



REPUBLIC OF KENYA
MINISTRY OF HEALTH

Kenya National Guidelines

for Research and Development of HIV/AIDS Vaccines



March 2005



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Kenya National **Guidelines** for Research and Development of HIV/AIDS Vaccines

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Abbreviations

AAVP	African AIDS Vaccine Programme	MoH	Ministry of Health
AG	attorney general	MoP	Ministry of Planning and National Development
AIDS	acquired immunodeficiency syndrome	MRC	Medical Research Centre
ARV	antiretroviral	MVA	modified vaccinia Ankara
CAB	community advisory board	NACC	National AIDS Control Council
CDC	Centers for Disease Control and Prevention	NASCOP	National AIDS/STD Control Programme
CTL	cytotoxic T lymphocytes	NCST	National Council for Science and Technology
DNA	deoxyribonucleic acid	NEPHAK	Network of People Living with HIV / AIDS in Kenya
DSMB	Data and Safety Monitoring Board	NGO	non-governmental organization
ELISA	enzyme-linked immunosorbent assay	NIH	National Institutes of Health
env	envelope	NOPE	National Organization of Peer Educators
GCLP	good clinical and laboratory practices	OHERS	Organization for Health, Education and Research Services
GCP	good clinical practice	PI	principal investigator
GLP	good laboratory practice	PLWHA	people living with HIV / AIDS
GMP	good manufacturing practice	PPB	Pharmacy and Poisons Board
HB	haemoglobin	RADA	research and development agreement
HIV	human immunodeficiency virus	SACODEN	Strategic Community Development Network
HLA	human leucocyte antigen	SOP	standard operating procedure
IAVI	International AIDS Vaccine Initiative	STI	sexually transmitted infection
IRB	institutional review board	SWAK	Society of Women and AIDS in Kenya
IT	information technology	UN	United Nations
KANCO	Kenya AIDS NGOs Consortium	UNAIDS	Joint United Nations Programme on HIV / AIDS
KAVI	Kenya AIDS Vaccine Initiative	UoN	University of Nairobi
KDHS	Kenya demographic and health survey	USA	United States of America
KELIN	Kenya Ethical and Legal Issues Network on HIV / AIDS	VCT	voluntary counselling and testing
KEMRI	Kenya Medical Research Institute	VEE	Venezuelan equine encephalitis
KICOSHEP	Kibera Community Self-Help Programme	VSC	Vaccine Subcommittee
KIPI	Kenya Industrial Property Institute	WB	western blot
KMA	Kenya Medical Association	WBC	white blood cells
KNCHR	Kenya National Commission on Human Rights	WHO	World Health Organization
KNH	Kenyatta National Hospital	WRP	Walter Reed Project

Foreword

In recent times, no disease has had such an impact on humankind as HIV / AIDS. It is the most important infectious disease globally. No country in the world has been spared from the disease and it is now the fourth most common cause of premature death in the world, and the leading cause of death in Africa. In Kenya, the first AIDS case was identified in 1984, and by 2003 over 1.5 million people had died of the disease and an estimated 2.5 million were living with the virus, giving a national prevalence of about 9.4%.

The HIV / AIDS pandemic has had various negative social and economic effects on our country. By the year 2003, there were over 1.5 million children orphaned by HIV / AIDS. Many of these orphans and other vulnerable children survive on the minimum of basic human needs. Patients with HIV-related illnesses occupy about 50 to 70% of hospital beds in medical wards. The country has continued to lose a large percentage of its productive citizens through HIV / AIDS illness and deaths. The health budget is overstretched and the success of poverty reduction programmes seriously jeopardized.

The government through the National AIDS Control Council (NACC) has established a multisectoral intervention programme in both public and private sector organizations. Together with the Ministry of Health's National AIDS and STI Control Programme (NASCOP), NACC has carried out various measures on HIV prevention and care for AIDS patients, such as awareness campaigns and antiretroviral (ARV) treatment. These measures have had a positive impact on HIV / AIDS incidence, prevalence and clinical presentation. However, some of them such as ARV treatment are still expensive and the majority of those infected are unable to afford them. It is therefore clear that other complementary methods to control the pandemic are required. An HIV / AIDS vaccine could be a major contribution to prevent the high rates of HIV transmission and infection among our population.

The government has a central role to play in creating an enabling environment for the successful conduct of HIV / AIDS vaccine trials in Kenya. Therefore, the Ministry of Health in playing this role has developed these guidelines to provide a framework for developing and evaluating HIV / AIDS vaccines. The guidelines will also provide a blueprint for government agencies and non-governmental organizations to collaborate with HIV / AIDS vaccine research and development partners to accelerate the research and development of HIV / AIDS vaccine.

The ministry wishes to recognize and appreciate the financial and logistic support from the International AIDS Vaccine Initiative (IAVI) in preparing these guidelines.



Hon. Charity K. Ngilu, EGH, MP
Minister for Health

Preface

In Kenya, it was observed that some commercial sex workers in Nairobi's Majengo slum were resistant to HIV infection despite repeated exposure. This observation led to research on possible immune mechanisms involved in resistance and the development of a vaccine construct. The resultant HIV / AIDS vaccine entered human trials conducted by the Kenya AIDS Vaccine Initiative (KAVI) in collaboration with the Medical Research Council-UK and the International AIDS Vaccine Initiative (IAVI) in 2001 in Nairobi. This marked the beginning of the search for an HIV / AIDS vaccine in Kenya.

At that time it was noted that there were no clear and specific guidelines to aid in developing and evaluating HIV / AIDS vaccines. Therefore the Ministry of Health began developing the relevant guidelines. This was done by a process that involved setting up the HIV / AIDS Vaccine Subcommittee and consulting stakeholders through a series of workshops held under five themes—clinical, biomedical, law and ethics, community, and policy. A two-day national consensus workshop was held to deliberate on the document in November 2004. It was attended by over 100 stakeholders comprising government ministries, researchers, health care workers, public and private universities, NGOs, community representatives, professional societies and faith-based organizations from all provinces.

The deliberations from these meetings were then incorporated into this document, the *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines*. These guidelines will be widely distributed and are expected to be used by all organizations, institutions and individuals involved in developing and evaluating such a vaccine. This is the first edition of these guidelines, and comments and suggestions are welcome. They should be forwarded to the Department of Standards and Regulatory Services (DSRS), Ministry of Health, to help review for future editions.



Dr James Nyikal, MBS
Director of Medical Services

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Contributors

Job Akuno (NOPE)	Eva Mwai (St John Ambulance)
Erastus O. Amayo (UoN)	David Nalo (MoP)
Julia Amayo (SACODEN)	J.O. Ndinya-Achola (UoN / KAVI)
Pauli N. Amornkul (CDC / KEMRI / Kenya)	Elizabeth Nganga (AG's Chambers)
Omu Anzala (UoN / KAVI)	Susan Ngugi (ActionAid)
Elizabeth Aroka (Rachier & Co. Advocates)	Rispah Oduwo (NCST)
Bonnie Bender (IAVI)	Cleophas Ojode (KIPI)
Kiran Bhatt (UoN / KAVI)	Tom Mboya Okeyo (MoH)
F. Babu Bora (KMA)	James Ombega (UoN)
Job Bwayo (UoN / KAVI)	Gloria Omosa-Manyonyi (KAVI)
K.L. Chebet (NASCOP)	Kepha Ombacho (MoH)
Rose Dorcas Cheche (OHERS)	Dennis Onwenga (KELIN)
Gina Foglia (WRP / KEMRI / Kenya)	P.A. Orege (NACC)
Esther Gatua (Policy Project)	L.S. Otieno (KMA)
Muriithi Gatumo (NASCOP)	D.M. Owili (AAVP)
Anastasia Guantai (UoN)	Anne Owiti (KICOSHEP)
H. Irimu (KNH)	John O. Owuor (MoP)
Pauline Irungu (KANCO)	Mark Rabudi (St John's Community Centre)
Walter Jaoko (UoN / KAVI)	Ambrose Rachier (Rachier & Co. Advocates)
James Jowi (KNH)	Allan Ragi (KANCO)
Sam Kalibala (IAVI)	Nelly Rangara (MoH)
Chrispin Kambili (IAVI)	Edward Saunders (KEMRI)
Anuja Kapila (Clinician)	Julia Stout (IAVI)
Christine Kigundu (UoN)	Grace Thoithi (UoN)
Micah K. Kisoo (NACC)	Annalisa Trama (UNAIDS)
Nellie Luchemo (Maendeleo ya Wanawake Organization)	Peter Tukei (KEMRI)
Florence Manguyu (IAVI)	Mercy Wahome (SWAK)
Inviolata Mmbavi (NEPHAK)	K.A. Wakoli (UoN)
Wanjuki Muchemi (Solicitor General)	Rhoda Wanjala (Maendeleo ya Wanawake Organization)
Lucy Muchiri (UoN)	Monique Wassuna (KEMRI)
Sobbie Mulindi (UoN)	S. Mwangi Watene (KMA)
Catherine Mumma (KNCHR)	S.E. Waweru (UoN)
Lawrence Muthami (KEMRI)	Edwin O. Were (Moi University)
Mugambi Mutuma (Kenya Methodist University)	Sylvia Yolanda (OHERS)

Executive summary

HIV / AIDS has become one of the most devastating infectious diseases globally. In 2004 approximately 4.9 million people were newly infected with HIV. Of these, 4.3 million were adults and 640,000 were children under 15 years of age. The pandemic is devastating sub-Saharan Africa, which is home to about 10% of the world's population but had 60% of all the people living with HIV in 2004.

A preventive HIV / AIDS vaccine could contribute substantially in preventing HIV infections in Africa, and more needs to be done to accelerate its research and development. Developing such a vaccine requires conducting multiple clinical trials to assess the efficacy of different vaccines against different HIV subtypes, and in diverse populations, some of which must be in developing countries.

Soon after HIV was identified as the cause of AIDS, the search for a vaccine began. Progress, however, has not matched initial hopes. HIV integrates into the human genome, making it difficult for the immune system to detect and eliminate it. The extensive genetic variability of the virus is further compounded by its high mutation rate in an infected person.

A wide range of candidate vaccines have been developed. Before a candidate vaccine is evaluated in humans, tests to assess its safety, toxicity and immunogenicity are conducted on small animals and non-human primates. Results obtained from animals, however, cannot accurately predict the degree of vaccine-induced protection in humans. It is therefore necessary to conduct human trials. Phase I trials, primarily for safety data, are conducted among 10 to 100 volunteers at low risk of HIV infection; phase II safety and immunogenicity trials are conducted in about 100 to 500 volunteers; candidate vaccines that progress to phase III trials are usually double-blind placebo-controlled trials, involving thousands of volunteers at moderately high risk of HIV infection; phase IV studies are on post-marketing matters.

Three principal HIV/AIDS vaccine approaches have been tested in three successive waves, dominated by different vaccine development models: antibody-inducing vaccines, CTL-inducing vaccines, and a combination of antibody and CTL-inducing vaccines. (Cytotoxic T lymphocytes (CTLs) are immune system cells that can destroy virus-infected cells.)

People have the right to make their own informed decisions as to whether they want to participate in HIV / AIDS vaccine research. They must therefore be informed about the background of the study, what benefits and risks are involved, how long the study will go on, and they must be able to comprehend the information given. To facilitate dialogue between community members, study volunteers and researchers, community advisory boards are created comprising community representatives who advise and guide implementation of a given research protocol.

The *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines* spell out a number of policy issues affecting vaccine research: the roles of government, regional and subregional intergovernmental organizations, the African AIDS Vaccine Programme, WHO, UNAIDS, vaccine manufacturers, funding organizations, investigators, and collaborating institutions.

A candidate vaccine must undergo a rigorous regulatory process before it is approved for testing in humans. The guidelines detail this process, which in Kenya involves the National Council for Science and Technology, the Pharmacy and Poisons Board, and the Kenya HIV / AIDS Vaccine Subcommittee.

International guidelines have been established on ethical and scientific standards for carrying out biomedical research on human subjects. They require ethical and scientific review of the research to protect participating persons and communities. Ethics review boards are set up to safeguard the dignity, rights, safety and well-being of research participants by ensuring that research is carried out according to the highest ethical and international scientific standards. Their review covers the scientific design and conduct of the study; how participants are recruited, cared for, their confidentiality protected; and culture considerations of the community.

Before an HIV / AIDS human vaccine trial begins, virological, immunological, epidemiological, clinical and sociobehavioral studies should be conducted. The director of the primary laboratory should be a specialist in a branch of laboratory science or medicine. Virological studies are necessary, including isolation and characterization, as different HIV subtypes are prevalent in different parts of the world. Baseline epidemiological studies are needed to characterize HIV infection in populations that are potential vaccine trial sites. Sociobehavioural studies gather data on public knowledge, attitudes, perceptions and practices regarding sexually transmitted infections and HIV / AIDS, particularly in the sex and age groups at greatest risk of infection in the study population. Studies also need to be done to assess what the community expects from the outcome of the trial.

The guidelines go into some detail on how to conduct phase I and II clinical trials and phase III efficacy trials, including giving check lists. They explain the need for counselling and what 'informed consent' entails. Guidelines for monitoring trials are spelled out, including the duties of a data and safety monitoring board.

If a candidate vaccine is assessed ready to market, the guidelines point out what must be done to make it available and affordable to the public, and how to transfer the technology for producing it to pharmaceutical manufacturers.

Sociological and counselling issues are covered, including details of the informed consent process. Operational and logistic issues are dealt with, such as laboratory support required, clinical support, data management, administrative issues, and public relations that will invariably surround the trial. The last chapter goes into detail on training that is needed, not only for study and non-study personnel but also for members of both regulatory and scientific review boards.

Five appendices cover an outline of a concept plan, an informed consent checklist, guidelines on participant consent, a form setting forth the subject's rights as a participant, and a sample agreement form for biological material transfer.

1 Introduction and background

Kenya is playing a key role in the research and development of HIV / AIDS vaccines. Enacting an important part of this role, the government has developed guidelines to facilitate and support research in this field.

RESEARCH AND DEVELOPMENT OF HIV/AIDS VACCINES

1.1 Vision

Research and development of HIV/AIDS vaccines that are effective, safe, affordable, accessible and acceptable.

1.2 Mission

To promote ethical research, development, production and evaluation of suitable HIV / AIDS vaccines and ensure sufficient availability of the vaccine for the country through strategic planning and national, regional and international collaboration.

1.3 Objectives

- To facilitate research and development of vaccines that can either prevent HIV infection or delay progression of disease.
- To build national consensus on a comprehensive, well-coordinated, long-term strategy for developing and evaluating safe, efficacious and affordable preventive, therapeutic and perinatal HIV / AIDS vaccines.
- To develop and provide the legal framework for regulatory approval of research trials, manufacture and licensing of HIV / AIDS vaccines and vaccine products.
- To advise on populations suitable for clinical evaluation of HIV / AIDS vaccines.
- To provide guidelines for scientific and ethical review of protocols for HIV / AIDS vaccine trials including biosafety committees.
- To provide guidelines for monitoring the conduct of HIV / AIDS vaccine trials according to scientifically and ethically acceptable standards.
- To establish ways and means of building local infrastructure and the transfer of knowledge and technology regarding HIV / AIDS vaccines.
- To establish ways and means of ensuring availability, accessibility and affordability of an efficacious HIV / AIDS vaccine.
- To develop indicators for monitoring and evaluating implementation of the national HIV / AIDS vaccine guidelines.

1.4 Strategies

Strategies for achieving the above objectives include the following:

- Develop clear national policy and implementation guidelines regarding vaccine research, development, testing, evaluation, production and utilization.
- Identify national, regional and international research institutions and other organizations, including vaccine manufacturers, that are willing to collaborate and have the

capacity to participate in HIV / AIDS vaccine-related research and evaluation.

- Mobilize and commit national resources
- Mobilize international resources.
- Identify potential cohorts suitable for evaluation of promising HIV / AIDS candidate vaccines.
- Identify what clinical support systems are necessary for developing an HIV / AIDS vaccine.
- Assess national and international institutions for their ability to:
 - Conduct relevant research
 - Enhance local capacity and improve infrastructure and communication
 - Collaborate with relevant partners and donor agencies for technical, financial and logistic support.
 - Engage in equitable and mutually beneficial collaboration.
- Regularly monitor and evaluate the implementation of these guidelines.
- Periodically update the public and the international communities on the progress of vaccine research and development through appropriate channels.

1.5 The HIV/AIDS pandemic and the need for an HIV/AIDS vaccine

Since HIV / AIDS was recognized in 1981, it has become one of the most devastating infectious diseases globally. It is the fourth most common cause of premature death in the world, and the leading cause of death in Africa. Of approximately 60 million people who had been infected with HIV since the beginning of the epidemic, more than 20 million had died of AIDS by the end of 2003 (UNAIDS / WHO 2003). In 2004, there were about 3.1 million (2.8–3.5 million) AIDS deaths. In the same year, about 4.9 million (4.3–6.4 million) new HIV infections occurred—approximately 14,000 per day—resulting in more than 39.4 million (35.9–44.3 million) people living with HIV / AIDS worldwide. In that year, 60% or some 25.4 million (23.4–28.4 million) of the infected people were living in sub-Saharan Africa, where the pandemic is causing particular devastation. The average HIV prevalence among the adult population across sub-Saharan Africa is 7.4% (UNAIDS / WHO 2004).

Current measures of HIV prevention and care have affected HIV / AIDS incidence, prevalence and clinical presentation positively. However, despite recent positive trends of falling prevalence among young people, especially in adolescent girls in Uganda and South Africa, overall about three times as many young women as men are infected in sub-Saharan Africa. In 2004, an estimated 3.1 million (2.7–3.8 million) people in the region became newly infected, while 2.3 million (2.1–2.6 million) died of AIDS. Among young people aged 15–24 years, an estimated 6.9% (6.3–8.3%) of women and 2.2% (2.0–2.7%) of men were living with HIV at the end of 2004. Several factors contribute to this high HIV prevalence, but it seems apparent that an HIV / AIDS vaccine could contribute in a major way towards preventing HIV infections among young people in Africa.

The high rate of HIV transmission throughout sub-Saharan Africa emphasizes the need to develop additional simple, affordable, accessible and effective biomedical preventive tools, such as microbicides and preventive vaccines. Because an HIV / AIDS vaccine offers the best long-term hope for controlling the AIDS pandemic on the continent, more needs to be done to accelerate research and development of a preventive HIV / AIDS vaccine.

To develop a safe and effective HIV / AIDS vaccine, multiple clinical trials must be conducted to assess the efficacy of different vaccines against different HIV subtypes, and

in populations diverse in risk and in genetic, nutritional or health backgrounds. To take into account all these variations, multiple phase III trials must be conducted in both industrialized and developing countries. These trials will require intensive international cooperation and collaboration.

Vaccine research and trials in developing countries are necessary because 1) the majority of infections occur in these countries, 2) an effective vaccine would be particularly beneficial for these populations, 3) phase III trials need to be conducted in populations with a relatively high incidence of HIV infection, 4) the variability of HIV necessitates testing candidate vaccines in different areas of the world where different subtypes are prevalent, 5) it may be necessary to evaluate how different routes or cofactors for HIV transmission and host genetic background would influence vaccine-induced protection, and 6) relevant research from countries with similar epidemiologic conditions may facilitate licensing and fulfilment of regulatory requirements.

The Kenyan situation

The first AIDS case was identified in Kenya in 1984, and by the year 2003 over 1.5 million people had died of the epidemic and 2.5 million were estimated to be living with the virus, giving a national prevalence of about 9.4% (fig. 1). About 80% of the transmission is by heterosexual contact and the highest rates of infection are between the ages 20–24 years in women and 30–39 years in men. Figure 1 shows a marked decrease in prevalence in the last two years. Estimates of HIV / AIDS prevalence are prepared by the National AIDS and STDs Control Programme (NASCOP) each year to assess the ongoing impact of the HIV / AIDS epidemic on the country. In 2003, a technical working group developed new estimates using data gathered for the Kenya Demographic and Health Survey (KDHS 2003) in addition to the results of sentinel surveillance conducted annually at antenatal clinics throughout the country. The new estimates have been revised downward. These estimates, however, reflect new, more comprehensive information used for calculating the rate. Prevalence has declined somewhat, but it still is high, and the revised rate should not give rise to a sense of complacency.

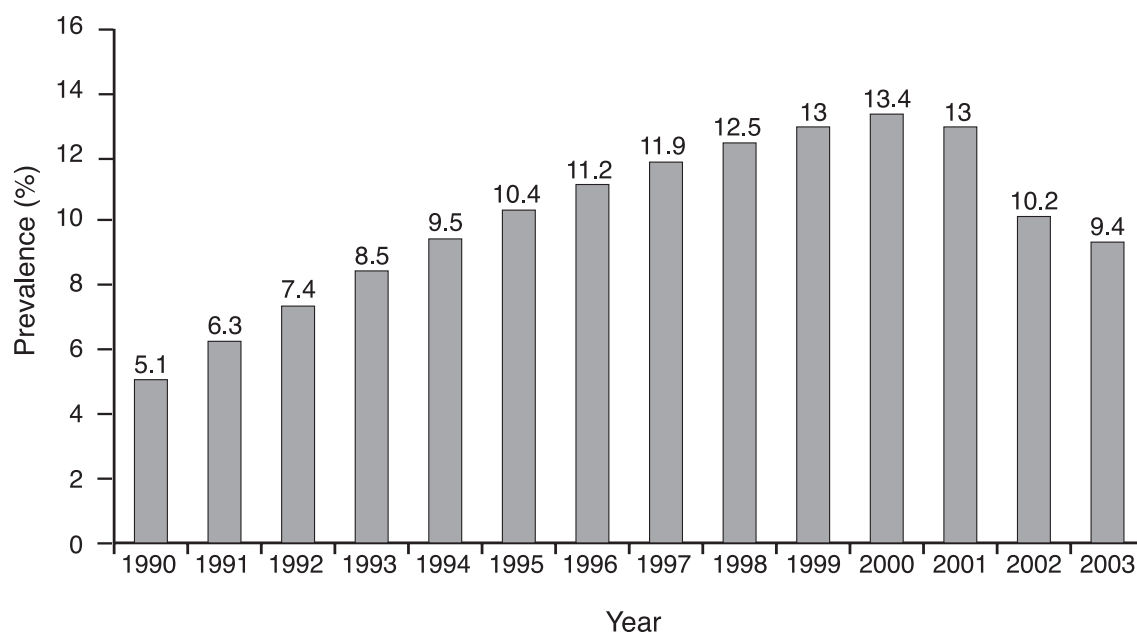


Figure 1. Trend of HIV prevalence (%) by year in the 15–49 age group, Kenya. Percentages for 2002–2003 are calculated using a method inclusive of a broader population sample (Ministry of Health, *HIV/AIDS Surveillance in Kenya*, 2003).

One of the specific objectives of the Kenya Demographic and Health Survey (KDHS) 2003 was to estimate the prevalence of HIV at national and provincial levels. This was the first time such estimates were obtained in the country's demographic health survey. Regional heterogeneity in HIV prevalence is significant (KDHS 2003).

Trends in prevalence by age and sex

Women are more vulnerable to HIV infections than men, particularly in younger age groups (fig. 2), for several reasons including biological, economic and sociocultural.

HIV prevalence in women age 15–49 is nearly 9%, while for men age 15–54 it is under 6% (KDHS 2003). Young women are particularly vulnerable to HIV infection compared with young men, as illustrated in figure 2. Prevalence in the 15–19 age group indicates that 3% of women are infected as compared with 0.4% of men. The overall prevalence among youth (15–24) is 4%. However, for women in the same age group it is 6% compared with slightly over 1% among men.

The peak prevalence among women is at age 25–29 (13%), while prevalence rises gradually with age among men to peak at age group 40–44 (9%). In age group 45–49, prevalence among men (5.2%) is higher than that among women (3.9%).

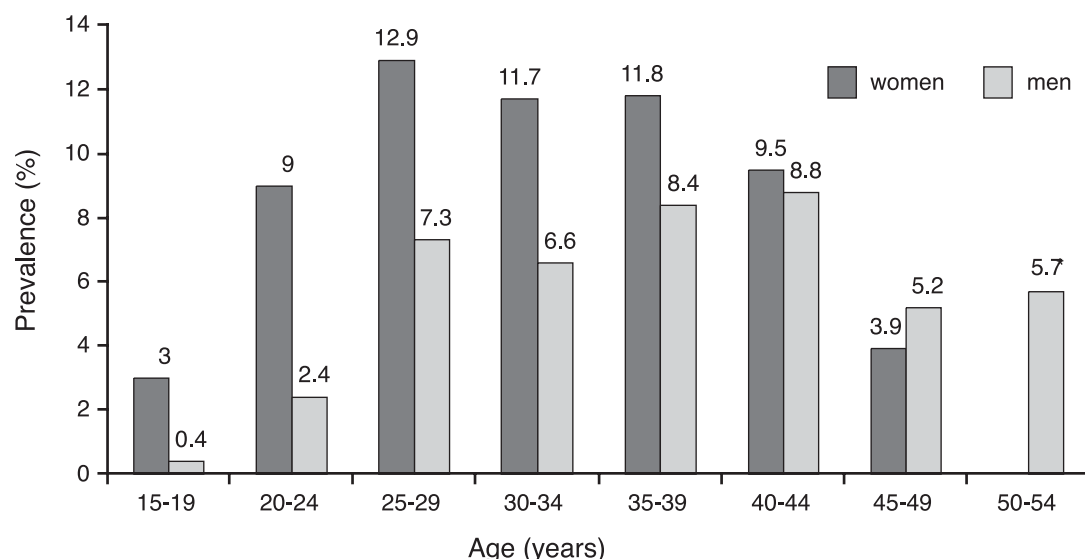


Figure 2. HIV prevalence by age and sex according to the Kenya Demographic 2003. Data on women 50 and above were not given in the report (KDHS 2003).

Trends in prevalence by province and sex

HIV epidemic shows regional heterogeneity (fig. 3). Nyanza Province has the highest overall prevalence of 15% followed by Nairobi with 10%. All other provinces have levels between 4% and 6% overall except for North Eastern with none of the respondents testing positive, an indication that the rate is very low in the province. However, gender differences persist in all regions.

The negative social and economic effects of the epidemic are worsening, with over 1.5 million children having been orphaned by the year 2003. Many of these orphans, like other vulnerable children, survive on minimum basic human needs.

Patients with HIV-related illnesses occupy about 50–70% of hospital beds in medical wards. This percentage is expected to increase as increasing numbers of people currently infected with the virus succumb and develop full-blown AIDS.

The National AIDS Control Council (NACC) has established a multisectoral intervention programme in both public and private sector organizations. Intricate and complex sociocultural beliefs and practices in multi-ethnic Kenyan society continue to have both direct and indirect implications in the spread of the epidemic, especially in rural areas, where 80% of the Kenyan population lives. Although the average national prevalence is decreasing, some districts continue to exhibit an increase in HIV infections despite a high level of awareness. To complement efforts to change behaviour, we need biomedical strategies to curb the spread of HIV and to treat infected persons.

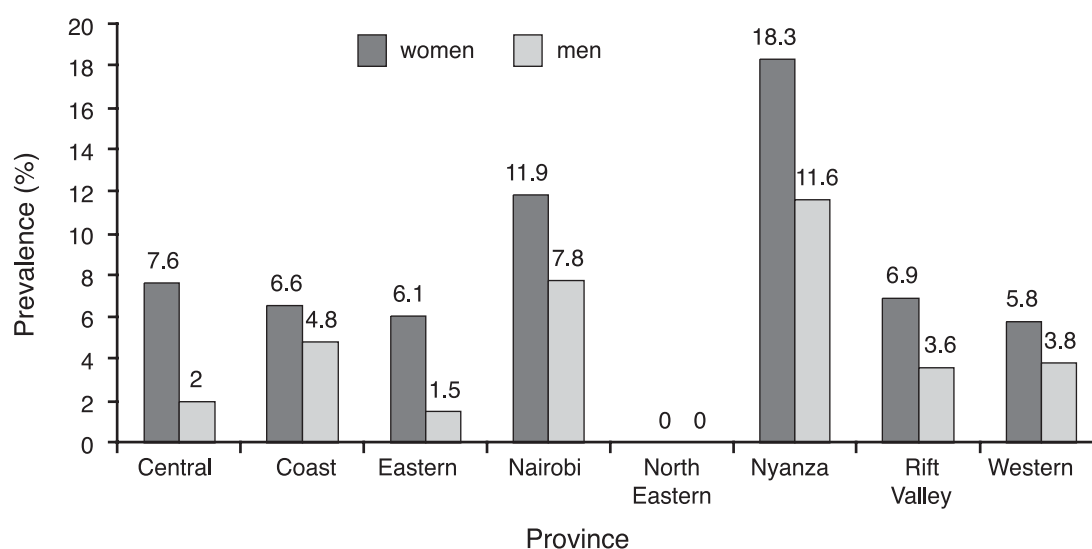


Figure 3. HIV prevalence by province and sex according to the Kenya Demographic Health Survey 2003 (KDHS 2003).

1.6 Problems and opportunities in the work to develop an HIV/AIDS vaccine

Scientific problems and opportunities

Soon after HIV was identified as the cause of AIDS, the search for an HIV/AIDS vaccine began with great optimism. In 1987 the first HIV/AIDS vaccine was tested in humans in the USA. Later it became recognized that some people resisted infection despite exposure and others were infected but remained relatively healthy despite persistent infection (non-progressors). This resistance, noted among commercial sex workers in the Majengo slum of Nairobi, led to new approaches for developing a vaccine. This observation plus other vaccine concepts have yielded a number of vaccine candidates that have been tested in many countries, including Kenya.

Progress, however, has not matched the initial hopes. A number of scientific, financial and logistical problems have beset research and development of an HIV/AIDS vaccine. Scientific problems include poor understanding of correlates of protection; genetic diversity of the virus, particularly of isolates from different populations or different geographical regions; and lack of an animal ideally suitable as a model.

HIV integrates into the human genome, making it difficult for the immune system to detect and eliminate it. The virus invades the CD4⁺ T lymphocytes and macrophages—cells central to immune defences against other microbes and to response to vaccines. AIDS differs from diseases that vaccines currently can prevent in that HIV infection may persist, and AIDS may develop, despite a broad range of immune responses from the

host. Therefore, a major conceptual problem in working to develop an HIV / AIDS vaccine is the lack of information on immune responses known to correlate with protection against HIV or AIDS.

Another obstacle in developing broadly protective HIV / AIDS vaccines is the extensive genetic variability of the virus, which is further compounded by the high mutation rate in an infected person. Phylogenetic analysis of the nucleotide sequence of the envelope genes (*env*) of numerous HIV-1 strains from different parts of the world has resulted in their classification within a major or M group and two minor groups (O and N). HIV-1 strains belonging to the M group are subdivided into at least nine pure genetic subtypes or clades (A,B,C,D; F,G,H; J,K). Strains belonging to the same subtype can differ by up to 20% in their *env* sequences; subtypes can differ as much as 35%. Analysis of other HIV-1 genes demonstrates a higher degree of conservation, which for the *gag* gene that codes for HIV core proteins is between 85 and 90%. Full-length genome sequence of HIV-1 has also revealed frequent inter- and intra-subtype recombinational events, resulting in a variety of mosaic viruses. In areas where more than one HIV subtype co-circulate, it is frequent to observe a wide range of inter-subtype unique recombinant forms of the virus, resulting from numerous mixed infections in the community.

It is important to emphasize that HIV is constantly evolving, increasing the genetic distance between strains and generating new inter- and intra-subtype recombinant viruses. In 2000, it was estimated that nearly half of the new HIV infections in the world, approximately 47%, were caused by subtype C viruses, which are prevalent mostly in southern Africa, Ethiopia and India. Subtype B viruses are prevalent in the Americas and western Europe, while subtypes A and D are prevalent in central and eastern Africa.

The key questions are: Is it possible to develop candidate vaccines specific for each HIV subtype, or to design immunogens capable of inducing broad cross-clade protective immunity?

The *env* gene codes for gp120 and gp41, which are responsible for inducing neutralizing antibodies. Because of the high variability of the *env* gene, it is generally assumed that vaccine approaches based on *env* will be subtype or even strain specific.

Conversely, vaccine approaches aimed at inducing cytotoxic T lymphocytes (CTLs) against *gag* gene products and other relatively conserved HIV-1 proteins are usually assumed to be more cross-reactive, offering hope that broadly protective vaccines can be developed. Immune responses to CTL epitopes, however, are restricted by the human leucocyte antigen (HLA) makeup of the host, and this may require the design of specific candidate vaccines for use in different populations.

HIV strains also exhibit significant biological differences. The most relevant observation for vaccine development is that, in addition to the CD4 molecule, HIV-1 uses different cell surface co-receptors to gain entry into target cells. Most HIV-1 strains use the chemokine receptor CCR5 (R5 strains), and these strains (also known as primary or clinical isolates) are usually found in recently infected individuals. Virus variants that switch to use CXCR4 as co-receptor (X4 strains) are usually found at advanced stages of the disease and among laboratory strains adapted to T-cell culture. The first generation of envelope-based candidate vaccines used cell culture-adapted X4 strains. They were found to induce antibodies capable of neutralizing X4 viruses, with only negligible ability to neutralize R5 strains, which are considered more clinically and epidemiologically relevant. For that reason, new generations of envelope-based vaccines also include antigens derived from R5 viruses. In Kenya, the predominant subtype is A, accounting for 70%; next is D, 20%; then C and others, 5% each.

To address some of the above issues, attempts have been made to match candidate vaccines with strains prevalent in the sites where phase III efficacy trials are to be conducted. Other approaches addressing this problem include using cocktail vaccines containing antigens representative of several genetic subtypes, designing candidate vaccines targeting conserved HIV epitopes, or basing candidate vaccines on consensus or ancestor sequences selected to minimize the genetic differences between vaccine strains and contemporary isolates.

Sociocultural, economic and political problems

Social challenges to HIV/AIDS vaccine trials include seroconversion of study participants to being HIV positive on a commercial HIV serological test after receiving the vaccine. This may have a negative effect on future health and life insurance, employment, immigration, marriage prospects and child bearing. Deliberate efforts should be made to allay fears related to sociocultural and economic issues before recruiting participants.

Vaccine study participants may engage in increased risky sexual behaviour if they believe that the study vaccine has life-long protective effects. Participatory education on vaccine research and development should be provided to all categories of people such as the youth, religious leaders, policy-makers and politicians.

Policy and political issues regarding identification and recruitment of the study populations and future assurance regarding access to a successful vaccine need to be addressed. Partnership should be equal between local investigators and sponsoring or partner investigators. The research should promote collaboration between governments and institutions, including universities and research organizations in developing and industrialized countries. Research results must be disseminated continuously to research organizations and study communities. This collaboration should ensure that it is policy to protect the study population.

1.7 Process of vaccine research and development

Despite the scientific uncertainties described above, a wide range of candidate vaccines have been developed and tested in animals used as models and in humans. Before a candidate HIV/AIDS vaccine is evaluated in humans, tests to assess the safety, toxicity and immunogenicity of the vaccine are conducted on small animals and on non-human primates. The efficacy of a vaccine can generally be assessed to a limited degree in these non-human primates. Testing is done by vaccinating chimpanzees with HIV/AIDS vaccines and challenging them experimentally with HIV, or by vaccinating macaque monkeys and challenging them with the analogous simian immunodeficiency virus (SIV) or with SIV/HIV chimeric hybrid virus-SHIV, which has an HIV envelope and an SIV core.

Several experimental vaccines have induced degrees of protection in primate models. It is important to note that most experimental vaccines tested in macaques have failed to protect fully against infection ('sterilizing immunity'). Instead, such vaccines reduce the amount of virus and consequently slow progression to disease in immunized animals that become infected after challenge. Animal experiments have also failed to provide clear information on potential immune correlates of protection. Moreover, it is unclear whether the results obtained from animals will be predictive of vaccine-induced protection in humans.

Such information can be obtained only from human trials. Consequently, the most promising products from these animal trials have moved to clinical trials in humans. Preventive vaccines are tested on healthy human volunteers through three sequential

clinical trial phases (table 1). The decision to progress through these phases of vaccine evaluation should be based on pre-established criteria. Phase I trials, which primarily provide safety data (and occasionally preliminary immunogenicity data), are conducted among small numbers of volunteers (10 to 100) at low risk of HIV infection. Phase II safety and immunogenicity trials are conducted in about 100 to 500 volunteers, including those at high risk of HIV infection. During phase I and II studies, different doses of the vaccine candidate are tested. Depending on safety and immunogenicity results, candidate vaccines may progress to phase III trials, to obtain definitive information about their efficacy in inducing protection against infection or disease. Phase III trials are usually double-blind placebo-controlled trials, involving thousands of volunteers at higher risk of HIV infection. They present a number of scientific, logistic and ethical problems. Post-marketing phase IV studies provide additional safety data and effectiveness data and are especially important for identifying rare adverse events. Although the various phases of clinical trials are described above as distinct, in reality, the phases often overlap.

Table 1. Phases of HIV/AIDS vaccine trials

Phase	Sample size range (no.)	Sample characteristics	Endpoints	Duration
I	10–100	Healthy, HIV uninfected at low risk of HIV infection	Safety; preliminary immunogenicity	18–24 months
II	100–500	Healthy, HIV uninfected at low to high risk	Safety; immunogenicity	18–24 months
III	5000–20,000	HIV uninfected, at risk— discordant couples, commercial sex workers, general population	Expanded safety; efficacy; correlates of protection	3–5 years
IV	unlimited	Post-marketing surveillance	Impact on epidemic; rare side effects	unlimited

Phase I

Trials are the first human test of a candidate vaccine, generally conducted on small numbers (< 100) of healthy adult volunteers who are not at risk for the disease in question. The main goal is to evaluate safety; to a lesser extent it is to analyse immune responses evoked by the vaccine and different vaccine doses and immunization schedules. A phase I trial usually takes 18–24 months to complete.

Phase II

Testing involves a larger number of volunteers (100–500), usually a mixture of low-risk and higher-risk people from the population where 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 18–24 months, with the increase over phase I due primarily to the addition time required for screening and enrolling large numbers of trial participants.

Phase III

Phase III trials are the definitive test of whether a vaccine is effective in preventing disease. Using thousands (5000–20,000) of volunteers from high-risk populations in geographic regions where HIV is circulating, the incidence of HIV in vaccinated people is compared with 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 3 years for enrolment, immunizations and assessments of efficacy.

The first phase III HIV / AIDS vaccine trials assessing the protective efficacy of two different versions of a gp120 candidate vaccine were initiated in North America and Europe in 1998 and in Thailand in 1999. Results from both trials showed that the vaccine failed to confer any protection.

Another phase III trial, using a Canary Pox 1521 prime with an AIDsVAX B/E gp 120 boost different vaccine regimen, started in Thailand in September 2003; results are expected in 2008.

1.8 Key issues in evolution of vaccine concepts and approaches

A variety of HIV/AIDS vaccine concepts (vaccine approaches) have been tested in three successive overlapping waves, which have been dominated by different vaccine development models.

Antibody-inducing vaccines

The first wave of candidate HIV/AIDS vaccines was based on the concept that antibodies would be sufficient to confer protection against HIV infection. This concept has worked with several other effective viral vaccines, such as those against polio and measles, and received early support from chimpanzee protection experiments and, more recently, from protection experiments using passive transfer of antibodies. Several candidate vaccines based on the envelope proteins of HIV-1 (gp120 or gp160) or on synthetic peptides representing the V3 loop of gp120 were designed on this concept.

The first generation of envelope vaccines were mainly monomeric molecules based on laboratory-adapted strains of HIV (X4 strains) produced by genetic engineering in mammalian cells. Because different strains of HIV-1 use different co-receptors, novel envelope candidate vaccines included primary isolates (R5 strains) of HIV.

Envelope-based candidate vaccines were found safe and immunogenic in diverse populations, inducing neutralizing antibodies in essentially 100% of the volunteers, but not cytotoxic T lymphocytes (CD8+ CTLs). A limitation of the existing envelope vaccines is that the antibodies they induce are mostly directed to laboratory-adapted strains of HIV, with weak or no ability to neutralize primary isolates. The neutralizing antibodies produced are subtype specific, with little cross-reactivity with other subtypes.

CTL-inducing vaccines

The second wave of HIV/AIDS vaccine research and trials started in the mid-1990s with the recognition of the importance of CD8+ T-cell responses in controlling HIV infection. This concept led to developing (or refining) live recombinant viral vectors, especially poxvirus vectors, capable of delivering HIV-1 antigens in the context of the major path-

way of the class 1 histocompatibility complex. Prime examples of this approach have been the development of different constructs using replication-defective canarypox and HIV-recombinant vectors from Aventis Pasteur, collectively known as ALVAC-HIV.

Most trials with these ALVAC candidate vaccines have been conducted in prime-boost regimes, to assess the ability of the canarypox vector to induce CD8⁺ CTLs and to prime for boosting of antibody responses to subsequent immunization with recombinant envelope antigens. These trials have shown that the prime boost combinations are safe and well-tolerated, producing proliferative responses and binding antibodies to gp120 as well as neutralizing antibodies to the HIV-MN strain in almost 100% of the volunteers but little or no neutralization of primary HIV isolates. A large body of data with this approach indicates that ALVAC-HIV vectors are able to elicit detectable CTL responses to different HIV proteins, but only in about 20–40% of vaccinees. These candidate vaccines have, however, been found to elicit cross-reactive CTL responses against different HIV subtypes, providing some encouragement regarding the possibility of developing broadly protective vaccines.

Other more recent candidate vaccines being developed under the CTL concept include using the attenuated modified vaccinia Ankara (MVA) virus as a vector, usually in combination with DNA, different types of DNA vaccines and lipopeptide vaccines.

Combination antibody and CTL-inducing vaccines

The third wave of HIV/AIDS vaccines started with the new century. It aims at optimizing immune responses to existing or potential candidate vaccines. The goal of this new wave of research is to develop candidate vaccines that can induce 1) antibodies capable of neutralizing primary (R5) and X4 strains from all HIV subtypes, and /or 2) high levels of long-lasting cross-reactive CTL responses against different HIV-1 structural and regulatory proteins. One such vaccine uses replicates of incompetent adenovirus type 5 vector developed by Merck. This DNA-prime, adenovirus-boost regimen in the SHIV macaque model induced high levels of CTLs, resulting in reduced infection after challenge. This candidate vaccine induces high levels of cross-subtype CTL reactivity in seronegative volunteers.

Other viral and bacterial vectors that are being explored include Venezuelan equine encephalitis (VEE) replicons, salmonella, shigella and bacillus Calmette-Guerin. Other researchers are exploring the use of *tat* and other regulatory proteins or novel genetic vaccine designs.

1.9 International efforts in HIV/AIDS vaccine evaluation

The first human trial of an HIV/AIDS vaccine was conducted in the United States in 1987. By 2003, more than 30 different HIV/AIDS candidate vaccines had been tested in approximately 80 phase I and II trials. The first phase I and II vaccine trial in a developing country was conducted in China in 1993. Since then, more than 20 phase I and II trials have been completed in developing countries including Brazil, Cuba, Haiti, Kenya, Peru, Thailand, Trinidad and Uganda (table 2). Concurrent efforts to develop and evaluate candidate vaccines involve extensive collaboration between organizations and governments in and outside Africa. Such collaboration includes infrastructural development, capacity building, laboratory research, cohort development and community education and mobilization. In Africa HIV / AIDS vaccine research activities are ongoing in a number of countries (table 3).

Table 2. HIV/AIDS vaccine trials in developing countries

Year of Initiation	Candidate vaccines	HIV subtype	Countries
1993–1996	Envelope-based candidate vaccines (gp120, V3 peptides and V3 protein)	B	Brazil, China, Cuba, Thailand
1997–1998	Envelope-based candidate vaccines (gp120)	B, E	Thailand
1999–2002	Canary pox and modified vaccinia Ankara vectors, DNA constructs, and prime-boost combinations	B, E, A	Brazil, Haiti, Kenya, Peru, Thailand, Trinidad, Uganda
2003	Multi-epitope DNA vaccine; adenovirus vectors; VEE vectors; DNA/MVA	multiclade, B, C	Several countries in Africa, Asia and the Americas

Table 3. African countries with ongoing HIV/AIDS vaccine research activities, as of March 2004

Have already initiated HIV/AIDS vaccine trials	Are planning specific vaccine trials	Have various levels of vaccine research activities
Botswana	Cameroon	Burkina Faso
Kenya	Cote d'Ivoire	Central African Republic
South Africa	Malawi	Ethiopia
Uganda	Nigeria	Gabon
	Rwanda	Ghana
	Tanzania	Senegal
	Zambia	Zimbabwe

By 2003, four phase I and II HIV / AIDS vaccine trials had been conducted in Africa. The first one, conducted in Uganda in 1999, was sponsored by the US National Institute of Health (NIH). This ALVAC-HIV preventive vaccine trial used a canarypox vector containing subtype B antigens. Immunogenicity was low, but the vaccine elicited CD8+ T-cell responses with detectable cross-reactivity against subtype A and D antigens in a significant proportion of vaccine recipients. Three other trials, sponsored by the International AIDS Vaccine Initiative (IAVI), were conducted in Kenya and Uganda between 2001 and 2003. The vaccine concept was based on a prime-boost combination using DNA and MVA candidate vaccines expressing a number of genes from subtype A.

In Kenya, the agencies and institutions working in HIV / AIDS vaccine research and development include IAVI, the NIH-sponsored HIV / AIDS Vaccine Trials Network, the US Centers for Disease Control and Prevention (CDC), the Walter Reed Project (WRP), the Medical Research Council, UK (MRC), Wellcome Trust, the French Agency for Research on AIDS (ANRS), the Harvard AIDS Institute and the European Union.

1.10 Kenyan efforts in HIV/AIDS vaccine evaluation

In Kenya, it was observed that some female commercial sex workers in Nairobi's Majengo slum were resistant to HIV-1 infection despite repeated exposure. This observation led to research on possible immune mechanisms involved in resistance. Further studies identified CTLs thought to be responsible for the resistance in these women. Subsequently, a subtype A DNA-MVA vaccine construct was developed. This vaccine entered human trials conducted by MRC UK in Oxford in 2000, and by the Kenya AIDS Vaccine Initiative (KAVI) in Nairobi in 2001. This DNA vaccine was the first HIV/AIDS vaccine trial con-

ducted in Kenya. By April 2004, two other phase I and one phase IIA vaccine trials were ongoing.

KAVI is locating a cohort of high-risk individuals in Nairobi (Kangemi) in preparation for a phase III trial of potential future vaccine candidates. The Walter Reed Project, CDC and Wellcome Trust are collaborating with the Kenya Medical Research Institute (KEMRI) and are in various stages of cohort and vaccine site development in Rift Valley (Kericho), Nyanza (Bondo and Siaya), and Coast (Kilifi) Provinces.

2 Political, economic, sociocultural and policy issues in HIV/AIDS vaccine research and development

2.1 Political commitment and involvement

Political support is critically important for the research and development of HIV / AIDS vaccines. It is needed to create an enabling environment for researchers, research partners, funding agencies and research institutions as well as volunteers and study communities.

One purpose of setting national vaccine guidelines is to involve leaders at all levels, including government officials, parliamentarians, administrators and community leaders. Women and youth leaders need to be involved at all these levels. The guidelines promote involvement and consultation with other stakeholders including, but not limited to, people living with HIV / AIDs, lawyers, journalists, health professionals, faith-based organisations and activists.

The guidelines recognize the various economic, social and cultural situations that may affect HIV / AIDS vaccine research and outline appropriate measures to create an enabling legal and ethical environment. Building political support and commitment includes:

- Working within the national decision-making processes and policies.
- Identifying government bodies responsible for formulating and implementing policies.
- Identifying the key members in those bodies for advocacy.
- Initiating open and honest discussions with the scientific community, key policy-makers and other stakeholders, and providing them with comprehensive information.
- Approaching and involving gradually widening circles of opinion leaders and stakeholders at various levels.
- Providing information on risks versus benefits to individuals, communities and the country.
- Providing regular updates to appropriate government bodies and stakeholders.
- Developing appropriate media strategies.
- Advocating HIV / AIDS vaccine research and development as a priority in the national political agenda.
- Advocating HIV / AIDS vaccine research and development in the national and strategic development plans.

2.2 Social mobilization and sensitivity to culture

Community support and participation

People have the right to be protected from harm and exploitation, and to make their own decisions regarding how they will participate in HIV / AIDS vaccine research. They must therefore be informed about vaccine research and about the risks and benefits resulting from it. The rights and responsibilities of vaccine volunteers must be formally recognized and safeguarded. No person should be stigmatized or discriminated against during the vaccine research process.

To ensure the ethical and scientific quality of any proposed research, a continuing forum of communication, consensus building and problem solving should be established to assist the study community in understanding and accepting the relevance of the research. Such a forum should include community representatives, people living with HIV / AIDS (PLWHA), and non- governmental organizations (NGOs) involved in HIV / AIDS work. These stakeholders should be consulted and involved in an early and sustained manner in designing, developing and implementing the research, and in disseminating the results.

To ensure full community participation and support, it is important to:

- Present the protocol in simple, culturally acceptable and understandable language.
- Create a forum for informing the community about the science of vaccine research and development, legal and ethical issues, and access issues including recruiting participants and retaining their participation through the trial.
- Create links between vaccine research trials, opinion leaders and community organizations who could facilitate preparing community participation in vaccine research.
- Ensure that communities continue to advocate preventive measures to curb further spread of HIV / AIDS
- Ensure that there is a clear link between policy formulation and implementation regarding policy towards HIV / AIDS vaccine research and development.

Community advisory board

To facilitate dialogue between community members, study volunteers and researchers, a community advisory board (CAB) shall be created. Such a board is a committee of community representatives who are selected to advise and guide implementation of a given research protocol.

The CAB shall:

- Provide input into the design of the protocol including the appropriate informed consent process.
- Inform the community about the proposed research and create a supportive environment.
- Provide feedback to researchers from the community.
- Create trust between the study community and researchers.
- Provide information to the researchers regarding traditional health beliefs of the study population.
- Provide advice and support regarding recruiting trial participants and retaining their participation through the trial.
- Advise on gender equity in selecting trial participants.
- Advise on effective methods for disseminating the research results.
- Inform the community of the advantages and risks involved in the proposed research and on the legal implications.

CAB members shall be identified through community forums by the community in consultation with the principal investigator or designee. The principal investigator shall write letters of appointment for CAB members including draft terms of reference that clearly state the roles and expectations for the board. The CAB should be made of 10 to 15 members including a study team member for coordination. At the first meeting, the CAB shall elect a chairperson and secretary and review and confirm the terms of reference. The study project should help the CAB carry out its functions by providing such assistance as

a meeting place, transportation expenses and facilities for communication as appropriate. The CAB should represent gender equitably and comprise people who are able to understand the study, know the local culture and are sensitive to community perspectives.

Members may include:

- Human rights activists
- People with an understanding of ethics and national laws
- Gender advocacy group representatives
- Youth group representatives
- Role models
- Religious leaders
- PLWHA
- Representatives of trial participants
- Health care workers in the community
- People who understand and respect local cultural values and norms
- Other professionals or people who understand scientific issues of research
- A government representative at community level

Dissemination of information

To prevent misinformation, it is essential to have an information strategy for the scientific community, regulatory bodies, the media, the public, volunteers and other stakeholders. The strategy should include:

- Advocating, seeking consensus and disseminating information before the trial is initiated.
- Educating and updating the local media regularly on various aspects of the trial from inception to completion.
- Using the CAB as a link between researchers and the community.
- Continuous education efforts directed at the media to provide regular updates on various aspects of the trial.
- Active involvement of the media throughout the vaccine research process, from planning to implementation, to ensure accurate and fair reporting.
- Making use of the CAB to provide useful links between researchers and the public.
- A strategy for advocacy and consensus seeking as well as information dissemination before trial initiation.
- Training and preparing of researchers to prepare them for effective and accurate interaction with the media.
- Communicating a unified and consistent message from the Director of Medical Services to the media through the public relations office of the Ministry of Health (MoH).
- Maintaining an MoH website with accurate and regularly updated information about HIV / AIDS vaccines.
- Releasing accurate and updated research findings from the PI to the national ethics and regulatory bodies.

2.3 Policy issues

Role of the government

The government has a central role to play in creating an enabling environment for successful conduct of HIV / AIDS vaccine trials. It also has the responsibility of ensuring the availability and accessibility of efficacious HIV / AIDS vaccines in the future. In carrying out these responsibilities, the government will:

- Assure political commitment to support the vaccine research, development and evaluation efforts.
- Formulate and disseminate policies supportive of research, development and evaluation of HIV / AIDS vaccines.
- Integrate research and development of HIV / AIDS vaccines into the Kenya National HIV / AIDS Strategic Plan.
- Provide an environment conducive to long-term collaborative research from phase I through phase IV studies as appropriate.
- Define guidelines for scientific and ethical review of research proposals.
- Ensure protection of trial participants by developing strategies to prevent stigmatization and exploitation.
- Establish a legal framework to ensure adequate compensation in case of research related injuries and provide protection against discrimination in insurance, employment and migration.
- Provide appropriate legal framework to address researcher liability and protection from undue exposure to litigation.
- Provide a legal framework for material transfer agreements regarding movement and use of biological specimens.
- Empower, support and facilitate regulatory and ethics boards such as: the National Council for Science and Technology (NCST), institutional review boards (IRBs), the Pharmacy and Poisons Board (PPB) and any other relevant bodies to carry out their functions with respect to vaccine research, to facilitate expedited vaccine research and development.
- Facilitate provision of infrastructure and training of personnel required for the successful transfer of technology.
- Liaise with vaccine manufacturers or vaccine trial sponsors and the principal investigator to ensure availability, affordability and accessibility of safe and effective HIV / AIDS vaccines.
- Work in collaboration with WHO-UNAIDS HIV Vaccine Initiative, the African AIDS Vaccine Programme (AAVP) and other HIV / AIDS vaccine development partners to accelerate HIV / AIDS vaccine research and development.

Role of regional and subregional intergovernmental organizations

Partnership and collaboration through regional and subregional intergovernmental organizations, such as the African Union and the East African Community, is critical for HIV / AIDS vaccine research and development. These links can:

- Provide forums for sharing lessons learned and exchange scientific information.
- Enable sharing of material and human resources.
- Facilitate and support multicentre studies.
- Provide platforms for regional and subregional centres of excellence.

- Help harmonize standards in ethics, clinical, laboratory and other aspects of research in the region.

Role of the African AIDS Vaccine Programme

AAVP was conceived in 2000 as a network of African experts working together to promote and facilitate HIV / AIDS vaccine research and evaluation in Africa through capacity building and regional and international collaboration. AAVP advocates and supports a coordinated global effort to contribute to the research and development of an appropriate HIV / AIDS vaccine, affordable and accessible in Africa within the shortest possible time.

The main activities of AAVP are:

- Providing a forum for collaboration and coordination.
- Strengthening sites and infrastructure for promoting the research and development of appropriate vaccines for Africa.
- Developing a normative framework (political, legal, regulatory and ethical) to facilitate HIV vaccine research and trials, in the context of the overall response of African countries to the HIV / AIDS epidemic.
- Promoting training and exchange of information.
- Providing an advisory and advocacy role to government and intergovernmental bodies.

Role of WHO and UNAIDS

Since 1990, WHO and UNAIDS have been playing an important role in facilitating international HIV / AIDS vaccine activities, focusing on collaborating with developing countries, to ensure that trials are conducted at the highest scientific and ethical standards. Key to this role was collaboration that led to the early development, in 1992, of 'National AIDS Vaccine Plans' in Brazil, Thailand and Uganda—countries in which the majority of developing-country trials have been conducted.

The WHO-UNAIDS HIV Vaccine Initiative, established as joint activity in 2000, receives scientific, technical and strategic advice from an international vaccine advisory committee composed of high-level representatives of the lead HIV / AIDS vaccine programmes in industrialized and developing countries. This initiative implements activities in the following areas:

- Advocacy, guidance and coordination of the international HIV / AIDS vaccine effort with equitable participation of multiple partners, from the public and private sector.
- Promotion of simultaneous research, development and evaluation of candidate vaccines appropriate for developing countries, according to the highest ethical and scientific standards.
- Facilitation of scientifically and ethically acceptable clinical trials through capacity building and development of norms and standards.
- Assistance and advice to governments regarding intellectual property issues and rights and access to future HIV / AIDS vaccines.

Role of vaccine manufacturers

In some situations the manufacturer of the candidate vaccine also funds the study. In that case the issues stated under 'Role of funding organizations', next, would apply to the

manufacturer as well. The responsibilities and expectations of the vaccine manufacturer shall be specified in a written agreement as early as possible in developing the protocol and certainly before the protocol is implemented. In addition to the above agreement, the manufacturer, funding organization and collaborating research institutions should have regular dialogue through a study steering committee.

Issues to consider include:

- Provision of study products manufactured according to good manufacturing practice (GMP).
- Archive of vaccine sample(s) from each batch produced.
- Ensured legal categorization and licensing or registration of product in country.
- Assurance of care of product-related injury.
- Insurance of study participants and liability of researchers.
- Intellectual property rights.
- Material transfer agreements.
- Affordability and accessibility of the vaccine if registered or licensed.
- Confidentiality of data and proprietary information.
- Guidelines for disposal of unused vaccine(s).
- Assurance that trials are conducted according to national guidelines, rules and regulations.

Role of funding organizations

Funding organizations or sponsors are the agencies that provide funding for most aspects of the trial. It should be noted, however, that other institutions also provide resources, such as infrastructure and personnel, that are crucial for the trial. Funding organizations play a central role in assuring that before a protocol is implemented, formal agreements are reached on the responsibilities and expectations of the various parties.

They also:

- Provide oversight to ensure that trials are conducted according to good clinical practice (GCP).
- Support local capacity building (training and infrastructure).
- Support archive of samples from research participants.
- Assure care for research-related injury.
- Ensure that adequate data and record keeping are maintained.
- Ensure adherence to importation requirements into Kenya.
- Ensure that trials are carried out according to the laws, regulations and guidelines of Kenya.
- Ensure independent monitoring of trials.
- Insure study participants and liability of researchers.

Role of investigators

Investigators should be based in and affiliated to local institutions where the trials are to be conducted. International principal investigators must work with equivalent local co-investigators. The principal investigator is the researcher who takes overall responsibility for the ethics and science of the trial by working together with other investigators to:

- Assure in-country regulatory approval by submitting the proposal to and responding to comments from the scientific and ethics review committees.
- Convene study steering committee meetings.

- Take full responsibility for the study at the site and be answerable to national authorities and collaborators
- Provide regular study progress reports to the scientific and ethics review committees, collaborators and the media.
- Provide the sponsor with audited financial reports.
- Assure confidentiality of data and proprietary information.
- Collaborate with sponsors and manufacturers and ensure that there is a Data and Safety Monitoring Board (DSMB) where applicable.
- To ensure that policies regarding use, disclosure and dissemination of study information are followed.
- Comply with Material Transfer Agreement
- Assure consent from trial participants for current and / or future use of stored study specimens.

Role of collaborating institutions

Collaborating institutions may include local and international research institutions that are neither sponsors nor manufacturers. The contributions of the different collaborating institutions should be clearly stated in writing. Their contributions include:

- Providing study personnel, especially the key investigators.
- Recruiting, training and supervising study personnel.
- Providing technical assistance.
- Providing infrastructure and office and laboratory space.
- Ensuring equal partnership and ownership of data and publications.
- Ensuring that intellectual property rights are respected by all partners.
- Assuming legal responsibility for the trial.
- Establishing an institutional biosafety committee.

3 Regulatory process in Kenya

Implementation of these guidelines shall be subject to prevailing Kenyan laws.

Figure 4 summarizes the regulatory process for scientific and ethical approval for a candidate vaccine before it is tested in humans.

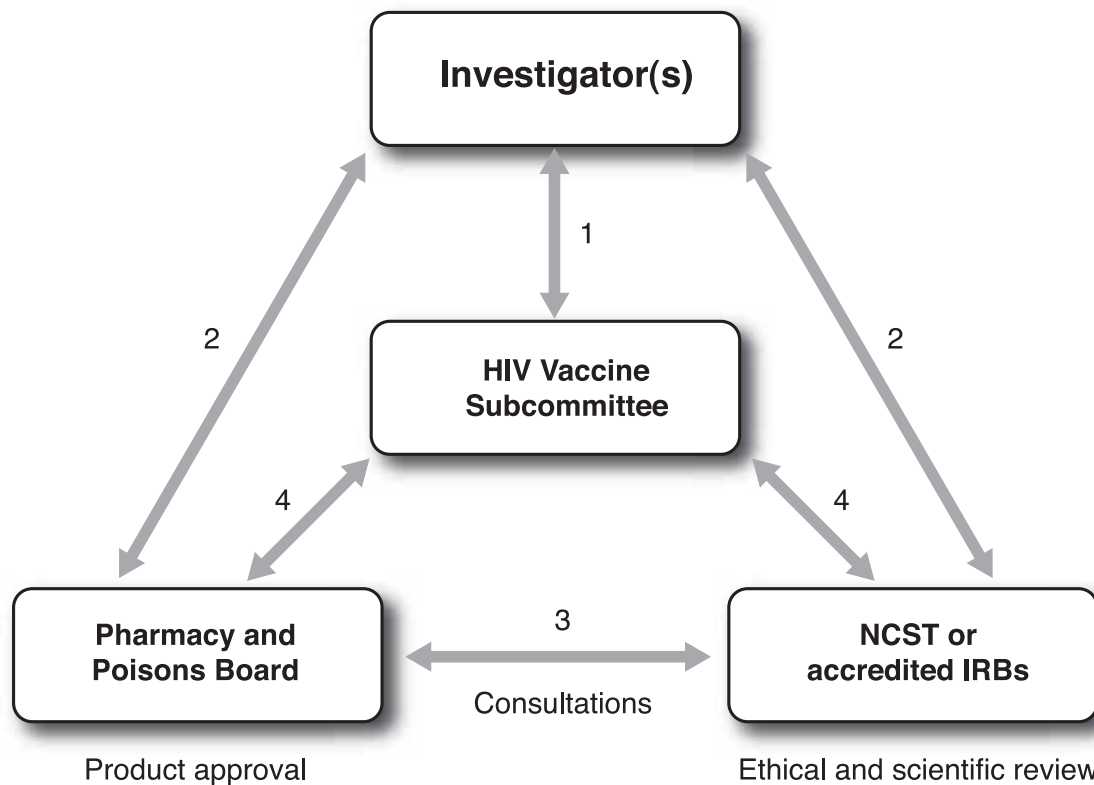


Figure 4. Flow chart for approval for HIV/AIDS vaccine research in Kenya (see following box).

Stages for approval

Given the urgency of responding to the HIV/AIDS epidemic, strategies should be put in place to expedite processing of HIV/AIDS vaccine proposals. One strategy is simultaneous submission and review by both the Pharmacy and Poisons Board (PPB) and the National Council for Science and Technology (NCST) or designated institutional review board (IRB). When a committee receives a proposal or concept paper, it should immediately send the investigator(s) a letter acknowledging receipt. The timelines shown below refer to the range within which the proposal should be reviewed and the response provided.

Stage 1

a: The investigator(s) submits a concept paper (not the full proposal) to the Kenya HIV/AIDS Vaccine Subcommittee of the Ministry of Health. The subcommittee reviews the concept paper, giving particular attention to preclinical safety and immunogenicity data and relevance of the trial to the country. The subcommittee has among its member representatives from NCST, PPB, and IRBs. This ensures that these bodies receive advance information regarding proposed vaccine trials before the full protocol is submitted.

b: The response of the subcommittee is communicated to the investigator(s) within 3 to 4 weeks. This response is in the form of advice and should not be construed to represent formal approval of the trial. It is sent with copies to PPB and NCST or accredited IRBs.

Stage 2

a: The investigator(s) submits the full proposal simultaneously to the PPB and the NCST or designated IRB with a copy to the HIV/AIDS Vaccine Subcommittee.

b: The PPB provides a response to the investigator(s) regarding the candidate product and sends a copy to the NCST or designated IRB. This response may be in the form of an approval, comments for amendments, or rejection. It should be provided within 6–8 weeks from receipt of the proposal.

c: The NCST or accredited IRB provides a response to investigator(s) regarding the ethics and science of the proposal and sends a copy to the PPB. This response may be an approval, comments for amendment, or rejection and should be provided within 6–8 weeks from receipt of the proposal. A proposal that has been reviewed and approved by an accredited IRB shall be forwarded to the NCST for record and information.

Stage 3: During the 6–8-week review period, the PPB and NCST or designated IRB consult each other to avoid delay in conveying the two responses.

Stage 4: Copies of responses from PPB (2a) and NCST or accredited IRBs (2b) should be sent to HIV vaccine subcommittee for its information and record only.

Note

Approval from both the PPB and the NCST (or accredited IRB) is mandatory before any trial can commence.

Fees

Adequate funds are needed to support the regulatory, scientific and ethical review boards. The respective bodies will set the appropriate fee structure.

A standardized financial mechanism is needed to support the regulatory and ethical review bodies. This requires resource mobilization through collaboration with national and international partners. Systematically solicited support will avoid potential conflict of interest between sponsors, investigators and reviewers.

3.1 National Council for Science and Technology

Legal provisions

The National Council for Science and Technology (herein referred to as the Council) is empowered under the Science and Technology Act (1979) to coordinate all research work in Kenya and advise the government on all matters of science and technology. This among other things entails authorizing and documenting all research work in Kenya.

The Council is responsible for assessing technical and ethical aspects of proposals submitted for clearance and authorization. It is illegal to conduct research in Kenya without clearance. The offence is punishable as provided for in the Science and Technology Repeal Act Cap. 250 of the Laws of Kenya.

Objectives of research clearance and authorization

Under the Science and Technology Act, the objectives of research clearance are to:

- Facilitate coordination of research.
- Encourage quality research that will directly benefit Kenya and increase the body of scientific knowledge as a whole.
- Make secure the data and results of research work undertaken in Kenya.

- Document and monitor all research work going on in the country and have centrally available information on such work.
- Facilitate useful research work and discourage projects that are not in the national interest.
- Ensure maximum benefit and dissemination of knowledge and technology to users from research activities in the country.
- Eliminate unauthorized collection and transfer of research information and materials.
- Ensure that research in Kenya is conducted according to professional ethics.
- Ensure that relevant national institutions are informed of intended and ongoing research work in their areas of responsibility and that they are given an opportunity to influence the course of research work in their areas of interest.
- Discourage unnecessary duplication of data collection for ongoing research projects or research already undertaken or research about to be undertaken.
- Protect national interests in general and as far as possible discourage clandestine activities that may be undertaken under the cover of research.

Monitoring and evaluation of authorized projects

- The government of Kenya shall have access to the data and the research premises of the project.
- The Council may from time to time visit the research projects to get familiar with the work going on and make appropriate recommendations on the project.
- The affiliating institutions will be required to give progress reports to the Council and to indicate areas that need further action if considered necessary.
- Final research reports will be deposited in the Council library with copies to affiliating institutions, the National Archives and the relevant ministry.

Issuance of research permit

- The research permit will be issued in the name of the holder of the permit as defined below.
- The holder of the permit will be the project leader, or the expedition leader or the leader of the institution in the case of standing research clearance.
- The holder of the research permit will be held responsible for making sure that the regulations governing the permit are observed.

Termination of research permits

The government reserves the right to withdraw a research clearance permit (individual or standing) without giving notice or reasons to the researcher or institution.

Work permits

Foreigners working in Kenya are required by law to secure work permits. Granting of a research permit does not in any way absolve the researcher from the requirement of a work permit. It is up to the researcher to secure the necessary work permit upon arrival in Kenya.

Application for clearance for non-Kenya assistants in research projects will be carefully considered but is generally disapproved where it is obvious that Kenyans can be recruited for such tasks.

Acknowledgement of collaborators

Researchers are required to acknowledge Kenyan collaboration and participation in all papers and books that emanate from the research.

- The Kenyan government research permit must be acknowledged.
- The affiliating institution must be acknowledged and its mailing, physical and e-mail addresses and the telephone contact must be given.

3.2 Pharmacy and Poisons Board

Legal provisions

The Pharmacy and Poisons Board (PPB) is empowered, under the Pharmacy and Poisons Act Cap. 244 (2002) to regulate the manufacture, importation, exportation, registration, distribution and sale of all pharmaceuticals and medical devices including vaccines and vaccine products.

Roles and responsibilities

No vaccine shall be tested in humans without regulations to ensure safety, immunogenicity, potential efficacy and environmental biosafety.

The main functions of the PPB relating to vaccines are:

- Evaluate candidate vaccines by reviewing all preclinical and clinical data and results of previous trials in human volunteers.
- Review research proposals, select and authorize candidate vaccines and monitor their use in clinical trials.
- Receive and review from the sponsor evidence of GCP of prior clinical trials and GMP for the proposed candidate vaccine.
- Monitor the manufacture of vaccines and vaccine products to ensure that they are produced according to GMP.
- Inspect and license manufacturing facilities.
- Establish biosafety committee and oversee its activities.
- Develop guidelines on disposal of unusable vaccine products and other hazardous products relating to the research.
- Process importation and exportation documents relating to the vaccine product.
- Standardize and ensure quality control of vaccines and vaccine products through the National Quality Control Laboratory.
- Inspect and license distributors of vaccines and vaccine products.
- Oversee compliance with national and international regulations.
- Review academic and professional credentials of the researchers involved in these trials.
- Where necessary, solicit, receive and consider comments and/or recommendations from other regulatory authorities regarding the proposed vaccine.
- Consult with the WHO-UNAIDS Vaccine Advisory Committee, AAVP and other partners.
- Work closely with other national regulatory bodies, especially the ethics and science committees.
- Register and license vaccines and vaccine products.
- Carry out post-marketing surveillance to monitor quality of product and rare or late adverse reactions.

Selection criteria for candidate vaccines

The Pharmacy and Poisons Board will collaborate with regulatory authorities from countries with similar epidemiological and population characteristics to explore ways of pooling scientific and regulatory expertise with a view of adopting common or similar approval processes. PPB will ensure sufficient human and financial resources to support its functions.

The main criteria for selecting a candidate vaccine for evaluation are that the vaccine must:

- Be manufactured under GMP.
- Have data on safety and immunogenicity in small animals and in human phase I/II trials if applicable.
- Be relevant to the country or region in terms of virus subtype or circulating HIV strains.

Other important considerations are:

- Relevance to the country or region in terms of HLA types, nutritional status and prevalent parasitic and other diseases.
- Effects of studies that would involve minors, pregnant women, breastfeeding women.
- Humoral and cellular immunogenicity, using various routes of administration such as intramuscular, intradermal, intravaginal, intrarectal or oral-mucosal.
- Flexibility of routes of administration such as orally, intranasally, intramuscularly and intradermally.
- Schedule of administration and ease of implementation (single or multiple doses of vaccine).
- Robustness of the immune response generated, including duration and rate of decay of antibodies, T cells or other factors.
- Protection in animal challenge experiments against infections acquired through various routes.
- Prevention of mother-to-child transmission of HIV.
- Ability to distinguish HIV infection from vaccine immune responses.
- Feasibility of combining with other vaccines in an expanded programme of immunization.
- Storage: need for cold chain, and potency at room temperature.
- Stability in adverse conditions such as transport on rough roads for long distances and in tropical conditions.

Essential information required for evaluating vaccine manufacturers or sponsors

- Capacity for GMP production.
- Assurance for treating and managing all vaccine-related adverse events and injuries.
- Commitment to capacity building and transfer of technology.
- Assistance to the government to develop and implement vaccine distribution plans.
- Willingness to discuss equitable distribution of benefits arising from intellectual property issues regarding a given vaccine.
- Willingness to discuss provision of antiretroviral (ARV) therapy to volunteers who become infected with HIV during the trial.
- Commitment to provide free vaccine for phase III trials where indicated.
- Willingness to provide phase III participants with free preventive vaccine, where indi-

cated, that is safe and efficacious, after successful trial completion.

- Willingness to allow bulk purchases of efficacious vaccine at an affordable price for the country.
- Commitment to conduct post-study surveillance for rare and long-term side effects

3.3 Kenya HIV/AIDS Vaccine Subcommittee

The Kenya HIV / AIDS Vaccine Subcommittee (VSC) was constituted by the director of Medical Services in January 2004. The subcommittee functions as an advisory body to the Ministry of Health regarding HIV / AIDS vaccine research and development.

Terms of reference

The functions of the VSC are to advise and assist the Ministry of Health in formulating a national framework for HIV / AIDS vaccine research and development. Its tasks include:

- Developing policies on pertinent issues in vaccine research and development such as scientific and ethical review of HIV / AIDS vaccine research proposal; regulatory approval of candidate HIV / AIDS vaccines and eventual licensing and use of a successful vaccine.
 - Developing plans for putting the above policies into operation.
 - Developing a long-term national plan for implementing HIV / AIDS vaccine research and development in the country.
 - Developing technical guidelines for selected sections of the plan as deemed necessary by the subcommittee.
 - Providing advice on other issues relating to HIV / AIDS vaccines as requested by the director of Medical Services.
 - Soliciting, receiving and considering comments and /or recommendations from other national or international drug regulatory authorities, where necessary, regarding the proposed vaccine.
 - Consulting with the WHO-UNAIDS Vaccine Advisory Committee, AAVP or other partners.
 - Working closely with other national regulatory bodies and IRBs in reviewing proposed research and exchanging information regarding ongoing research on HIV / AIDS vaccines in the country.
 - Assisting the government to develop and implement vaccine distribution plans.
 - Updating information on HIV / AIDS vaccine research and its health and economic impact to the Ministry of Health.
 - Monitoring ongoing vaccine trials.
- To accomplish the above duties, the VSC shall:
- Meet regularly every month.
 - Appoint small groups to work on specific tasks.
 - Seek advice from experts in different fields relating to the above functions.
 - Consult relevant stakeholders.
 - Provide regular technical updates to key stakeholders on HIV / AIDS vaccine research and development through workshops, meetings, Internet, websites and other networks.
 - Establish a secretariat at the Ministry of Health.
 - Apply any other method of work the VSC deems fit.

Membership

Membership shall include persons with expertise in biomedicine, policy, community affairs, clinical practice, legal matters, and ethics who represent the various institutions involved in developing HIV / AIDS vaccines. The chairperson shall be the Director of Medical Services.

Membership shall consist of representatives from the following institutions:

- African AIDS Vaccine Programme (AAVP)
- Attorney General's Office
- Centres for Disease Control and Prevention–Kenya (CDC / Kenya)
- International AIDS Vaccine Initiative (IAVI)
- Joint United Nations Program on HIV / AIDS(UNAIDS)
- Kenya AIDS NGOs Consortium (KANCO)
- Kenya AIDS Vaccine Initiative (KAVI), University of Nairobi
- Kenya Intellectual Property Institute (KIPI)
- Kenya Inter-Religious AIDS Consortium (KIRAC)
- Kenya Medical Association (KMA)
- Kenya Medical Research Institute (KEMRI)
- Kenyatta National Hospital (KNH)
- Law Society of Kenya (LSK)
- Ministry of Health (MoH)
- Moi University
- National AIDS Control Council (NACC)
- National Council for Science and Technology (NCST)
- Network of People Living with HIV / AIDS (NEPHAK)
- Pharmacy and Poisons Board (PPB)
- Walter Reed Project (WRP / KEMRI / Kenya)
- World Health Organization (WHO)

The DMS may co-opt other members as and when necessary.

The role of the Vaccine Subcommittee

The role of the VSC in reviewing research will be to advise the investigator(s) regarding the science and ethics of the concept paper and the draft proposal. The secondary aim of the review will be to advise the MoH, PPB and NCST or its designated IRBs regarding the proposed research. The purpose of this review is to expedite review of HIV / AIDS vaccine research in the country by providing the national authorities with prior knowledge of the proposed research before the full proposal is submitted. The VSC will respond to the concept paper or draft proposal by a letter to the investigator copied to the regulatory and ethics boards listed above. The VSC communicates with these boards through members representing the boards.

The method of the review within the VSC shall be as follows:

- The secretariat receives and acknowledges receipt of the concept paper.
- The chair designates two members as official reviewers.
- The official reviewers turn in their comments within 2 weeks.
- The VSC meeting discusses reviewer comments.
- The secretariat gives the investigator a written response, copied to PPB and NCST or its designated IRBs.

Where a VSC member is directly involved in the research under review, that member does not attend the pertinent reviewing meeting.

4 International guidelines for scientific and ethical review of proposals

International guidelines have been developed and established on ethical and scientific standards for carrying out biomedical research on human subjects. Some institutions have joint science and ethics review committees while others have separate scientific and ethics review bodies.

International guidelines require the ethical and scientific review of biomedical research to protect persons and communities participating in research.

The guidelines for scientific and ethical review should clearly describe the following:

- Review process
- Essential documents required for review
- Information that must regularly be communicated to the review committee
- Authority, process and criteria for appointing scientific and ethics committee members
- Powers and functions of the ethics and research committee
- Process of monitoring and evaluation

4.1 Mission of a science and ethics committee

To safeguard the dignity, rights, safety and well-being of research participants through the review of research proposals and their supporting documents and ensure that research is carried out according to the highest ethical and international scientific standards.

4.2 Terms of reference for a science and ethics committee

- Safeguard the dignity, rights, safety and well-being of research participants.
- Provide independent, competent and timely review of the research and ethics of proposed studies, in accordance with national guidelines.
- Verify ethical integrity of HIV / AIDS vaccine trial protocols in accordance with internationally accepted ethical guidelines, such as:
 - Declaration of Helsinki
 - Council for International Organization of Medical Sciences (CIOMS) publication: *International Ethical Guidelines for Biomedical Research Involving Human Subjects*
 - World Health Organization (WHO) pamphlet: *Proposed International Guidelines for Biomedical Research Involving Human Subjects*
 - WHO and International Conference on Harmonization Guidelines for GCP, GMP, Good Clinical and Laboratory Practice (GCLP)
 - UNAIDS guidance document: *Ethical considerations in HIV Preventive Vaccine Research*
 - Any other relevant or applicable internationally accepted documents that may come into force hereinafter
- Review research proposals and their supporting documents with emphasis on:
 - Scientific design, objectives, statistics and methods

- Storage, disposal and repository of biological materials
- Recruitment of participants
- Care and protection of participants
- Maintenance of confidentiality
- Informed consent process
- Vulnerable groups
- Community considerations
- Monitor ethical adherence through:
 - Regularly reviewing the principal investigator's adherence to approved protocol and other aspects of the implementation of the HIV / AIDS vaccine trial
 - Supervising interim reports through systematic analysis
 - Appointing a committee to supervise the vaccine trial
- Receive and review reports from an independent monitor appointed by the sponsor
- Receive and review reports from the investigator regarding:
 - Protocol amendments, deviations and violations
 - Serious and unexpected adverse events
 - Periodic and final reports
 - New information that may affect risk-to-benefit ratio
- Receive and consider recommendations from the Data and Safety Monitoring Board (DSMB) and where necessary, make recommendations to the DSMB.
- Work closely with the WHO ethical review committee, the WHO-UNAIDS Vaccine Advisory Committee and other relevant bodies on HIV / AIDS vaccine research and development.

4.3 Membership

A science and ethics committee should be multidisciplinary, multisectoral and pluralistic with balanced age and gender distribution. Members should be independent from political, institutional, professional and market influences. Reviewers should abide by existing national legal and regulatory requirements.

Membership should include:

- Social or behavioural scientist
- PLWHA
- Clinician
- Laboratory scientist
- Pharmacist
- Lawyer
- Ethicist
- Community representatives
- Advocate for vulnerable groups such as children and youth
- Gender advocate

4.4 Development of standard operating procedures

Scientific and ethics committees should develop standard operating procedures (SOPs) for their own function using guidelines such as the *WHO operational guidelines for ethics committees that review biomedical research* (WHO:TDR / PRD / ETHICS / 2000). These procedures must include the following elements:

- Membership and term of office

- Quorum requirements
- Qualification of members
- Requirements for submission of proposals
- Timeline for the review process
- Expeditious review process
- Fees for review of research protocols if applicable
- Required institution capacity for research implementers
- Required documentation such as:
 - Synopsis of protocol including ethical considerations
 - Data collection instruments
 - Brochures on investigative product
 - Material for recruitment including advertisements
 - Process to obtain and document consent
 - Information about compensation, indemnity and insurance
- Appeal process
- Material transfer agreement
- Termination or suspension of research
- Renewal or continuation process
- Monitoring
- Modification
- Levels of approval

4.5 Essential elements of the review

Scientific design and conduct of the study

- Appropriateness and relevance of:
 - Objectives and rationale
 - Study population and sample size
 - Study procedures
 - Statistical methods
 - Site
 - Research personnel
- Risk vs. benefit justification
- Criteria for premature termination
- Adequate safety monitoring plan
- Provision for monitoring by DSMB

Recruitment of research participants

- Characteristics of study population: gender, age, social status, race
- Information given to the community and potential participants
- Criteria for inclusion or exclusion

Care and protection of research participants

- Adequate qualification and experience of investigators
- Medical care during and after research
- Care and support of participants who become infected with HIV while participating in the study

- Product availability to participants
- Justification for withholding standard treatment, if indicated, for purpose of research
- Description of any financial costs to the volunteer
- Compensation for participation without coercion (undue inducement)
- Provision for compensation and /or treatment in case of study-related injury
- Insurance and indemnity arrangements
- Referral to psychosocial and legal support where necessary
- Safety monitoring
- Provision of address of contact person(s) in case of study related injury
- Provision of periodic information and results to participants
- Safeguard against conflict of interest
- Reporting of adverse events

Protection of research participant confidentiality

- Policy on access to personal data and samples
- Measures to ensure confidentiality and security of personal information

Informed consent process

- Description of process for obtaining consent
- Adequacy, completeness and understandability of written and verbal information given to participants or legally acceptable representative. Other methods of communication for special groups such as sign language and Braille where necessary should be availed.
- Justification for and desirability of inclusion of minors and socially or legally vulnerable groups such as refugees, prisoners and soldiers
- Steps to protect the dignity, safety and welfare of the above vulnerable groups from exploitation
- Strategies for informing participants of new information during study concerning their rights and safety
- Provision for receiving and responding to questions and complaints from participants
- Information on the voluntary nature of the research and the right to withdraw at any stage of the research without losing any benefits to which they are otherwise entitled.

Community and cultural considerations

- Consultations with concerned communities during the design and implementation of the research to obtain their input and assess their acceptance of the study.
- Impact and relevance of the research to the local community or study population.
- Assessment of what contribution the research will make to the community.
- Availability, affordability and accessibility of successful study product to the concerned community.
- Dissemination of research findings to study participants and to the concerned communities.
- Appointment of a community advisory board.
- Sensitivity of research team to relevant sociocultural issues.
- Strategy for disseminating new information and results of the trial to the community during the study
- Protection from exploitation of the vulnerable and the poor.

5 Research activities in preparation for HIV/AIDS vaccine trials

In preparing to implement an HIV / AIDS vaccine trial it is essential to conduct virological, immunological, epidemiological, clinical, sociobehavioural studies using a multidisciplinary approach.

5.1 Virological and immunological studies

In preparing for HIV / AIDS vaccine trials, virological studies on HIV are necessary, including isolation and characterization.

Different subtypes of HIV are prevalent in different parts of the world. The viral mutation rate is high within an individual and a population, resulting in antigenic variations of HIV strains within the country. Ongoing HIV isolation and characterization studies are thus needed to monitor the genetic, biological and antigenic variation of these HIV strains.

By collaborating with the WHO Network for HIV Isolation and Characterization, HIV isolation and characterization of strains can be undertaken by obtaining samples from newly infected persons in potential study populations representing different risk groups and geographical areas as well as different modes of transmission, such as mother-to-child transmission.

Virological and immunological studies among HIV-exposed seronegative persons, serodiscordant couples and long-term non-progressors can provide valuable information for vaccine design. Humoral (neutralizing antibodies) and cellular immune response (CTL response) studies among HIV-infected persons can provide insights in the understanding of virus and host interactions.

Exposure to micro-organisms considered as vectors for the HIV candidate vaccines should be determined for potential study population. In addition, determining the HLA profile of the potential study populations may be necessary.

There should be adequate laboratory equipment, sufficient cold storage capabilities, trained technical staff, and data management and communication infrastructure to support these activities.

5.2 Epidemiological studies

Baseline epidemiological studies are required to characterize HIV infection in potential populations for HIV / AIDS vaccine trials. Such studies should include HIV seroincidence and seroprevalence, routes of transmission and associated risk behaviour or risk factors for HIV transmission. For phase III trials, identification and access to populations with high HIV seroprevalence and incidence are important. Continuous HIV prevalence and incidence surveillance studies including those conducted in the community should also be carried out during vaccine trials. This will contribute to knowledge of the dynamics of the epidemic and of the prevalent and incident HIV subtypes and / or immunotypes.

5.3 Sociobehavioural studies

Before initiating a vaccine trial, it is important to gather data or review available data on public knowledge, attitudes, perceptions and practices regarding sexually transmitted

infections (STIs) and HIV / AIDS, particularly in the sex and age groups at greatest risk of infection in the study population. Such information will help in the following:

- Understanding how to obtain informed consent.
- Identifying factors, including gender concerns, that may influence participation in trials.
- Assessing feasibility of conducting placebo-controlled trials.
- Assessing perceptions, understanding and acceptability of the vaccine or placebo in a trial.
- Designing public information counselling and education messages in vaccine trials.
- Assessing perceptions, attitudes and cultural concerns towards the use of contraceptives.
- Understanding views regarding delaying pregnancy as a result of participating in the vaccine trials.
- Assessing community attitude towards vaccine trials on children and minors.
- Designing comprehensive care including support groups, ARV therapy and counselling.

Studies should also be carried out on acceptance of voluntary counselling and testing (VCT) among targeted populations, on misconceptions, and willingness to participate in vaccine trials. Assessment of community preparedness for a vaccine study should identify strategies to recruit targeted populations into the study and retain their participation for the length of it. Lessons learned from community mobilization for other HIV / AIDS programmes should also be used to prepare people for vaccine trials. Additional social behavioural studies would include evaluation of non-vaccine preventive measures, vulnerability studies and the overall social dynamics of the epidemic.

The investigators and other study personnel should fully understand local social and behavioural attitudes to HIV / AIDS among the study population, and to vaccines in particular. People's knowledge of vaccines, and their attitudes towards them should be studied. Possible fears that vaccines could lead to disease should be examined. It is also important to explore beliefs in the community that the vaccine will provide adequate protection against HIV / AIDS and thus negate the need for other, proven preventive measures. HIV counselling and testing may be new in many communities and researchers need to explore ways of introducing the service.

It is also important to get the local views of PLWHA on preventive vaccines. PLWHA may feel that priority efforts should also be put into looking for therapeutic vaccines.

5.4 Studies on community expectations regarding participation in vaccine trials

Such studies should solicit community views on:

- Impact and relevance of the research to the local community or study population.
- Eventual availability, affordability and accessibility of any successful study product to the community.

5.5 Defining laboratory reference ranges in study populations

Before initiation of HIV / AIDS vaccine trials, a full determination of laboratory reference ranges (haematology, biochemistry, CD4 count, and so on) should be undertaken unless already characterized in a similar population.

5.6 Dissemination of findings from preparatory studies

Data from preparatory research should be:

- Disseminated to the communities where it was collected as soon as possible.
- Utilized in designing:
 - Other community-based studies
 - Informed consent materials
 - Clinical trial proposals
 - Community education materials for creating a positive attitude towards vaccine research
 - Community education materials for mobilizing vaccine study volunteers

6 Implementation issues in HIV/AIDS vaccine trials

6.1 Identification and establishment of trial cohorts and sites

Identification and establishment of HIV-uninfected cohorts including perinatal and paediatric subjects at risk of HIV infection is needed to determine prospective HIV incidence. It is also important in these cohorts to assess the effect of other preventive interventions on HIV incidence. Cohorts are necessary for exploring the feasibility of recruiting and retaining sufficient numbers of volunteers. Cohorts of HIV-infected individuals are required for therapeutic vaccines.

The investigator(s) should select sites with high HIV incidence (> 1%) for phase III trials to ensure a manageable sample size. Specific groups with high incidence such as discordant couples, STI patients and sex workers should be identified to achieve smaller sample sizes.

The field sites must have capacity for recruiting, enrolling and conducting surveillance to monitor HIV seronegative persons longitudinally. Major requirements for these field sites include the following:

- Access to an appropriate medical facility where the study population can receive appropriate care for medical problems that arise during a vaccine trial.
- Adequate facilities for collecting and processing laboratory samples.
- Sufficient infrastructure including power, water, communication, security, transport, shipping, procurement, storage and safe waste disposal.
- High standard of confidentiality.
- Capacity for continuous monitoring of HIV incidence in the cohort studies.
- Appropriate referral mechanisms should be available for those identified as HIV infected during cohort development studies and cross-sectional studies
- Capacity to manage data from multidisciplinary studies.
- Counselling and interventions to prevent HIV infection in the study population.
- A cohort with moderate stability and limited mobility.
- Stable and long-term funding for the cohort.
- Ongoing sociobehavioural studies.
- Community involvement in the planning and implementation.

6.2 Conducting phase I and II clinical trials

Early clinical phases of HIV vaccine research should generally be conducted in communities that are least vulnerable to harm or exploitation from research activities. Since HIV strains vary and populations can differ in their response to vaccination, Kenya may consider conducting phase I and II trials and eventually phase III efficacy trials of promising HIV / AIDS vaccines. These trials may be conducted in the country for the first time, simultaneously with other countries, or repeated where similar studies have been conducted elsewhere. Kenya may initiate any phase of a study within its populations, provided there are sufficient scientific justification, capacity, infrastructure and ethical safeguards.

Evaluation of potential vaccine candidates requires well-trained and experienced personnel at all levels of an HIV vaccine trial, together with adequate and appropriate clinical and laboratory facilities. These are required for screening for HIV status and other

inclusion or exclusion criteria as well as monitoring side effects and assessing laboratory end points. For these reasons, Kenya is committed to working with its partners to develop its capacity.

Site initiation checklist

Before a research study commences its recruitment, screening and enrolment activities, the site must demonstrate that the following elements are in place:

- Protocol with regulatory approval by the PPB and an IRB accredited by NCST
- Approval by the PPB to import the candidate vaccine
- Infrastructure needs as listed in the following section, 'Clinical monitoring and site facilities'
- Data collection forms, case report forms and laboratory requisitions
- Fully equipped laboratory (see section 8.1)
- Staff recruited and trained in relevant areas, such as technical training, GCP, GCLP, counselling, confidentiality
- Staff trained on SOPs pertinent to the study
- SOPs developed for laboratory, clinic and data management activities
- SOPs developed for use of outside laboratories and medical facilities
- Master file for site including roles and responsibilities of study team
- Monitoring mechanisms for the study
- Quality assurance and quality control procedures encompassing personnel, clinical, laboratory and information technology (IT)
- Adverse-event reporting system
- Post-exposure prophylaxis programme for staff

Clinical monitoring and site facilities

Adequate provision should be made for monitoring and managing medical, social and psychological problems among the study populations. Well-trained personnel in trial implementation, monitoring and volunteer follow-up are crucial for clinical trials. The personnel includes doctors, clinical officers, nurses, clinical research coordinators, counsellors, laboratory staff, data managers, administrative and fiscal support staff and radiation safety officers where necessary. Trial sites require infrastructure and appropriate equipment: adequate and appropriate reception and waiting areas, health education and seminar rooms, counselling rooms that ensure confidentiality, clinical examination rooms, phlebotomy rooms, areas for assessing participants' clinical vital signs, laboratory space, a data processing area, and storage and filing areas. There should be immediate on-site access to emergency cardiac and respiratory care.

Trial sites should also provide biosafety facilities and expertise. Other considerations include reliable utilities including power, water, telephone, IT facility and Internet connection. In addition, trial sites should have access to outpatient, inpatient, pharmacy and X-ray facilities.

Safety end points

Parameters for determining safety in phase I and II vaccine trials include:

- Medical history and physical examination for evidence of local or systemic reactogenicity

- Haematology (for example, Hb, WBC, total and differential)
- Biochemistry (for example, creatinine, liver function tests)
- Urinalysis (for example, proteins, glucose, microscopy)
- Pregnancy test
- HIV diagnostics (for example, ELISA, Western Blot)
- Any other testing as needed to diagnose or follow up an adverse event

Immunological studies and immunogenicity end points

Vaccine-induced humoral (neutralizing antibodies) and cellular (CTL) responses of the immune system to HIV play an important role in HIV vaccinology. An ideal candidate vaccine should induce adequate, effective and durable immune responses that cross-react with Kenyan isolates. Studies should be conducted during the course of the trials to determine CTL killing activity, neutralizing antibody responses, antiviral factor secretion of cytokines or beta chemokines, and other CD8+ T-cell antiviral factors, and induction of both secretory IgA and mucosal CTL response. However, for each candidate vaccine, the end points should be clearly stated in the approved study protocol.

6.3 Conducting phase III efficacy trials

It is urgent to conduct phase III efficacy trials on vaccines relevant for use in Africa and other heavily affected areas of the world. To accelerate research, development and future access to HIV vaccines, it is essential to increase efforts to move additional candidate vaccines to clinical trials, including phase III trials. Phase III trials will need large numbers of trial participants and may require intra- and intercountry collaboration in multicentre studies.

Possible outcomes that might be observed in an HIV / AIDS vaccine phase III efficacy trial should be documented. These possibilities include:

- Prevention of infection
- Prevention of chronic infection (limited to a transient infection)
- Occurrence of infection, but prevention or delay of AIDS, assessed by candidate surrogate markers such as viral loads, or by clinical findings such as AIDS or mortality
- Occurrence of infection but by a less infectious virus
- Combinations of the above

Because of the concerns about seroconversion from the vaccine, researchers should protect volunteers from possible discrimination in insurance, employment and migration. Such mechanisms include identity cards for trial participants and laboratory tests to distinguish vaccine-induced seropositivity from true infection.

Criteria for conducting phase III efficacy trials

Prerequisites for conducting phase III trials include the following:

- Political support, commitment and involvement.
- Community support and participation.
- Moderately stable, well-defined population with sufficiently high HIV incidence rates.
- Capability and feasibility of collecting and characterizing HIV strains prevalent in the potential study population or region.
- Availability of candidate vaccines that have successfully completed toxicity and safety studies in animals, are safe and have promising immunogenicity profile in phase II human trials.

- Capacity to manufacture sufficient amounts of candidate vaccines according to GMP.
- Capacity to monitor side effects during and after the trial.
- Scientifically competent and ethically acceptable investigators from reputable institutions or organizations with sound collaborative links.
- Access to a medical facility to treat intercurrent illness.
- Provision of counselling and interventions to prevent HIV infection among the study population.
- Ability to respond to psychological and medical needs of those people who are either HIV-infected at screening or who become HIV-infected in the course of the trial.
- Provision of psychological support for those who seroconvert due to the vaccination.
- Ability to manage data.
- Equal gender participation in vaccine trials.

6.4 Monitoring guidelines for HIV/AIDS vaccine trials

Data and Safety Monitoring Board

Vaccine trials must be monitored to ensure the safety of participants and the validity and integrity of the data. Although not strictly necessary for all trials, external monitoring by a DSMB should always be considered. Monitoring should be commensurate with the level of study risk, which is related to study size and complexity and to the absolute degree of risk of the intervention.

Vaccine trials should have a DSMB composed of experts appointed by sponsors, in consultation with collaborating national and international scientists. DSMB members must be independent of the vaccine trial to avoid conflict of interest. The DSMB is an independent body that should provide the sponsors and investigators with reports that go through them to the IRB and NCST.

The DSMB should be multidisciplinary with appropriate representation from all scientific disciplines needed to interpret the data and ensure patient safety, including:

- Clinical trial experts
- Biostatisticians
- Bioethicists
- Clinicians knowledgeable in HIV / AIDS
- Epidemiologists
- Virologists
- Immunologists
- Social and behavioural scientists
- Community representatives

Terms of reference for the Data and Safety Monitoring Board

The DSMB will:

- Review the research protocol and the plans for data and safety monitoring.
- Receive and review regular periodic progress reports from the investigators.
- Have access to and review all data generated from the trial for quality and integrity.
- Monitor data regarding safety (adverse reactions), immunogenicity and efficacy.
- Receive and review unblinded results of interim analyses to determine continuation or termination of the trial.
- Evaluate trial progress, including:

- periodic assessments of data quality and timeliness
- participant recruitment, accrual and retention
- participant risk versus benefit
- performance of trial sites
- other factors that can affect study outcome such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study
- Give recommendations to the sponsor, IRB or NCST, and investigators concerning continuation or conclusion of the trial(s).
- Ensure confidentiality of trial data and monitoring results.

Other monitoring agencies

Scientific and ethical monitoring by the sponsor, manufacturer and collaborator institution is recommended. This is better done as a team but needs to be agreed upon before the research starts, as different groups may have different interests. This team could include representatives from WHO-UNAIDS and other interested parties such as regulatory authorities who may need to monitor the trials for licensing purposes.

6.5 Potential availability, affordability and accessibility of HIV/AIDS vaccines

Developing an HIV / AIDS vaccine incurs financial and logistical risks. Additional problems include identifying and addressing potential regulatory obstacles to ensure appropriate evaluation of the proposals. Mechanisms should be developed to ensure future availability, affordability and accessibility of HIV / AIDS vaccines in Kenya.

Early planning is essential to ensure that future effective HIV / AIDS vaccines are made available to all populations in need without unnecessary delay. This planning should include the following:

- Development of policies and strategies for vaccine introduction and use in different communities.
- Estimates of need and probable vaccine uptake based on varying levels of vaccine efficacy.
- Coordination of future vaccine introduction with an overall HIV / AIDS prevention intervention programme.

Financial support is necessary, not only to develop new candidate vaccines, but also to strengthen appropriate infrastructures in Kenya where vaccine trials may be carried out and where future effective vaccines will have to be eventually used as a matter of urgency. One approach to mobilizing financial resources is to create or increase financial incentives to stimulate more active industry participation in the quest for an HIV / AIDS vaccine. Financial mechanisms, such as tax breaks for investments in HIV / AIDS vaccine research and development, could persuade industry to make more investments in the field. A new purchase fund for buying vaccine for adults on a wide scale may have to be created with the assistance of the World Bank, other UN agencies and other interested private organizations.

6.6 Technology transfer

At present the local capacity to produce vaccines needed for human clinical testing is inadequate, and resources devoted to taking a research construct through the rigors of

vaccine production are insufficient. Therefore the resources and the facilities involved in manufacturing candidate HIV / AIDS vaccines must be increased markedly. The importance of building infrastructure has become even more acute as the major focus of HIV / AIDS vaccine research and development has shifted from large pharmaceutical corporations to small biotechnology companies and to non-profit or academic organizations. The government of Kenya aims to put in place incentives and collaborative arrangements to attract these companies and organizations to set up base in Kenya. Such collaborative arrangements could bring to Kenya the technology it needs to start manufacturing small amounts of vaccines for research.

Technology transfer to Kenya may provide a long-lasting solution. However, this requires agreement between the manufacturer or sponsor and the government of Kenya. Where technology transfer is not possible, negotiations towards purchasing in bulk from the manufacturing company and repackaging locally will have to be considered.

Early negotiations with vaccine manufacturers, funding agencies and collaborators should be undertaken to ensure overall availability, accessibility and affordability of relevant vaccines to persons at risk of HIV in Kenya.

Post-marketing studies should be conducted to evaluate the vaccine in public health use, documenting late, rare and long-term side effects as well as logistics of distribution after a product has been put on the market.

7 Sociocultural and counselling issues in HIV/AIDS vaccine trials

7.1 Sociocultural concerns

Counselling in Kenya as a whole is compounded by a variety of sociocultural factors. Health care recipients tend to be largely agreeable to any suggestion made by the health care provider. Patients do not usually openly question suggestions made by health care providers, considering it rude and unappreciative of the care provided. There is often worry about displeasing the health care provider and fear of losing out on possible beneficial medical attention.

The role of spouses and partners in decision-making needs to be considered in light of different local sociocultural norms. Consultations with spouses or partners and other family members where appropriate should be taken into consideration in the informed consent process, if that is agreeable to the volunteer, to avoid future misunderstanding and conflicts.

Couples intending to participate in HIV / AIDS vaccine research are welcome and should be advised of their responsibility to each other. It is desirable that they are counselled as couples and that they obtain their HIV results as such. Should this not be feasible, each member of the couple has the moral obligation to disclose their serostatus to the partner.

7.2 Counselling

Participants in HIV / AIDS vaccine research need to be counselled regarding their serostatus, to avoid risky behaviour and to use HIV prevention methods. They need to understand the importance of early diagnosis and treatment of STIs, and consider how to provide support to oneself and the family.

Pre-test HIV counselling is essential for those who volunteer to participate in either preventive or therapeutic vaccines. Post-test HIV counselling is equally essential. Those taking part in preventive HIV / AIDS vaccine trials will specifically be counselled regarding risk reduction. Counselling of HIV-infected individuals should address the need to avoid transmitting HIV to others.

During HIV / AIDS vaccine trials, some participants will develop antibodies to some HIV antigens and hence test antibody positive. All volunteers should understand that this does not necessarily denote HIV infection. Some volunteers may attempt to find out whether they are on the active candidate vaccine and therefore consider themselves protected. It is therefore important that all participants be counselled on the fact that antibodies to the vaccine may not necessarily protect them from natural infection.

Support and post-testing centres and clubs should provide for those who are HIV positive, whether symptomatic or still asymptomatic, by counselling them to live positively, adhere to reasonable self-health care such as minimizing alcoholic intake, practise health-seeking behaviour such as prompt treatment of opportunistic infections, avoid reinfection, and consider starting ARV therapy.

7.3 Informed consent process

General aspects

- Consent from a person to join any study should be voluntary, informed and documented.
- Informed consent must be based on complete, accurate and appropriately conveyed information in a language and format that the participant clearly understands.
- Often the person counselled does not take time to read a lengthy consent form as required by the regulatory bodies, which even when translated into the local language may make heavy reading.
- Some medical terms translated into a local language may not mean as much to the reader as it does to the medically oriented translator.
- The over-enthusiastic participant who opts not to read the consent form, hardly listens to the counsellor, and is over-eager to sign and enter the study may in reality not be prepared to be an HIV / AIDS vaccine trial participant.
- Potential participants may have misconceptions, perceiving more protection than may be received. End points of the vaccine trial should be clearly explained. If the end point is immunogenicity, participants should not assume this implies 'protection' and should be counselled not to relax or veer from behaviour that has kept them free from HIV infection
- A person being considered for inclusion in an HIV / AIDS vaccine trial should be appropriately counselled, with all aspects of the study discussed in detail in at least two or three sessions.
- The potential study participant must then be given adequate time, not less than 48 hours, in between at least two counselling sessions, to think (and consult) about participating in the study.
- After signing the consent form, there should be at least two counselling sessions before the potential participant is enrolled into the study. This break serves as a reflection period that gives prospective participants time to change their mind if they so wish.
- A person who seeks out the study team to enrol should be counselled to look introspectively for any other motives for joining the study.
- The counsellor needs to evaluate the level of understanding of the consenting volunteer.
- For minors (< 18 years), written consent should be obtained from parents or guardians according to existing legal provisions, in addition to written assent from the minor where applicable.
- For mature minors (< 18 years but married, pregnant, a parent or engaging in behaviour that puts them at risk for STI/ HIV infection), consent should be obtained from the minor.
- There must be a plan for monitoring the adequacy of the informed consent process (for example, test of understanding) and risk reduction interventions including access to prevention methods throughout the trial period.
- Researchers should not be volunteers in the trials, as this would create a conflict of interest.
- No biological material transfer shall be done without informed consent of the trial participants.

Technical aspects

- Counsellors must point out issues that the layperson may not specifically raise, such as effect of the vaccine on future HIV tests.
- The concept of placebos in trials must be clearly explained, so the participant does not feel that those in the study arm have an advantage over those in the placebo arm.
- Short- and long-term planning for future pregnancies should be discussed in detail with participants.
- The issue of compensation should be clearly discussed at the beginning of the counselling sessions. Monetary benefit could be an inducement for participation in a trial and thus would negate free consent. The potential participant should therefore understand that the studies do not carry monetary benefit and the reasons behind this policy.
- Issues such as transport refund, compensation for work hours lost and for injuries from the study, medical treatment and benefits for self as well as family should all be clearly discussed at the beginning of the study and during follow up. Times for follow-up visits should be flexible.
- It is important that participants be accorded privacy and confidentiality, both at home and at work.

8 Operational and logistic issues

8.1 Laboratory support

For proper functioning, all laboratories require staff well trained in haematology, immunology, clinical chemistry and virology. Laboratories also require adequate equipment including refrigerators and freezers with generator back-up. Training in GCLP, quality assurance and control, documentation and regular laboratory monitoring are essential. All laboratories should be accredited by relevant legal boards or bodies. International accreditation is especially desirable for secondary laboratories. Certification should include evidence of participation in external quality assessment schemes that include proficiency and validation tests. The director of the primary laboratory should be a specialist in a branch of laboratory science or medicine.

Laboratories should have a computer network for entering test results, as well as for easy communication with different centres. Accountability and tracking of samples from participants, appropriate collection and storage, identification of missing or pending results, and shipping records are crucial.

Storage facilities for samples should include sufficient rooms, with cold rooms and freezers, and an adequate power supply with back-up generators. As secondary laboratories will be used as repositories for serum samples and cells from all study volunteers, they need to have liquid nitrogen tanks for storage, or freezers at -70°C . Samples must be stored for reference and for any other studies that might be determined in future. Collaborative international reference laboratories may also need to repeat some of the tests for quality control.

Evaluation of HIV/AIDS vaccines requires a high level of laboratory rigour. The following issues should be considered as minimum requirements for establishing laboratory capacity for HIV/AIDS vaccine trials:

- Staff fully trained and regularly updated in GCP, GCLP and new techniques.
- Staff registered and licensed by their appropriate boards or bodies.
- Laboratories inspected and accredited by the appropriate boards or bodies.
- Comprehensive SOPs for all aspects of the research laboratory functions including specimen transport and waste disposal.
- Standardization and validation of diagnostic assays.
- Establishment of laboratory reference values for the study population.
- Establishment of an appropriate HIV testing algorithm based on standardized tests.
- Reliable computer network for storing and transmitting data.
- Capacity to generate cellular and humoral immunological data.
- Availability of laboratory facilities to perform all assays required for screening and follow-up of volunteers.
- Ability to track all specimens received, stored, used and shipped.
- Availability of either regional or international reference laboratory for quality assurance and quality control.
- Ability to monitor disease progression as required by protocol.
- Adequate facilities to ensure cold chain for specimens, reagents and vaccines.
- Availability of GCLP-compliant back-up laboratory facilities.
- Requirements for specimen transport if necessary.
- Access to reliable means of communication (telephone, e-mail, fax).

- Mechanisms in place to ensure prompt reporting of laboratory results to clinic staff.
- Back-up power supply to maintain full laboratory function.
- Mechanisms in place for quality assurance and quality control.

8.2 Laboratory network

The primary laboratories at the vaccine trial site may not necessarily need to perform all laboratory assays, but they should ensure that quality assurance and control are adequate. Depending on the resources available, the primary laboratory may collect biological samples with the ability to process the specimens and send samples to secondary laboratories for serology, microbiology, haematology, biochemistry and other required tests. Secondary laboratories are expected to uphold standards of GCLP with well-understood agreements between laboratories.

8.3 Material transfer agreements

- Biological material transfer agreements must be in place on all transferred materials and specimens used for vaccine studies.
- Material transfer agreements should state:
 - The materials or specimens are for scientific, educational and non-commercial purposes only.
 - Any other use of materials and specimens or research results, including but not limited to commercial development, may proceed only after concluding a cooperative research and development agreement (RADA). Negotiations must be completed and the RADA executed before commercial sale of the products. This agreement must be binding on all parties with respect to intellectual property rights.
 - Any unauthorized commercial use of the materials and specimens or results without the said agreement will be subject to financial penalty by court of law.
 - No material transfer will be done without the consent of the trial participant.
 - No material transfer will be done without approval of the protocol and in accordance to the Ministry of Health guidelines on transfer of biological material.

8.4 Clinical support

Clinical support for an HIV / AIDS vaccine trial requires:

- A qualified and registered medical practitioner with appropriate credentials and previous clinical experience
- An adequate number of staff fully trained and regularly updated in all aspects of GCP
- An adequate number of staff well trained in counselling and in all aspects of tracing and following up participants
- Well-developed SOPs for all aspects of the trial clinic
- Reliable transportation for tracing of volunteers, follow-up and emergencies
- Resuscitation and emergency equipment present at vaccine trial site
- Access to emergency care and referral
- Cold chain for vaccine handling and storage
- Proper and timely submission of biological specimens according to SOPs
- Access to reliable means of communication (telephone, e-mail, fax etc)
- Appropriate means for disposing of bio-hazardous material
- Appropriate pharmaceutical support systems

8.5 Data management

The principal investigator in conjunction with co-sponsors and collaborators will decide on who will analyse and publish the data and where data will be published. The data should be handled according to the ethics of intellectual property rights. The government shall have access to the data through its regulatory and ethical scientific bodies.

The research site must have a central computerized data management system with computers, relevant software and peripherals, handled by a trained data management staff. The computers should have sufficient storage capacity, with high-quality printers, and adequate data-saving and back-up systems in case of power failure, fire or other catastrophe. There must be reliable generator power back up and an uninterrupted power supply for the computer systems.

Data need to be managed by persons well trained in this aspect of research. The raw data must be kept by the principal investigator with back-up sets stored in collaborating and coordinating centres.

The research team should have a policy in place before the research starts as to who may access and retrieve data, who may enter the data entry room, and who will perform the appropriate back up. Data usage, exportation and destruction will be in accordance with the national regulatory policy.

Minimum data management requirement should include:

- Data collection and storage according to GCP with appropriate source documents
- Confidentiality of data as dictated by GCP including adequate security and limited access
- Well-developed SOPs related to data management
- Adequate facilities for storing both electronic and paper documents and data
- Quality assurance and quality control of data
- Adequate facilities (appropriate IT) for transmitting data
- Adequate personnel for data management who are trained in GCP

Study sites must have state-of-the-art information and communication systems.

8.6 Administrative issues

To ensure that infrastructure is adequately developed the study sponsor and investigators should take into consideration the logistical challenges inherent in performing high technology research in a setting that is not highly developed technologically. The following should be considered:

- Availability of adequate numbers of qualified personnel and a well-defined organogram
- Availability of electricity, back-up power, a reliable water supply and other utilities including telephone and IT at the study site
- Policies to ensure the entire staff is given appropriate training in confidentiality
- Transport management system
- Adequate funding and clear guidelines for financial management and reporting
- Procurement policies to ensure proper stock of study supplies
- Personnel policies that provide motivation and encourage employees to stay on
- Adequate provisions for employee orientation and technical training
- Adequate and appropriate communication between the study team and outside partners
- Regular meetings between study team members at the site and collaborators

8.7 Public and media relationships

Effective communication between investigator(s) and the public requires:

- Media training
- Media updates and briefing on the study
- Community education
- Response to media enquiries
- Volunteer information campaigns
- Methods to control damage from adverse public information (accurate or inaccurate)

9 Training

9.1 Study personnel

HIV / AIDS vaccine-related research is multifaceted and therefore to address the various needs it requires personnel trained in a multiplicity of disciplines. All staff in the research unit need to have initial and ongoing training. The training may be formal leading to degree courses or it may be in the form of in-house short courses to strengthen specified capabilities at research sites. The sponsor and the principal investigator are responsible for facilitating all forms of training for the staff in the research unit.

Following are key areas where training is required to build capacity for HIV / AIDS vaccine trials.

Public relations courses

Public relations courses are required for all staff in the research unit. This training is necessary for efficient interactions with volunteers, spouses or partners of participants, and communities in which trials may be conducted. The training may also help in recruiting volunteers. Each research site should designate a public relations officer.

Research training

GCP training should be provided and documented for all clinical and health care staff, and GCLP training for laboratory staff before volunteer screening starts. This should be followed by GCP and GCLP and updates—regularly, annually or at some other agreed frequency. Support staff also needs to be given appropriate training.

General training

All support staff, for example, drivers, office personnel, need to receive this type of training:

- GCP
- GCLP
- Confidentiality
- SOPs
- Communication skills in techniques such as e-mails, speakerphones, teleconferences
- Any other appropriate training for various cadres
- Data and specimen handling
- Protection of human subjects
- Ethical issues and guidelines
- Handling, storage, shipment of hazardous materials
- Teamwork
- Policy issues
- Radiation safety
- Handling, storage, shipment and disposal of vaccines

Specific training

- Data fax requirements
- Protocol specific guidelines
- Risk reduction counselling
- Data handling and management
- Quality assurance
- Scientific communication skills
- Report writing
- Record keeping

Basic science research training

- Cell and molecular biology
- Virology
- Immunology and vaccinology
- Specialized training of laboratory technologists in various techniques
- Radiation safety

Social and behavioural training

- Social science research
- Bioethics
- Anthropology
- Counselling in HIV / AIDS
- Cultural sensitivity issues
- Gender and youth issues
- Legal issues

Epidemiological training

- Biostatistics
- Clinical research methodologies
- Monitoring and evaluation

Data management and information technology

- Data collection, entry and analysis and quality control
- Filing and archiving of data
- Compilation of progress reports

Administration

- Management courses
- Social administration
- Radiation safety

9.2 Non-study personnel

For the community, the community advisory board, and peer leaders:

- General HIV education, prevention, epidemiology, disease progression, care and treatment, vaccines

- Study protocol
- Ethics
- Public relations
- Informed consent process
- Human rights
- Gender issues
- Critical role of the community in study success

9.3 Regulatory and scientific review board members

Board members should receive training in:

- Ethics
- Informed consent
- Conflict of interest
- Coercion
- Vulnerable populations
- Human rights
- Gender
- Use of the *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines*

Quality management

For all staff in the research unit, there should be:

- Quality assurance, which involves:
 - Periodically reviewing various components of research process
 - Ensuring adherence to policies, protocols, SOPs
 - Determining accuracy of records and their transmission
 - Overall planning, reviewing partial or complete records
 - Responding in a timely way to periodic monitoring visits and reports
- Quality control
- Daily process of ensuring accuracy and timely transmission of forms, including all records
- Timely response to regular reports from statistical centre

Appendices

Appendix 1 CONCEPT PLAN OUTLINE

Following is a 15-step guideline on preparing and presenting a concept paper to the HIV subcommittee of the Ministry of Health for review. The subcommittee will give early feedback to the protocol team regarding issues of key importance in developing the protocol. The concept paper should be approximately 10 pages long, exclusive of the study capsule.

1 Study title and research team contact list

2 Description of product or intervention

Indicate the study agents and provide background information about the product, including previous studies with the product. (half to two pages)

3 Study capsule

Executive summary: specify the principal objectives, rationale, relevant background, overall design for phase I and II trials; describe critical pathway to efficacy evaluation; indicate relevance to the long-term goals of the research institution. A study schema would be helpful. (about one page)

4 Study objectives

Specify primary and secondary objectives. (about half page)

5 Design

Specify the type of study proposed, for example, whether it is phase I, IIA, IIB or III, a randomized clinical trial, observational, nested case control study; immunization dose and schedule. (a quarter to half a page)

6 Study population and eligibility criteria

Specify sample size, principal inclusion and exclusion criteria, recruitment source(s), appropriateness of proposed study population for the proposed concept and other salient characteristics. (half to one page)

7 Specify end points

Specify the primary end points such as seroincidence, dose-limiting toxicity, specific behavioural outcomes (either primary or secondary end points). (about a quarter page)

8 Statistical considerations and analyses plan

For each study objective, justify statistical design characteristics (for example, sample size, comparison groups, estimate of effects size). (one to two pages)

9 *Participation requirements*

Specify the number and duration of study visits, and the specimens and data to be collected (including any invasive procedures for collecting specimens). (half to one page)

10 *Participating sites and institutions*

Specify the proposed study sites and investigators; specify role of other core or shared resources with regard to implementation (special assays to be done, data management, coordination, materials development, specify other collaborating organization(s) and pharmaceutical companies). (half to one page)

11 *Ethical considerations*

Identify any special ethical problems that may be associated with study implementation. Specify plans for providing follow-up care for participants who become HIV infected and for people who are screened, determined to be HIV infected and not enrolled. How long? For phase III vaccine trials, will the intervention be accessible to the community in which the study is being implemented after completion of the study? Will it be sustainable? (about one page)

12 *Product-related considerations*

Are an investigational new drug (IND) review and approval needed? Are the product and placebo available in sufficient quantity for the proposed study? From whom is there a plan to manufacture sufficient quantities for any proposed follow-up studies? (about half a page)

13 *Time frame*

Specify a time line for making the product available, developing the protocol and implementing the trial. Include time anticipated as needed for follow-up. Anticipate contingencies for development and implementation, such as selecting the final product and awaiting results of the ongoing study to determine dosage. (about half a page)

14 *Special considerations*

Identify special considerations for safety, regulatory, pharmacy and assay requirements. (about half a page)

15 *Budget considerations*

Provide an estimated total budget by year.

Appendix 2 INFORMED CONSENT CHECKLIST

Following is the checklist IRB panel members use when they review consent forms.

SECTION I – *Basic elements of informed consent*

Element

- ✓ A statement that the study involves research
 - ✓ An explanation of the purposes of the research
 - ✓ An explanation of the expected duration of subject's participation
 - ✓ A description of the procedures to be followed
 - ✓ The trial procedures to be followed, including all invasive procedures
 - ✓ Identification of any procedures that are experimental
 - ✓ The trial treatment(s)
 - ✓ The probability for random assignment to each treatment
 - ✓ The subject's responsibilities (for clinical studies)
 - ✓ A description of any reasonably foreseeable risks or discomforts to the subject
 - ✓ A description of any benefits to the subject or to others which may reasonably be expected from the research
 - ✓ The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this
 - ✓ A disclosure of appropriate alternative procedures or courses of treatments, if any, that may be advantageous to the subject
 - ✓ The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks
 - ✓ A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
 - ✓ That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and /or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential (for clinical studies)
 - ✓ A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and that notes the possibility that the IRBs may inspect the records;
- (for clinical studies)*
- ✓ For research involving more than minimal risk, an explanation as to whether any compensation is available if injury occurs, an explanation as to whether any medical treatments are available if injury occurs, and if so, what they consist of, OR where further information may be obtained
 - ✓ An explanation of whom to contact for answers to pertinent questions about the research
 - ✓ An explanation of whom to contact for answers to pertinent questions about research subjects' rights

- ✓ An explanation of whom to contact in the event of a research-related injury to the subject
- ✓ A statement that participation is voluntary
- ✓ A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; a statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

SECTION II – *Additional elements of informed consent*

Additional element

- ✓ A statement that the particular treatment or procedure may involve risks to the subject (or embryo, or foetus, or nursing infant if subject is or may become pregnant) that are currently unforeseeable
- ✓ Anticipated circumstances under which a subject's participation may be terminated by the investigator without regard to the subject's consent
- ✓ Any additional costs to the subject that may result from participation in the research
- ✓ The anticipated prorated payment, if any, to the subject for participating in the trial
- ✓ The consequences of a subject's decision to withdraw from the research
- ✓ A description of the procedures for orderly termination of participation by the subject
- ✓ A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject or the subject's legally acceptable representative in a timely manner
- ✓ Approximate number of subjects involved in the study

SECTION III – *Additional elements, including documentation of informed consent*

Additional element

- ✓ This legislation applies to 'medical experiments' and mandates the use of an 'Experimental subject's rights as a participant'. There is no exception from this requirement.

Documentation of informed consent

- ✓ Informed consent shall be documented by use of a written consent form approved by the IRB and signed and dated by subject, or subject's legally authorized representative. A copy shall be given to the person signing the form.
- ✓ The information given to a subject or the subject's representative shall be in language understandable to the subject or representative (i.e., lay terms).
- ✓ No informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Appendix 3SAMPLE CONSENT INFORMATION GUIDELINES

Consent to participate in a medical research study with an experimental HIV/AIDS vaccine

Title of study: A randomized, placebo-controlled, double-blind, phase # trial to evaluate and compare the safety and immunogenicity of injections of an experimental HIV-1 vaccine versus placebo in HIV uninfected, healthy volunteers.

Study number: #####

Sponsor: _____

Study protocol date: _____

Principal investigators: _____

Study site: _____

Introduction

You are being asked to participate in a clinical research study to test a human immunodeficiency virus preventive vaccine. Human immunodeficiency virus is often called HIV. HIV is the virus that causes people to eventually become sick with the disease called acquired immunodeficiency syndrome (AIDS).

Over 40 million people worldwide are currently infected with HIV. The number of new cases continues to rise at an alarming rate. Other infectious diseases, such as smallpox or poliomyelitis, have been controlled, or even eliminated, by vaccination programs. A vaccine is a substance that is introduced into the body (usually orally or by injection) to stimulate the body's immune system to prevent or control a specific infection. Many experts believe that an HIV vaccine offers hope in controlling the epidemic. Currently, there is no licensed and available HIV vaccine that can protect people against the virus that causes AIDS.

Many different types of HIV vaccines are currently being developed and tested. This study is one of several studies that will test HIV vaccines in humans. More research studies will have to be carried out before the vaccines can be used in the general population.

Before you agree to participate in this research study, it is important that you read and understand the purpose of the study and the study procedures. You should also know your rights as a participant. Please ask Dr _____ or a member of the research team to explain any words or information that you do not understand.

Purpose of this research study

The goal of this study is to evaluate if the study vaccine is safe and to evaluate how the immune system responds to the study vaccine.

Requirements to participate

You must be a healthy male or female who is not infected with HIV. You must not have any behaviour that puts you at risk of HIV infection. You must be between the ages of 18 and 60 years. If you are a woman you must not be pregnant or breastfeeding and must agree to delay pregnancy for at least _____ months after the last injection by using effective

tive birth control. This is because the effect of the test vaccine on your unborn child is not yet known. You must be well informed about this study and willing and able to provide written consent to participate in this study.

Length of participation

This study will require that you make approximately ——— visits to the research centre unless you are ill and have to return to the clinic more frequently. The doctors or nurses at the centre will speak to you about when these visits will occur. This trial will be approximately ——— months long.

Study procedures

About ## volunteers are expected to participate in this clinical research study.

This consent form gives information about the study that will be discussed with you and read to you if you are unable to read. If you agree to participate, you will sign your name or make your mark on two copies of this consent form confirming that you agree to take part. Before you consent to participate in the study, you will be assessed to determine whether you have understood all the information that has been made available to you. You may keep one copy and the study clinic will keep a copy at the clinic. If you do not wish to keep a copy, the study clinic will keep it for you in a safe and secure place. If you wish to have a person who is not part of the study team present to assist you in understanding the study, they may be present with your permission throughout the consent process and will be required to sign your consent as a witness. Your participation is voluntary and it is entirely up to you to decide whether to participate in this study or not.

If you decide not to participate, none of your rights will be compromised and the care that would otherwise be available to you will not be affected. If you decide not to participate, there might be another HIV vaccine trial or a licensed vaccine in the future. There is no alternate licensed HIV vaccine currently available. It is not known whether receiving this vaccine would make you respond better or worse to a future vaccination.

Before you can be enrolled into the study, the doctor and the nurse will determine if you are eligible to participate in this study by performing the following procedures:

Screening visit/s

- You will be asked questions to see if you qualify for the study.
- A blood specimen will be collected for an HIV test.
- You will be asked questions about your risk of exposure to HIV.
- A complete medical history and physical examination will be performed.
- (An amount of) blood will be collected and tested for the function of your organs and to ensure that you are healthy.
- Urine samples will be also collected. The urine will be tested to make sure your kidneys are functioning normally.
- If you are a woman, you will have a urine pregnancy test prior to receiving vaccine to make sure that you are not pregnant. This is being done because the safety of these vaccines for pregnant women and their babies is not yet known.

At the injection visits

There will be ## visits where you will be given injection(s) of the test vaccine or placebo for a total of ## injections. A placebo is prepared to look like the vaccine, but it does not contain the vaccine. You will be assigned by chance to one of three groups. The group

you are assigned to will be kept secret. Neither your doctor or nurse nor you will know whether you are getting vaccine or placebo until the end of the study. The Principal Investigator may request this information in the case of a medical emergency where it will help him / her make decisions regarding your medical care. You may request this information after the end of the whole study when all the volunteers have completed all their visits and all the results are available.

Before you are given an injection, the following procedures will be performed:

- A brief medical history and physical examination.
- (An amount of blood) of blood may be taken. The blood will be tested for the function of your organs, for HIV and the effect of the vaccine on your organs and the immune system.
- Urine samples will be collected at some visits.
- If you are a woman, you will have a urine pregnancy test prior to receiving a dose of vaccine to make sure you are not pregnant. This is being done because the safety of these vaccines for pregnant women and their babies is not yet known.
- You will be tested for HIV at established intervals. You will be counseled on HIV risk reduction before and after each HIV test.
- You will be asked questions about your potential risk of getting HIV before each HIV test and at any time that you may have been exposed.
- Your blood will be tested for immune responses several times during the study.
- The study nurse or study doctor will give you a dose(s) of vaccines or placebo in the upper arm during the study using a sterile needle. You will be required to remain in the clinic for one hour after the injections to ensure you are not having any immediate health problems. The study nurse or study doctor will take your blood pressure before each injection and 30 minutes after each injection and at your request.
- After each injection you will be given a diary card to record any symptoms, any visits to a health care provider or any medication use. You will be asked to record this information for ##†days and to return with it to the clinic ## days after each injection.
- If you experience any unusual, alarming or unexpected symptoms that your nurse / doctor will tell you about, or require hospitalization during the course of the study, you should notify your study clinic immediately.

Follow-up visits

You will be asked to return to the study clinic at #, ##, ### and #### months after your first injection.

The following procedures will be performed:

- Brief medical history and physical examination.
- Blood samples collected to test for safety and immune response.
- Blood for HIV testing at the last study visit. HIV risk reduction counseling will be offered before and after the HIV test.

The study vaccines

The HIV candidate vaccine for this study does not contain any material from live HIV, no material from individuals who are infected with HIV or who are found to be resistant to HIV. The vaccine does not contain any blood or blood products. The vaccine contains artificially made genetic information, which resembles a small part of the genetic mate-

rial of HIV. Because of this resemblance, the vaccine may produce a response from your immune system when injected into your arm.

Storage of blood

After completion of the initial laboratory tests on your blood specimens, some of the remaining blood will be stored in accordance with the instructions contained in the *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines*. A number, rather than your name, will be used to label this blood to maintain your confidentiality. The stored samples may be used in the future for quality control purposes and other tests related to approved HIV vaccine research and development. Samples may be shipped to national or international laboratories for additional testing.

Risks and discomforts

With any new medicine or vaccine, there is a possibility of unexpected side effect(s). This study will show us how well the vaccine is tolerated (safety) and your body's ability to make a response to it. It is not investigating if the vaccine can prevent HIV infection or disease. Until larger studies have been performed we will not know whether this vaccine is effective in preventing HIV infection or disease.

THEREFORE YOU SHOULD CONTINUE TO AVOID ANY BEHAVIOUR THAT MAY PUT YOU AT RISK OF CONTRACTING HIV. YOU SHOULD NOT CONSIDER YOURSELF PROTECTED FROM HIV AFTER HAVING PARTICIPATED IN THIS STUDY.

We do not know what effect the vaccine would have on an unborn child if given to a pregnant woman. Women who may be able to bear children should use a reliable form of contraception until ## months after the last injection. A pregnancy test will be done before the study begins and prior to each injection. If you become pregnant during the injection period, you will not receive any further injections. You will be followed up until the end of the study or until delivery of the baby, whichever is last.

Following the injections, you may test positive on a routine HIV antibody test although this is not likely to happen with this particular vaccine candidate. However, if this were to happen, it could mean that your body has been exposed to the vaccine and has produced antibodies to it. In case of a positive result on a routine HIV test, an independent laboratory will confirm whether your positive test is a result of the vaccine or whether you were naturally infected with HIV. Should you test HIV positive due to vaccine-induced antibodies, you will be followed up until the test becomes negative.

Should you become naturally infected with HIV due to exposure in the community, and have not received all your injections, you will not receive further injections, and will be followed up until the end of the study. The number of immune cells in your body and the amount of virus in your blood will be measured.

You will be referred for care and support, including the provision of antiretroviral medications according to the *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines*.

Should you require an HIV test outside the study for whatever reason, we strongly recommend you contact the study team first. We will offer HIV testing and counselling or recommend a laboratory that can distinguish between a positive result from a vaccine and HIV infection. To avoid any problems, you will be offered an identification card that shows that you joined this study. A contact number in case of queries or medical emergencies will be provided.

It is unknown whether receiving this HIV vaccine will alter your immune response to any future HIV vaccine that you might receive.

Benefits

There are no direct benefits for you in taking part in the study except that you will get information about your general health and your HIV status. You will receive HIV counselling and family planning counselling including free condoms. The information that we collect from this study may help to develop an effective HIV vaccine.

Injuries

We do not expect you to suffer any injury as a result of participating in this study. However, in case you are injured as a result of being in this study, you will be given the necessary treatment for your injuries including emergency treatment without charge. If the study clinic cannot provide the type of treatment you need you will be referred to a clinic where treatment will be provided for you at no cost to you. The study site and their funding agencies and collaborators have made no provision for monetary compensation in the event of injury resulting from the research.

If you have any symptoms or medical problems that you think are due to getting these vaccines, you should report them right away to Dr _____ at the following telephone number _____ or mobile number _____.

Circumstances for discontinuation from injections or withdrawal from the trial

Your participation in the trial is entirely voluntary. You may withdraw from the study at any time without giving a reason. Withdrawal will NOT compromise any rights or benefits you may be entitled to or influence any current or future medical care you may need.

You may be removed from the study without your consent for the following reasons:

- If your doctor feels that staying in the study is harmful to your health
- If you don't keep appointments
- If you have serious side effects from the injection
- If the Data Monitoring and Ethics Committee feels that the study should be stopped
- If the study sponsor decides to stop or cancel the study
- If you become pregnant
- If you become HIV infected

If injections have been discontinued you will be followed until the end of the study, if possible.

New information

You will be told of any new information gained during the course of the study that might cause you to change your mind about staying in the study. You will be told about new information gained in this trial and trials elsewhere as well as information on any other HIV vaccines. You will also be informed if a safe and effective vaccine becomes available.

Supervision of the study

An outside group of experts called a Trial Steering Committee will supervise the conduct of the study. Independent monitors will regularly check all data collected and an independent group of experts called the Data Monitoring and Ethics Committee.

Confidentiality

Your participation in the study, all information collected about you as well as all results of laboratory tests will be kept strictly confidential to the extent permitted by law. You will be identified by a unique identity number known only to you and the clinic staff. Apart from the study team members that you meet, other staff from national or international government regulatory agencies, members of the Ethics Committee, study monitors, auditors, inspectors and representatives of the sponsor will check the records to make sure that the trial was conducted properly. They are equally bound to respect your confidentiality. Your identity will not be disclosed in any publication or presentation of this study.

End of study

At the end of the study, you will be told whether you received the vaccine or placebo, a process called unblinding. The analysis of the data may take several months after the end of the study and after all volunteers have completed their visits. You will then be informed about the results.

Reimbursement

You will be reimbursed Ksh_____ for each scheduled protocol visit. These reimbursements will continue for as long as you continue to participate in the study; the exact amount and nature of the reimbursements may be modified in light of changes in bus fares, cost of living, or hospital coverage.

Contact numbers

If you have any questions regarding the study or your participation in the study, you can call Dr _____, the Principal Investigator, at _____ or mobile:_____.

If you have a medical problem related to your participation in the study, please contact Dr _____ at the _____.

Nurses and counsellors are available at the _____ at tel: _____.

If you have a question about your rights as a research subject you should contact Dr_____, the chairperson of the Ethics Committee, at _____, tel:_____.

Enrolment consent form signature

I, (name of volunteer) _____ ,

of (address) _____

agree to take part in the research project entitled: A randomized, placebo-controlled, double-blind, phase # trial to evaluate and compare the safety and immunogenicity of injections of high dose of an experimental HIV-1 vaccine versus placebo in HIV uninfected, healthy volunteers.

I confirm that the nature and demands of the research have been explained to me and I understand and accept them. I understand that my consent is entirely voluntary and that I may withdraw from the research project if I find that I am unable to continue for any reason and this will not affect the legal rights I may otherwise have.

Volunteer

Print name: Signature:

Date: |__|__| / |__|__|__| / |__|__|__| Time: |__|__: |__|__| (24-hour clock)
DD / MMM / YYYY

Witness

I have explained the nature, demands and foreseeable risks of the above research to the subject:

Print name: Signature:

Date: |__|__| / |__|__|__| / |__|__|__| Time: |__|__: |__|__| (24-hour clock)

Person obtaining consent

Print name: Signature:

Date: |__|__| / |__|__|__| / |__|__|__| Time: |__|__: |__|__| (24-hour clock)

Principal investigator

Print name: Signature:

Date: |__|__| / |__|__|__| / |__|__|__| Time: |__|__: |__|__| (24-hour clock)

Appendix 4 PARTICIPANT'S RIGHTS

As a human subject you have the following rights. These rights include but are not limited to the subject's right to: (The following bill of rights may be added onto the informed consent form)

- be informed of the nature and purpose of the experiment
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used
- be given a description of any attendant discomforts and risks reasonably expected
- be given an explanation of any benefits to the subject reasonably expected, if applicable
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits
- be informed of the avenues of medical treatment, if any are available to the subject, if complications should rise after the experiment
- be given an opportunity to ask questions concerning the experiment or procedures involved
- be instructed that the subject may at any time withdraw consent to participate in the medical experiment and discontinue participation without prejudice
- be given a copy of the signed and dated consent form
- be given the opportunity to decide to consent or not to consent to a participate in a medical experiment without intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision

Your signature indicates that you have read and that you understand the above information, that you have discussed this study with the person obtaining consent, that you have decided to participate based on the information provided, and that a copy of this form has been given to you.

Signature of subject

Date

ID / PIN or any other form of identification

Person obtaining consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied—that the subject has been provided with the experimental subject's rights as a participant, if appropriate; that I have discussed the research project with the subject and explained to him or her in non-technical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the subject to ask questions and that all questions asked were answered.

Signature of person obtaining consent

Date

IRB approval date:

IRB expiration date:

Appendix 5 BIOLOGICAL MATERIAL TRANSFER AGREEMENT

A Biological Material Transfer Agreement (BMTA) is a generic term for documents used in the context of the transfer of any kind of biological material (animals, plants, microbes) from one institution to another, nationally as well as internationally. Since these materials may be commercially valuable, few are willing to provide them without some form of legal contract in place. The contractual agreement signed between the provider and the recipient of a biological material is what is generally referred to as the BMTA, and is binding to both parties.

A BMTA lays down mutually agreed upon terms and conditions of transfer of the biological material. It sets out the rights and obligations of both the provider and the recipient of the material. It also aims to facilitate access to biological materials and to allow fair and equitable sharing of the benefits derived from their use. Any deviation from the defined terms and conditions of a BMTA without prior written approval from both parties is a violation of the binding contract and the provider may invoke the Governing Law clause and formally punish the recipient, or may work with the recipient to reach a satisfactory settlement.

The provider; who may be an individual, an institution or a company, decides on the type of BMTA to be used, which must conform to Public Health Act Cap. 242 of the Laws of Kenya. A BMTA may be simple or complex but its basic terms are quite similar. A Biological Material Agreement Implementing Form accompanies the terms and conditions of every BMTA as shown below.

I. Definitions

A. PROVIDER: Organization providing the ORIGINAL MATERIAL. The name and address of this party will be specified on the MTA Implementing Form.

B. PROVIDER SCIENTIST: The name and address of this party will be specified on the MTA Implementing Form.

C. RECIPIENT: Organization receiving the ORIGINAL MATERIAL. The name and address of this party will be specified on the MTA Implementing Form.

D. RECIPIENT SCIENTIST: The name and address of this party will be specified on the MTA Implementing Form.

E. ORIGINAL MATERIAL: The description of the material being transferred will be specified on the MTA Implementing Form.

F. MATERIAL: ORIGINAL MATERIAL, PROGENY, and UNMODIFIED DERIVATIVES. The MATERIAL shall not include (a) MODIFICATIONS, or (b) other substances created by the RECIPIENT through the use of the MATERIAL which are not MODIFICATIONS, PROGENY, or UNMODIFIED DERIVATIVES.

G. PROGENY: Unmodified descendant from the MATERIAL, such as virus from virus, cell from cell, or organism from organism.

H. UNMODIFIED DERIVATIVES: Substances created by the RECIPIENT, which constitute an unmodified functional subunit or product expressed by the ORIGINAL MATERIAL. Some examples include: subclones of unmodified cell lines, purified or fractionated subsets of the ORIGINAL MATERIAL, proteins expressed by DNA/RNA supplied by the PROVIDER, or monoclonal antibodies secreted by a hybridoma cell line.

I. **MODIFICATIONS:** Substances created by the RECIPIENT which contain/incorporate the MATERIAL.

J. **COMMERCIAL PURPOSES:** The sale, lease, license, or other transfer of the MATERIAL or MODIFICATIONS to a for-profit organization. COMMERCIAL PURPOSES shall also include uses of the MATERIAL or MODIFICATIONS by any organization, including RECIPIENT, to perform contract research, to screen compound libraries, to produce or manufacture products for general sale, or to conduct research activities that result in any sale, lease, license, or transfer of the MATERIAL or MODIFICATIONS to a for profit organization. However, industrial sponsored academic research shall not be considered a use of the MATERIAL or MODIFICATIONS for COMMERCIAL PURPOSES *per se*, unless any of the above conditions of this definition are met.

K. **NON-PROFIT ORGANIZATION(S):** A university or other institution of higher education or any non-profit scientific or educational organization, qualified under a state non-profit organization statute. As used herein, the term also includes government agencies.

II. Terms and conditions of this Agreement

A. The PROVIDER retains ownership of the MATERIAL, including any MATERIAL contained or incorporated in MODIFICATIONS.

B. The RECIPIENT retains ownership of: (a) MODIFICATIONS (except that, the PROVIDER retains ownership rights to the MATERIAL included therein), and (b) those Substances created through the use of the MATERIAL or MODIFICATIONS, but which are not PROGENY, UNMODIFIED DERIVATIVES, or MODIFICATIONS (i.e., do not contain the ORIGINAL MATERIAL, PROGENY, UNMODIFIED DERIVATIVES). If either 2(a) or 2(b) results from the collaborative efforts of the PROVIDER and the RECIPIENT, joint ownership may be negotiated.

C. The RECIPIENT and the RECIPIENT SCIENTIST agree that the MATERIAL:

1. is to be used solely for teaching and academic research purposes;
 2. Will not be used in human subjects, in clinical trials, or for diagnostic purposes involving human subjects without the written consent of the PROVIDER;
 3. Is to be used only at the RECIPIENT organization and only in the RECIPIENT Scientist's laboratory under the direction of the RECIPIENT SCIENTIST or others working under his/her direct supervision;
- and
4. Will not be transferred to anyone else within the RECIPIENT organization without the prior written consent of the PROVIDER.

D. The RECIPIENT and the RECIPIENT SCIENTIST agree to refer to the PROVIDER any request for the MATERIAL from anyone other than those persons working under the RECIPIENT Scientist's direct supervision. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agrees to make the MATERIAL available, under a separate implementing form, to this Agreement or other agreement having terms consistent with the terms of this Agreement, to other scientists (at least those at NONPROFIT ORGANIZATION(S)) who wish to replicate the RECIPIENT Scientist's research; provided that such other scientists reimburse the PROVIDER for any costs relating to the preparation and distribution of the MATERIAL.

E. Distribution

1. The RECIPIENT and/or the RECIPIENT SCIENTIST shall have the right, without restriction, to distribute substances created by the RECIPIENT through the use of the ORIGINAL MATERIAL only if those substances are not PROGENY, UNMODIFIED DERIVATIVES, or MODIFICATIONS.

2. Under a separate implementing form to this Agreement (or an agreement at least as protective of the PROVIDER's rights), the RECIPIENT may distribute MODIFICATIONS to NONPROFIT ORGANIZATION(S) for research and teaching purposes only.

3. Without written consent from the PROVIDER, the RECIPIENT and/or the RECIPIENT SCIENTIST may not provide MODIFICATIONS for COMMERCIAL PURPOSES. It is recognized by the RECIPIENT that such COMMERCIAL PURPOSES may require a commercial license from the PROVIDER and the PROVIDER has no obligation to grant a commercial license to its ownership interest in the MATERIAL, incorporated in the MODIFICATIONS. Nothing in this paragraph, however, shall prevent the RECIPIENT from granting commercial licenses under the RECIPIENT's intellectual property rights claiming such MODIFICATIONS, or methods of their manufacture or their use.

F. The RECIPIENT acknowledges that the MATERIAL is or may be the subject of a patent application. Except as provided in this Agreement, no express or implied licenses or other rights are provided to the RECIPIENT under any patents, patent applications, trade secrets or other proprietary rights of the PROVIDER, including any altered forms of the MATERIAL made by the PROVIDER. In particular, no express or implied licenses or other rights are provided to use the MATERIAL, MODIFICATIONS, or any related patents of the PROVIDER for COMMERCIAL PURPOSES.

G. If the RECIPIENT desires to use or license the MATERIAL or MODIFICATIONS for COMMERCIAL PURPOSES, the RECIPIENT agrees, in advance of such use, to negotiate in good faith with the PROVIDER to establish the terms of a commercial license. It is understood by the RECIPIENT that the PROVIDER shall have no obligation to grant such a license to the RECIPIENT, and may grant exclusive or non-exclusive commercial licenses to others, or sell or assign all or part of the rights in the MATERIAL to any third party(ies), subject to any pre-existing rights held by others and obligations to the Government of Kenya.

H. The RECIPIENT is free to file patent application(s) claiming inventions made by the RECIPIENT through the use of the MATERIAL, but agrees to notify the PROVIDER upon filing a patent application claiming MODIFICATIONS or method(s) of manufacture or use(s) of the MATERIAL.

I. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. The PROVIDER *makes no representations and extends no warranties of any kind, either expressed or implied. There are no express or implied warranties of merchantability or fitness for a particular purpose, or that the use of the MATERIAL will not infringe any patent, copyright, trademark, or other proprietary rights.*

J. Except to the extent prohibited by law, the RECIPIENT assumes all liability for damages which may arise from its use, storage or disposal of the MATERIAL. The PROVIDER will not be liable to the RECIPIENT for any loss, claim or demand made by the RECIPIENT, or made against the RECIPIENT by any other party, due to or arising from the use of the MATERIAL by the RECIPIENT, except to the extent permitted by law when caused by the gross negligence or willful misconduct of the PROVIDER.

K. This Agreement shall not be interpreted to prevent or delay publication of research findings resulting from the use of the MATERIAL or the MODIFICATIONS. The RECIPIENT SCIENTIST agrees to provide appropriate acknowledgment of the source of the MATERIAL in all publications.

L. The RECIPIENT agrees to use the MATERIAL in compliance with all applicable statutes and regulations, including Public Health Service and National Institutes of Health regulations and guidelines such as, for example, those relating to research involving the use of animals or recombinant DNA.

M. This Agreement will terminate on the earliest of the following dates: (a) when the MATERIAL becomes generally available from third parties, for example, through reagent catalogs or public depositories, or (b) on completion of the RECIPIENT's current research with the MATERIAL, or (c) on thirty (30) days written notice by either party to the other, or (d) on the date specified in an implementing form, provided that:

1. if termination should occur under M(a) above, the RECIPIENT shall be bound to the PROVIDER by the least restrictive terms applicable to the MATERIAL obtained from the then-available sources; and
2. if termination should occur under (b) or (d) above, the RECIPIENT will discontinue its use of the MATERIAL and will, upon direction of the PROVIDER, return or destroy any remaining MATERIAL.

The RECIPIENT, at its discretion, will also either destroy the MODIFICATIONS or remain bound by the terms of this agreement as they apply to MODIFICATIONS; and

3. in the event the PROVIDER terminates this Agreement under M(c) above other than for breach of this Agreement or for cause such as an imminent health risk or patent infringement, the PROVIDER will defer the effective date of termination for a period of up to one year, upon request from the RECIPIENT, to permit completion of research in progress. Upon the effective date of termination, or if requested, the deferred effective date of termination, RECIPIENT will discontinue its use of the MATERIAL and will, upon direction of the PROVIDER, return or destroy any remaining MATERIAL. The RECIPIENT, at its discretion, will also either destroy the MODIFICATIONS or remain bound by the terms of this agreement as they apply to MODIFICATIONS.

N. Paragraphs F, I, and J of these terms and conditions shall survive termination.

O. The MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested by the PROVIDER, the amount will be indicated in an implementing form.

Biological material agreement implementing form

The purpose of this form is to provide a record of the biological material transfer, to memorialize the agreement between the PROVIDER SCIENTIST (identified below), and the RECIPIENT SCIENTIST (identified below) to abide by all terms and conditions of the accompanying Biological Material Transfer Agreement (BMTA), and to certify that the RECIPIENT (identified below) organization has accepted and signed an unmodified copy of the BMTA. The RECIPIENT organization's Authorized Official also will sign this form if the RECIPIENT SCIENTIST is not authorized to certify on behalf of the RECIPIENT organization. The RECIPIENT SCIENTIST (and the Authorized Official of RECIPIENT, if

necessary), should sign three copies of this form and return one signed copy to the PROVIDER. The PROVIDER SCIENTIST will forward the material to the RECIPIENT SCIENTIST upon receipt of the signed copy from the RECIPIENT organization. This implementing form is effective when signed by all parties. The parties executing this form certify that their respective organizations have accepted and signed the copy of the BMTA, initialing where modifications have been negotiated, and further agree to be bound by the terms of the BMTA, for the transfer specified above. Please fill in all of the blank lines below.

Original material: (describe and quantify)

Intended use(s) of the material:

Optional termination date:

Amount of optional transmittal fee: (indicate currency)

Provider (organization providing the ORIGINAL MATERIAL):

a. Name of organization:

b. Address:

c. Signature:

Date:

Provider scientist:

a. Name and title:

b. Address:

d. Signature:

Date:

Recipient scientist:

a. Name and title:

b. Address:

d. Signature:

Date:

8. Recipient organization certification (organization receiving the ORIGINAL MATERIAL):

I hereby certify that the RECIPIENT ORGANIZATION has accepted and signed (initialing modifications) a copy of the BMTA.

a. Name of organization:

b. Address:

c. Signature:

Date:

d. Name and title (recipient):

Glossary

AIDS vaccine	A substance that is introduced into the body (usually orally or by injection) to stimulate the body's immune system to prevent or control HIV infection.
ALVAC-HIV	A genetically engineered HIV vaccine composed of a live, weakened canarypox virus (ALVAC) into which parts of genes for non-infectious components of HIV have been inserted.
canarypox	A virus that infects birds and is used as a live vector for HIV vaccines. It can carry a large quantity of foreign genes. Canarypox virus cannot grow in human cells—an important safety feature.
CD4+ T	Immune cell that carries a marker on its surface known as 'cluster differentiation of 4' (CD4). These cells are the primary target of HIV. Also known as helper T cells.
CD8+ T	Immune cell that carries the 'cluster differentiation of 8' (CD8) marker. CD8+ T cells may be cytotoxic (killer) T cells or suppressor T cells.
clade	Subtype. A group of related HIV viruses classified by their degrees of genetic similarity.
cohort	Group of persons who share one or more characteristics in a research study and who are followed over time.
CTL	Cytotoxic T lymphocyte. Immune system cells that can destroy cancer cells and cells infected with viruses, fungi or certain bacteria.
cytokine	A soluble, hormone-like protein produced by white blood cells that acts as a messenger between cells.
DNA	Deoxyribonucleic acid. The double-stranded, helical molecular chain found within the nucleus of each cell. DNA carries the genetic information that encodes protein and enables cells to reproduce and perform their functions.
ELISA	Enzyme-linked immunoabsorbent assay. A blood test that detects antibodies based on a reaction that leads to detectable colour change in a test tube.
env (envelope) gene	Outer surface of a virus, also called the coat. Not all viruses have an envelope.
epitope	A specific site on an immunogen that stimulates a specific immune response such as the production of antibodies or the activation of immune cells.
gag gene	An HIV gene that codes for p55, the precursor of HIV proteins p7 and p6 that form HIV's core, the inner protein shell surrounding the viral ribonucleic acid (RNA).
gp	Glycoprotein. A protein molecule with a single sugar molecule or branches of such molecules attached to it. Many cellular and viral proteins are glycoproteins, including the outer-coat proteins of HIV. A number after the gp is the molecular weight of the glycoprotein.
HLA	Human leukocyte antigen.

immunogen	A substance capable of provoking an immune response.
immunogenicity	The extent to which an immunogen or vaccine stimulates immune responses.
MHC	Major histocompatibility complex. The gene cluster that controls certain aspects of the immune response. Among the products of these genes are the histocompatibility antigens, such as HLA class I antigen, which are present on every cell with a nucleus and serve as markers to distinguish self from non-self.
placebo	An inactive substance administered to some study participants while others receive the agent under evaluation, to provide a basis for comparison of effects.
seroconversion	Development of antibodies to a particular antigen. When people develop antibodies to HIV or an experimental HIV vaccine they seroconvert from antibody negative to antibody positive.
SHIV	A genetically engineered hybrid virus with an HIV envelope and an SIV core. SHIV is widely used for testing vaccines in monkeys.
SIV	Simian immunodeficiency virus. An HIV-like virus that infects and causes an AIDS-like disease in some species of monkeys.
T cell	CD4 ⁺ T cells and CD8 ⁺ T cells. The T stands for thymus.
<i>tat</i> gene	A regulatory gene whose protein product is not required for but helps regulate viral replication in infected cells.
vaccinia	A cowpox virus, formerly used in human smallpox vaccines. Employed as a vector in HIV vaccines to transport HIV genes into the body.

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DSRS

Department of Standards and
Regulatory Services (DSRS)
Ministry of Health
Afya House, Cathedral Road,
PO Box 30016, Nairobi, Kenya
Tel: +254 20 2717077
Fax: +254 20 2722986
Email: dsrs@africaonline.co.ke
Website: www.dsrs.org