HIV Vaccines in Canada: Legal and Ethical Issues

An Overview

Canadian Strategy on HIV/AIDS

CANADIAN HIV•AIDS LEGAL NETWORK | RÉSEAU JURIDIQUE CANADIEN VIH•SIDA

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An Overview

Published by the Canadian HIV/AIDS Legal Network

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Website: www.aidslaw.ca

Further copies can be retrieved at www.aidslaw.ca
or obtained through the Canadian HIV/AIDS Clearinghouse
(www.clearinghouse.cpha.ca)

ISBN 1 896735-41-X

Canadian Cataloguing in Publication Data

Garmaise, David

HIV Vaccines in Canada: legal and ethical issues: an overview

Text in English and French, on inverted pages.

ISBN 1-896735-41-X

1. AIDS vaccines – Research – Law and legislation – Canada. 2. AIDS vaccines – Research – Moral and ethical aspects – Canada. 3. Human experimentation in medicine – Law and legislation – Canada. I. Canadian HIV/AIDS Legal Network. II. Title: Vaccins anti–VIH au Canada.

QR189.5.A33G37 2002 616.97'92027 C2002-940699-4E

Acknowledgments
This paper was written by David Garmaise, and is an adaptation of a longer paper by David Thompson entitled *HIV Vaccines in Canada: Legal and Ethical Issues – A Backgrounder*. The Canadian HIV/AIDS Legal Network wishes to thank Jane Rowley for her advice and guidance throughout the preparation of this paper; Sam Avrett, Chris Collins, Dale Guenter, Craig McClure, Sophia Musaka Monico, David Patterson, Paul Sandstrom, and Michael R Smith for reviewing a draft of the paper; Garry Bowers for copyediting the English text; Jean Dussault for translating the original English text into French; and C & G Graphics, Montréal, for layout.

Funding for this project was provided by Health Canada under the Canadian Strategy on HIV/AIDS.
The opinions expressed in this document are those of its authors and do not necessarily reflect the views or policies of the Minister of Health or the Canadian HIV/AIDS Legal Network.

Cover design by Reinhard Blumenschein

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Why an Overview on Vaccine-Related Legal and Ethical Issues?

Current prevention efforts – including education about safer sex and provision of condoms, making sterile injection equipment available to people who inject drugs, peer counselling, providing HIV treatments to reduce mother-to-child transmission, and making blood supplies safer – have slowed the spread of HIV but have not stopped it. The best long-term hope for controlling AIDS is the development and widespread distribution of a safe, effective, and affordable preventive vaccine.

Research aimed at developing a preventive HIV vaccine is accelerating. Over the coming decade, Canadians will likely be involved in vaccine clinical trials both here and abroad. In fact, HIV vaccine trials in Canada have already begun. The existing trials, the likelihood of further trials, and the potential impact of a preventive HIV vaccine on HIV prevention programs all raise a number of legal and ethical issues that need to be addressed.

About This Overview

This overview is designed to provide a summary of the major legal and ethical issues related to the development and delivery of an HIV vaccine in Canada. The main target audience is people working in community-based HIV/AIDS organizations. Secondary target audiences are researchers working on HIV vaccines and government officials working in HIV/AIDS. For a more in-depth examination of the topics discussed in this paper, readers should consult *HIV/AIDS and Vaccines: Legal and Ethical Issues: A Background Paper* (see box, page ii).

The overview deals with HIV vaccines in Canada, but many of the issues it raises also apply to other developed countries, and some of them will resonate with people working on

The *Background Paper*

This overview has been adapted from *HIV/AIDS and Vaccines: Legal and Ethical Issues – A Background Paper*, prepared by David Thompson for the Canadian HIV/AIDS Legal Network. There are frequent references to the *Background Paper* within the text of this paper.

The *Background Paper,* which is in English only, is available on the website of the Canadian HIV/AIDS Legal Network (www.aidslaw.ca/Maincontent/issues/vaccines.htm).

vaccine issues in developing countries. It focuses primarily on HIV preventive vaccines; however, the issues with respect to therapeutic vaccines are very similar.

Section 1.0 – The **Introduction** provides explanatory information on vaccines and clinical trials, a brief summary of the current state of HIV vaccine research globally and in Canada, and a description of the AIDSVAX® trial now underway in Canada and other countries.

Section 2.0 – Investing in HIV Vaccine Development and Delivery discusses the need for Canada to invest more resources in HIV vaccines and to develop a Canadian HIV Vaccine Strategy.

Section 3.0 – HIV Vaccine Clinical Trials examines legal and ethical issues that arise during the conduct of large-scale HIV vaccine efficacy trials on humans. The subsection on "Working with Target Communities" describes how governments, trial organizers, and communities can work together to ensure that the trials are of the highest quality. The subsection on "Recruitment" discusses which communities should participate in HIV vaccine trials and what compensation should be offered to participants for taking part in the trial. The subsection on "The Informed Consent Process" examines measures that can be used to ensure that consent is truly informed, and describes what information should be disclosed as part of the process of obtaining consent. The subsection on "Obligations to Participants during and after the Trial" examines four specific obligations – the provision of preventive counselling, the provision of care and treatment to participants who become HIV-positive during the trial, the provision of compensation to any participants who suffer a vaccine-induced injury, and the dissemination of information on the results of the trial.

Section 4.0 – HIV Vaccine Delivery examines legal and ethical issues related to the eventual delivery of an HIV vaccine, and discusses the need for a formal HIV vaccine delivery plan.

Recommendations have been inserted throughout the text. A complete list of the recommendations is presented at the end of the paper. Only limited references have been included in this overview. Please see the *Background Paper* for full references. Suggestions for further reading have been provided in the text.

What Does This Overview Conclude?

The most significant conclusion of the overview is that Canada needs a formal HIV vaccine plan. The paper calls on Health Canada to coordinate, and provide funding for, a Canadian HIV Vaccine Plan by 1 October 2003. The Plan should address both the development of vaccines and the delivery of an eventual vaccine. It should be developed in consultation with the provinces and territories, HIV/AIDS community organizations, HIV researchers, and other stakeholders.

The overview also concludes:

- that Canada should substantially increase its investment in HIV vaccine research and development in Canada and internationally;
- that all populations with significant HIV infection rates should be involved in human testing of candidate HIV vaccines;
- that communities should be involved in the design and implementation of HIV vaccine trials being conducted in their midst;
- that consent obtained for participation in an HIV vaccine trial should be truly informed, meaning that all reasonable steps must be taken to ensure that potential participants understand the nature, benefits, and risks of taking part in a trial;
- that trial organizers must provide high-quality preventive counselling to all participants in an HIV vaccine trial;
- that trial organizers must ensure that high-quality care and treatment is provided to participants who become HIV-infected during the course of the trial;
- that the federal government should establish a no-fault vaccine-related injury-insurance program covering all experimental and licensed vaccines (both HIV-related and other); and
- that trial organizers should work with insurance companies to minimize the risks of discrimination for participants in an HIV vaccine trial.

Note on Terminology

The term "**trial organizers**" is used throughout this overview to refer to both the sponsors of clinical trials and the researchers associated with the trials. The following is a short glossary of other terms used extensively in this overview.

- The **arms** of a clinical trial refer to the different groups into which trial participants are divided in order to test the effectiveness of a candidate vaccine.
- **Candidate vaccine** refers to the experimental vaccine being tested in a clinical trial.
- **Cohort** refers to the participants at a given site in a vaccine clinical trial.
- **Seroincidence** or **HIV incidence** refers to the number of new HIV infections occurring over a period of time (usually one year).
- **Seroprevalence** or **HIV prevalence** refers to the number of HIV infections in the general population or a particular subpopulation at a given moment in time.

Further Reading

- For additional information on issues raised throughout this overview, consult *HIV Vaccine Handbook: Community Perspectives in Participating in Research, Advocacy and Progress*. B Snow (ed). AIDS Vaccine Advocacy Coalition. December 1999 (2nd printing) (available at www.avac.org). The Handbook contains a series of articles, some of which relate directly to topics addressed in this paper: Working with Communities; Community Advisory Boards; Vaccine Preparedness Studies, HIV Vaccines and Human Rights; Participants Bill of Rights; and Social, Ethical and Political Considerations.

- For a discussion of global strategies to promote HIV vaccine research and access to an eventual HIV vaccine, consult *HIV Vaccines for Developing Countries: Advancing Research and Access*. S Avrett. Canadian HIV/AIDS Legal Network, 2002 (www.aidslaw.ca/Maincontent/issues/vaccines.htm).

The following publications provide useful ethical guidance for the conduct of clinical trial research and are referenced extensively in this overview.

- *Ethical considerations in HIV preventive vaccine research*. UNAIDS Guidance Document. Joint United Nations Programme on AIDS (UNAIDS). Geneva: May 2000 (available at www.unaids.org).

- *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization, Geneva: 1993 (available at www.cioms.ch).

- *Tri-Council Policy Statement: Ethical conduct for research involving humans*. Medical Research Council of Canada, National Science and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, August 1998 (available at www.nserc.ca).

Section 1.0 Introduction

This section provides an explanation of vaccines and clinical trials. It has been adapted from information on the websites of the International AIDS Vaccine Initiative and the Canadian HIV Trials Network; and from *Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups*, a publication of the International Council of AIDS Service Organizations. (See the details on page 3 on how to access these resources.) This section also summarizes the current state of HIV vaccine research globally and in Canada, and describes the AIDSVAX trial now underway.

1.1 Vaccines

A vaccine is a medicine that teaches the body's immune system to recognize and protect against a disease caused by an infectious agent. When people are given a vaccine against a particular disease, this provokes responses from their immune systems. The immune systems are then "on alert." If these people are later exposed to the infectious agent that causes that disease, their immune systems are ready to protect them from infection.

Vaccines save millions of lives each year and prevent many more people from getting sick. They are one of the most powerful and cost-effective health interventions available in medicine. For example, extensive use of the smallpox vaccine eradicated that disease from the world. As well, widespread vaccination against polio has reduced the number of cases of polio dramatically and has eradicated it from the Americas. Vaccines exist for many other diseases, including measles, chicken pox, influenza, hepatitis A and B, mumps, pertussis, and rubella. However, there are a number of important diseases for which there are still no effective vaccines, including HIV/AIDS, malaria, hepatitis C, and tuberculosis – the most deadly infectious diseases in the world. (There is a partially effective vaccine against

tuberculosis, but it needs improvement.) When properly manufactured and used, vaccines are among the safest of medicines.

Vaccine development is a long and complicated process. For example, after more than 15 years of research on HIV, only two candidate vaccines are currently undergoing large-scale efficacy testing in humans. It is likely that the first generation of HIV vaccines will be only partially effective – this means that they will not protect against HIV infection or disease progression in everyone who is vaccinated and exposed to HIV.

A vaccine is a medicine that teaches the body's immune system to recognize and protect against a disease caused by an infectious agent.

Is a vaccine a cure? Most of the time, when one talks about vaccines one is referring to preventive vaccines – ie, medicines that protect people who do not have a disease from getting that disease. Preventive vaccines do not provide a cure for people who are already infected. Scientists are also trying to develop what are called "therapeutic vaccines" for HIV, hepatitis, cancer, addiction, and a number of other conditions. Therapeutic vaccines are designed to treat disease, not to prevent it. However, therapeutic vaccines for HIV are still in the early stages of development.

1.2 Clinical Trials

Clinical trials are research studies designed to evaluate experimental vaccines (or therapeutic agents) in humans. The purpose of vaccine clinical trials is to determine whether the candidate vaccine is both safe and effective. New vaccines are tested in humans only after laboratory and animal studies show promising results.

Clinical trials for a candidate preventive vaccine are divided into three distinct phases. (The following text is taken verbatim from the website of the International AIDS Vaccine Initiative at www.iavi.org.)

- **Phase I** trials are the first human tests of a candidate vaccine, generally conducted on small numbers (10 to 30) of healthy adult volunteers who are not at risk for the disease in question. The main goal is evaluation of safety, and to a lesser extent, analysis of the immune responses evoked by the vaccine and of different vaccine doses and immunization schedules. A Phase I trial usually takes eight to twelve months to complete.

- **Phase II** testing involves a larger number of volunteers (50 to 500), usually a mixture of low-risk people and higher-risk individuals from the population in which Phase III (vaccine efficacy) trials will eventually be conducted. Phase II trials generate additional safety data as well as information for refining the dosage and immunization schedule. Although not set up to determine whether the vaccine actually works, Phase II trials are sometimes large enough to yield preliminary indications of efficacy. These trials generally take 18 to 24 months, with the increase over Phase I due primarily to the additional time required for screening and enrolling larger numbers of trial participants.

- **Phase III** trials are the definitive test of whether a vaccine is effective in preventing disease. Using thousands of volunteers from high-risk populations in geographic regions where HIV is circulating, the incidence of HIV in vaccinated people is compared to that in people who receive a placebo. Successful demonstration of efficacy in a Phase III trial can then lead to an application for licensure of the vaccine. Phase III trials of AIDS vaccines are generally expected to require a minimum of three years for enrolment, immunizations, and assessments of efficacy.

Clinical trials for therapeutic agents operate in the same fashion.

The detailed plan for a trial is called a protocol. The protocol outlines the rationale and purpose of the trial and lays down procedures for how the vaccine will be given, who is eligible to take part, what the timetable is for tests and clinical visits by participants, how long the study will last, how the results will be assessed, and so forth.

Further Reading

- For more information on HIV vaccines and on efforts to accelerate HIV vaccine research, go to the website of the International AIDS Vaccine Initiative at www.iavi.org.
- For more information on clinical trials in general, go to the website of the Canadian HIV Trials Network at www.hivnet.ubc.ca/ctn.html.
- To obtain a copy of *Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups*, go to the website of the International Council of AIDS Service Organizations at www.icaso.org.

To determine the efficacy of an HIV vaccine in a clinical trial, organizers randomly divide the participants into two arms: one that will receive the vaccine in addition to HIV-prevention measures (the vaccine arm), and one that will receive a "control" in addition to HIV-prevention measures (the control arm). The control arm may receive a placebo (an inactive or inert substance), another HIV vaccine that is known to be effective (if one has been developed), or a vaccine for a condition other than HIV. Randomization is the best way to make sure that people in different arms of the trial are broadly similar, so that the effects of the vaccine can be reliably measured. In most trials, neither the researchers nor the participants know who is getting the vaccine. This is called double-blinding. The purpose of double-blinding is to make sure that the expectations of the researchers and participants do not bias the results of the trial.

Clinical trials are usually sponsored (ie, designed and paid for) by the private company or public research institution that developed the experimental vaccine. The principal investigator is the researcher who supervises the trial, usually a doctor with experience in running clinical trials. Phase III clinical trials of vaccines are usually conducted in multiple locations (often in more than one country). Each of these locations is called a trial site. Most HIV-related clinical trials in Canada take place in cities that have university teaching hospitals with clinics specializing in HIV disease. Each site has a doctor, called a site investigator, in charge of the trial,. Usually, staff are hired at each site to help the site investigator run the trial. Sometimes, family doctors can be site investigators and can run trials from their offices. The trial participants at a given site are often referred to as a cohort.

In Canada, all clinical trials must be approved in advance by the Therapeutics Products Directorate (TPD) of Health Canada. TPD reviews the safety, efficacy, and quality data submitted by the sponsor and approves the distribution of the experimental vaccine to the principal investigator. Federal regulations also require that clinical trials be approved in advance by research ethics boards (REBs), sometimes called institutional review boards (IRBs). In the case of a multi-centre trial, approval is usually required from an REB at each site. (Please see the *Background Paper* at www.aidslaw.ca/Maincontent/issues/vaccines.htm for a more thorough discussion of the regulatory framework for clinical trials in Canada.)

What are research ethics boards? Research ethics boards (REBs) are a mechanism established to protect people who participate in research. Typically, they are composed of at least five volunteers representing the fields of research, ethics, and law, in addition to one or more representatives from the community. REBs can be established in universities, government agencies, community organizations, hospitals, and pharmaceutical companies. There are more than 300 REBs in Canada.

A REB is mandated by its institution to approve, reject, or propose modifications to any proposed research involving human subjects that is conducted within the institution or by members of the institution. REBs review the research protocol, the informed consent document to be signed by research participants, any advertisements to be used to recruit participants, and other relevant documents. REBs ensure that any risks participants may incur are warranted in relation to the anticipated benefits, and they attempt to minimize the risk and maximize the benefits without jeopardizing the research planned. REBs also monitor clinical trials after the research protocols have been approved, and have the authority to terminate a trial if they believe that participants are being subjected to unnecessary or inappropriate risks.

1.3 Current Status of HIV Vaccine Research

Some progress has been made in the global effort to find an HIV vaccine. A number of experimental vaccines have been and are being developed in the laboratory, some of which have progressed to clinical trials. Since 1987, when the first HIV vaccine trial was conducted, about 30 candidate vaccines have been tested in approximately 60 Phase I/II clinical trials involving more than 10,000 healthy human volunteers. Two candidate vaccines are currently undergoing Phase III efficacy evaluation in North America, the Netherlands, and Thailand. The final results of these trials are expected within one to two years. (See the description of the AIDSVAX trials below.) One additional Phase III trial is scheduled to start in early 2003 in Thailand, with results expected by 2007.[1]

No precise figures are available about how much is being spent on HIV vaccine research globally, but estimates range from $US450 to 600 million a year.[2] This represents less than one percent of the spending on all global health research and development.[3]

In Canada, some work is being done to develop candidate HIV vaccines in the laboratory and to test these vaccines on animals. There have been no Phase I/II clinical trials of candidate HIV vaccines in Canada. There is one Phase III HIV vaccine trial currently operating in Canada – a multinational trial of the AIDSVAX B/B Gp 120 experimental vaccine produced by VaxGen Inc.

Aside from the AIDSVAX trial, about $CAN 2.14 million is being spent each year in Canada for HIV vaccine research. The Canadian Network for Vaccines and Immunotherapeutics (CANVAC) has been investing about $CAN 1.3 million annually in HIV

vaccine biomedical research and $CAN 140,000 annually in HIV vaccine behavioural research.[4] The Canadian Institutes of Health Research (CIHR) has been investing about $CAN 700,000 annually in HIV vaccine research.[5]

In addition, the Canadian International Development Agency has been providing an annual grant of about $CAN 2.5 million to the International AIDS Vaccine Initiative to support international HIV vaccine development.

No precise figures are available about how much is being spent on HIV vaccine research globally.

1.3.1 The AIDSVAX Trials

AIDSVAX B/B is a candidate vaccine designed to prevent HIV infection. It was developed by VaxGen, a California biotechnology company. The vaccine is designed to work against the B subtype of HIV, found primarily in North America, Western Europe, Australia, the Caribbean, and South America. A similar vaccine, AIDSVAX B/E, is designed to prevent infection with HIV subtypes B and E, primarily the latter (which is found extensively in Asia). Two Phase III clinical trials are underway, one in Canada, the United States, and the Netherlands (AIDSVAX B/B); and the other in Thailand (AIDSVAX B/E).

The North America/Netherlands trial started in 1999 and is scheduled to be completed at the end of 2002. The trial has enrolled over 5400 participants, of whom 291 are in Canada. There are three Canadian trial sites: Vancouver, Toronto, and Montréal. The primary objectives of the trial are:

- to determine if the vaccine helps to prevent HIV infection in people who are at risk for getting HIV through sexual activity; and
- to determine if the vaccine is safe compared to the placebo when given to large numbers of people who are at risk for HIV infection.

In addition, the trial is trying to determine if the vaccine also helps to slow the rate of disease progression in persons infected with HIV, and if people change their sexual activity or other risk behaviours while they are in the study.

The three Canadian sites recruited only men who have sex with men and who, in the 12 months preceding enrolment, had a relationship with an HIV-positive sexual partner or had engaged in anal intercourse with someone other than their regular HIV-negative partner. The US sites had similar entry criteria but also recruited some HIV-negative women who had HIV-positive sexual partners or who were considered to be at higher risk of HIV infection. In contrast, the trial in Thailand recruited HIV-negative injection drug users with a high risk for bloodborne transmission of HIV.

Results from the North America/Netherlands trial are expected in early 2003.

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[1] Esparza J. An HIV vaccine: How and when? *Bulletin of the World Health Organization*. 2001; 79:1133-1137.

[2] Communication from Jose Esparza, Co-ordinator, WHO – UNAIDS HIV Vaccine Initiative, 26 February 2002.

[3] Avrett S. *HIV Vaccines for Developing Countries: Advancing Research and Access*. Canadian HIV/AIDS Legal Network, 2002.

[4] Communication from Aline Rinfret, Associate Scientific Director, CANVAC, 27 March 2002.

[5] Communication from Jennifer Gunning, Program Officer, Collaborative Research Programs, CIHR, 5 April 2002.

Section 2.0
Investing in HIV Vaccine Development and Delivery

This section presents a rationale for investing in HIV vaccine development and delivery and concludes that Canada needs a formal HIV vaccine Plan.

Canada needs an HIV vaccine for the following reasons:

- **HIV/AIDS poses a threat to the health of Canadians.** As of the end of 1999, it was estimated that there were almost 49,000 people with HIV/AIDS in Canada. The epidemic in Canada is growing among women, Aboriginal people, and men who have sex with men, and remains a serious problem among injection drug users, prisoners, street youth, and immigrant communities from endemic countries.
- **Existing treatments have limitations.** The antiretroviral treatments available today are unable to cure the disease or eliminate the virus entirely. Treatment is costly and lifelong, and the treatment regimens are difficult to follow. The treatments can produce adverse effects, some of which can be severe. As well, the treatments can fail due to the emergence of drug-resistant strains of HIV.
- **Prevention efforts have had limited success.** Behaviour is influenced by many factors – environmental, social, religious, cultural, economic, educational, and psychosocial – so getting people to use condoms and sterile injection equipment regularly is a formidable challenge. It is often difficult for people to maintain safer sexual behaviour over a lifetime.

The rise in infection rates among specific populations (Aboriginal people, women, men who have sex with men, etc) is evidence of the fact that current prevention and treatment strategies have not been successful in stemming the tide of the epidemic. In addition to strength-

ening our current efforts (including by addressing the underlying causes of disease – such as poverty, marginalization, discrimination, etc) – new strategies such as vaccine research and development must be urgently explored.

Up to now, work on HIV vaccines in Canada has been fairly limited. No funds have been specifically earmarked for HIV vaccine research. No Phase I/II human trials of HIV vaccines have taken place in Canada. No work has been done to plan for the delivery of an eventual HIV vaccine. Canada can and should do more. For this to happen, a stronger political commitment is required.

Conducting more research on HIV vaccines in Canada would benefit not only Canadians but also people from other countries. HIV/AIDS is the world's most deadly infectious disease. As of December 2001, over 40 million people were living with HIV/AIDS. Already, 25 million people have died of AIDS-related causes. An estimated five million people were newly infected with HIV in 2001 – more than 13,500 people a day. More than 13 million children worldwide have been orphaned by HIV/AIDS. The number of orphaned children is expected to top 40 million in the next decade. In 16 African countries, between 10 and 20 percent of the adult population has HIV.

Further Reading

➢ For the latest HIV/AIDS epidemiological information for Canada, go to the Health Canada website at www.hc-sc.gc.ca. For international epidemiological information, go to the website of the United Nations Joint Programme on HIV/AIDS (UNAIDS) at www.unaids.org.

AIDS is overwhelming health-care systems and national economies. The United Nations estimates that the medical and human costs of AIDS have already reversed social and economic development in twenty countries. In sub-Saharan Africa, household incomes have fallen by half and business profits have decreased by 20 percent due to AIDS deaths. By 2010, South Africa's gross national product will be more than 17 percent smaller than it would have been without AIDS.[6]

Furthermore, most people with HIV or AIDS in the developing world do not have access to antiretroviral drugs or even most of the treatments for opportunistic infections, at least in part because of the high cost of these treatments. A preventive vaccine is likely to be more affordable than current treatments.

As one of the richest nations in the world, Canada has a moral obligation to contribute generously to the international effort to develop an HIV vaccine. Canada should also play a leading role in efforts to ensure global coordination of the HIV vaccine effort.

As one of the richest nations in the world, Canada has a moral obligation to contribute generously to the international effort to develop an HIV vaccine.

There is a growing scientific consensus that an HIV vaccine is possible. Advances in molecular biology and basic HIV research have led to the development of promising strategies for effective HIV vaccines. Experimental vaccines have been used to protect non-human primates from infection by a virus closely related to HIV. A number of candidate vaccines have been shown to be safe in small-scale clinical trials and to trigger HIV-specific immune

responses. Some people repeatedly exposed to HIV resist infection and mount HIV-specific immune responses, providing important clues for the design of an effective AIDS vaccine. Our experience with other infectious diseases is encouraging. Smallpox was eradicated in 1977 because of an effective vaccine. Polio has been eliminated in the Americas and projections are that it will be eliminated globally by the end of 2005. Measles and yellow fever have been controlled by vaccines. Yet only two candidate HIV vaccines have reached the final stages of testing in humans: large-scale efficacy trials. The pace of research needs to be accelerated.

HIV vaccine research should not be seen as competing with other prevention efforts or with the search for new treatments.

Some people have argued that increasing the investment into HIV vaccine research will divert scarce resources from other prevention and treatment programs. However, HIV vaccine research should not be seen as competing with other prevention efforts or with the search for new treatments. For one thing, vaccine research will advance basic science. The knowledge gained will likely benefit the search for both vaccines and treatments (for HIV disease as well as for other diseases). Furthermore, by virtue of the infrastructures that they will create, large-scale HIV vaccine trials will have spillover effects – they will bolster other prevention efforts, improve access to HIV-antibody testing, improve access to care, facilitate other research, and contribute to community development. They will also provide opportunities to administer vaccines for other diseases and to diagnose and treat other health conditions, particularly sexually transmitted infections. Finally, the spread of the epidemic and the threat it poses to human health, economic development, and political security dictate that substantial new resources be invested. Some of these additional resources should be used to support HIV vaccine research.

A failure to intensify efforts to find an HIV vaccine could be construed as a violation of the rights to life and health as proclaimed in numerous international human rights covenants and treaties. The Charter of the United Nations, the Universal Declaration of Human Rights, the United Nations General Assembly Declaration of Commitment on HIV/AIDS, and other United Nations declarations and treaties – all support the legal obligation to research and develop new technologies for health.[7]

Canada was one of 189 countries that endorsed the United Nations Declaration of Commitment on HIV/AIDS in June 2001. The Declaration of Commitment calls on governments to "increase investment and accelerate research on the development of HIV vaccines, while building national research capacity, especially in developing countries."[8]

Further Reading

➢ For further information on why we need to invest more in HIV vaccine development and delivery, consult *HIV Vaccines for Developing Countries: Advancing Research and Access*. S Avrett. Canadian HIV/AIDS Legal Network, 2002. Available at www.aidslaw.ca/Maincontent/issues/vaccines.htm.

Canada should commit significant additional resources to HIV vaccine research, both in Canada and in developing countries, and should develop an agenda for HIV vaccine development and delivery. This would best be accomplished through the creation of a formal Canadian HIV Vaccine Plan. The Plan should be coordinated by Health Canada and should be developed in consultation with, and with the full participation of, the provinces and territories, community HIV/AIDS organizations, HIV researchers, and other relevant stakeholders. The Plan should be developed by 1 October 2003.

The drafters of the Canadian HIV Vaccine Plan should consider the benefits of developing partnerships between the public and private sectors in Canada for vaccine research and development, or for vaccine delivery, or for both. These partnerships can address many factors that influence decisions concerning private-sector investment in HIV vaccine development and delivery, including:

- the high costs of research and development;
- the potentially high costs of vaccine production;
- the anticipated demand for an HIV vaccine;
- expectations about pricing; and
- the opportunity costs of researching and developing an HIV vaccine.[9]

Such partnerships exist in other countries. One example is the Australian AIDS Vaccine Consortium, which includes private-sector companies, academic research institutions, and a community advocacy organization, and is focused on developing a candidate vaccine for clinical trials in Sydney, Australia by the end of 2002.

Canada should also consider participating in international HIV vaccine development partnerships like the Kenya/Oxford partnership, which links the United Kingdom Medical Research Council and the University of Nairobi with vaccine manufacturers in the United Kingdom and Germany, and is focusing on testing a candidate vaccine in the United Kingdom and Kenya.

As well, consideration should be given in the Plan to the use of "push" and "pull" incentives – ie, policies and program tools designed to encourage more private-sector involvement in HIV vaccine development and delivery. Examples of push and pull incentives include: direct government funding of private-sector research; tax credits for vaccine research; efforts to improve international intellectual property laws; and development of infrastructures to ensure that HIV vaccines can be appropriately delivered.[10]

Finally, the Plan should include measures to mobilize public opinion and support for HIV vaccine development and delivery. Community HIV/AIDS organizations should be engaged and supported in the attainment of this objective.

Increased Canadian funding for vaccine development and delivery should be directed to:

- national research agencies, to support increased vaccine research in Canada;
- community HIV/AIDS organizations, to enable them to participate fully in the development and implementation of a Canadian HIV Vaccine Plan;
- domestic and international HIV vaccine development partnerships;
- developing countries, through bilateral aid, to support vaccine development and delivery in these countries; and
- multilateral agencies, such as the HIV Vaccine Initiative of the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Global Alliance for Vaccines and Immunizations (GAVI).

Recommendation 1

Governments, the pharmaceutical industry, researchers, and HIV/AIDS community organizations should make a firm commitment to an accelerated and sustained program of HIV vaccine research in Canada.

Recommendation 2

Federal and provincial governments and the pharmaceutical industry should substantially increase their investment in HIV vaccine research in Canada.

Recommendation 3

Health Canada should coordinate, and provide funding for, the development of a Canadian HIV Vaccine Plan. The Plan should be prepared in consultation with the provinces and territories, HIV/AIDS community organizations, HIV researchers, and other relevant stakeholders, and should be developed by 1 October 2003. The Plan should contain a development component and a delivery component. The development component of the Plan should focus on those areas where Canada has experience and expertise.

Recommendation 4

Health Canada, through the Canadian HIV Vaccine Plan, and with the participation of HIV/AIDS community organizations, should mobilize public opinion and support for HIV vaccine development and delivery.

Recommendation 5

The federal government should significantly increase funding for international HIV vaccine efforts. It should participate actively in attempts to ensure global coordination of HIV vaccine development.

Note: Subsequent sections of this paper advance additional recommendations concerning the content of the proposed Canadian HIV Vaccine Plan.

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[6] This text is taken from the website of the International AIDS Vaccine Initiative (www.iavi.org).

[7] Avrett, supra, note 3.

[8] *Declaration of Commitment on HIV/AIDS*. United Nations General Assembly. June 2001, paragraph 70. Available at www.unaids.org under "UN Special Session on HIV/AIDS."

[9] Avrett, supra, note 3.

[10] Ibid.

Section 3.0
HIV Vaccine Clinical Trials

This section examines legal and ethical issues that arise during the conduct of large-scale (Phase III) efficacy trials. Some of the issues discussed in this section also apply to Phase I/II trials.

3.1 Working with Target Communities

> Community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research.… Involvement of community representatives should not be seen as a single encounter, nor as one-directional. The orientation of community involvement should be one of partnership towards mutual education and consensus-building regarding all aspects of the vaccine development program.[11]

This subsection describes how the involvement of target communities and people living with HIV/AIDS in the design and implementation of HIV vaccine trials can contribute to the success of the trials. It also discusses how communities can become involved, and examines one particular model for structuring community involvement: community advisory boards. Finally, the subsection outlines how governments and trial organizers can prepare communities for an HIV vaccine trial. (Please see part 2 ("Clinical Trials") of the *Background Paper* for a discussion of what constitutes a "community.")

3.1.1 Why Community Involvement in the Design and Implementation of Vaccine Trials Is Important

For a vaccine trial to be successful, governments, trial organizers, and communities need to work together. Communities should be involved because they can make a meaningful contribution to the success of the trial. They can help to ensure that: (a) the trial meets appropriate scientific and ethical standards, including adequate informed consent, education on safer sex and needle use, and protection from harm; (b) the trial is relevant to the targeted population; and (c) the trial is accepted by that population. Communities can help to improve the design of a trial, which in turn can lead to better recruitment and retention of volunteers. The involvement of the community will generate grassroots support for the development and eventual delivery of an HIV vaccine. This support is critical to obtaining scientific, political and economic support at higher levels.

For a vaccine trial to be successful, governments, trial organizers, and communities need to work together.

Another reason for involving the communities that will be targeted by a vaccine trial is that the trial may generate undue optimism, which may make it necessary to modify prevention messages. The presence of an HIV vaccine trial in a community, and the potential this offers for the discovery of a successful vaccine, might engender a false sense of security on the part of the trial participants and the community at large. Undue vaccine optimism – this false sense of security – is similar to treatment optimism, which refers to the belief that the advances in treatments of the last six or seven years (eg, protease inhibitors, triple cocktails) make HIV infection a manageable, chronic disease and that it is therefore acceptable to subject oneself to greater risks when having sex or injecting drugs. There is some evidence that recent increases in HIV incidence among men who have sex with men may be due in part to treatment optimism. It is possible that undue vaccine optimism could lead people to think that they are no longer at risk for HIV infection or that the risk has been significantly reduced. This in turn might lead to a greater assumption of risk by individuals and by the community. Unfortunately, not much is known about the possible effects of undue vaccine optimism; more research on this area is needed.

Recommendation 6

Trial organizers should involve community representatives in the design and implementation of HIV vaccine trials.

Recommendation 7

Trial organizers should work closely with communities and public health officials to minimize potential harms caused by undue vaccine optimism.

Recommendation 8

As part of the Canadian HIV Vaccine Plan, the Canadian Institutes of Health Research should fund sustained qualitative psychosocial research to investigate the potential impact of undue vaccine optimism on individual and collective risk assessment and risk assumption. The research should also look at ways to sustain behaviour change in the face of undue vaccine optimism.

3.1.2 How Communities Can Become Involved

Members of the community who could make a contribution to a vaccine development process include representatives of the research population eligible for the trial, the intended beneficiaries of the vaccine, relevant non-governmental organizations, persons living with HIV/AIDS, community leaders, public health officials, and persons providing health care and other services to people living with and affected by HIV/AIDS. In order to be involved in a meaningful way in the design and implementation of an HIV vaccine trial, community representatives first need to become knowledgeable about the vaccine research process and about the issues involved in HIV vaccine development.

Community representatives can contribute to the design and implementation of an HIV vaccine trial by:

- participating on research ethics boards that review trial protocols;
- educating people in the community about the proposed trial;
- relaying the concerns of the community to trial organizers;
- providing input to trial organizers on the design of the trial (eg, procedures for informed consent, plans for recruitment);
- supporting recruitment to the trial;
- monitoring the trial as it is being implemented;
- working to minimize the possibility that undue vaccine optimism could lead to increased risk behaviour among trial participants or in the community generally;
- helping to disseminate the trial results; and
- advocating for effective delivery when a vaccine becomes available.

Community organizations will need to be supported in their efforts to fulfil these roles. One way to structure community involvement in HIV vaccine trials is through the use of community advisory boards. These are described below.

Recommendation 9

Trial organizers and governments should provide funding for community organizations to educate communities about HIV vaccine research and to participate in the design and implementation of HIV vaccine trials.

3.1.3 The Role of Community Advisory Boards

UNAIDS recommends that trial organizers facilitate the establishment in the community

> of a continuing forum for communication and problem-solving on all aspects of the vaccine development program from Phase I through Phase III and beyond, to the distribution of a safe, effective, licensed vaccine.[12]

These "continuing forums" often take the form of community advisory boards (CABs), which are usually made up of volunteers from the target community. In the case of the AIDSVAX trial, for example, CABs were established in each of the three Canadian sites: Vancouver, Toronto, and Montréal. The mandates and activities of the CABs vary considerably, reflecting differences in local cultures and approaches.

Each of the CABs established in the three Canadian sites of the AIDSVAX trial shared a mandate to advise organizers on the aspects of the trial that most concerned participants and

target communities (eg, the informed-consent process, recruitment, the dissemination of information in the community). However, while the Vancouver site defined "community" as the participants in the trial, the other sites interpreted the term more broadly.

In Vancouver, the CAB is made up entirely of trial participants. The people involved in the CAB are from various backgrounds, including education, health care, law, and government.

In Toronto, the CAB includes a counsellor from a local AIDS service organization; a trial participant who is also an HIV/AIDS activist; an epidemiologist from a local university; a basic science and clinical researcher; and a local public health officer. The mandate of the CAB refers to liaising between trial organizers and the gay and HIV-affected communities.

In Montréal, half of the membership of the CAB comes from trial participants, while the other half comes from the larger gay community. One of the members is a physician. The mandate of the CAB refers to conducting education in the larger gay community. (See part 2 of the *Background Paper* for a detailed description of the Montréal CAB, and for an analysis of some of the differences between the Montréal and Vancouver CABs.)

CABs can help researchers better understand the target communities. Specifically, CABs can provide researchers with advice on: (a) how to recruit and retain research subjects; (b) how to provide prevention counselling to trial participants; (c) how to undertake community relations; and (d) how best to disseminate information about the trial in the community. CABs can educate researchers on the cultural sensitivities of the target communities. In a multi-centre trial, local CABs can help researchers understand the variations among sites in HIV epidemiology, ethnicity, cultures, community organization, patterns of socialization, delivery of health services, etc. CABs can also help to facilitate meetings between researchers, public health, and community leaders.

CABs can assume a leadership role in the design of some aspects of the trial, including: (a) measures to minimize risk to trial participants; (b) disclosure of information about the trial to participants; and (c) the informed-consent process. CABs can also vet the written materials produced by researchers for use before and during the trial.

CABs are composed of volunteers who are motivated to contribute to their communities. CABs can educate the community about vaccine research issues in general and about the specific vaccine trial they are involved with. They can provide a forum for trial participants to raise issues or concerns.

CABS can only be effective in providing advice to researchers and in educating communities if they are adequately supported and resourced. Funding can be a major challenge. Some other challenges CABs can face are as follows:

- It would be difficult for CABs to function effectively in the absence of strong community leadership and a well-defined community structure of HIV prevention and other HIV-related services.
- In the context of a multi-centre trial, a local CAB would have only limited ability to request changes to reflect local conditions (eg, changes to consent forms and procedures). Substantive changes to trial protocols and procedures at one site would likely have to be made at all sites (and would have to be approved by regulatory authorities in one or more countries).
- Depending on how the members of the CAB are selected, there may be issues of accountability to the target community (or communities).
- If the trial is recruiting people from target communities with widely divergent cultures and characteristics, it may be difficult to construct a functional CAB.

- A CAB will only be effective if it has a good working relationship with the sponsor, the researchers, and the trial staff; and if it has good partnerships with local prevention and health services.

In and of themselves, CABs do not constitute "community involvement." CABs are composed of a small number of volunteers and there are limits to how much work volunteers can realistically be expected to contribute. Rather, CABs should be seen as one element of an overall program of community involvement in HIV vaccine research.

Recommendation 10

At each trial site, trial organizers should help facilitate the establishment of a community advisory board (CAB). This should include providing the CABs with adequate training and resources to carry out their functions of advising organizers, educating target communities, maintaining links with local prevention and health services, and preparing materials to educate CAB members on their role.

Recommendation 11

At each trial site, community organizations should advocate for the establishment of a community advisory board (CAB) where communities, NGOs, and researchers can share information, problem solve, and work to improve the trial. Community organizations should support existing CABs by providing feedback to CAB members, attending meetings between the CAB and the broader community, etc.

Recommendation 12

In multi-centre trials, trial organizers should prepare and disseminate directories of the members of CABs in various cities involved in the trials. Organizers should encourage CAB members to correspond and exchange ideas with people working on CABs in other cities.

3.1.4 Why People with HIV/AIDS Should Be Involved in the Design and Implementation of Preventive Vaccine Trials

People with HIV/AIDS should participate in the design and implementation of preventive vaccine trials because they are an integral part of the community. For one thing, because HIV-positive persons play a role in prevention and transmission, they – as much as HIV-negative persons – need to hear the message that testing an experimental vaccine does not mean that a cure is on the horizon. For another, the involvement of people with HIV/AIDS will enable the community to speak with a strong voice in advocating for more vaccine research; for the simultaneous study of new agents as both preventive and therapeutic vaccines (wherever possible); for the highest ethical standards in vaccine research; and for the maximum involvement of the community.

Research on preventive vaccines may yield information that can be used to develop therapeutic vaccines, particularly with regard to how the preventive vaccines stimulate the immune system. People with HIV/AIDS will be interested obtaining and disseminating the

scientific information generated by the preventive vaccine trials.

As well, having HIV-positive people involved at the outset can help ensure that the allocation of resources to vaccine research does not detract from the provision of care, treatment, and support to people with HIV/AIDS. This may help avoid schisms between HIV-positive and HIV-negative people in the community.

Recommendation 13

Trial organizers should involve people with HIV/AIDS in the design and implementation of vaccine trials.

3.1.5 Building Capacities within Target Communities to Participate in the Design and Implementation of Vaccine Trials

Communities should be able to function as equal partners in a collaborative process with trial organizers. In Canada, some communities (such as the gay community in some cities) may already be able to function in this fashion. However, other communities that could become settings for future vaccine trials – such as Aboriginal people on reserve, injection drug users, and street youth – may lack the leadership and skills required to take on the work involved in collaborating in a vaccine trial. In trials involving one or more of these communities, it would be in the interest of trial organizers to help develop a capacity within the community to conduct scientific research and to undertake scientific and ethical review of research protocols. In fact, existing international ethical guidelines on the conduct of research state that trial organizers have an obligation to do so.[13] Governments can also play an important role in building capacities.

Communities should be able to function as equal partners in a collaborative process with trial organizers.

Recommendation 14

Where warranted, trial organizers and governments should collaborate on the development and implementation of capacity-building programs to enable target communities to participate in the design and implementation of HIV vaccine trials. Organizers should encourage and support the development of leadership within communities likely to be targeted for vaccine trials.

3.1.6 How Trial Organizers Can Prepare a Community for Recruitment

Once a decision has been made to proceed with an HIV vaccine trial in a given community, there are several steps that should be taken prior to initiating the recruitment process.

Trial organizers need to anticipate and address the direct or indirect harms that the research may cause individuals. One example of these harms is the possible repercussions of a diagnosis of HIV. The organizers need to make sure that potential participants who test HIV-positive at the time of recruitment, and participants who become HIV-positive during the trial, will be able to promptly access appropriate care, treatment, and support. This requires developing links with service providers. Another example is the potential harm arising from undue vaccine optimism. Organizers need to establish links with the community in

order to prepare the programs that will be required to educate people about the need to maintain safe behaviours.

To facilitate recruitment, organizers need to be prepared to address the concerns potential participants may have about risks. Volunteers are likely to be worried about issues such as the possibility of vaccine-induced injury and the potential for discrimination. (These issues are discussed in Sections 3.4 and 3.5.)

One tool that has been used to prepare a community for a vaccine trial is the vaccine preparedness study (VPS). A VPS is an epidemiological study that typically evaluates HIV infection rates, risk behaviours, and incentives or barriers to participation in a vaccine trial. VPSs can take many forms; some studies are more intensive than others. In a more intensive VPS, participants are educated about vaccine trials and are informed of recent scientific developments. They are tested at regular intervals in order to generate the data scientists need to prepare the research protocol. And they are counselled on the importance of maintaining HIV-preventive behaviours. Investing resources in a VPS makes sense if there is a reasonable expectation of a substantial trial being conducted in the community.

In a community where there has been little advance preparation, trial organizers, public health, and community leaders will need to be able to mobilize quickly to respond to a proposal for a vaccine trial. All the steps described above will still need to be done, but in a compressed time frame.

Recommendation 15

Prior to commencing recruitment, trial organizers should: (a) anticipate potential harms to participants and establish links with service providers and community leaders to minimize these harms; and (b) take steps to address the concerns of potential participants about risks associated with the trial.

Recommendation 16

Trial organizers should consider undertaking vaccine preparedness studies in communities where there is a reasonable expectation of an HIV vaccine trial being conducted.

Further Reading

- ET Juengst. Commentary: What "community review" can and cannot do. *Journal of Law, Medicine & Ethics* 2000; 28(1): 52-54.

3.2 Recruitment

This subsection deals with legal and ethical issues that can arise during recruitment for an HIV vaccine trial. A brief description of the recruitment processes used for the Canadian sites of the AIDSVAX trial is provided. This is followed by a discussion of which communities should be participating in HIV vaccine trials. Finally, the subsection examines the question of what compensation should be offered to participants for taking part in the trial.

3.2.1 How Recruitment Was Done for the AIDSVAX Trial in Canada

At the three Canadian sites in the AIDSVAX trial, the following approaches were used to recruit participants: direct referrals from physicians; direct referrals from workers at AIDS service organizations; distribution of brochures and posters in STD clinics and gay venues; community forums; advertisements in the gay press; publicity through media articles; and word of mouth.

In Vancouver and Montréal, existing cohort studies involving gay and bisexual men were also a source of recruitment. In Montréal, some people enrolled simultaneously in the cohort study and the AIDSVAX trial.

At the three Canadian sites of the AIDSVAX trial, participants had to fulfil the following entry criteria:

- men who have sex with men
- 18-60 years old
- HIV-negative
- at risk of HIV infection
- not an injection drug user
- available to participate in the study for three years

"At risk of HIV infection" was defined as having engaged in anal intercourse with someone other than a regular HIV-negative partner in the 12 months preceding enrolment.

3.2.2 Who Should Participate in HIV Vaccine Trials?

Recently, there have been growing demands from people in all communities affected by HIV/AIDS to be able to access HIV vaccine trials. These demands echo calls advanced earlier in the epidemic (and still being made) for greater access to treatments and for accelerated research and approval of new drugs. The demands for greater access are based on human rights and ethical arguments, including the right to health and the principle of distributive justice. (Distributive justice refers to the fair distribution of burdens and benefits in society).

In the last few years, national and international ethical guidelines on the conduct of research have begun to address the need for an equitable and inclusive approach to recruitment. According to these guidelines,[14, 15, 16] the principle of distributive justice requires not only that no segment of the population be unfairly burdened with the harms of research, but also that data from clinical trials should benefit all the groups affected by the research. The guidelines also refer to the duty not to discriminate against disadvantaged groups. However, these guidelines are meant to apply to research generally. They do not say that each individual trial has to be open to all affected groups.

Technically, HIV vaccine trials recruit individuals, not entire communities, so the decision to participate is an individual one. Nevertheless, trials often target specific populations. Decisions about where a trial is done and who is recruited into a trial are linked to scientific factors such as what type of trial is being conducted (Phase I, II or III), what the specific research questions are, what the potential risks are, and what type of vaccine is being tested.

Costs, time, and ethics are additional factors that influence the choice of target populations. Organizers are trying to do a trial as quickly as possible and are trying to use their resources as efficiently as possible without putting anyone at risk. As a result, organizers have a predisposition to work with populations where they feel they can achieve high uptake

and retention rates. If organizers can find a population with an incidence of HIV infection that is higher than the incidence in the general population, they can reduce the sample size they need for the trial.

It seems reasonable to conclude, therefore, that the decision about which populations are targeted *for an individual trial* must be made by balancing a number of factors, only some of which relate to ethics. In terms of the *overall HIV vaccine research effort,* however, there is an ethical imperative to ensure that trials are conducted in different populations in order to find out whether the vaccine is safe and effective in these populations.

It would be clearly unethical to exclude women from HIV vaccine research.

In Canada and other industrialized countries, gay men have one of the highest rates of new HIV infections. The gay community is relatively cohesive and well organized, and gay men are well represented in AIDS service organizations. There is a perception that gay men would be easier to recruit and retain in the trial than certain other populations – eg, injection drug users, street youth, Aboriginal people. It would not be surprising, therefore, if the organizers of a vaccine trial decided to target primarily gay men. However, a decision to focus the vaccine research effort in industrialized countries entirely on gay men would only provide information on how effective the vaccine is in preventing homosexual transmission of HIV; it would not provide information on the impact of the vaccine on heterosexual transmission or transmission through the sharing of injection equipment.

Development of an HIV vaccine is a high priority for women. Globally, women account for about a half of the number of people with HIV/AIDS and more than a half of new infections. In Canada, although women constitute a minority of people with HIV/AIDS, the proportion of new infections represented by women has been increasing significantly since 1995. Women in this country have historically been under-represented in clinical trials. There is evidence that suggests that the pathology of HIV differs along lines of gender and route of infection. Therefore, if women are excluded from HIV vaccine trials, the research data obtained from male-oriented studies may not be generalizable to women. For this reason, national and international ethical guidelines on the conduct of research in human subjects now acknowledge that, in the absence of a compelling scientific reason, it would be clearly unethical to exclude women from HIV vaccine research.[17, 18]

The high HIV incidence rates that have been reported among injection drug users indicate that this is an important population to target with a preventive vaccine. These rates could justify delivery of even a low-efficacy vaccine to this population in some cities. Many of the candidate vaccines being developed today attempt to stimulate mucosal immunity – ie, immunity in the membranes founds in various parts of the body, including the vagina and rectum. The cells and chemicals that predominate in the mucosa are not present in the blood, which is the route by which HIV can enter the body when people share injection equipment. The only way to find out if these candidate vaccines are effective in preventing HIV infection in injection drug users is to conduct clinical trials in this population.

Concerns have been raised about the challenges of recruiting and retaining injection drug users in HIV vaccine trials. These concerns are not unique to HIV vaccine research; in any event, research and experience suggest that any obstacles to the inclusion of injection drug users in clinical trials can be overcome with good planning.

(Please see the *Background Paper* for a discussion of recruitment issues pertaining to street involved youth, Aboriginal people, and prisoners.)

Recommendation 17

The Canadian HIV Vaccine Plan should emphasize the need to ensure that all populations with significant rates of HIV infection participate in human testing of candidate HIV vaccines.

Recommendation 18

For individual trials, to the extent that the criteria permit, trial organizers should recruit participants from the various populations with significant rates of HIV infection.

Although individuals can decide whether or not to participate in an HIV vaccine trial (or any trial), there are no provisions in human rights legislation that give them the "right" to participate. On the other hand, if illegal discrimination is being exercised in the selection of trial participants on the basis of any of the grounds listed in human rights codes – eg, disability, race, ethnicity, sex, sexual orientation – then it would be possible to seek redress under these codes. (Please see the *Background Paper* for a discussion of whether the sponsors or the researchers would be held liable in the event of such discrimination.)

3.2.3 What Compensation Is Appropriate for Participants in an HIV Vaccine Trial?

Trial participants are sometimes offered financial or other compensation to offset the inconvenience of participating, or to cover any costs they may have incurred while taking part in the trial. Examples of compensation are: (a) a token sum of money for each appointment (eg, $20); (b) bus tickets or taxi vouchers for transportation to appointments; (c) condoms; (d) sterile injection equipment; (e) on-site child care; (f) preventive HIV counselling; and (g) diagnosis and treatment (or referrals) for STD and other infections. In the AIDSVAX trial at the three Canadian sites, the only compensation offered was token sums (up to $20) as reimbursement for travel expenses incurred to attend appointments. Most participants refused the offer.

What level of compensation is appropriate? If the compensation is too great, it could constitute an undue incentive to participate in the trial – ie, an incentive that corrupts the process of obtaining free and informed consent. Could compensations such as those described above constitute an undue incentive? Possibly. For one thing, even small financial compensations can become a significant incentive to people living in dire poverty. For another, in places where health services are less than ideal or difficult to access, the prevention and care services provided by the trial could influence a person's decision to join the trial. To minimize the danger of compensation becoming an undue incentive, trial organizers should work with the target community to identify what compensation would be appropriate.

Recommendation 19

Trial organizers and community leaders should work together to design a compensation package that is reasonable but that will not create an undue incentive to participate in the trial.

Other Issues Concerning Recruitment

Please see the section "Recruitment" of the *Background Paper* for a discussion of the following issues:

- Is it appropriate to provide different levels of compensation for different populations taking part in the trial?
- Is there a need to take the specific values and cultural realities of a community into account when designing the compensation package?
- What are the obligations of trial organizers toward volunteers who are not accepted into the trial?
- What are advantages or disadvantages of recruiting via the Internet?
- What would the impact be of variances in HIV prevalence levels among injection drug users in different cities on recruitment for a multi-centre HIV vaccine trial in which injection drug users were taking part?

3.3 The Informed-Consent Process

Individuals recruited for an HIV vaccine trial must provide informed consent to participate in the trial. This subsection examines the legal and ethical issues that can arise during the informed-consent process. The subsection explains the importance of informed consent and describes the informed-consent process used for the AIDSVAX trial. It then outlines the information that should be disclosed during the informed-consent process. This is followed by a description of the measures that can be taken to ensure that the consent is truly informed. Finally, the subsection discusses the issue of whether the search for personal protection is an appropriate reason for participating in an HIV vaccine trial.

3.3.1 What Is Informed Consent and Why Is It Important?

The process of informed consent is the most important way of protecting the interests of participants.

In the context of a clinical trial, informed consent is the process whereby potential participants are provided relevant information about the trial and agree to participate in the trial. The concept of informed consent is grounded in the fundamental human right of individuals to control what is done to their own bodies. In Canada, informed consent is required by law for any clinical trial that involves the administration of a vaccine or any other experimental medicine.

To provide informed consent, the individual must be accurately informed of the purpose and methods of the trial, and of the risk and benefits of participating in the trial; must understand this information and its implications for his or her own health; and must make a voluntary, uncoerced decision whether to participate.

The process of informed consent is the most important way of protecting the interests of participants as well as those of trial organizers. Informed consent empowers research subjects to make enlightened and autonomous decisions related to their health. As well, because of the nature of the process and the fact that trial organizers have to make a full disclosure of pertinent information, informed consent promotes self-scrutiny and rational decision-making among the researchers involved in the trial.

3.3.2 The Informed Consent Process Used in the AIDSVAX Trial

The following process was used to obtain informed consent at the three Canadian sites in the AIDSVAX trial:

1. An initial screening of potential participants was performed by telephone.
2. An on-site appointment was set up for each potential participant. At that time, each person was given a complete description of the trial and had an opportunity to pose questions.
3. At that same appointment, the site investigator (or his or her representative) reviewed the entry criteria with the potential participant and presented the consent form (a document of 10 to 15 pages). The person could sign the consent form at that time, or the person could take the consent form home to review and discuss with others, and then come back to sign it in a couple of days. (In Montréal, potential participants were not allowed to sign the consent form at the initial appointment; they had to take it home and return later to sign it.)
4. After signing the consent form, potential participants were given a comprehension test (also known as a consent understanding test) to see if they fully understood the information that was provided to them about the trial. The test consisted of 10 to 12 written questions. If a potential participant failed this test, the test questions and the consent form were reviewed with that person and he or she was asked to take the test again. Potential participants had to pass the test to gain entry to the trial.

3.3.3 Information that Must Be Disclosed as Part of the Informed-Consent Process

Canadian law requires extensive disclosure of information for an HIV vaccine trial, as it does for any vaccine trial and, indeed, for any research that has a high risk-to-benefit ratio. This means that all risks must be disclosed, even risks that are considered rare or remote. International ethical guidelines on the conduct of research contain similar provisions.

The obligation to provide extensive disclosure pertains not only to information available at the outset of the trial, but also to any new information that may emerge during the course of the trial that could influence a participant's decision to continue taking part (eg, a revelation that the vaccine causes serious side effects).

Potential participants need to be informed of the objectives of the trial and the relative importance of the objectives. For example, if the major objective of the trial is to generate information about the correlates of immunity (correlates of immunity are immune responses that appear to correlate with protection from disease) for future vaccines – as opposed to evaluating the effectiveness of the candidate vaccine – the participant has a right to know this. Participants also need to understand the research hypothesis (ie, how the researchers think the candidate vaccine might work to achieve efficacy); the results from prior research; the results trial organizers are hoping to achieve; and the end points of the trial. Participants should be told what phase of clinical research they are involved in and what phases will follow.

Potential participants need to be informed about the research methodologies being used. For instance, they must comprehend the double-blind, randomized, placebo-controlled methodology of the trial (if that is the methodology being used), and hence the importance

of not unblinding their status. Participants should be told the probability of assignment to each arm of the clinical trial.

The role of the principal investigator or site investigator should be explained. There may be confusion about whether the investigator is acting solely as a scientist or also providing some clinical services. The potential participant needs to understand exactly what kind of relationship to expect. Potential participants should be provided with the administrative details of the trial, including the identities of the sponsor, its parent corporation (if applicable), and the principal or site investigator. Participants should also be made aware of any conflicts of interest linking these parties (eg, does the principal investigator have a current financial interest in the sponsor company?).

It is critical that potential participants be provided with a detailed overview of the potential benefits and risks of participating in the trial. (See the boxes for examples of the benefits and risks). The nature, magnitude, and probability of all known potential harms should be spelled out as fully as possible.

Benefits of Participating

The following are examples of the benefits of participating in an HIV vaccine trial. The precise benefits will vary depending on the trial.

- ➢ It is an opportunity to contribute to science and to the fight against HIV/AIDS.
- ➢ It is an opportunity to become more directly involved in the research process.
- ➢ Participants will have access to HIV prevention materials, including male and female condoms and sterile injection equipment.
- ➢ Participants will have access to periodic HIV-antibody testing, accompanied by state-of-the-art counselling over a period of several years.
- ➢ Should a participant become HIV-positive during the course of the trial, the infection will be detected early.
- ➢ In the event of vaccine-induced injury or HIV infection, participants will be able to access care and treatment at a level agreed to before the trial started.
- ➢ If health problems arise during the trial, these will be diagnosed and participants will be provided with referrals to ancillary health, social, and community services.
- ➢ If the vaccine should prove effective, participants who had been receiving the placebo will be offered the vaccine free of charge.

Risks of Participating

The following are examples of the risks of participating in an HIV vaccine trial. The precise risks will vary depending on the trial.

- Participants may experience mild pain or discomfort at the injection site.
- Participants may incur a vaccine-induced injury.
- There is a remote possibility that vaccination might actually make the participant more susceptible to HIV infection.
- Because they are taking part in the trial, participants could reduce or abandon the practice of safer sexual and drug-taking behaviours.
- Participants might be exposed to stigma and discrimination simply by virtue of taking part in the trial, or because of the way in which HIV-antibody test results are interpreted during or after the trial.
- Participants may not be able to take part in future clinical trials of experimental vaccines.
- There is a possibility (though remote) that the vaccine might interact with the body in a way that would reduce the efficacy of a future vaccine.
- The vaccine may interact negatively with other drugs.

Potential participants should be informed about the obligations of the trial organizers. For example, they should be told: (a) how the confidentiality of their identity and personal information will be maintained; (b) who will care for them if they become ill as a result of the vaccine, what level of care will be provided, and whether and to what degree they will be compensated for loss of income, medical costs, and other suffering; and (c) what help will be provided in the event that the participant faces stigma or discrimination as a result of participation in the trial. (The issues concerning compensation and level of care are discussed in more detail in Section 3.4. Please also see Section 3.5 for a discussion of HIV vaccine–related stigma and discrimination.)

Potential participants should be informed of what their own obligations are, including: (a) the nature, timing, frequency, and duration of appointments and examinations they are expected to attend; and (b) the diagnostic tests they are expected to undergo. Participants should be told that during the trial they would be expected to use the trial facilities as the only site for HIV-antibody testing (to prevent unblinding of their HIV status within the trial).

Potential participants need to be informed about the importance of maintaining safer behaviours to avoid contracting HIV infection throughout the trial. The experimental nature of vaccine trials and the uncertainties concerning the efficacy of the candidate vaccine should be stressed. (See Section 3.4 for a discussion of the obligation to provide preventive counselling.)

3.3.4 The Need to Ensure That the Consent Obtained for Participation in an HIV Vaccine Trial Is Truly Informed

Trial organizers have an obligation not only to disclose all pertinent information but also to ensure that the consent is truly informed. This means that organizers must take all reasonable steps to ensure that potential participants understand the information about the trial and appreciate the nature, benefits, and risks of the experiment to which they are submitting.

Various means can and should be used to convey the information. The use of a signed consent form is an important method, but it should be seen as only one part of the process. Other methods include: (a) interviews with the principal or site investigator and trial staff; (b) community forums; (c) explanatory videos; and (d) written materials. The choice of methods will be shaped by factors such as the culture, language, traditions, and levels of education of the target community and the prior experience of the community with vaccination and clinical research. In order to ensure that potential participants fully understand the information and are not overwhelmed by the sheer volume of data, trial organizers will need to find ways to make the information readily accessible to people.

Potential participants should be partners in the informed-consent process. Ideally, informed consent will take the form of a dialogue between the researcher and the participant in which the participant feels free to ask questions. Researchers will anticipate the questions that a "reasonable person" from the target community might ask before consenting to participate.

The use of a "participant's bill of rights" may enhance the informed-consent process. Such a bill could explicitly state the potential participant's right to free, voluntary, and informed consent; summarize the representations made by the organizers; and outline the procedures by which participants can raise questions or lodge complaints. Organizers may also want to make use of a test or other type of assessment to determine whether the potential participants understand all the relevant information about the trial (as was done in the AIDSVAX trial).

The consent forms themselves should be written in a way that makes them easily understandable and should be pre-tested on the target populations. Potential participants should have the opportunity to take the consent form and other relevant materials home to study for at least 48 hours before signing the form. Participants should be encouraged to discuss the form and the materials with their doctors, partners, families, and friends.

The informed-consent process needs to be adapted to different cultures. Information should be communicated in a culturally appropriate manner and in appropriate languages, which means that written materials may need to be translated or adapted.

To help ensure that the consent is truly informed, organizers should consult with the target communities on the design of the informed-consent process. Community advisory boards can play a useful role in this process.

Recommendation 20

Trial organizers should work with people from each target community to obtain input on the informed-consent process and to ensure that the process is adapted to the particular culture of that community.

Recommendation 21

Trial organizers should ensure that the trial protocols spell out in detail the process for obtaining informed consent, including a description of the methods that will be used to ensure that the consent is truly informed.

Canadian researchers wishing to conduct HIV vaccine trials in Aboriginal communities will have to take into consideration traditional values and decision-making processes in these communities concerning risks, health, and ownership of research materials and data. A vaccine clinical trial may generate ancillary epidemiological data that, if not presented in a culturally contextualized manner, could stigmatize certain Aboriginal communities. Researchers should consider undertaking a process of obtaining general community assent according to local values and traditions at the same time as individual consent is sought from each volunteer.

3.3.5 The Search for Personal Protection

Studies have shown that a desire for protection is one of the factors motivating willingness to participate in an HIV vaccine trial. These studies also show that individuals willing to participate are more likely to be younger, to be unemployed, to live in unstable housing, to have practised unsafe sexual or drug-use behaviours, and to have low self-esteem. This means that the people most likely to respond to a recruitment campaign may be among the most marginal members of the target population and may be more vulnerable to HIV infection than other members of that population.

It would not be surprising, therefore, if many of these people were looking for personal protection in a vaccine trial. However, this is not a good reason for joining a trial. The trial may not offer any protective benefit to participants. For one thing, a participant may be randomized into the placebo arm of the trial and therefore not receive the vaccine at all. For another, even if the participant is in the arm of the trial that receives the vaccine, there is no certainty that the vaccine will be effective. Furthermore, it may take many years of testing before the trial will yield significant results.

A better motivation for participating in an HIV vaccine trial is a desire to help society find a vaccine that works against HIV. As part of the informed-consent process, trial organizers have an obligation to educate potential participants about what it means to take part in a clinical trial and about how they can best guard against becoming HIV-infected. Organizers should inform potential participants that vaccine research is a lengthy process and that it may not offer participants any therapeutic value, but that it is worthy of support because it will improve knowledge of what works and what does not work, and could eventually lead to the development of an effective vaccine.

Recommendation 22

During the informed-consent process, trial organizers should educate participants about the randomized, placebo-controlled nature of a clinical trial. Organizers should stress the altruistic reasons for participating in a trial. They should inform participants that their best hope for preventing HIV lies in avoiding risk behaviours or adopting harm-reducing behaviours.

Other Issues Concerning Informed Consent

Please see the *Background Paper* for a discussion of the following topics:

- What legal recourse is available if consent is improperly obtained.
- The need for multiple or separate consents for various interventions during the trial and for any additional research undertaken with the same cohort.
- The differences between Canadian common law and Québec civil law with respect to the standards for evaluating the scope of disclosure of information about the trial.

Further Reading

➢ EJ Emmanuel et al. What makes clinical research ethical? *Journal of the American Medical Association* 2000; 283(20): 2701-2711.

3.4 Obligations to Participants during and after the Trial

This subsection examines four specific obligations that trial organizers or governments have toward participants during or after an HIV vaccine trial: (a) the provision of preventive counselling; (b) the provision of high-quality care to participants who become HIV-positive during the trial; (c) the provision of compensation for any participant that suffers a vaccine-related injury; and (d) the dissemination of information on the results of the trial.

Organizers are ethically obligated to take all reasonable actions to reduce HIV risk behaviours among HIV vaccine trial participants.

3.4.1 The Need to Provide Preventive Counselling

Organizers are ethically obligated to take all reasonable actions to reduce HIV risk behaviours among HIV vaccine trial participants.[19] Preventive counselling is one way of doing this.

The potential for HIV risk behaviours among trial participants is significant. For scientific reasons, large-scale vaccine efficacy trials often deliberately recruit populations at greater risk of contracting HIV. For example, in the AIDSVAX trial in Canada, recruitment was limited to gay and bisexual men who had engaged in penetrative anal intercourse (with or without a condom) with someone other than their regular, HIV-negative sexual partner during the 12 months preceding enrolment.

There is also the phenomenon of undue vaccine optimism which, as discussed in Section 3.1, can create a false sense of security among trial participants. One way that undue vaccine optimism can manifest itself is as follows. If participants were involved in one or more incidents of risky behaviour during the course of the trial, successive negative HIV-antibody tests might lead them to assume that they were receiving the experimental vaccine and that it was effective. Such an assumption would of course be premature (at best) or completely false (at

worst) and, therefore, dangerous. For these reasons, the trial must provide a very high standard of preventive counselling.

The obligation to promote prevention starts when participants consent to take part in the trial and continues throughout the trial. All HIV vaccine trials require participants to undergo periodic testing for HIV infection. The pre- and post-test counselling sessions that accompany the tests are the ideal venue for stressing prevention. However, participants should be able to request counselling sessions at any time during the trial (not just when HIV-antibody tests are being conducted).

Preventive counselling should be conducted by trial staff who are trained to understand the culture of the target community, including attitudes toward sexuality, illness, family, and injection drug use. The training could come from local health-care providers and AIDS service organizations who are already doing HIV-antibody testing and counselling in the community. During the course of the trial, staff should continue to meet with these providers and organizations to update their skills. Having an external expert evaluate the counselling would help to identify where further training is required.

In a multi-centre trial, organizers could elaborate basic standards for preventive counselling to be applied at every site. However, local sites should be permitted some flexibility to adapt the standards to local conditions.

Researchers and trial staff must ensure the protection of the confidentiality of information gathered during the pre- and post-test counselling interviews. This will encourage free and frank discussions with participants.

If the mid-term statistical review of results from a large-scale efficacy trial revealed any inordinately high levels of HIV incidence, trial staff could then take steps to revise and intensify preventive interventions. This could be done without unblinding the study. It may also be possible for the study to contain a small, parallel unblinded arm solely for the purpose of evaluating the efficacy of counselling over time.

It is important to ensure that community organizations carefully monitor whether trial organizers are fulfilling their obligation to provide high-quality preventive counselling. The reason for this is that the organizers face a real dilemma. They are ethically obligated to counsel safer behaviours, but if participants do not take risks the trial will not reveal anything useful. This is one reason why Phase III HIV vaccine trials recruit extremely large numbers of people. The expectation is that with so many people participating, even if only a very small percentage of them engage in risky behaviour, the actual numbers will still be large enough to provide scientifically valid results concerning the effectiveness of the candidate vaccine being tested.

Recommendation 23

Trial organizers should develop a comprehensive plan for preventive counselling prior to the start of the trial. The plan should be developed in consultation with local health-care providers and AIDS service organizations.

Recommendation 24

Trial organizers should ensure that the staff providing preventive counselling are knowledgeable about the cultures of the target communities.

Recommendation 25

Trial organizers should protect the confidentiality of the information gathered during counselling sessions.

3.4.2 The Need to Ensure that Participants who Become HIV-Positive during the Course of an HIV Vaccine Trial Are Provided High-Quality Care

International ethical guidelines on the conduct of research require that organizers ensure that care and treatment are provided to participants who become HIV-infected during an HIV vaccine trial.[20] The level of care to be provided is an issue in some countries (see below), but in Canada, with its publicly funded health-care system and relative affluence, there is no reason why the highest quality care available anywhere cannot be provided. High-quality care includes the provision of the latest drugs that have been approved for sale in Canada, including both antiretroviral medications and drugs for the treatment of opportunistic infections. Most of these drugs are covered under provincial and territorial drug reimbursement programs, but some drugs are not covered (or are not fully covered) in some jurisdictions. Organizers have an obligation to ensure that participants who become HIV-infected during the trial are able to access all drugs available in Canada. In some cases, this may require organizers to subsidize the cost of individual drugs.

The level of care that should be provided to participants *in developing countries* who become HIV-infected during a vaccine trial is a subject of considerable debate and controversy. There is disagreement about whether the care and treatment should be: (a) "best available" – ie, the level of care and treatment available in the host country; or (b) "best proven" – ie, the highest level of care and treatment available anywhere in the world. There is no agreement on who is obligated to provide (and pay for) the care and treatment.

The UNAIDS Guidance Document, *Ethical considerations in HIV preventive vaccine research*,[21] states that participants should ideally be provided best proven care and treatment, but at the very least should be provided best available care and treatment. The guidelines also state that the care and treatment package should be agreed upon through a dialogue involving the host country, the sponsor, and the target communities.

Recommendation 26

Trial organizers should ensure that high-quality care and treatment are provided to any participant who becomes HIV-infected during the course of the trial. Where necessary to ensure access, organizers should subsidize the cost of any antiretroviral medications or drugs for the treatment of opportunistic infections not already covered under provincial and territorial drug reimbursement programs.

3.4.3 The Need for Compensation for Participants in an HIV Vaccine Trial Who Suffer a Vaccine-Related Injury

Every effort is made to ensure that vaccines tested in large-scale efficacy trials are safe. It is very unlikely that these vaccines would cause adverse events compromising the health of

trial participants. However, should it happen, participants will expect trial organizers to ensure that they are well cared for.

Every effort is made to ensure that vaccines tested in large-scale efficacy trials are safe.

Depending on the severity of the injury, participants may feel that they are entitled to compensation for loss of income, for loss of enjoyment of life, or for health services they require that are not provided as part of the trial's treatment package and not covered by public insurance or the participants' private insurance. It is unlikely that a participant's private disability insurance would provide protection in this situation because the damages would not have arisen from an accidental occurrence or work-related hazard, but rather as a result of a voluntary decision by the participant to incur an avoidable risk.

If the trial organizers have taken every precaution to avoid injury, and have fully disclosed all potential risks known to them, injured participants would not be able to allege negligence. In this situation, therefore, trial organizers would appear to have no legal obligation to compensate for a vaccine-related injury. In fact, the arguments in favour of compensation are primarily ethical rather than legal. Two principal arguments have been advanced to support compensation:

- Because of the non-therapeutic nature of preventive vaccine research, a volunteer in an HIV vaccine trial is acting less out of self-interest and more out of altruism than a volunteer in a clinical trial for an experimental therapy. Because participants in an HIV vaccine trial stand to gain so little, governments or industry are ethically obliged to care for them in the event of injury.
- HIV vaccine trials are critical to society's efforts to control the HIV/AIDS epidemic. To encourage people to volunteer for such trials, compensation should be provided to participants who experience adverse effects.

International ethical guidelines on the conduct of research state that participants have a right to "equitable compensation" in the event of a vaccine-induced injury or any injury that results directly from participation in a trial.[22, 23] The guidelines state that participants should not be required to waive their right to compensation, and that the informed consent form should not contain any wording that would absolve trial organizers from their responsibility in case of injury. The guidelines also state that participants should not be obliged to show negligence on the part of trial organizers in order to claim compensation.

Participants have a right to "equitable compensation" in the event of a vaccine-induced injury.

Although there is general agreement that compensation ought to be provided, questions have been raised about who should provide it. Compensation could potentially involve huge amounts of money. For this reason, the pharmaceutical industry is reluctant to offer compensation. The profit margins involved in the development and marketing of vaccines tend to be very small compared with profit margins for therapeutic medications. In the United States over the last 30 years, pharmaceutical companies have been pulling out of the market for childhood vaccinations; among the reasons cited have been the skyrocketing litigation costs and damage awards associated with injuries.

Concerns about the potential costs of compensation extend beyond the pharmaceutical industry. In 1976, the insurance industry refused to provide liability insurance for a vaccine manufactured to combat an anticipated epidemic of the swine flu in North America. The

swine flu was a new pathogen, and there was considerable uncertainty about the potential effectiveness and adverse effects of the vaccine. The manufacturer, in turn, refused to dispense the vaccine without insurance coverage. Ultimately, the United States government accepted liability for injury and the vaccine was released.

To require the sponsor to offer compensation could deter industry from investing in vaccine research.

Some people have argued that to require the sponsor to offer compensation would deter industry from investing in vaccine research. However, as the swine flu example attests, it may not be necessary to have the sponsor bear the entire burden of compensation. The alternative could be a no-fault insurance plan that offers compensation and that is funded jointly by industry and government, or by government alone. Under a no-fault plan, participants would not need to prove negligence. In exchange, participants could be asked to waive the right to sue (except in cases of gross negligence or malevolence). California has instituted a no-fault insurance plan specifically for persons injured by an HIV vaccine used in a clinical trial. Québec has a no-fault insurance plan for persons injured by vaccines, but it is not specific to HIV and it covers only licensed vaccines (not experimental ones). Because the payouts could be huge, it is likely that any no-fault insurance plan established in Canada would set limits on the amount of compensation that would be provided to any given individual. This means that trial participants would still be absorbing a share of the risk.

There are several advantages to a no-fault insurance plan. First, if access to compensation is determined by a schedule of side effects and corresponding pre-set levels of payment, the plan should be comparatively easy to administer. Second, obtaining payment should be fairly rapid. Third, the legal costs of participants would be kept low. Fourth, the risks for industry to get involved in vaccine research would be reduced and would be more easily evaluated in advance.

Potential drawbacks to a no-fault insurance plan include the following: (a) setting aside money today for a problem that may not even occur tomorrow carries an opportunity cost; and (b) if industry is participating in the plan, industry's contribution will ultimately be factored into the price of the vaccine.

One of the biggest obstacles to the establishment of a no-fault insurance plan for HIV vaccine trials is the potential cost. Other barriers include the following:

- Unknown risks make it difficult to determine the size of the fund required.
- If there are many unexpected adverse effects, the size of the contributions to the fund may need to be increased, or the payments decreased, to keep the fund solvent.
- The public may not support a fund that limits benefits to injuries incurred solely from HIV vaccine research.

The best course of action would be for the federal government and the pharmaceutical industry to jointly fund a no-fault insurance plan that covers not only HIV vaccines but also vaccines for other diseases; and that covers both vaccines in human testing and vaccines that have been licensed for sale.

Recommendation 27

The federal government should establish a no-fault vaccine-related injury insurance program in Canada. The program should cover all experimental and licensed vaccines. Pharmaceutical companies should contribute to this fund.

3.4.4 The Need to Provide Participants with Information on the Results of the Trial

Trial participants are volunteers. Organizers would not be able to do the trial without them. At the conclusion of the trial, organizers therefore have an ethical obligation to provide participants with the results of the trial.

Recommendation 28

Trial organizers should provide participants with detailed information on the results of the trial. The information should be provided in a format that is accessible to the target audience.

3.5 Stigma and Discrimination Resulting from Participation in an HIV Vaccine Trial

Stigma and discrimination have been associated with AIDS since the start of the epidemic. People with HIV/AIDS have been discriminated against in a variety of ways. As a result of their participation in an HIV vaccine trial, HIV-negative volunteers may also be stigmatized or discriminated against. This subsection provides a brief overview of why discrimination can arise in this situation and how the discrimination can manifest itself, particularly with respect to insurance coverage. (Please see the *Background Paper* for a more detailed analysis of these issues.)

Further Reading

➢ T de Bruyn. *HIV/AIDS and Discrimination: A Discussion Paper*. Montréal: Canadian HIV/AIDS Legal Network and Canadian AIDS Society, 1998. Available at www.aidslaw.ca/Maincontent/issues/discrimination.htm.

If a volunteer's participation in an HIV vaccine trial becomes known, people may associate participation in the trial as an indication of HIV infection, probable infection or the likelihood of becoming infected, and may discriminate on that basis. Or people may strongly disapprove of HIV risk practices and view trial participants as people likely to engage in such practices. As well, the trials may occur in marginalized communities that already experience stigma and discrimination; if the research process and its attendant publicity identify these communities, the stigma and discrimination could be further exacerbated.

How would the discrimination manifest itself? For the most part, HIV-negative participants would be subject to the same kinds of discrimination as people with HIV – such as harassment, denial of housing, refusal of service, loss of employment, denial of insurance, and denial of a promotion. Participants could also be stigmatized within their own communities. Research shows that potential recruits fear unfavourable social reaction to their involvement in HIV vaccine research and consider this to be a primary risk associated with participation in a vaccine trial.

With respect to the workplace, there is no need for participants in an HIV vaccine trial to divulge their participation to their employers. But word can nevertheless get around. One way to help preserve the confidentiality of this information would be for trial organizers to ensure that participants are able to make trial-related appointments outside their normal working hours.

With some (but not all) HIV vaccines, there is a possibility that some HIV-negative participants in a trial will falsely test positive on the standard HIV-antibody tests that are used. When this happens, the tests are merely indicating the presence of antibodies against the vaccine (as opposed to antibodies against HIV disease). This raises the possibility of discrimination when trial participants apply for insurance coverage. Under Canadian law, insurance companies are legally entitled to deny insurance to anyone who has a "pre-existing condition" such as HIV infection. If a participant applied for insurance and needed to take an HIV-antibody test as part of the application process, discrimination could result (ie, coverage could be denied) if the insurance company wrongly interpreted the applicant's test result as being indicative of HIV infection.

However, there are special tests available that can distinguish between a vaccine-elicited immune response and an immune response that is due to infection from HIV. While there is no guarantee that today's special tests will work for future vaccine candidates, it should be possible to develop other tests that will. Obviously, at any HIV-antibody testing site established or used by organizers during the trial itself, these special tests would be available and would be used in the event that the standard HIV test produced a positive result. Otherwise, the organizers would not know how to interpret the results of the trial. However, insurance companies are not legally compelled to use the testing facilities of the vaccine trial or to accept its test results. In order to protect against possible discrimination, trial organizers should (a) provide trial participants with documentation that shows that they are participating in an HIV vaccine trial; (b) educate insurance companies about this issue; (c) encourage insurance companies to use the HIV-antibody testing sites where the special tests are available; and (d) ensure that access to sites where the special tests are available continues even after the trial ends.

One way for the organizers to deal with discrimination that might arise as a result of participation in an HIV vaccine trial is to give participants an identification card containing a phone number where they can obtain assistance.

Recommendation 29

Trial organizers should ensure that during the informed-consent process potential participants are provided with full information on the types of stigma and discrimination that could result from their participation in an HIV vaccine trial.

Recommendation 30

Trial organizers should ensure that support is provided to people who experience discrimination during the course of an HIV vaccine trial.

Recommendation 31

Trial organizers should ensure that appointment hours are flexible enough to allow participants to attend appointments outside the participants' working hours.

Recommendation 32

Trial organizers should provide trial participants with documentation that shows that they are participating in an HIV vaccine trial. This could take the form of an identification card. The card should include a phone number participants can call in the event they experience discrimination related to their participation in the trial.

Recommendation 33

When testing candidate vaccines that can produce a false positive result on an HIV-antibody test, trial organizers should educate insurance companies about the issue; encourage insurance companies to use the HIV-antibody testing sites where special tests are available that can distinguish between a vaccine-elicited immune response and an immune response that is due to infection from HIV; and ensure that participants are able to access the sites where special tests are available even after the trial ends.

Other Issues Concerning HIV Vaccine Clinical Trials

Please see the *Background Paper* for a discussion of the following issues:

- Which candidate vaccines should be chosen for clinical trials?
- What type of clinical trials should be conducted?
- Should sponsors who are refused permission to conduct a trial in one country be permitted to solicit approval for the same protocol in another country?
- What level of risk is ethically acceptable in a vaccine clinical trial?

[11] *Ethical Considerations in HIV Preventive Vaccine Research*. UNAIDS Guidance Document. Geneva: UNAIDS, May 2000, guidance point 5 and accompanying notes, at 19.

[12] Ibid.

[13] *Ibid*, guidance point 3 at 15.

[14] *Ibid*, content notes at 7; guidance point 2 and accompanying notes at 13-14; guidance point 4 and accompanying notes at 17-18; and guidance point 7 and accompanying notes at 22-23.

[15] *Tri-Council Policy Statement: Ethical conduct for research involving humans*. Medical Research Council of Canada; Natural Sciences and Engineering Research Council of Canada; Social Sciences and Humanities Research Council of Canada. August 1998, at i.6.

[16] *International Ethical Guidelines For Biomedical Research Involving Human Subjects*. Council for International Organizations of Medical Sciences in collaboration with World Health Organization. Geneva: 1993, guideline 10.

[17] *Tri-Council Policy Statement*, supra, note 15, articles 5.1 and 5.2.

[18] *Ethical Considerations*, supra, note 11, guidance point 17 at 45.

[19] *Ibid*, guidance point 14 at 38.

[20] *Ibid*, guidance point 16 at 41.

[21] Ibid.

[22] *Ibid*, guidance point 9 and accompanying text at 27-29.

[23] *International Ethical Guidelines*, supra, note 16, guideline 13.

Section 4.0
HIV Vaccine Delivery

> Any HIV preventive vaccine demonstrated to be safe and effective … should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.[24]

This section of the paper explains that the delivery of many effective vaccines in Canada has been less than ideal, and concludes that Canada needs a vaccine delivery plan to ensure that an eventual HIV vaccine reaches the people who most need it. The section then provides suggestions concerning what should be included in a vaccine delivery plan. This is followed by a description of how the level of efficacy of an HIV vaccine can affect decisions on how best to deliver the vaccine. Finally, the section describes some of the potential obstacles to delivery of an HIV vaccine.

4.1 The Need for a Vaccine Delivery Plan in Canada

Discovery of an HIV vaccine will not automatically lead to effective delivery of that vaccine in Canada. There is no guarantee that the vaccine will reach the people who are most at risk of contracting HIV. Experience with other vaccines in Canada reveals many instances of less than optimal coverage. For example:

- Even though the measles vaccine has been around for a long time and is readily available, epidemics of measles broke out across the country in the late 1980s. In Québec alone, there were more than 10,000 cases and 50 deaths.

- Despite extensive promotion, influenza vaccination rates among health-care professionals remain relatively low.
- Infant vaccination rates for standard vaccines (diphtheria, measles, tetanus, etc) are high, but still below national targets.
- Vaccination rates decline abruptly as people progress from infancy to adolescence to early adulthood.
- Vaccination rates among adults vary substantially among different geographic areas and populations.
- Among men who have sex with men, where the risk of infection with hepatitis A and hepatitis B is fairly high, the proportion of men who have received the full series of vaccinations for both diseases remains relatively low. One cohort study among gay and bisexual men in Montréal revealed hepatitis B vaccination rates of 49 percent, of which only three-fifths had received all three inoculations required; and hepatitis A vaccination rates of 38 percent, of which less than three-tenths had received both inoculations required. Similar (or worse) coverage rates have been documented among gay men in several US cities.

A low-efficacy vaccine could be on the market in a few years from now.

Given the history and the global scale of the HIV/AIDS epidemic, the large number of people infected worldwide, the lack of resources and medical infrastructure in some of the hardest-hit nations, and the mobility of people in the modern world – even with the best of delivery strategies, it will take years to bring the global HIV epidemic under control with a highly effective preventive vaccine. HIV vaccination programs will probably have to extend through several generations. Generating and maintaining public interest and high levels of vaccine delivery and uptake over such a long period will be a challenge.

Although it is not possible to predict exactly when an effective vaccine will be available, it is not unreasonable to expect that a low-efficacy vaccine could be on the market as soon as a few years from now, and that a higher-efficacy vaccine could become available not too many years after that. Canada needs to be prepared for the day when an effective vaccine is ready to be delivered. Given the complexities of vaccine delivery, Canada needs a formal HIV vaccine delivery plan. Health Canada should start immediately to coordinate the development of such a plan, in consultation with the provincial and territorial governments, health-care providers, public health officials, and organizations representing target communities. If Canada waits any longer to develop a plan, useful HIV vaccines will almost certainly emerge without Canada having in place a plan to get the vaccine to the people who most need protection from the virus.

Health Canada should start immediately to coordinate the development of an HIV vaccine delivery plan.

Initially, the plan will have to be fairly general. It will not be possible to develop detailed strategies until more is known about the characteristics of the vaccine that will be delivered – characteristics such as effectiveness, duration of protection, number of doses required, and method of delivery. It is now possible, however, to develop the broad outlines of a delivery plan and to develop hypothetical delivery models based on different scenarios of vaccine efficacy.

The plan should outline how the vaccine will be delivered. It should provide answers to questions such as:

- Who will be vaccinated and under what conditions?

- How will vaccine delivery be financed?
- How will Canada ensure that there is sufficient manufacturing capacity to guarantee a supply of the vaccine?
- How will the vaccine be distributed? What strategies will be required in vulnerable and marginalized communities, and in resource-poor settings? What strategies will be required in multicultural communities?
- What should the delivery timelines be?
- What measures will be required to encourage the highest possible levels of vaccine uptake?
- What strategies will be required to ensure that coverage remains at a high level if multiple doses need to be administered over a long period of time?
- Who will coordinate vaccine delivery and what will the roles and responsibilities of key players be? What public–private community partnerships need to be developed?
- What efforts will be undertaken to prepare communities for vaccine delivery? What information, education, and training strategies need to be developed? What social marketing strategies need to be developed?
- If a limited supply of the vaccine is available, what criteria will be used to determine what delivery strategies should be employed or which communities should be prioritized?
- What measures need to be put in place to ensure that any vaccine-induced adverse events (ie, adverse reactions, serious side effects) are promptly identified and reported?
- How will issues of liability be handled? How will individuals be compensated for vaccine-induced adverse events?
- What measures need to be put in place to protect those who have been vaccinated from discrimination?
- What monitoring and evaluation systems need to be developed?

The plan should consider using a variety of settings to deliver the vaccine, in addition to physicians' offices and community health clinics. Such settings could include pharmacies, workplaces, schools, colleges and universities, adult education classes, family planning clinics, methadone maintenance programs, needle exchange and safe injection sites, mobile vans working with the homeless or street-involved youth, homeless shelters, outdoor sites where the homeless meet or sleep, food banks, community-based organizations, community and government service centres for recently arrived immigrants, Native friendship centres, First Nations and Aboriginal communities, gay pride events, summer camp grounds, and gymnasiums or community sports centres.

There is a danger that inoculation with a vaccine that offers less than complete protection against infection – and particularly with a comparatively low-efficacy vaccine – might actually increase HIV incidence if it encouraged a significant number of people who have been vaccinated (and others in the community) to relax safer sexual and needle sharing practices. It will be critical, therefore, to ensure that vaccine recipients are counselled to maintain risk-reduction behaviours. It will also be important to address the impact of vaccine delivery on collective risk assessment in the community. The plan will need to spell out how this will be done.

Given current HIV vaccine research patterns, it is quite possible that an effective HIV vaccine will emerge from a trial conducted in just one or two target communities. Therefore, the vaccine delivery plan will need to provide for "bridging studies" that could be rapidly mounted to determine whether the vaccine is effective in other communities.

The framers of the vaccine delivery plan should study the record of vaccine distribution for hepatitis A and hepatitis B. There are considerable similarities between the epidemiology of hepatitis and HIV, so valuable lessons could be learned. It may be possible to combine the HIV vaccine with hepatitis vaccines or with vaccines for other infections.

During the development of the vaccine delivery plan, it may be helpful to undertake some research in potential target communities. Possible research topics could include: (a) how levels of vaccine uptake will vary as a function of vaccine efficacy; and (b) what follow-up methods would work best if booster inoculations are required.

Development of the plan should be coordinated with the Canadian National Immunization Strategy being developed by Health Canada in collaboration with provincial and territorial governments. The Immunization Strategy is currently focusing on childhood vaccinations, but there are plans to address adult vaccinations as well. A Canadian HIV vaccine delivery plan must also take into account the global dimensions of the epidemic. In order to reap the greatest possible public health benefit, a national plan for domestic delivery will need to be firmly anchored in a global delivery strategy.

Recommendation 34

As part of the Canadian HIV Vaccine Plan, Health Canada should begin immediately to coordinate the development of a plan for the delivery of an HIV vaccine. The plan should be developed in consultation with the provincial and territorial governments, health-care providers, public health officials, and organizations representing target communities. Once it has been developed, the plan should be updated regularly to reflect the latest developments in HIV vaccine research.

Further Reading

➢ *Future Access to HIV Vaccines*. Report from a WHO–UNAIDS Consultation, Geneva, 2-3 October 2000. (Final draft, 5 February 2001). Health Technology and Pharmaceuticals, World Health Organization.

4.2 How Vaccine Efficacy Might Affect Delivery of an HIV Vaccine

There are a number of possible scenarios with respect to the degree and type of protection that an HIV vaccine could confer. Some of these scenarios are:

- The vaccine provides complete or near complete protection against acquiring HIV infection (known as "sterilizing immunity").
- The vaccine does not provide protection against acute infection, but it stimulates the immune system to control viral replication to the point where chronic infection is not established.

- The vaccine provides only partial protection against acquiring chronic infection, but prevents or delays disease progression.
- The vaccine provides only partial protection against acquiring chronic infection, and does not prevent or delay disease progression.
- The vaccine does not provide any protection against chronic infection, but prevents or delays disease progression.
- The vaccine does not provide protection against chronic infection or disease progression, but reduces the infectiousness of the individual.

The ideal vaccine will benefit both the individual and the community. However, as can be seen from the scenarios listed above, some vaccines may benefit one more than the other. The level of efficacy of the vaccine and the type of protection it provides will obviously have an impact on the vaccine delivery strategy. If a vaccine confers proportionately greater benefit to public health than to individual health, then vaccination campaigns will have to appeal to values such as community solidarity, altruism, and the desire to protect future generations. This may make delivery a much more difficult task, particularly among vulnerable populations where people may not access community support and health services.

The level of efficacy of the vaccine and the type of protection it provides will have an impact on the vaccine delivery strategy.

It is also possible that the efficacy of preventive vaccines will vary according to the subtype of HIV. This would require development and delivery of multiple vaccines (or a cocktail vaccine) in Canada and elsewhere.

The level of efficacy of the vaccine being delivered will influence the strategies that Canada uses in its vaccine delivery plan. Vaccines with high efficacy may stop or reverse the progress of the HIV/AIDS epidemic even with less than optimal coverage. The higher the level of vaccine efficacy, the lower the proportion of people in a given community that will need to be vaccinated in order to obtain significant reductions in new infections. Consequently, the best strategy for a highly effective vaccine might be to deliver the vaccine to broad segments of the overall population.

On the other hand, the lower the efficacy of the vaccine, the more coverage will be required for it to have a significant impact on the epidemic. Therefore, a vaccine with a low level of efficacy would need to be targeted to people at high risk in populations where the HIV-incidence rates are high. In these populations, even modest reductions in HIV incidence can save many lives. The lower the level of vaccine efficacy, the greater the proportion of the targeted high HIV-incidence populations that must be vaccinated in order to achieve a significant public health impact. Also, the lower the level of vaccine efficacy, the harder it will be to persuade people to be vaccinated.

4.3 Potential Obstacles to Delivering an HIV Vaccine

Perhaps the greatest obstacle to delivering an HIV vaccine in Canada is scepticism and distrust. Popular opposition to vaccines has existed throughout history. This opposition is based primarily on concerns about the safety of the vaccines. One of the most commonly expressed fears is that the vaccine might actually give people the disease it is designed to prevent. (Unfortunately, this actually happened to a very small number of people who received the first polio vaccine, but it is an extremely rare occurrence.) The scepticism is fuelled by

misconceptions about vaccines held by the public (and even health-care professionals) and by a lack of accurate information about vaccines.

In the case of an HIV vaccine, people may simultaneously overestimate the risks of vaccination and underestimate the risks and consequences of HIV infection. They may not consider themselves at risk of HIV infection. Or they may reason that HIV is not contagious; that it is not suddenly catastrophic; that it can have a relatively long asymptomatic period; and that it can be treated. These attitudes could affect vaccine uptake, especially if the vaccine being delivered had a relatively low efficacy.

To overcome the obstacles outlined above, and to achieve the degree of public confidence and support needed to ensure a high level of vaccine coverage, the case for HIV vaccination will need to be presented in a manner that clearly outlines the potential benefits and disadvantages both for individuals and for public health.

If insufficient resources were made available to implement a comprehensive vaccine delivery program, this would constitute a significant barrier to delivery. The stigma associated with HIV/AIDS could also be an obstacle. It is possible that the vaccine delivery strategy would call for vaccination to be carried out initially in those communities with the highest rates of infection (eg, gay men, people who inject drugs, prisoners, sex trade workers). However, because these communities are already marginalized, it may be difficult to rally public and political support to release the budgets needed for effective vaccine delivery in these populations. Furthermore, the stigma could make people reluctant to agree to be vaccinated. People who are vaccinated could be exposed to some of the same risks of discrimination faced by participants in a vaccine trial (see Section 3.5).

Delivery of an HIV vaccine in marginalized communities will present a series of challenges.

Encouraging vaccination in settings where there is widespread poverty may be an extremely difficult task. In a population of injection drug users where hepatitis C rates are 80 percent or higher, or in a population of women coping with physical and sexual abuse, despair and fatalism could make it difficult to convince people that they should be vaccinated against HIV.

Delivery of an HIV vaccine in marginalized communities will likely present a series of challenges. In some of these communities, living circumstances are complicated, housing is precarious, incomes and education levels are relatively low, and people may be fighting diseases other than HIV/AIDS. People in these communities may access health-care services only inconsistently. The services may be provided by a variety of uncoordinated programs.

Recommendation 35

Public health officials and affected communities should work together to advocate for vaccine delivery in those communities where it is most needed.

Recommendation 36

Prior to implementing a vaccine delivery program, governments should ensure that the target communities are provided with (a) clear and comprehensive information about the benefits, efficacy, safety, and risks of the HIV vaccine; and (b) information on the risks of not being vaccinated.

Other Issues Concerning HIV Vaccine Delivery

Please see the *Background Paper* for a discussion of the following issues:

- Would there be public support for a program of childhood HIV vaccination in primary or secondary schools?
- What would be the impact on delivery of the durability of immunity conferred by the HIV vaccine?
- Would mandatory HIV vaccination programs be appropriate for the general public or for specific populations?
- Should health professionals be offered financial incentives in order to bolster HIV vaccine delivery?
- Should people in difficult-to-reach target populations be offered financial incentives to be vaccinated?

[24] *Ethical Considerations*, supra, note 11, guidance point 2 at 13.

Summary of Recommendations

Investing in HIV Vaccine Development and Delivery

1. Governments, the pharmaceutical industry, researchers, and HIV/AIDS community organizations should make a firm commitment to an accelerated and sustained program of HIV vaccine research in Canada.
2. Federal and provincial governments and the pharmaceutical industry should substantially increase their investment in HIV vaccine research in Canada.
3. Health Canada should coordinate, and provide funding for, the development of a Canadian HIV Vaccine Plan. The Plan should be prepared in consultation with the provinces and territories, HIV/AIDS community organizations, HIV researchers, and other stakeholders, and should be developed by 1 October 2003. It should contain a development component and a delivery component. The development component of the Plan should focus on those areas where Canada has experience and expertise.
4. Health Canada, through the Canadian HIV Vaccine Plan, and with the participation of HIV/AIDS community organizations, should mobilize public opinion and support for HIV vaccine development and delivery.
5. The federal government should significantly increase funding for international HIV vaccine efforts. It should participate actively in attempts to ensure global coordination of HIV vaccine development.

HIV Vaccine Clinical Trials

Working with Target Communities

6. Trial organizers should involve community representatives in the design and implementation of HIV vaccine trials.
7. Trial organizers should work closely with communities and public health officials to minimize potential harms caused by undue vaccine optimism.
8. As part of the Canadian HIV Vaccine Plan, the Canadian Institutes of Health Research should fund sustained qualitative psychosocial research to investigate the potential impact of undue vaccine optimism on individual and collective risk assessment and risk assumption. The research should also look at ways to sustain behaviour change in the face of undue vaccine optimism.
9. Trial organizers and governments should provide funding for community organizations to educate communities about HIV vaccine research and to participate in the design and implementation of HIV vaccine trials.
10. At each trial site, trial organizers should help facilitate the establishment of a community advisory board (CAB). This should include providing the CABs with adequate training and resources to carry out their functions of advising organizers, educating target communities, maintaining links with local prevention and health services, and preparing materials to educate CAB members on their role.
11. At each trial site, community organizations should advocate for the establishment of a community advisory board (CAB) where communities, NGOs, and researchers can share information, problem solve, and work to improve the trial. Community organizations should support existing CABs by providing feedback to CAB members, attending meetings between the CAB and the broader community, etc.
12. In multi-centre trials, trial organizers should prepare and disseminate directories of the members of CABs in various cities involved in the trials. Organizers should encourage CAB members to correspond and exchange ideas with people working on CABs in other cities.
13. Trial organizers should involve people with HIV/AIDS in the design and implementation of vaccine trials.
14. Where warranted, trial organizers and governments should collaborate on the development and implementation of capacity-building programs to enable target communities to participate in the design and implementation of HIV vaccine trials. Organizers should encourage and support the development of leadership within communities likely to be targeted for vaccine trials.
15. Prior to commencing recruitment, trial organizers should: (a) anticipate potential harms to participants and establish links with service providers and community leaders to minimize these harms; and (b) take steps to address the concerns of potential participants about risks associated with the trial.
16. Trial organizers should consider undertaking vaccine preparedness studies in communities where there is a reasonable expectation of an HIV vaccine trial being conducted.

Recruitment

17. The Canadian HIV Vaccine Plan should emphasize the need to ensure that all populations with significant rates of HIV infection participate in human testing of candidate HIV vaccines.

18. For individual trials, to the extent that the criteria permit, trial organizers should recruit participants from the various populations with significant rates of HIV infection.
19. Trial organizers and community leaders should work together to design a compensation package that is reasonable but that will not create an undue incentive to participate in the trial.

Informed Consent

20. Trial organizers should work with people from each target community to obtain input on the informed-consent process and to ensure that the process is adapted to the particular culture of that community.
21. Trial organizers should ensure that the trial protocols spell out in detail the process for obtaining informed consent, including a description of the methods that will be used to ensure that the consent is truly informed.
22. During the informed-consent process, trial organizers should educate participants about the randomized, placebo-controlled nature of a clinical trial. Organizers should stress the altruistic reasons for participating in a trial. They should inform participants that their best hope for preventing HIV lies in avoiding risk behaviours or adopting harm-reducing behaviours.

Obligations to Participants

23. Trial organizers should develop a comprehensive plan for preventive counselling prior to the start of the trial. The plan should be developed in consultation with local health-care providers and AIDS service organizations.
24. Trial organizers should ensure that the staff providing preventive counselling are knowledgeable about the cultures of the target communities.
25. Trial organizers should protect the confidentiality of the information gathered during counselling sessions.
26. Trial organizers should ensure that high-quality care and treatment are provided to any participant who becomes HIV-infected during the course of the trial. Where necessary to ensure access, organizers should subsidize the cost of any antiretroviral medications or drugs for the treatment of opportunistic infections not already covered under provincial and territorial drug reimbursement programs.
27. The federal government should establish a no-fault vaccine-related injury insurance program in Canada. The program should cover all experimental and licensed vaccines. Pharmaceutical companies should contribute to this fund.
28. Trial organizers should provide participants with detailed information on the results of the trial. The information should be provided in a format that is accessible to the target audience.

Stigma and Discrimination

29. Trial organizers should ensure that during the informed-consent process potential participants are provided with full information on the types of stigma and discrimination that could result from their participation in an HIV vaccine trial.

30. Trial organizers should ensure that support is provided to people who experience discrimination during the course of an HIV vaccine trial.
31. Trial organizers should ensure that appointment hours are flexible enough to allow participants to attend appointments outside the participants' working hours.
32. Trial organizers should provide trial participants with documentation that shows that they are participating in an HIV vaccine trial. This could take the form of an identification card. The card should include a phone number that participants can call in the event they experience discrimination related to their participation in the trial.
33. When testing candidate vaccines that can produce a false positive result on an HIV-antibody test, trial organizers should educate insurance companies about the issue; encourage insurance companies to use the HIV-antibody testing sites where special tests are available that can distinguish between a vaccine-elicited immune response and an immune response that is due to infection from HIV; and ensure that participants are able to access the sites where special tests are available even after the trial ends.

HIV Vaccine Delivery

34. As part of the Canadian HIV Vaccine Plan, Health Canada should begin immediately to coordinate the development of a plan for the delivery of an HIV vaccine. The plan should be developed in consultation with the provincial and territorial governments, health-care providers, public health officials, and organizations representing target communities. Once it has been developed, the plan should be updated regularly to reflect the latest developments in HIV vaccine research.
35. Public health officials and affected communities should work together to advocate for vaccine delivery in those communities where it is most needed.
36. Prior to implementing a vaccine delivery program, governments should ensure that the target communities are provided with (a) clear and comprehensive information about the benefits, efficacy, safety, and risks of the HIV vaccine; and (b) information on the risks of not being vaccinated.