AIDS Legal Network.

During the meeting a working group discussed the paper and the issues raised, and made further observations and recommendations. The report of the working group rapporteur, Ann Strode, is attached as Annex 4.

2. Purpose of This Paper, Key Issues, and Basic Assumptions

2.1 Purpose

At the end of 1999, UNAIDS and WHO estimated that over 33 million people were living with HIV infection. About 95 percent live in the developing world, with little access to essential AIDS medications and other necessary treatment and care. Over 16 million people have already died of AIDS-related illnesses. This includes about 14 million people in sub-Saharan Africa, which has close to 70 percent of the global total of HIV-positive people.¹

In the absence of a cure for AIDS, attention has turned to the possibility of developing a preventive vaccine for HIV infection. It is well known that vaccines have been used successfully to fight serious infectious diseases such as smallpox and poliomyelitis. These public health victories have raised hopes for an inexpensive and effective vaccine against HIV infection or AIDS. Yet many scientific, ethical, legal, and economic obstacles remain.² At the current rate of research, the development and production of an effective vaccine could take 15-20 years or longer. If tens of millions more HIV infections and deaths are to be avoided in the coming decades, vaccine research needs to be greatly expedited. Furthermore, it must be undertaken ethically, and the products of this research must benefit people in developing countries.

The purpose of this paper is to review legal, ethical, and human rights challenges in HIV vaccine research, and to identify actions that need to occur in order to overcome these challenges. The paper specifically addresses challenges arising in the context of **HIV preventive vaccine research in developing countries**. It does not aim to address clinical research in developing countries relating to treatments or therapeutic vaccines.³ Nor does it address legal and ethical issues relating to HIV vaccine research in industrialized countries, although similar issues arise in both contexts.⁴

¹ *AIDS epidemic update: December 1999* Geneva: UNAIDS/WHO, 1999, www.unaids.org

² For a succinct summary see *AIDS Vaccines in the Developing World*, Fact Sheet, Interagency Coalition on AIDS and Development, 1999, www.icad-cisd.com

³ See generally, *The ethics of clinical research in developing countries*, Nuffield Council on Bioethics, 1999, www.nuffieldfoundation.org

⁴ The Canadian HIV/AIDS Legal Network, in partnership with the Centre for Bioethics of the Clinical Research Institute of Montréal, will publish a paper in 2000 on the legal, ethical, and human rights issues raised by the development and eventual availability of a vaccine for HIV/AIDS. See also Kerns A. *Ethical Issues in HIV Vaccine Trials*. New York: St Martin's Press, 1997; Grady C. *The Search for an AIDS Vaccine*. Bloomington: Indiana University Press, 1995.

The terms “industrialized country” and “developing country” are used as shorthand in this paper. This crude distinction is admittedly inadequate for discussing the specific vulnerability of a population, community, or country to HIV/AIDS. Nonetheless, these terms are used to distinguish broadly those countries with greater wealth and experience in research from those countries in which research is proposed to take place, and which may have greater vulnerability to harm resulting from such research.

An overview of the key issues is given briefly below. The next section notes the main documents in which legal, ethical, and human rights principles relevant to HIV vaccine clinical research are set out, or from which they can be derived. These principles do not themselves provide ready answers to conflicts of interest or ethical dilemmas, but offer standards by which proposed solutions to such conflicts and dilemmas can be evaluated. Only international documents have been reviewed: regional and national statements, policies, and laws are important but space limitations do not permit their consideration here.

The key issues are then examined with respect to these legal, ethical, and human rights principles, followed by a more general discussion and draft recommendations for consideration at the satellite meeting. The paper concludes that while ethical codes are silent on the obligation to undertake research and development, international law provides strong legal obligations, particularly on industrialized states, which should be invoked to accelerate HIV vaccine development and distribution.

2.2 Key Issues

The major challenges to developing a safe, effective and accessible vaccine can be divided into three areas.

1. **The development of HIV vaccines suitable for developing countries.** In the absence of commercial incentives, the private sector is not investing sufficiently in the development of vaccines for the relevant HIV subtypes. There are few candidate vaccines in the development pipeline specifically designed for developing countries.⁵ More than ten distinct genetic subtypes of HIV have been described worldwide. The major subtype of HIV in industrialized countries is subtype B, whereas other subtypes predominate in developing countries. Originally, most research focused on a vaccine for subtype B because not much was known

⁵ Esparza J. and Bhamarapavati N. Accelerating the development and future availability of AIDS vaccines: Why, when, where, and how? *Lancet* 2000: 355; generally, 7 years and counting: how can we overcome obstacles to an AIDS vaccine? AIDS Vaccine Advocacy Coalition, 2000, www.avac.org

about genetic variability and because the only well-characterized virus strains available for vaccine development were subtype B North American isolates.⁶

2. **The rights and protection of subjects and communities during research.** Trial participants and their communities may face discrimination, or participation in a vaccine trial may have a negative impact on preventive behaviour. It will be crucial to ensure that participants understand they may receive a placebo, and that the vaccine may not be effective. The impact of trials on women and girls must be considered, and concerns about the participation of children must be addressed. Arrangements must be made for people who test HIV-positive either during volunteer screening or while the trial is taking place. Finally, competent local ethics review mechanisms must be established to review research protocols and to monitor the research as it takes place.
3. **Equity in research and access to the benefits of vaccine research.** There are major challenges in ensuring that a successful vaccine, once developed, is made available as quickly as possible to vulnerable communities. Recent research has suggested that it may be possible to design a polyvalent vaccine, which would be effective against a range of subtypes.⁷ In the worst case, such a vaccine might be developed in developing countries and only later made available in industrialized countries.⁸ Benefits should also accrue to communities participating in research, such as the strengthening of local technical expertise and research facilities.

2.3 Basic Assumptions

This paper is based on the following assumptions:

1. State-of-the-art treatments for HIV infection (including HAART) will not be widely available in developing countries in the foreseeable future.
2. With sufficient funding, leadership, and commitment, a vaccine could probably be developed that could provide at least some level of protection from the types of HIV found in developing countries.

⁶ Personal communication, J. Esparza, UNAIDS, 11 May 2000.

⁷ Jordan Report 2000, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, at 90, www.niaid.nih.gov

⁸ Esparza J., and Bhamarapavati N. Accelerating the development and future availability of AIDS vaccines: Why, when, where, and how? *Lancet* 2000; 355: 2061.

3. The traditional course of market-driven research and development will not result in the development and distribution of a suitable vaccine in the developing world in the near future.⁹
4. Early vaccines may be less than 100 percent effective, and safer sex and other prevention measures must continue alongside HIV vaccine development and implementation programs in order to limit the spread of both HIV and other infectious diseases.

Because we may not have an HIV vaccine for many years, and because such a vaccine is unlikely to be 100 percent effective, vaccine research must complement, not displace, our present prevention, treatment, and care programs. The development of an HIV vaccine is a long-term goal that will require substantial financial, scientific, political, and societal commitment and resources over many years. In the interim, many more people will become infected with HIV. Research into other prevention strategies, and treatments for AIDS, must continue, as well as efforts to reduce the cost of, and increase access to, present and future therapies.

⁹ Ainsworth M. et al. "Accelerating an AIDS vaccine for developing countries: Recommendations for the World Bank" World Bank AIDS Vaccine Task Force, 2000, www.iaen.org

3. Relevant Legal, Ethical, and Human Rights Principles

In the last 50 years, international laws and ethical guidelines have been developed which set out the rights and responsibilities of researchers and research subjects before, during, and after clinical research, as well as the duties of states to make the benefits of that research available nationally and internationally.¹⁰ The following principles are drawn from two sources: public international law, and internationally recognized codes of ethics.

International law and codes of ethics address both the rights of individual participants in human trials of HIV vaccines and broader issues of equity and access affecting whole populations.¹¹ While codes of ethics are directed more toward the relationships between individuals (researcher/research subject), the human rights framework addresses state responsibility. These two sources complement each other. As Jonathan Mann observed,

rather than seeing human rights and ethics as conflicting domains, it seems more appropriate to consider a continuum, in which human rights is a language most useful for guiding societal level analysis and work, while ethics is a language most useful for guiding individual behavior.¹²

This section will first consider the legal obligations on states arising from international law. The moral obligations on individuals and institutions arising from international codes of ethics will be addressed in the following section.

3.1 International Law

The International Covenant on Economic, Social and Cultural Rights and the International Covenant on Civil and Political Rights impose on those states that ratify them the obligation to respect, protect, and fulfil a comprehensive set of rights based on the rights set out in the Universal Declaration of Human Rights. Further, some principles are so general that they form part of *customary international law*, which is binding on *all* states (including those that have not ratified specific treaties).

¹⁰ Kelly R., Fluss S. and Gutteridge F. The regulation of research on human subjects: a decade of progress. *Ethics and Research on Human Subjects: International Guidelines* Proceedings of the XXVth CIOMS Conference, Geneva: CIOMS, 1992, at 127-170; for a comprehensive list see Fluss S. International guidelines on bioethics *EFGCP News*, Supplement, December 1999, www.efgcp.org/workingparties/ethics/bioethgl.htm

¹¹ Beloqui J., Chokevivat V. and Collins C. HIV Vaccine Research and Human Rights: Examples from Three Countries Planning Efficacy Trials. *Health and Human Rights* 1998; 3(1): 39-58 at 41.

¹² Mann J. Medicine and Public Health, Ethics and Human Rights. *Hastings Center Report*. 1997; 27(3): 6-13 at 10.

Other international treaties also contain relevant provisions. For example, the “right to health” is addressed in the International Convention on the Elimination of All Forms of Racial Discrimination (Article 5(e)(iv)); the Convention on the Elimination of All Forms of Discrimination Against Women (Articles 11 & 12); the Convention on the Rights of the Child (Article 24); as well as regional human rights instruments in Europe, Africa, and the Americas. These other international and regional treaties, although important, are not discussed further here.

International Covenant on Economic, Social and Cultural Rights, 1966

As of 15 March 2000, 142 states had accepted the obligations of the International Covenant on Economic, Social and Cultural Rights. These include all OECD countries except the United States of America.

Article 12 of the Covenant refers to “the right of everyone to the highest attainable standard of physical and mental health.” Article 15(b) refers to “the right of everyone ... to enjoy the benefits of scientific progress and its applications.”

Article 2(1) states:

Each State Party to the Covenant undertakes to take steps, individually and through international assistance and co-operation, especially economic and technical, to the maximum of its available resources, with a view to achieving progressively the full realization of the rights recognized in the present Covenant by all appropriate means, including particularly the adoption of legislative measures.

The Committee on Economic, Social and Cultural Rights, which monitors the implementation of the Covenant, has issued several General Comments to aid in the interpretation of the Covenant. In particular, the Committee has noted that

in accordance with Articles 55 and 56 of the Charter of the United Nations, with well-established principles of international law, and with the provisions of the Covenant itself, international cooperation for development and thus for the realization of economic, social and cultural rights is an obligation of all States. It is particularly incumbent on those States which are in a position to assist others in this regard.¹³

Most recently, the Committee has noted in relation to Article 12:

¹³ Committee on Economic, Social and Cultural Rights, General Comment 3 (5th session, 1990), para. 14.

Depending on the availability of resources, States should facilitate access to essential health facilities, goods and services in other countries, wherever possible and provide the necessary aid when required.¹⁴

Although Article 2(1) refers to the *progressive implementation* of the rights in the Covenant, the Committee has noted that it imposes obligations that are of *immediate effect*, such as the principle of non-discrimination. Further, “progressive realisation means that States parties have a specific and continuing obligation ‘to move as expeditiously and effectively as possible’ towards the full realisation of article 12.”¹⁵

The UN General Assembly has also addressed these issues. Although the resolutions of the General Assembly do not have the same legal status as treaties, they are strong statements of international concern that should guide the actions of Member States. For example, the UN Declaration on Social Progress and Development (1969) calls for national and international action to ensure:

- equitable sharing of scientific and technological advances by developed and developing countries (Article 13(a)); and
- increased utilization of science and technology for social and economic development; arrangements for the transfer and exchange of technology, including know-how and patents, to developing countries (Article 24(c)).¹⁶

Similarly, the UN Declaration on the Right to Development (1986) notes that “States have the duty to take steps, individually and collectively, to formulate international development policies with a view to facilitating the full realization of the right to development” (Article 4(1)).¹⁷

There is thus a legal basis for the moral and ethical obligations on industrialized states to promote the health, not only of their own citizens, but of people in developing countries. This includes promoting research into diseases (and HIV subtypes) specific to developing countries.¹⁸

¹⁴ Committee on Economic, Social and Cultural Rights, General Comment 14 (22nd session, 2000), para. 39. See generally, Toebes B. Towards an improved understanding of the international human right to health *Human Rights Quarterly* 1999: 21; 661-679.

¹⁵ Committee on Economic, Social and Cultural Rights, General Comment 14 (22nd session, 2000), para. 31.

¹⁶ United Nations General Assembly resolution 2542 (XXIV) of 11 December 1969. Although the Covenant came into force in 1976, it was opened for signature in 1966, three years before the Declaration.

¹⁷ United Nations General Assembly resolution 41/128 of 4 December 1986; see generally Häusermann J. *A Human Rights Approach to Development* London: Rights and Humanity, 1998.

¹⁸ See Attaran A. Human Rights and Biomedical Research Funding for the Developing World: Discovering State Obligations under the Right to Health. *Health and Human Rights* 1998; 4(1): 27-58.

International Covenant on Civil and Political Rights, 1966

As of 15 March 2000, 144 States had accepted the obligations of the International Covenant on Civil and Political Rights.

Article 5 of the Universal Declaration of Human Rights states that “No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment.” Article 7 of the Covenant restates this right and adds: “In particular, no one shall be subjected without his [sic] free consent to medical or scientific experimentation.” Other relevant rights include the principle of non-discrimination (Article 2) and the right to life (Article 6).

Although the Committee on Economic, Social and Cultural Rights and the Human Rights Committee (which monitors the implementation of the International Covenant on Civil and Political Rights) cannot force states to take specific action, both committees report to the Commission on Human Rights, which can in turn refer serious matters to the UN Economic and Social Council.

International Guidelines on HIV/AIDS and Human Rights, 1996

The International Guidelines on HIV/AIDS and Human Rights provide a framework for a multi-sectoral response, including national law and policy reform, and community and private-sector involvement, based on the rights and obligations contained in international human rights treaties.¹⁹ The Guidelines address vaccines in the context of law reform relating to protection of research subjects (Guideline 5) and to fraudulent products (Guideline 6).

3.2 Internationally Recognized Codes of Ethics

In the last century, medical experimentation during the Nazi period and subsequent infamous studies such as the Tuskegee study in the United States (in which black patients with syphilis were left untreated in order to follow the natural history of the disease), left a legacy of distrust of medical research and researchers in many communities.

The following international codes of ethics were designed to govern biomedical research involving human subjects in order to ensure that the rights of research subjects are respected. The application of these codes to HIV preventive vaccine research is discussed in the next section.

The Nuremberg Code, 1947

In 1947 the War Crimes Tribunal at Nuremberg convicted the German defendants, most of whom were physicians, of war crimes and crimes against humanity. The Tribunal proposed ten

¹⁹ *HIV/AIDS and Human Rights: International Guidelines* Geneva and New York: UNAIDS and the Office of the High Commissioner for Human Rights, 1998 www.unaids.org

standards to guide physicians in carrying out experiments on human subjects.²⁰ In particular, informed consent was identified as an absolute precondition for the conduct of research involving human subjects. The Nuremberg Code has since been amplified and extended by other authoritative guidelines. Its usefulness today is limited, other than to remind us of the dangers of unchecked medical experimentation.

Declaration of Helsinki 1964, 2000 (last amended)²¹

The Declaration of Helsinki provides basic principles for the conduct of medical research on human subjects. The Declaration notes (section A (5)): “In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.”

The Declaration is divided into three sections. Section A contains an introduction. Section B provides basic principles for all medical research, which would include HIV vaccine research. Section C contains additional principles for medical research combined with medical care, which would not be applicable to HIV preventive vaccine research, as this is conducted on healthy subjects (not receiving medical care.)

Ethical Principles and Guidelines for the Protection of Human Subjects in Research (the Belmont Report), 1979

The Belmont Report was prepared by the (US) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Because of its clarity and authority, the Belmont Report is a standard reference on ethics in research involving human subjects.

The Report sets out three basic ethical principles to guide research: the principles of respect for persons, beneficence, and justice.²² Respect for persons requires that individuals should be treated as autonomous agents (unless of diminished autonomy) and hence requires informed consent based on information, comprehension, and voluntariness. The principle of beneficence entails the obligation to do no harm and to maximize benefits and minimize harms. The principle of justice addresses the question: Who ought to receive the benefits of research and bear its burdens?

Regarding the principle of justice, the Commission noted that “whenever research *supported by public funds* leads to the development of therapeutic devices and procedures, justice demands

²⁰ *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10.* Nuremberg, October 1946 - April 1949. Washington D.C.: U.S. G.P.O, 1949-1953. See www.ushmm.org/research/doctors/index.html

²¹ World Medical Association www.wma.net

²² *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (U.S.A.), 1979.

both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research” (emphasis added).²³ Disappointingly, the Report does not provide particular guidance in this respect for research funded by the private sector.

International Ethical Guidelines for Biomedical Research Involving Human Subjects (the CIOMS Guidelines), 1982, 1992 (last amended)

These Guidelines are published by the Council for International Organizations of Medical Sciences.²⁴ They expand and extend the ethical principles embodied in the Declaration of Helsinki, particularly to research in developing countries. The CIOMS Guidelines were revised in 1992 in part to address specific concerns about HIV/AIDS research, and are again under revision. A preliminary consultation was held in March 2000. The background papers to this consultation will be published later in 2000, and a further conference on the issues may be held in 2001.²⁵

Ethical considerations in HIV preventive vaccine research: UNAIDS Guidance Document, 2000

In 1998, UNAIDS conducted a series of regional and international consultations to try to achieve a global consensus on key ethical issues in HIV preventive vaccine research.²⁶ Although consensus was not achieved on all issues, the resulting UNAIDS Guidance Document sets out UNAIDS policy in 18 guidance points that address a wide range of issues, including international response, access, capacity development, community representation, benefits, harms, consent, and care and treatment.²⁷ The application of the Guidance Document to key issues is addressed in the next section.

²³ Belmont Report, supra, section B3. See also Ethical and policy issues in international research. National Bioethics Advisory Commission, draft report 29 September 2000 <http://bioethics.gov/report.html>

²⁴ International Ethical Guidelines for Biomedical Research Involving Human Subjects *Ethics and Research on Human Subjects: International Guidelines*. Geneva: CIOMS, 1993.

²⁵ Personal communication, J. Gallagher, CIOMS, 30 May 2000.

²⁶ UNAIDS Sponsored Regional Workshops to Discuss Ethical Issues in Preventive HIV Vaccine Trials. UNAIDS, 2000 www.unaids.org; Guenter D., Esparza J. and Macklin R. Ethical considerations in international HIV vaccine trials: summary of a consultative process conducted by the Joint United Nations Programme on HIV/AIDS (UNAIDS) *Journal of Medical Ethics* 2000; 26(37): 37-43; Bayer R. Ethical challenges of HIV vaccine trials in less developed nations: conflict and consensus in the international area *AIDS* 2000; 14(8):1051-1057.

²⁷ Ethical considerations in HIV preventive vaccine research: UNAIDS guidance document, 2000, www.unaids.org; see letter of 11 February 2000 from Lurie P. and Wolfe S., Public Citizen, to Piot P., UNAIDS, (HRG publication #1508); www.citizen.org; see generally Patterson D. New Guidelines on Ethical Considerations in HIV Preventive Vaccine Research *Canadian HIV/AIDS Policy and Law Review* 2000 (forthcoming), www.aidslaw.ca

An international code of ethics for business: The Global Compact

In 1999, the UN Secretary-General launched the Global Compact, intended to “safeguard open markets while at the same time creating a human face for the global economy.”²⁸ The Global Compact challenges individual corporations and representative business associations to support nine key principles relating to human rights, labour, and the environment, “which emanate from universally agreed standards found in United Nations documents.” In relation to human rights, the Global Compact states:

1. businesses should support and respect the protection of international human rights within their sphere of influence; and
2. make sure their own corporations are not complicit in human rights abuses.²⁹

The application of the Global Compact to HIV vaccine research and development has yet to be explored.

²⁸ www.unglobalcompact.org Business promises UN boss to be good citizens, Reuters, Geneva, 5 July 1999, cited in The Global Compact: The UN’s new deal with ‘Global Corporate Citizens’, Corporate Europe Observer, 5 October 1999, www.corpwatch.org

²⁹ The Office of the High Commissioner for Human Rights regularly participates in meetings with key business organisations such as the World Business Council on Sustainable Development and the International Chamber of Commerce; see Business and HIV/AIDS: a progress report, Office of the United Nations High Commissioner for Human Rights, January 2000.

4. Application of Principles to Key Issues

In this section, key issues are discussed in the light of the above-mentioned international legal and ethical standards.

4.1 The Development of HIV Vaccines Suitable for Developing Countries

None of the ethical codes provide any *obligation* to undertake research. Only international human rights law and, in particular, the International Covenant on Economic, Social and Cultural Rights, carries obligations to undertake research to promote the right to health in developing countries. Although they do not refer specifically to HIV, the declarations of 1969 and 1986 also provide guidance as to the duties of states to respond to HIV as potentially the biggest single threat to development.

4.2 The Rights and Protection of Research Subjects and Communities

Trial participants may face discrimination. Many commentators have observed that if a candidate vaccine generates HIV antibodies to certain envelope proteins in an uninfected research participant, this may result in a false-positive HIV test (eg, for matters such as insurance and employment) when an ELISA or similarly sensitive but not highly specific test is used. In this case, a Western blot or other specific test could be used to distinguish a “vaccine-positive” result. However, such tests are substantially more expensive than the simpler screening tests, and in developing countries it may not be feasible to propose that a more expensive test be used routinely to distinguish vaccine-positive from HIV-positive results.

Discrimination may also be encountered due to mere enrolment in a vaccine trial, especially where trial participants are identified as being at increased risk of HIV infection (eg, injection drug users in the VaxGen trial in Thailand). On the other hand, given that preventive vaccine trials only enrol HIV-negative volunteers, known exclusion from a trial might also lead to stigma and discrimination. Confidentiality is key, and there is a need to share experiences of ways in which confidentiality can be preserved in such circumstances. Social harm should be monitored throughout the trial with the same vigilance as physical harm.³⁰

The UN Commission on Human Rights has affirmed that the broad prohibition against discrimination in international human rights law is to include HIV/AIDS.³¹ The International

³⁰ Sheon A. et al. Preventing discrimination against volunteers in prophylactic HIV vaccine trials: lessons from a Phase II Trial. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 1998; 19(5): 519-526 at 524.

Guidelines on HIV/AIDS and Human Rights require states to introduce appropriate legislation to protect “people living with asymptomatic HIV infection, people living with AIDS, or those merely suspected of HIV or AIDS” – which could also address discrimination in the context of vaccine trials.³²

Vaccine trials may have a positive or negative impact on preventive behaviour. Early surveys of potential trial participants indicated that some people might want to enrol in a trial in the mistaken belief that participation would guarantee them some immunity against HIV infection. It was feared that a trial could result in a net increase in HIV incidence if people took more risks as a result of their participation.³³ In practice these fears have not been substantiated from results obtained in the US and Thailand.³⁴

Vaccine trial protocols must stress the need for education and counseling of all trial participants (active vaccine and placebo recipients) to ensure safer sexual practices and a reduction in harm related to injection drug use. But how much further should these efforts go? If no infections result in either group (a triumph for education), the trial will fail to produce meaningful results. Given that education and counseling themselves have limited impact on vulnerability, should the trial participants be given other services and assistance to reduce the health and socioeconomic factors that increase their risk of HIV infection (eg, STD monitoring and treatment,³⁵ clean needles and syringes for injection drug users, or financial assistance for girls to continue schooling)? The direct cost of such benefits may be relatively small and their personal impact large – but the indirect cost will be that a much larger number of volunteers will be needed to generate meaningful results, or the trial might take much longer.

Vaccine trials may result in a disproportionate impact on women and girls. Women and girls are often at greater risk of HIV infection than same-aged male counterparts for a range of biological, social, cultural, economic, and legal reasons. Particular concerns arise in the context of preventive vaccine trials. For example, consent may be coerced, or as a result of enrolling in the trial a woman may be under more pressure from her partner to have unprotected sexual intercourse. There are also concerns about the participation of women of child-bearing age in trials, owing to undetermined risks to the fetus. The CIOMS Guidelines stress that such clinical

³¹ Resolutions 1995/44 and 1996/43.

³² *HIV/AIDS and Human Rights: International Guidelines* Geneva and New York: UNAIDS and the Office of the High Commissioner for Human Rights, 1998, Guideline 5, www.unaids.org

³³ See e.g. Kippax S. HIV and technology: the issue of prophylactic vaccines. *Development Bulletin* 2000; 52:24-25 <http://devnet.anu.edu.au>

³⁴ Personal communication, J. Esparza, UNAIDS, 11 May 2000.

³⁵ Angell M. Investigators' responsibilities for human subjects in developing countries. *New England Journal of Medicine* 2000; 242(3) www.nejm.org

and ethical concerns must be addressed, and women included in trials, in order for women to benefit equally from advances in scientific knowledge.³⁶

Informed consent will be crucial. The Nuremberg Code places particular emphasis on the principle of voluntary consent. The Belmont Report identified three components of informed consent: information, comprehension, and voluntariness.³⁷ With respect to obtaining informed consent, the Declaration of Helsinki addresses the disclosure of conflicts of interest, avoidance of duress, and the consent of minors and others. CIOMS Guideline 3 addresses the information to be given, the opportunity to ask questions, and issues of deception, undue influence, intimidation, documentation, and continuing consent. UNAIDS Guidance Point 12 notes the need for consultation between community representatives and researchers to design an effective informed consent strategy. In other words, there is a heavy burden on researchers to ensure that trial subjects fully understand and consent freely to their participation.

Fears that people in developing countries cannot understand the necessary concepts may be exaggerated. For example, Richter et al have developed a practical guide for obtaining consent in the South African context.³⁸

Undue inducement would render trials unethical. Participation in vaccine trials is assumed to be altruistic. Although participants are not normally regarded as benefiting materially from participation in a vaccine trial, UNAIDS has identified the benefits participants should receive. At a minimum, participants should:

- have regular and supportive contact with health-care workers and counselors throughout the course of the trial;
- receive comprehensive information regarding HIV transmission and how it can be prevented;
- receive access to HIV prevention methods, including male and female condoms, and clean injecting equipment, where legal;
- have access to a pre-agreed care and treatment package for HIV/AIDS if they become HIV-infected while enrolled in the trial;
- receive compensation for time, travel, and inconvenience related to participation in the trial; and
- if the vaccine is effective, develop protective immunity to HIV.³⁹

³⁶ Barrett K. Ethics and consent: women and vaccine research *Agenda* 1998; 39, www.oneworld.org/agenda/; see also International Ethical Guidelines for Biomedical Research Involving Human Subjects *Ethics and Research on Human Subjects: International Guidelines* Geneva: CIOMS, 1993, at 33-34 (commentary on Guideline 11).

³⁷ The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (U.S.A.), 1979. See generally Macklin R. *Against relativism: cultural diversity and the search for ethical universals in medicine* New York: Oxford University Press, 1999, Chapter 8.

³⁸ Richter L., Lindegger G., Abdool Karim Q. and Gasa N. Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials. Discussion paper, University of Natal, 1999, www.hs.unp.ac.za/mind/icunaid.htm

Undue inducement is a function of both the benefits offered and the material circumstances of the individuals and community from which the research subjects are drawn. At what level of impoverishment would these minimum benefits become an undue inducement to participate? There may be circumstances in which some populations can never, because of the degree of their impoverishment, give free and informed consent. This is because any treatment or compensation for participation in a trial would in such a context be an undue inducement to participation in the trial. It follows that research must not be undertaken in these populations. The state of poverty itself thus further contributes to their marginalization.

Further, although participation is altruistic, volunteers will expect that the benefits of the research will somehow and sometime flow to their communities. If there is no credible plan at the outset to distribute the successful products of the research in the community where the research is undertaken, can researchers maintain consent was freely given if it was based on such an assumption?⁴⁰

The participation of children in vaccine trials raises particular concerns. Children will also be potential HIV vaccine trial participants, and require particular arrangements for obtaining informed consent from them and/or their parents/guardians. UNAIDS notes that:

Children, including infants and adolescents, should be eligible for enrolment in HIV preventive vaccine trials, both as a matter of equity and as a function of the fact that in many communities throughout the world children are at high risk of HIV infection. Infants born to HIV-infected mothers are at risk of becoming infected during birth and during the post-partum period through breast-feeding. Many adolescents are also at high risk of infection due to sexual activity, lack of access to HIV prevention education and means, and engagement in injecting drug use.⁴¹

Yet the CIOMS Guidelines state that “the investigator must ensure that ... children will not be involved in research that might equally well be carried out in adults...”⁴² One option would be to hold a Phase IV trial in children, once a Phase III trial in adults has demonstrated the efficacy of a particular vaccine. This would entail a delay of at least several years in the commencement

³⁹ Ethical considerations in HIV preventive vaccine research: UNAIDS guidance document, 2000, www.unaids.org Guidance Point 10. Of course, trial participants will only develop protective immunity if they are administered an effective vaccine during the trial. If they are part of the control (placebo) group, they should be given free access to the vaccine, if it is subsequently approved for use.

⁴⁰ Annas G. & Grodin M. Human rights and maternal-fetal HIV transmission prevention trials in Africa, in Mann J. et al, eds. *Health and Human Rights*. New York: Routledge, 1999, 373 at 374.

⁴¹ Ethical considerations in HIV preventive vaccine research: UNAIDS Guidance Document, 2000, www.unaids.org. Guidance Point 18.

⁴² International Ethical Guidelines for Biomedical Research Involving Human Subjects *Ethics and Research on Human Subjects: International Guidelines* Geneva: CIOMS, 1993, Guideline 5.

of trials in children. How many more children will become infected before a vaccine is approved for them?

Volunteers who test positive for HIV infection on applying to join the trial must receive attention. All trial volunteers will be initially tested for HIV, and only those who are negative will continue in the trial. This initial screening must be accompanied by pre-and post test counseling. It is not clear what further obligations are owed to these people: this issue is not addressed by the Declaration of Helsinki, the CIOMS Guidelines, or the UNAIDS Guidance Document. On the one hand, their willingness to take part in the trial should be acknowledged. On the other, special treatment (eg, medical care above the local standard) would encourage persons in the community who know or suspect they may be HIV-positive to volunteer for the trial in order to receive special medical attention. The resulting financial burden might threaten the viability of the trial itself.

Treatment and care issues for participants infected during the trial must be addressed. In spite of the counseling, some trial participants are expected to contract HIV infection through sexual contact or injection drug use during the trial (breakthrough infections, not from the vaccine itself). In industrialized countries, these people would usually receive a standard of care that, although it varies, now includes highly active antiretroviral therapy (HAART).

Some argue that this standard should also apply to trial participants in developing countries, irrespective of local conditions. During the UNAIDS-sponsored regional workshops to discuss ethical issues in preventive HIV vaccine trials, the participants in the April 1998 Brazil workshop felt strongly that preventive risk-behaviour counseling, general HIV care and treatment, post-exposure prophylaxis, and antiretroviral therapy were all subject to the same ethical imperative; that is, all should be provided to the trial participants according to the best scientific evidence for effectiveness available at the time of the trial.⁴³

The contrary view is that this is an unrealistic standard in many developing countries for reasons that include the cost of these drugs and the fact that the sophisticated medical monitoring that should accompany antiretroviral therapy is often not available. The UNAIDS Guidance Document proposes that

Sponsors should seek, at a minimum, to ensure access to a level of care and treatment that approaches the best proven care and treatment that are attainable in the potential host country.⁴⁴

⁴³ UNAIDS Sponsored Regional Workshops to Discuss Ethical Issues in Preventive HIV Vaccine Trials. UNAIDS, 2000 www.unaids.org

⁴⁴ Ethical considerations in HIV preventive vaccine research: UNAIDS Guidance Document, 2000, www.unaids.org. Guidance point 16.

Standards of care change as new therapies are developed and the prices of existing drugs drop (eg, because the patent on them expires or they are added to the subsidized-drug list.) Some commentators fear that a lower than best-possible standard will be used by researchers to justify providing less than is practically possible.⁴⁵

The revised version of the Declaration of Helsinki continues to be silent on the issue, as the provision relating to the continuation of treatment after the study only applies to medical research that is combined with medical care, which is not the case in preventive vaccine research.⁴⁶

The CIOMS Guidelines themselves do not address the issue. CIOMS Guideline 13 refers to the right of subjects to compensation for “physical injury as a result of their participation.” The Commentary on Guideline 13 refers to accidental injury “due to procedures performed exclusively to accomplish the purposes of research...” HIV infection as a result of unprotected sex or injection drug use during the trial would not appear to fall within this definition of accidental injury.

Finally, even if treatment is provided during the remainder of the trial, what will happen to the participants once the study is finished – will the care and treatment be provided for life? There are serious concerns for both the individual and the community (due to the development of resistant virus strains) if treatment is interrupted. Will the national authorities agree to continue paying for treatments after the researchers leave?

Competent mechanisms in the host country must ensure that proposed research will be legal and ethical, monitor trials, and ensure follow up of promised support. The Declaration of Helsinki requires that the research protocol

should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. (section B(13))

Thus, the review committee has the right, but not the obligation, to monitor the trials it approves.

⁴⁵ See Brennan T. Proposed Revisions to the Declaration of Helsinki – Will They Weaken the Ethical Principles Underlying Human Research? *Lancet* 1999; 341(7): 527-530.

⁴⁶ This distinction was also made in the previous version of the Declaration. See ‘Annex 2. The Phases of Clinical Trials of Vaccines and Drugs’ in *Ethics and Research on Human Subjects: International Guidelines*. Geneva: CIOMS, 1993, at 52. The Commentary accompanying the CIOMS Guidelines notes that ‘...Phase III vaccine-trials do not conform to either of the categories defined in the Declaration of Helsinki.’ See also Levine R. The ‘Best Proven Therapeutic Method’ Standard in Clinical Trials in Technologically Developing Countries *IRB* 1998; 20(1): 5-9 reprinted in *AIDS & Public Policy Journal* 1998; 13(1): 30-35.

The UNAIDS Guidance Document provides that “HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent scientific and ethical review.” (Guidance Point 6)

Many questions remain. Which standards should apply? How will the community be represented? Even with a place on an ethics review board, community representatives may find themselves overwhelmed by the science and language of clinical research.

How can we guarantee independence from the commercial interests that fund much of the research? The pool of available expertise in some countries may be limited and there may be a real risk of conflicts of interest between persons in their review capacity and as researchers in their own right. The CIOMS Guidelines and Commentary address these issues in some depth.

Finally, what monitoring mechanisms will be established at the national and international levels to ensure that standards and agreements set out in the research protocols and other contracts are maintained? This is particularly important if benefits to individuals or communities are promised to arrive after the research is concluded.

4.3 Equity in Research and Access to the Benefits of Vaccine Research

Access to an effective vaccine must be assured. The principle of justice demands that those persons who are the subjects of research should also benefit from that research. The Declaration of Helsinki states (section B(19)): “Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.”

CIOMS Guideline 8 addresses “research involving subjects in underdeveloped communities.” The Commentary on Guideline 8 states:

As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out; exceptions to this general requirement should be justified, and agreed to by all concerned parties before the research is begun.

The UNAIDS Guidance Document states:

Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials, as well as to

other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.⁴⁷

Proposals to oblige pharmaceutical companies to provide a successful vaccine at low cost or no cost to the communities or countries where the research was undertaken may backfire within the present commercial framework, as such up-front requirements may diminish commercial interest in investing in vaccine development. This is particularly true if the research is specific to HIV subtypes found only in developing countries.

Provisions exist under international intellectual property law for the issuing of compulsory licences for the local manufacture of pharmaceutical products, including vaccines, or their import in competition with the patent holder. These mechanisms, although controversial, are legal if the necessary national legislation is in place and the prescribed procedures for issuing the licences to private-sector producers or importers are followed.⁴⁸ Alternatively, the government can legally issue a licence for non-commercial public use. The adoption of such measures might reduce incentives for further private-sector vaccine research and development, and hence reduce access to new vaccines from this source in the longer term.

Other social benefits should be negotiated. It may take many years after a Phase III trial for a successful vaccine to be licensed, manufactured in bulk, and made available to the community where the original research took place. What other benefits, such as the development of infrastructure and training, might be negotiated as part of the agreement to participate in the trials?

The Commentary to CIOMS Guideline 15 notes the obligations of external sponsors to train local people as investigators, research assistants, etc. Other benefits, such as financial, educational, and other assistance is expected to aid in the development of local ethics review capacity. Funds are to be channeled through the host country government or a host research institution. The Commentary also states:

The research protocol should specify what, if any, resources, facilities, assistance and other goods or services will be made available, during and after the research, to the community from which the subjects are drawn and to the host country. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when relevant, the community from which subjects are to be drawn. The ethical review committee in the host country should

⁴⁷ Ethical considerations in HIV preventive vaccine research: UNAIDS guidance document, 2000, www.unaids.org. Guidance Point 2. The requirement up-front for such plans is new.

⁴⁸ *Globalization and Access to Drugs: Perspectives on the WTO/TRIPS Agreement*, Health Economics and Drugs, DAP Series No. 7, Geneva: World Health Organization, 1997, 2nd edition. Contact: Documentation Centre, Essential Drugs and Other Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Email: darec@who.ch; see also Compulsory licensing and parallel importing: what do they mean? Will they improve access to essential drugs for people living with HIV/AIDS? ICASO, 1999, background paper, www.icaso.org

determine whether any or all of these details should be made part of the consent process.

5. Other Factors Affecting the Decision to Proceed with Trials

Two further issues deserve particular mention. The first concerns the scientific readiness for clinical trials, and the second how treatment for HIV infection might affect the quality of the data collected.

Basic science versus empiricism

There is ongoing debate in the scientific research community between those who believe more basic research is necessary before proceeding to clinical trials, and those who believe that much can be gained from clinical trials of present candidate vaccines, although substantial doubt exists as to whether they could actually prevent HIV infection or reduce the impact of infection.

According to the former view, clinical trials with candidate vaccines that do not show real promise are a waste of funds. Further, they may render trial participants ineligible to take part in later trials, thus reducing the pool of research subjects and making later trials even more difficult and expensive.

The contrary view is held by researchers who believe that we must start human trials of candidate vaccines now, in order to learn from this experience and to prepare the way for future trials. They point out that the history of vaccines demonstrates that many questions of basic science are often not resolved before a successful vaccine is developed and licensed. For example, the correlates of immunity for some vaccines in current use (eg, polio, hepatitis B) are still unknown.

The late Jonathan Mann was strongly of the view that the delay in moving to clinical trials was inexcusable, and in part due to the fact that most people contracting HIV infection today in the USA are from marginalized groups with relatively little political weight. He noted: “The key ethical concept of concern is the duty to help people in need, and the central human rights violations involve the rights ‘to share in scientific advancement and its benefits,’ and the rights to non-discrimination and to life.”⁴⁹

The VaxGen trial of AIDSVAX illustrates this issue. In 1994, the National Institutes of Health (NIH) decided not to pursue Phase III studies of a similar product because of doubts about its possible efficacy. The VaxGen candidate vaccine was then modified to match HIV subtypes

⁴⁹ Mann J. Paralysis in AIDS Vaccine Development Violates Ethical Principles and Human Rights, unpublished address to Presidential Advisory Council on AIDS, 15 March, 1998. <http://hivinsite.ucsf.edu/topics/vaccines/2098.3940.html>; DeNoon D. AIDS Vaccine Test Delay Called Human Rights Violation: Is it prudent scientific caution or human rights violation? *AIDS Weekly Plus*, 13 April 1998, www.aegis.com/pubs/aidswkly/1998/aw980404.html

prevalent in Thailand and North America and to improve its chances of success, yet some AIDS researchers still believed it was too early to go to Phase III clinical trials. Many others disagreed: even if the trial was unsuccessful, it would provide valuable data about undertaking such a vaccine trial, and pave the way for future trials with more promising vaccine candidates. Their attitude was summed up by VaxGen's president: "It works in a chimp, it's safe in humans, and it produces a better immune response in humans than in chimps. To sit back and wait for more lab tests would, I think, be unconscionable."⁵⁰

Primary and secondary endpoints

A vaccine that does not prevent infection (a "primary endpoint") could still be of value if it modified disease progression (a "secondary endpoint"). A vaccine that reduces viral load following infection, and hence progression to AIDS, would probably also reduce infectivity and hence could have a significant public health impact. Further, new data suggest that the first determination of viral load at the time of diagnosis is the best predictor of long-term disease progression, so the early administration of antiretroviral therapy (if available) may not drastically interfere with the interpretation of trial results.⁵¹

⁵⁰ See Jubilation, and Skepticism, Greet Announcement of First Phase III Trial of an AIDS Vaccine: Watershed or Waterworld? *Treatment Action Group* 1998; 5(6) www.aegis.com/pubs/tag/1998/tg980701.html

⁵¹ Personal communication, J. Esparza, UNAIDS, 11 May 2000; see also Lie R. Ethical issues in clinical trial collaborations with developing countries – with special reference preventive HIV vaccine trials with secondary endpoints, UNAIDS working paper, 1998.

6. An Example of National and Community Response: South Africa

With a good research infrastructure and relatively high rates of HIV infection, South Africa has been identified as an attractive environment for HIV vaccine clinical trials. Structures and processes have been established to address key ethical questions and to ensure that vaccine research in South Africa will ultimately benefit all South Africans.

In late 1998 a regional consultation on ethics and research was held in Durban. At this meeting the South African AIDS Vaccine Initiative (SAAVI) was created to promote vaccine development in South Africa. SAAVI receives funding from both government and non-government sources.

In 2000, SAAVI proposed to fund two projects on advocacy and ethics:

Community Mobilisation and Advocacy

This project comprises five components:

- broad-based advocacy;
- education and community mobilization;
- public health, legal, and human rights;
- communications and media; and
- supporting information system and knowledge network.

Participating groups include the Medical Research Council, the National AIDS Convention of South Africa (NACOSA), the AIDS Legal Network, the Centre for the Study of AIDS at the University of Pretoria, and the National Association for People with AIDS (NAPWA).

HIV/AIDS Vaccines Ethics Group (HAVEG)

Issues to be researched will include: informed consent; fair treatment of volunteers; confidentiality; developing a contract between researchers and research participants; fair selection of communities and individuals for research; legal and ethical obligations of researchers toward participants; and future access to any products developed through the trial.

As noted above, guidelines have already been prepared for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials.⁵²

⁵² Richter L., Lindegger G., Abdool Karim Q. and Gasa N. Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials, unpublished discussion paper, University of Natal, 1999. www.hs.unp.ac.za/mind/icunaids.htm

In March 2000, UNAIDS sponsored a capacity-building meeting jointly with AfriCASO in Pretoria, South Africa, for African NGOs. The meeting was part of a more comprehensive UNAIDS-driven process to develop an African AIDS Vaccine Strategy. The report of the meeting identified key challenges and provide recommendations for NGOs in four areas: assessment, collaboration, information sharing, and coordination.⁵³

In June 2000, a national series of workshops was to be held in South Africa for NGOs/CBOs on research and vaccine basics and ethics to facilitate meaningful community participation in the review process. Overall coordination of research was to be undertaken by the South African national AIDS program in the context of a national HIV vaccine development plan. In short, the South African experience has so far provided a good model of community consultation and engagement in HIV vaccine research and development.

⁵³ 'WHO-UNAIDS and AfriCASO NGO Consultative meeting on Community Role in the development and evaluation of Candidate HIV Vaccines in Africa, 21-22 March 2000' report compiled by AfriCASO Secretariat, Dakar, Senegal.

7. Discussion

The following factors and developments will influence efforts to develop and distribute a suitable HIV vaccine.

Prevention options have increased: from behaviour change to multiple prevention strategies. A preventive vaccine for HIV would be one of a range of available and emerging options, which include:

- education about behaviour change to reduce risky sexual and injection drug practices, together with the provision of condoms, safe and effective microbicides (when available), and clean injection equipment;
- interventions to prevent the transmission of HIV from mother to child; and
- the provision of antiretroviral therapies, which may reduce viral load and infectivity of people with HIV/AIDS.

Cofactors such as sexually transmitted diseases, and factors that impact on vulnerability such as the right to privacy, the right to work, and the right to an adequate standard of living must also be addressed.

Universal ethical standards in clinical research are being challenged. The urgent need for an HIV vaccine has led some people to question whether universal ethical standards should be maintained, given the differences in research contexts between industrialized and developing countries. For example, a spokesperson for the South African Medical Research Council has noted in relation to proposals for HIV vaccine trials in South Africa:

Existing international ethical guidelines, including those developed specifically for AIDS vaccine research, will be reviewed and modified to fit the specific needs of the South African population and the limitations of our health care system.⁵⁴

HIV vaccine research *is* arguably different from other biomedical research in developing countries because

- (i) the harm under discussion results from sexual activity or injecting drug use, not from any ill effects of the candidate vaccine itself;
- (ii) vaccine trials can be distinguished from research combined with medical care (and hence the obligations relating to treatment set out in the Declaration of Helsinki) because they involve healthy participants, who are presumed to participate for altruistic reasons, not because of any potential direct personal benefit;
- (iii) the HIV epidemic threatens the very fabric of society in some regions; and

⁵⁴ Galloway M. South African Initiative Makes First Vaccine Awards, International AIDS Vaccine Initiative, www.iavi.org

- (iv) such research, by focusing on local subtypes, is intended to benefit the community under study. It would not at present be possible for such research to be undertaken in the sponsoring country.⁵⁵

For example, those who would maintain the “best proven therapy” standard for participants infected during a trial need to be able to respond to those who are equally committed to ethical research but are also confronted by the realities of life and research in the developing-country context:

The need to improve health in developing countries requires informed public health decisions that will sometimes mean re-examining interventions proved effective under different conditions in resource-rich countries. Stopping trials in Africa that are trying to help improve the health of poor people so that those in affluent countries can have peace of mind seems a tortured form of ethical logic.⁵⁶

The solution proposed in the UNAIDS Guidance Document (ie, “a level of care and treatment that approaches the best proven care and treatment that are attainable in the potential host country”) only concerns HIV preventive vaccine research, and is thus a response to an exceptional case rather than an erosion of standards of clinical research in developing countries more generally.

Developing countries and communities now expect to have a substantive input into the design and implementation of research. It is increasingly expected that ethical approval should not only be obtained from the appropriate body in the sponsor country, but from a competent and independent review committee in the host country as well.

Yet because of disparities in wealth, scientific experience, and technical capacity, developing countries are still vulnerable to undue influence and exploitation.⁵⁷ There is an inherent contradiction between:

- (i) the recognition that communities are vulnerable due to a range of economic, social, legal and other factors (hence the increased risk of HIV infection and impact of AIDS), and
- (ii) the expectation that such communities can freely negotiate the terms and conditions of complex vaccine trials to their benefit and the benefit of others vulnerable in their country and even in other developing countries.

⁵⁵ In assessing appropriate standards of care, ethical factors such as distributive justice should be considered. Brennan T. Proposed Revisions to the Declaration of Helsinki – Will They Weaken the Ethical Principles Underlying Human Research? *Lancet* 1999; 341(7): 527-530 at 529.

⁵⁶ Gambian Government / Medical Research Council Joint Ethical Committee. Ethical issues facing medical research in developing countries. *Lancet* 1998; 351: 286-287 at 287.

⁵⁷ Ethical considerations in HIV preventive vaccine research: UNAIDS guidance document, 2000, www.unaids.org Guidance Points 3 & 7.

Indeed, the very concept of “community” requires careful consideration. Consider the difference between the gay male community in North America and a “community” of migrant workers or refugees – the latter may be hardly a community at all, if relocation has broken down the social structures and links that give people the sense and power of community identity.⁵⁸

The first Phase III vaccine trial in a developing country, among injecting drug users in Thailand, is a case in point. Participants are not provided with clean injection equipment,⁵⁹ will receive less than the best proven standard of care (double ARV, not HAART) if they become infected during the trial, and assurances from VaxGen (the pharmaceutical company sponsoring the trial) that any successful vaccine will be made “as inexpensive as possible” for Thailand are imprecise and difficult to enforce.⁶⁰

Yet communities are learning, and knowledge and expertise in negotiation will increase as more trials are planned and the necessary training and institutional development is undertaken.

There is insufficient research into vaccines suitable for developing countries. In spite of the demonstrated need for an HIV vaccine in the developing world, the limited demand (in economic terms, the ability and willingness of governments and individuals to pay) is a major reason why the private sector is reluctant to invest more in the development of an HIV vaccine.

This is not a new problem. In 1986 the Commission on Health Research for Development noted that although 93 percent of the world’s burden of preventable mortality occurred in the developing world, only 5 percent of investment in health research was devoted specifically to the problems of developing countries.⁶¹ The World Bank AIDS Task Force reports that in 1999, privately funded research and development on HIV vaccines was in the range of \$50-\$124 million per year, with fewer than 200 scientists worldwide in the private sector dedicated to HIV vaccine-related work.⁶² In the same year, total global research and development for HIV vaccines in both the public and private sectors was about \$300 million. Of this amount, IAVI estimates that only \$5-\$10 million a year is being spent on vaccines designed specifically for use

⁵⁸ Scott A. and Rosko M. In search of community action on HIV/AIDS in Asia. *International Social Science Journal* 1999; 161: 377-387.

⁵⁹ Provision of clean injecting equipment is illegal in Thailand (personal communication, J. Esparza, UNAIDS, 11 May 2000), however is reportedly freely available for sale at low prices.

⁶⁰ See Questions and Answers on the Thailand Phase III Vaccine Study and CDC’s Collaboration *CDC Update*, February 1999; Wehrwein P. and Morris K. HIV-1 vaccine trial go-ahead reawakens ethics debate *Lancet* 1998; 351: 1789.

⁶¹ Commission on Health Research for Development, *Health Research: Essential Link to Equity in Development* Oxford: OUP, 1990 at 29, cited in Attaran, supra at 29.

⁶² Ainsworth M. et al. Accelerating an AIDS vaccine for developing countries: Recommendations for the World Bank, World Bank AIDS Vaccine Task Force, www.iaen.org at 4.

in developing countries. An estimated \$2 billion annually is spent worldwide on research for AIDS treatments.⁶³

Further, although the economies of industrialized countries are presently fairly buoyant, and hence public-sector research funds more readily available, a downturn in the global economy in the next few years could see much tighter constraints on public-sector research funding.

In the face of the threats posed to national and global security by the HIV/AIDS epidemic, our response so far seems remarkably laissez faire when compared with other major initiatives to either promote scientific development (eg, in the field of space exploration) or constrain unethical or illegal research (eg, bans on chemical weapons development, atmospheric nuclear testing).

Are our development options limited either to downstream applications of random breakthroughs in “pure” science, or to private-sector, market-oriented, profit-driven research and development?⁶⁴ The World Bank AIDS Task Force acknowledges the market failure that constrains private-sector investment. In response, the Task Force identifies three roles for the World Bank: promote a policy dialogue on the key responsibility of government to prevent the epidemic; increase public- and private-sector funding to developing country governments and groups such as IAVI (“push” strategies), or make the commercial climate more attractive for private-sector investment through mechanisms such as vaccine purchase funds (“pull” strategies).⁶⁵ The World Bank stops short of directly proposing substantial funding of public-sector research into an HIV vaccine suitable for developing countries.

Yet such an initiative is no more ambitious than establishing an international space station, and patently more urgent (in this author’s view). International law (derived from customary law, treaty-based obligations, noted above, and other sources) is clear about state obligations to promote human rights, including the right to health, in developing countries. If the private sector proves an unsuitable vehicle for the development and delivery of the necessary technologies, governments (and intergovernmental organizations) must assume their responsibilities through direct funding of HIV vaccine development and distribution.⁶⁶

⁶³ Ainsworth M. et al. Accelerating an AIDS vaccine for developing countries: Recommendations for the World Bank, World Bank AIDS Vaccine Task Force, www.iaen.org at 4-5.

⁶⁴ Berting J. Technological Impacts on Human Rights: Models of Development, Science and Technology, and Human Rights, in Weeramantry C. *The Impact of Technology on Human Rights: Global Case Studies* Tokyo: United Nations University Press, 1993, 13-44 at 33.

⁶⁵ Ainsworth, supra 9. See also Public policy initiatives to accelerate the global search for an effective AIDS vaccine, IAVI Briefing Paper, undated, www.iaevi.org

⁶⁶ See generally The search for an HIV vaccine. Who pays? *Development*, European Commission, 3 February 1999 <http://europa.eu.int/comm/development/aids>

The following initiatives have been designed to accelerate the development and delivery of promising vaccines that would be effective against HIV subtypes in developing countries.

International AIDS Vaccine Initiative (IAVI)

Through vaccine development partnerships, IAVI can provide financial resources to move promising candidates through clinical trials to a point where additional resources and expertise may be attracted from large pharmaceutical companies. IAVI proposes to negotiate intellectual property and technology transfer agreements with such companies to provide either that a successful vaccine will be distributed at a given price, or that the licence can be made available to other manufacturers interested in doing so.⁶⁷ The following is an example of such arrangements:

IAVI [has] signed pricing agreements with Alpha Vax Human Vaccines and the Medical Research Council in Britain, under which the companies can only charge for the cost of production, plus a maximum of 10 per cent in profit. If the vaccines can be produced more cheaply elsewhere, IAVI can force the companies to move their production to those countries. This applies to sales in developing countries only.⁶⁸

Global Alliance for Vaccines and Immunization

The Global Alliance for Vaccines and Immunization (GAVI) was formed in 1999. It replaces the Children's Vaccine Initiative. In addition to the eradication of poliomyelitis and tackling common childhood diseases, GAVI will fund research and development into vaccines for other priority diseases, including HIV/AIDS. GAVI will also provide technical instructions to the Global Vaccine Fund, established in UNICEF for the purchase of newer vaccines. Initial financing has come from the Bill and Melinda Gates Foundation (which also funds the Children's Vaccine Program) and from the US government.⁶⁹

World Bank action

The World Bank AIDS Vaccine Task Force has recommended that the World Bank take four actions to promote HIV vaccine development and delivery:

⁶⁷ International AIDS Vaccine Initiative, www.iavi.org

⁶⁸ Foreman M. North South Initiative Sparks Hope for AIDS Vaccine, Panos Institute, London, 24 December 1998, www.aegis.com/news/panos/1998/ps981202.html

⁶⁹ See www.vaccinealliance.org ; Nossal, G. Global Alliance for Vaccines and Immunization – A Millennial Challenge, Jordan Report 2000, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, 131, www.niaid.nih.gov; "Vice-President Gore unveils new \$150 million initiative to combat AIDS and other infectious diseases" Office of National AIDS Policy (USA), media release, 10 January 2000.

1. Enable developing countries to be better partners in AIDS vaccine development, through policy dialogue and lending;
2. Expand childhood immunization rates in developing countries, through policy dialogue, lending, and participation in international initiatives, to strengthen the market and infrastructure for existing vaccines;
3. Generate new knowledge on the potential public and private demand for an AIDS vaccine in developing countries and its strategic use in AIDS prevention programs; and
4. Adopt new mechanisms to ensure adequate financing for an AIDS vaccine in developing countries that will serve as a credible assurance of a future market.⁷⁰

Developing countries must take the initiative, and be supported in doing so. There is increasing recognition that developing countries themselves must take active steps to encourage international research on local health problems. Twentieth-century discourse on technology and human rights was greatly influenced by such negative developments as nuclear weapons technology and threats to privacy from information technology.⁷¹ In the field of biomedical research, the emphasis has been primarily on the protection of research subjects. As a result, many communities may be suspicious of, and even hostile to, international private-sector vaccine research. Others may see it as a means of gaining benefits, such as AIDS medications, as well as promoting local institutional development. Both these approaches miss the point: the early development of an HIV preventive vaccine could save tens of millions of lives in the developing world.

Rather than characterize HIV vaccine research solely in terms of its immediate threats to human rights, a longer-term view would welcome and encourage investment in research and development in principle, while ensuring adequate protections in practice. In any case, researchers will continue to compare potential research sites in different developing countries when choosing where to undertake HIV vaccine research, and manufacturers will simply invest elsewhere, or not at all, if communities are too strident in their demands.⁷² Once substantial private-sector investment has been undertaken in a particular country, community and individual benefits from subsequent trials can, through skilful negotiation, be gently and persistently increased.

In short, developing-world governments and communities should explore all opportunities to invite and promote ethical and appropriate HIV vaccine research. Perhaps in recognition of this

⁷⁰ Ainsworth M. et al. Accelerating an AIDS vaccine for developing countries: Recommendations for the World Bank, World Bank AIDS Vaccine Task Force, www.iaen.org

⁷¹ See e.g. UN General Assembly, Declaration on the Use of Scientific and Technological Progress in the Interests of Peace for the Benefit of Mankind, Resolution 3384 (XXX), 10 November 1975 noted in Weeramantry C. *The Impact of Technology on Human Rights: Global Case Studies* Tokyo: United Nations University Press, 1993 at 3.

⁷² This is the case even if '(i)t is not ethical for researchers to conduct trials in developing countries merely because it is less expensive or more convenient.' See *Adverse Reactions to HIV Vaccines: Medical, Ethical and Legal Issues* Washington, DC: Office of Technology Assessment, 1995, background paper 11, www.wvs.princeton.edu/~ota

imperative, in June 2000 a meeting of 40 African government and community representatives and researchers convened to launch “The Nairobi Declaration: An African Appeal for an HIV Vaccine.”⁷³

International law and human rights are becoming increasingly relevant. Creative proposals to use international law to address the public health needs of developing countries include the suggestion of an international vaccine treaty. The treaty would mobilize nations to contribute to a global vaccine fund and bind signatories to minimum national levels of vaccination, thus stimulating further production, research, and development.⁷⁴

In early 2000, the US government identified the global spread of AIDS as a threat to US national security and global stability.⁷⁵ The threat posed by the HIV/AIDS epidemic was the subject of a full day’s discussion at the UN Security Council in January 2000. A three-day meeting of the UN General Assembly to discuss AIDS is proposed for June 2001. As the epidemic also threatens the very stability of some states, it is increasingly appropriate and urgent to respond at the international political level.

The actions states may take in response to such threats are governed by international law. The Charter of the United Nations provides that in the case of threats to peace, the Security Council may take certain actions to restore international peace and security, including calling on Member States to take measures deemed necessary or desirable. In the history of the United Nations, this provision has never been invoked in response to an epidemic. HIV/AIDS may prove the exception.

There will be increasing scrutiny and questioning of the role and responsibilities of the private sector, transnational corporations, and related multilateral organizations. This is already happening in the context of therapies for HIV/AIDS. Pharmaceutical research and development based on a mixed model of government and private sector–sponsored research, commercial marketing, and access to (state or private) health insurance, has had some success in developing and delivering treatments for people with HIV and AIDS in industrialized countries. However, this model has largely failed the 95 percent of the world’s population with HIV who live in developing countries.

Reflecting increasing concern about the impact of globalization, the civil society declaration of the Millennium Forum, adopted in May 2000, called on the United Nations “to reform and democratize all levels of decision making in the Bretton Woods institutions and the World Trade

⁷³ The Nairobi Declaration: An African Appeal for an HIV Vaccine www.unaids.org

⁷⁴ Barton J. Financing of Vaccines *Lancet* 2000; 355: 1269-70.

⁷⁵ Gellman B. AIDS Called US Security Threat *Washington Post* 4 April 2000, www.washingtonpost.com

Organization (WTO) and integrate them fully into the United Nations system, making these institutions accountable to the Economic and Social Council.”⁷⁶

The Global Compact, noted above, offers a potential framework for addressing global corporate responsibility in the context of HIV/AIDS, but the lack of any binding force has led to calls for binding international rules for transnational corporation activities, so far only in the areas of labour standards, fair trade, and environmental protection.⁷⁷ Much work remains to be done in the application of the Global Compact (and other mechanisms of influence on transnational corporations) to health, and specifically HIV/AIDS.

⁷⁶ Millennium Forum Declaration and Agenda for Action www.millenniumforum.org/index.html

⁷⁷ UNDP Human Development Report, cited in Corporate Europe Observer, 5 October 1999, www.corpwatch.org; see also Skeldon R. HIV/AIDS and Globalization, background paper, UN Inter-Agency Advisory Group on AIDS (IAAG), May 2000. In 2001, IAAG will again address the issue of globalization and AIDS.

8. Conclusions

The global HIV/AIDS pandemic poses an unprecedented challenge to human rights and development. A vaccine for HIV infection and AIDS offers a potential solution, but there are many obstacles to the development and distribution of an effective HIV preventive vaccine in developing countries.

Existing international ethical standards are designed to protect research subjects and ensure equitable access to the products of research. These ethical standards are living documents and should be adapted as required, following consultation with all stakeholders. National legislation should be reformed to make these standards legally binding. Protection of research subjects is paramount, but at the same time HIV preventive vaccine research should not be seen as a “back door” to treatments for HIV/AIDS.

International ethical standards are, however, silent on the obligation to develop HIV preventive vaccines. International human rights law imposes obligations on states to safeguard and promote the health not only of their own citizens and people within their borders, but of all people. There are clear legal and moral obligations on industrialized states and other actors to provide the necessary technical and financial assistance to developing countries to address the HIV epidemic, including through the development of HIV preventive vaccines as a feasible and cost-effective preventive measure.

States should take measures to encourage ethical private-sector HIV vaccine research and development. If the private sector cannot or will not undertake appropriate HIV vaccine research, the obligation falls on governments (particularly in industrialized countries) to direct, fund, and, if necessary, undertake this research. At the same time, adequate funding should be made available for existing prevention, care, and treatment programs.

Although the focus on HIV vaccines may divert attention away from difficult questions relating to sexuality and drug use,⁷⁸ it may also increase attention on the present global economic (dis)order and North–South disparities, which are, according to some views, responsible for developing-world impoverishment and the consequent rampant spread of HIV infection.⁷⁹ Above all, we must acknowledge that the development and distribution of an HIV preventive vaccine in developing countries will take many years, perhaps decades – or we may never have an effective vaccine for HIV/AIDS. We must strengthen, not relax, other prevention efforts. In 1995, Tony Klouda wrote:

⁷⁸ Kippax S. New antiviral therapy and the promise of vaccines: a challenge to HIV prevention for social sciences. Paper presented at XIth Annual Meeting of the Canadian Association for HIV Research, Montreal, April 2000.

⁷⁹ Figueredo R. and Cheru F. Debt relief and social investment, Report to the UN Commission on Human Rights, 2000, E/CN.4/2000/51, www.unhchr.ch

It is arrogant to maintain that there is a set of solutions for AIDS and HIV in the face of the catastrophically inadequate generalized support of the poorest and most marginalized. The world might be a better place for the abolition of grandiose and patronising statements about the eradication of HIV in favour of more honest statements about what can be achieved within defined areas of endeavour in particular situations, and in relation to the overwhelming influence of political realities.... On the broader political front, it should be recognized that the enemy in this case is not AIDS, but that very status quo that allows for the continuing imposition of inequities that leads to the inequalities in health.⁸⁰

Klouda proposes that AIDS activists recognize allies and learn to speak with and work alongside them so that problems seen to be of common interest can be tackled. This advice appears just as sound in the development and distribution of HIV preventive vaccines as in other areas of HIV/AIDS action and activism.

⁸⁰ Klouda T. Responding to AIDS: Are there *any* appropriate development and health policies? *Journal of International Development* 1995; 7(3): 467-487 at 486-7.

9. Key Resources

This section contains the most useful references cited in this paper.

Books, Articles, and Reports

AIDS Vaccines in the Developing World, Fact Sheet, Interagency Coalition on AIDS and Development, 1999, www.icad-cisd.org

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Bayer R. Ethical challenges of HIV vaccine trials in less developed nations: conflict and consensus in the international arena. *AIDS* 2000; 14(8): 1051-1057

Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups. International Council of AIDS Service Organizations, 2000, www.icaso.org

Ethical and policy issues in international research. National Bioethics Advisory Commission, draft report, 29 September 2000 <http://bioethics.gov/report.html>

Ethical Considerations in HIV Preventive Vaccine Research: UNAIDS Guidance Document Geneva: UNAIDS, 2000, www.unaids.org

Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the Belmont Report). (US) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979.

Ethics and Research on Human Subjects: International Guidelines. Geneva: CIOMS, 1993.

Guenter D., Esparza J. and Macklin R. Ethical considerations in international HIV vaccine trials: summary of a consultative process conducted by the Joint United Nations Programme on HIV/AIDS (UNAIDS) *Journal of Medical Ethics* 2000; 26(37): 37-43.

HIV/AIDS and Human Rights: International Guidelines. Geneva and New York: UNAIDS and the Office of the High Commissioner for Human Rights, 1998, www.unaids.org

Snow B. *HIV Vaccine Handbook.* Washington, DC: AIDS Vaccine Advocacy Coalition, 1999, www.avac.org

UNAIDS Sponsored Regional Workshops to Discuss Ethical Issues in Preventive HIV Vaccine Trials. UNAIDS, 2000, www.unaids.org

Websites

AIDS Vaccine Advocacy Coalition

Contains the HIV Vaccine Handbook and other useful resources

www.avac.org

Canadian HIV/AIDS Legal Network

Publishes a regular newsletter and comprehensive reports on legal and ethical issues.

www.aidslaw.ca

HIV InSite

Contains useful references on vaccines.

hivinsite.ucsf.edu

Interagency Coalition on AIDS and Development

Contains fact sheets on vaccines and related matters.

www.icad-cisd.com

International AIDS Economics Network

Information on the economic aspects of vaccine development.

www.iaen.org

International AIDS Vaccine Initiative

A major resource on vaccine development.

www.iavi.org

International Council of AIDS Service Organizations

Contains a community primer on vaccines.

www.icaso.org

UNAIDS

Contains the Guidance Document and other useful resources

www.unaids.org

World Medical Association

Contains the revised version of the Declaration of Helsinki

www.wma.net

Annex 1: Glossary and Abbreviations

The following glossary is based on the *HIV Vaccine Glossary*, prepared by the NIAID Office of Communications.⁸¹ Other terms used in this paper have also been added.

AfriCASO: African Council of AIDS Service Organizations

AIDS (acquired immunodeficiency syndrome): the late stage of HIV disease, characterized by a deterioration of the immune system and a susceptibility to a range of opportunistic infections and cancers.

antibody: an infection-fighting protein molecule in blood or secretory fluids.

arm: a group of participants in a clinical trial, all of whom receive the same treatment, intervention, or placebo. The other arm(s) receive(s) a different treatment.

blinded study: a clinical trial in which participants are unaware as to whether or not they are in the experimental or control arm of the study. (See also **double-blind study**.)

breakthrough infection: an infection, which the vaccine is intended to prevent, that occurs in a volunteer during the course of a vaccine trial. Such an infection is caused by exposure to the infectious agent and may occur before or after the vaccine has taken effect or all doses have been given.

CBO: community-based organization

CIOMS: Council for International Organizations of Medical Sciences

control: in vaccine clinical trials, the control group is given either the standard treatment for the disease or an inactive substance called a placebo. The control group is compared with one or more groups of volunteers given experimental vaccines to detect any effects of the vaccines.

correlates of immunity (correlates of protection): the immune responses that must be present to protect an individual from a certain infection. The precise correlates of immunity in HIV transmission are unknown.

double-blind study: a clinical trial in which neither the study staff nor the participants know which participants are receiving the experimental vaccine and which are receiving a placebo or another therapy. Double-blind trials are thought to produce objective results, since the

⁸¹ Office of Communications, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services, 2000, <http://www.niaid.nih.gov/factsheets/glossary.htm>

researcher's and volunteer's expectations about the experimental vaccine do not affect the outcome.

ELISA (enzyme-linked immunoabsorbent assay): a blood test that detects antibodies based on a reaction that leads to a detectable color change in the test tube. The HIV ELISA is commonly used as the initial screening test because it is relatively easy and inexpensive to perform. Because the HIV ELISA is designed for optimal sensitivity – that is, it detects all persons with HIV antibodies as well as some who don't have them (false positives) – a positive HIV ELISA test must be confirmed by a second, more specific test such as an HIV Western blot.

empirical: based on experience or observational information and not necessarily on proven scientific data. In the past, vaccine trials have been performed based exclusively on empirical data and without a full understanding of the disease processes or correlates of immunity.

endpoint: the results of an intervention such as vaccination compared among different study groups in a clinical trial. In early vaccine trials, common endpoints are safety and specific types and intensities of immune responses (neutralizing antibodies, CTL responses).

epidemiology: the study of the frequency and distribution of disease in human populations.

ethics review committee / IRB (Institutional Review Board): a committee of physicians, statisticians, community advocates and others that reviews clinical trial protocols before they can be initiated, and must ensure that the trial is ethical and that the rights of participants are adequately protected.

HAART: highly active antiretroviral therapy.

IAAG: United Nations Inter-Agency Advisory Group on AIDS.

immune deficiency: a breakdown or inability of certain parts of the immune system to function, thus making a person susceptible to diseases that they would not ordinarily develop.

immunity: natural or acquired resistance provided by the immune system to a specific disease. Immunity may be partial or complete, specific or nonspecific, long-lasting or temporary.

immunization: the process of inducing immunity by administering an antigen (vaccine) to allow the immune system to prevent infection or illness when it subsequently encounters the infectious agent.

incidence: the rate of occurrence of some event, such as the number of individuals who get a disease divided by a total given population per unit of time. (Contrast with **prevalence**.)

inclusion/exclusion criteria: the medical or social reasons why a person may or may not qualify for participation in a clinical trial.

informed consent: an agreement signed by prospective volunteers for a clinical research trial that indicates their understanding of (1) why the research is being done, (2) what researchers want to accomplish, (3) what will be done during the trial and for how long, (4) what risks are involved, (5) what, if any, benefits can be expected from the trial, (6) what other interventions are available, and (7) the participant's right to leave the trial at any time.

isolate: a particular strain of HIV-1 taken from a person.

NGO: non-governmental organization.

OECD: Organisation for Economic Co-operation and Development.

OHCHR: Office of the United Nations High Commissioner for Human Rights.

opportunistic infection: an illness caused by an organism that usually does not cause disease in a person with a normal immune system.

Phase I vaccine trial: a closely monitored clinical trial of a vaccine conducted in a small number of healthy volunteers. A Phase 1 trial is designed to determine the vaccine's safety in humans, its metabolism and pharmacologic actions, and side effects associated with increasing doses.

Phase II vaccine trial: controlled clinical study of a vaccine to identify common short-term side effects and risks associated with the vaccine and to collect information on its immunogenicity. Phase 2 trials enroll some volunteers who have the same characteristics as persons who would be enrolled in an efficacy (Phase 3) trial of a vaccine. Phase 2 trials enroll up to several hundred participants and have more than one arm.

Phase III vaccine trial: large controlled study to determine the ability of a vaccine to produce a desired clinical effect on the risk of a given infection, disease, or other clinical condition at an optimally selected dose and schedule. These trials also gather additional information about safety needed to evaluate the overall benefit-risk relationship of the vaccine and to provide adequate basis for labeling. Phase 3 trials usually include several hundred to several thousand volunteers.

placebo: an inactive substance administered to some study participants while others receive the agent under evaluation, to provide a basis for comparison of effects.

polyvalent vaccine: a vaccine that is produced from multiple viral strains, or is made to induce immune responses against multiple strains.

prevalence: the number of people in a given population affected with a particular disease or condition at a given time. Prevalence can be thought of as a snapshot of all existing cases at a specified time. (Contrast with **incidence**.)

preventive HIV vaccine: a vaccine designed to prevent HIV infection.

prophylaxis: prevention of disease.

protocol: the detailed plan for a clinical trial that states the trial's rationale, purpose, vaccine dosages, routes of administration, length of study, eligibility criteria, and other aspects of trial design.

randomized trial: a study in which participants are assigned by chance to one of two or more intervention arms or regimens. Randomization minimizes the differences among groups by distributing people with particular characteristics equally among all the trial arms.

seroconversion: the development of antibodies to a particular antigen. When people develop antibodies to HIV or an experimental HIV vaccine, they "seroconvert" from antibody-negative to antibody-positive. Vaccine-induced seroconversion does not represent an infection. Instead, vaccine-induced seroconversion is an expected response to vaccination that may disappear over time.

serostatus: positive or negative results of a diagnostic test, such as an ELISA, for a specific antibody.

sterilizing immunity: an immune response that completely prevents the establishment of an infection.

subtype: also called a clade. With respect to HIV isolates, a classification scheme based on genetic differences.

surrogate marker: an indirect measure of disease progression. In HIV disease, the number of CD4⁺ T cells per cubic millimetre of blood is often used as a surrogate marker.

therapeutic HIV vaccine: a vaccine designed to boost the immune response to HIV in a person already infected with the virus.

UNAIDS: Joint United Nations Programme on HIV/AIDS.

vaccine: a preparation that stimulates an immune response that can prevent an infection or create resistance to an infection.

virus: a microorganism composed of a piece of genetic material – RNA or DNA – surrounded by a protein coat. To replicate, a virus must infect a cell and direct its cellular machinery to produce new viruses.

Western blot: a blood test to detect antibodies to several specific components of a virus such as HIV. This test is most often used to confirm a positive ELISA.

WHO: World Health Organization.

Annex 2: Status of HIV Vaccine Clinical Research in Developing Countries (June 2000)

The following are some of the current and proposed HIV vaccine trials in developing countries. See also the websites of the International AIDS Vaccine Initiative and the AIDS Vaccine Advocacy Coalition.

(a) Brazil, Trinidad/Tobago, and Haiti

A multisite Phase II study of a canary pox with a gp120 boost vaccine is due to start in early 2000. Approvals have already been obtained from the national authorities in Haiti and Brazil.

(b) Kenya

Preparations are underway for Phase I clinical trials, funded by IAVI, which are expected to begin in Nairobi late 2000. The candidate vaccine is based on subtype A virus, and will follow a similar trial in Oxford, UK.

(c) South Africa

In 1997, the Medical Research Council secured the rural district of Hlabisa as a HIVNET trial site. The South Africa AIDS Vaccine Initiative has commenced a community consultation and consensus-building process to prepare the way for trials. South African scientists, in collaboration with Alphavax (US) and with partial support from IAVI, are also working on a subtype C candidate vaccine.

(d) Thailand

The first vaccine trial was conducted in Thailand in 1994. Since then eight vaccine trials have been conducted, including the most recent, which commenced in 1999. This is a Phase III trial of AIDSVAX, a clade B/E candidate vaccine, in a population of 2500 intravenous drug users in Bangkok.

The vaccine is produced by VaxGen (US) The trial does not include a needle and syringe exchange program; however, all participants “are automatically enrolled in drug treatment and maintenance programs at the Thai clinics to help them stop using drugs and reduce their risk for HIV infection.”⁸² No special medical care beyond that provided by the Thai public health system will be available for participants who become HIV infected during the trial.⁸³ VaxGen will make

⁸² Questions and Answers on the Thailand Phase III Vaccine Study and CDC’s Collaboration *CDC Update*, February 1999.

a small donation to the Bangkok Municipal Administration, and if the trial is successful, will make the vaccine as “inexpensive as possible” for Thailand.⁸⁴ The study protocol was reviewed by the institutional review boards and ethics committees of all the involved agencies, as well as the UNAIDS Vaccine Advisory Committee.⁸⁵

(e) Uganda

In 1999, Uganda began the first HIV vaccine trial in Africa with a Phase I/II study of a subtype B vaccine (ALVAC vCP205). The candidate vaccine has been extensively tested in the US and France. It is a clade B vaccine, intended to induce cell-mediated immunity, and researchers will be looking for reactions to subtypes A and D, the two subtypes that cause most HIV infections in Uganda. Recent research has suggested that “cross-reactivity” may permit the use of such vaccines in Uganda and other developing countries. If this is found not to be the case, future research will have to focus on subtypes specific to different countries.⁸⁶ Another proposed study will evaluate the safety and immunogenicity of an ALVAC HIV vaccine (vCP1452) in Ugandan infants.⁸⁷

⁸³ This includes prophylaxis for tuberculosis and pneumocystis carinii pneumonia and two antiretroviral drugs – AZT and ddI, ddC, or 3TC, as appropriate. Questions and Answers on the Thailand Phase III Vaccine Study and CDC’s Collaboration *CDC Update*, February 1999.

⁸⁴ Wehrwein P. and Morris K. HIV-1 vaccine trial go-ahead reawakens ethics debate *Lancet* 1998; 351: 1789.

⁸⁵ UNAIDS supports decision by Thai government to move ahead with large-scale human testing of AIDS vaccine, UNAIDS Press Release, 9 February 1999.

⁸⁶ NIAID opens first AIDS vaccine trial in Africa, NIAID media release, 8 February 1999.

⁸⁷ HIV Prevention Trials Network Leadership Group, RFA AI-98-015, at 12.
<http://resevoir.fhi.org/en/aids/hivnet/hptnag.pdf>

Annex 3: Draft Recommendations for Discussion at the Satellite Meeting

The following recommendations were offered as a starting point for discussions at the satellite meeting.⁸⁸

1. An independent international collaborative body comprising all relevant stakeholders (community, researchers, industry, UN system organizations, and international NGOs) be created to advise on legal and ethical issues related to HIV vaccines.
Action: UNAIDS, WHO, OHCHR, NGOs
2. Action be taken to revive and stimulate developing-world access to existing vaccines. Consideration be given to the creation of an international treaty on vaccines.
Action: WHO, UNICEF, health-sector NGOs
3. Integrate a consideration of HIV vaccine research and development and global corporate responsibility into the ongoing discussions about human rights, globalization, the Global Compact, and UN reform.
Action: OHCHR, NGOs, Global Business Council on HIV/AIDS
4. Assess industrialized-country contributions to research, development, and distribution of HIV vaccines as part of industrialized-country international obligations to promote the right to health.
Action: UN Committee on Economic, Social and Cultural Rights
5. All appropriate prevention and care efforts, based on the International Guidelines on HIV/AIDS and Human Rights, should be maintained and increased. HIV vaccines must be seen as a potential component of, not a replacement for, broad-based HIV prevention programs.
Action: Funding agencies and national AIDS programs
6. When considering the application of legal and ethical principles, distinguish research of little direct benefit to developing countries and communities from that intended to directly improve health in those contexts.
Action: Researchers, communities, ethics review committees
7. Introduce legislative reform as necessary to facilitate the research and development of HIV vaccines while prohibiting unproven vaccines and unethical medical experimentation.

⁸⁸ See also Langan M. and Collins C. Paving the Road to an HIV Vaccine: Employing Tools of Public Policy to Overcome Scientific, Economic Social and Ethical Obstacles, HIV InSite, 1998, <http://hivinsite.ucsf.edu/topics/vaccines/2098.400a.html>

Action: Developing country governments. UNAIDS/WHO may provide technical assistance.

8. Create a conducive research environment, in order to attract researchers and funding to develop an HIV vaccine specific to the local context, consistent with appropriate research standards.

Action: Developing countries' governments and communities

9. Promote appropriate research standards through the sharing of information and experiences about HIV vaccine research. Ways should be found to share experiences between communities with a view to maintaining minimum conditions. Existing regional networks could be used.⁸⁹

Action: Communities and ethics review boards

10. Industrialized countries should declare the HIV pandemic a global emergency and a national security issue, and specific and adequate funding and other incentives should be undertaken to develop and distribute an HIV vaccine suitable for developing countries.

Action: Industrialised countries

11. A Participants Bill of Rights should be developed for HIV vaccine trial volunteers.

Action: Researchers, community representatives, and ethics review boards

12. Include "benefit to developing countries" in criteria for selection of applications for pure and applied research grants.

Action: Research funders

⁸⁹ For example, the regional code on HIV/AIDS in the workplace adopted by the Southern African Development Community (SADC) see A human rights approach to AIDS prevention at work: The Southern African Development Community's Code on HIV/AIDS and Employment. UNAIDS, 2000 www.unaids.org

Annex 4: Rapporteur's Report on HIV Vaccine Workshop

1. INTRODUCTION

This is a brief report of the key areas on discussion in HIV vaccines parallel workshop held at the Putting Third First – Critical Legal Issues and HIV/AIDS satellite meeting on 7 July 2000 in Durban, South Africa.

2. KEY ISSUES AND DEBATES

A number of key issues emerged in the discussion, these included:

2.1 The Involvement of Communities in HIV Vaccine Development

A number of different points were raised with regard to the community, including:

- Participants felt that we needed to elaborate on and develop what we mean by “community involvement” in vaccine development.
- Community involvement will take different forms at different stages of the trials.
- Holding an HIV vaccine trial within a community may raise expectations regarding the development of a vaccine, which will in turn impact on safer-sex programs. Researchers need to ensure that they monitor the impact the trial is having on the sexual practices within the community at large.
- How do we manage information that is passed on to the community, eg, what information should be given?
- The language of ethics is very difficult and inaccessible. We need to find other ways of making these issues accessible, eg, using human rights concepts.
- Should 10 percent of a trial budget be spent on developing infrastructure within a community and should this become a standard for ethical research?

2.2 The Rights of Trial Participants after an Unsuccessful Trial

A number of different issues were raised with regard to unsuccessful trials, including:

- What access to treatment should such participants have?
- How will we ensure that the community remains committed to the trial after initial setbacks?
- Are participants excluded from being involved in future trials?

2.3 Need to Develop Partnerships and Collaborations

- To develop partnerships with both NGOs/community organisations and scientists.
- Need to ensure that proper partnerships are built between scientists and communities.

2.4 Informed Consent

- How do we ensure that proper consent is obtained from trial participants?
- The need to look at both the process and the formal aspect of giving consent.
- There is a need to look at the context of people's lives before developing informed-consent forms, eg, must understand whether women in that community are able to give consent freely and voluntarily.
- Should some communities be excluded from selection as trial sites because they are so poor that anything you offer them with regard to participation would be an incentive?
- What do we do about informed consent in collective communities?
- How do we ensure concepts such as placebo, randomisation, etc are explained properly before participants enter a trial?
- How do we deal with the tension between informed consent and inducements to enter a trial, particularly in developing countries where many participants will enter the trial because they see it as their only way of getting access to health-care services?

2.5 How to Encourage More Research into Developing an HIV Vaccine

- How to find a balance between trying to encourage research and ensure that it is undertaken in an ethical manner in developing countries?
- The need to develop networks around this issue.
- The need to look at both private and public sector funding.

2.6 How to Implement a Large-Scale HIV Vaccination Program

- At what point will we implement a large-scale HIV vaccination program? Ie, will it be done when the vaccine is still only partially effective?
- A polio vaccine was developed in 1954; however, it still took nearly 20 years before there was worldwide distribution of the vaccine.

2.7 Ensuring That Communities Benefit from HIV Vaccine Trials

- We need to ensure that communities benefit from participating in an HIV vaccine trial.
- We need to consider whether trials can be used as a means of developing infrastructure in a community.

2.8 Access to a Vaccine after Development

- There is a need to ensure that there is worldwide access to the vaccine.
- Agreements must be reached on access before the trial starts.
- We need further debate on intellectual property rights.

2.9 Access to Care/Treatment

- There is a need to ensure that the debates on treatment continue, particularly in developing countries.

2.10 When Should a Trial Be Stopped?

- Should a trial be stopped if the rates of unsafe sex become unacceptably high?

3. RECOMMENDATIONS

3.1 Create an International Collaborative Body on HIV Vaccines

It was recommended that a collaborative body be set up to advise on the ethical and legal issues related to HIV vaccine trials and to try to increase the funding set aside for vaccine development.

The functions of this body would be to:

- (a) lobby and increase impetus for HIV vaccine development;
- (b) build local capacity;
- (c) ensure fast flow of information on vaccine development; and
- (d) ensure that there is access to a vaccine after development and appropriate infrastructure for distribution and delivery.

3.2 Ensure that HIV Vaccine Development Is on the Agenda of Human Rights Groups

It was recommended that efforts be put into ensuring that the development of an HIV vaccine is put on the agenda of human rights groups throughout the world. In this regard the UNAIDS Guidelines can be used as a way of developing local capacity on these issues.

3.3 Building the Capacity of Local Communities to Participate in Vaccine Trials

It was recommended that efforts be put into building the capacity of local organizations to participate in HIV vaccine development as equal partners.

Ann Strode
August 2000