

THE UNITED REPUBLIC OF TANZANIA



MINISTRY OF HEALTH

**NATIONAL HIV VACCINE STRATEGIC
FRAMEWORK**

**(NACP) Dar es Salaam
February, 2005**

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National AIDS Control Programme
Dar es Salaam
February, 2005

Produced by:

Ministry of Health
National AIDS Control Programme
P.O. Box 11857
Dar es Salaam
Tanzania

National HIV Vaccine Strategic Framework

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ABBREVIATIONS

AAVP	-	African Aids Vaccine Programme
AIDS	-	Acquired Immune Deficiency Syndrome
ART	-	Antiretroviral Therapy
ARV	-	Antiretroviral
CAB	-	Community Advisory Board
CDC	-	US Centers for Disease Control and Prevention
COSTECH	-	Tanzania Commission for Science and Technology
CTL	-	CYTOTOXIC T LYMPHOCYTES
DNA	-	Deoxyribonucleic Acid
DSMB	-	Data and Safety Monitoring Board
ELISA	-	Enzyme Linked Immunosorbant Assay
Env	-	Envelope
GCP	-	Good Clinical Practice
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
HIV	-	Human Immunodeficiency Virus
HLA	-	Human Leucocyte Antigen
IAVI	-	International Aids Vaccine Initiative
IRB	-	Institutional Review Board
IT	-	Information Technology
MOH	-	Ministry of Health
MMRP	-	Mbeya Medical Research Project
MRCC	-	Medical Research Coordinating Committee
MNH	-	Muhimbili National Hospital
MUCHS	-	Muhimbili University College of Health Sciences
NACP	-	National AIDS Control Programme
HRESC	-	Health Research Ethics Sub-Committee
NIMR	-	National Institute for Medical Research
NGO	-	Non Governmental Organization
NIH	-	US National Institutes of Health
PI	-	Principal investigator
PLHA	-	People Living with HIV/AIDS
PMTCT	-	Prevention of Mother to Child HIV Transmission
SOP	-	Standard Operating Procedures
STI	-	Sexually Transmitted Infections
TACAIDS	-	Tanzania Commission for AIDs
TFDA	-	Tanzania Food and Drugs Authority
UN	-	United Nations
UNAIDS	-	Joint United Nations Programme on HIV/AIDS
US	-	United States of America
VCT	-	Voluntary Counseling and Testing
WHO	-	World Health Organization

FOREWORD

The continuing high rates of new HIV infections in Tanzania even in regions where falling incidence and prevalence are occurring and the very serious socio-economic impacts of HIV/AIDS in the country emphasize the need for additional biomedical tools such as preventive HIV vaccines and microbicides which are simple, affordable and effective to compliment on-going prevention and control efforts.

It is clear that development and availability of a safe and effective HIV vaccine offers the best and most cost effective strategy for prevention of new HIV infections in the country and throughout the world.

Since HIV vaccine trials began in 1987 more than 30 different HIV vaccine candidates have been tested in phase I and II clinical trials globally and mostly in developed countries. The primary goal of HIV preventive vaccines is to block infection and the secondary goal is to prevent progression of infection to disease (AIDS) through reduction of HIV viral load in the body and by maintaining high immunological status.

It is for this reason that a national workshop involving national and international experts was held in Bagamoyo, Tanzania on 15th – 17th September 2004 to review and improve on a draft National Framework for HIV/AIDS Vaccine Research in Tanzania including addressing key scientific and ethical aspects of conducting HIV Vaccine research and evaluations.

The objectives of the workshop were to review and discuss key points of Tanzania's draft National HIV Vaccine Plan which included:

- Roles and responsibilities of the Government in the promotion, review and regulation of HIV vaccine research.
- Roles and responsibilities of the local scientific and academic institutions and investigators, to ensure participation and sustainability of the process.
- Roles and responsibilities of international partners and investigators on conducting HIV vaccine research in Tanzania consistent with the highest scientific and ethical principles and standards.
- Overview of global HIV vaccine research activities and learn from previous phase I/II/III HIV vaccine trials in Africa and elsewhere.
- Update on HIV vaccine research and plans in Tanzania and
- Key ethical issues and strategies to promote broader community involvement in HIV vaccine research in Tanzania.

The workshop was expected to come up with an understanding that availability of a National HIV Vaccine Strategic Framework was an important step towards expanding national efforts against the HIV/AIDS epidemic. Availability of the framework is expected to provide strategic guidance on how to promote research, development, production and evaluation of safe, cost-effective and accessible HIV vaccines and ensuring the availability of vaccines for the population of Tanzania. Such a framework could also be useful in attracting and motivating international vaccine industry, research collaborators and funding agencies.

The Ministry of Health has a major responsibility of promoting, supporting and coordinating HIV vaccine research and development in the country in collaboration with national and international partners. Accordingly, I thank all those who in one way or the other enabled the workshop to be held and to accomplish its objectives. In particular I thank the WHO-UNAIDS-AAVP, the United Nations Development Programme in Tanzania through TACAIDS and the European Union through the HIVIS Project at MUCHS for financial and technical support to the workshop.



M. J. Mwaffisi
Permanent Secretary
Ministry of Health
February 2005

PREFACE

HIV/AIDS has serious and devastating political, social, economic, health and security consequences. It now threatens people's existence due to illness and death especially among adults in urban and rural areas in Tanzania. Hard won political and social economic gains of the past two decades are being arrested or reversed in life expectancy, education, agriculture, industrial production, business and other key areas of development due to HIV/AIDS. Treatment of HIV/AIDS including access to HAART is not yet readily available to most affected individuals and will therefore be unlikely to suffice in HIV prevention and control.

An AIDS vaccine is therefore urgently required and special efforts to support the development of such a vaccine relevant to Tanzania in the shortest possible period are needed. Participation of the country in vaccine trials requires an HIV vaccine plan in order to provide clear rules on regulatory approval, scientific and ethical reviews as well as monitoring guidelines. Such a plan will also facilitate the provision of human, financial, physical and other resources to implement the identified vaccine research activities.

There are at present on-going HIV-1 Phase I/II trial preparations at several sites in Tanzania including at Muhimbili University College of Health Sciences (MUCHS)/Muhimbili National Hospital (MNH), Mbeya Referral Hospital/Mbeya Medical Research Programme (MMRP)/National Institute for Medical Research (NIMR) and at the Kilimanjaro Christian Medical Centre (KCMC). These are part of on-going global, regional and national efforts to develop appropriate, effective, safe and accessible HIV vaccines within the framework of the HIV vaccine initiative of the World Health Organization (WHO) and the Joint United Nations Programme on AIDS (UNAIDS) and the African AIDS Vaccine Programme (WHO-UNAIDS-AAVP).

The WHO-UNAIDS-AAVP provided strategic and technical support to the workshop to develop Tanzania's HIV vaccine framework. Through the collaboration in the workshop which involved representatives from the Tanzania Government and several national institutions and international partner organizations, Tanzania's HIV Vaccine Framework based on the National HIV Vaccine Plan Template of WHO-UNAIDS-AAVP was finalized.

The workshop was opened by the Deputy Minister for Health, the Honorable Dr. Hussein Mwinyi on 15th September, 2004 by welcoming all participants representing the WHO – UNAIDS- AAVP, HIV Vaccine researchers from Walter Reed Army Institute in the USA, representatives of research institutions in Sweden, Kenya AIDS Vaccine Initiative (KAVI), International AIDS Vaccine Initiative (IAVI) based in Kenya, Makerere University Medical School, Uganda and experts involved in AIDS research, prevention and control from the United Republic of Tanzania.

The Deputy Minister for Health commended the HIV Vaccine research activities which had been going on in Tanzania in partnership with the International Scientific Community and challenged the workshop participants to finalize the National HIV Vaccine Framework for Tanzania.

At the end of the workshop the participants unanimously committed themselves to the finalization of the draft National Strategic Plan and agreed to the establishment of a working group to be called "Tanzania AIDS Vaccine Initiative (TAVI)" to come up with activity plans to implement the mission of the National HIV Vaccine Framework for Tanzania. The vaccine framework includes HIV Vaccine research priority needs, key ethical issues and strategies to enable community participation in vaccine research and evaluation.

The workshop was organized by the National AIDS Control Programme (NACP) in the Ministry of Health in collaboration with the Muhimbili University College of Health Sciences (MUCHS), Tanzania Commission for AIDS (TACAIDS) and the National Institute for Medical Research (NIMR), the Tanzania Foods and Drugs Authority (TFDA) and the Tanzania Commission for Science and Technology (COSTECH). It was sponsored by the WHO-UNAIDS-AAVP, MUCHS – HIVIS Project and TACAIDS/UNDP.

It was attended by 63 Tanzanian scientists, policy makers and public health experts from Tanzania mainland and Zanzibar including representatives of AIDS Service Organizations and AIDS Civil Societies as well as representatives of People Living with HIV/AIDS (PLHAs). Four mass media organizations were represented by 4 journalists and photographers who were invited to the workshop and provided wide publicity. The workshop was also attended by 11 representatives from the WHO-UNAIDS, WHO-AFRO, the Walter Reed Army Institute of the USA and scientists from Universities in Sweden, Uganda and Kenya.

The Executive Chairman, TACAIDS Major General H. Lupogo (Rtd) closed the workshop, emphasizing multisectoral efforts in HIV prevention, control, impact mitigation and care to reduce the impact of HIV/AIDS in the country.

The workshop would not have succeeded without the efforts of the members of the Organizing Committee, including support from the Ministry of Health, MUCHS-HIVIS Project, TACAIDS/UNDP, WHO Country office and all participants at the workshop who were highly committed for the production of the National HIV Vaccine Framework (Plan) for Tanzania.



Dr. Rowland Swai,
Programme Manager
National AIDS Control (MOH) and Chairman of the
Workshop Organizing Committee

ACKNOWLEDGEMENTS:

The Ministry of Health and Tanzania Commission for AIDS acknowledges with thanks the support and contributions of the World Health Organization and the Joint United National AIDS Programme and the African AIDS Vaccine Programme as well as the United Nations Development Programme in Tanzania and the Muhimbili University College of Health Sciences through Project support from the European Union to the HIV Immunogenicity Study (HIVIS) for contributing financially to the Development of the Tanzania National Vaccine Strategic framework.

Special thanks go to the international experts from the WHO-UNAIDS, Geneva and WHO-AFRO Harare, from Sweden, the USA, Kenya and Uganda for agreeing to participate at the workshop for the development of Tanzania's HIV vaccine strategic framework. We also thank the various Tanzanians who contributed their ideas in shaping the Tanzanian's strategic framework.

The development of the Strategic framework would not have been possible without the contributions of various individuals who constituted the secretariat and participated at the workshop, which developed the strategic framework.

NATIONAL STRATEGIC FRAMEWORK FOR HIV VACCINE DEVELOPMENT, UNITED REPUBLIC OF TANZANIA

EXECUTIVE SUMMARY

Purpose of Document

This document is a publication of the Government of the United Republic of Tanzania developed in collaboration with WHO-UNAIDS and the African AIDS Vaccine Programme. The purpose of the document is to provide guidance to Government sectors and scientific groups in Tanzania working with international and national stakeholders, civil societies and communities and non-Government organizations in the development and evaluation of candidate HIV vaccines relevant to Tanzania.

This guidance document is to be used by authorities responsible for the approval coordination and supervision of the conduct of HIV vaccine trials in the country. It provides a useful resource to members of scientific and ethics review committees as well as to national drug regulatory and biosafety authorities in regulating HIV vaccine development and trials in the country.

Magnitude of the HIV epidemic in Tanzania

AIDS has had a serious negative impact on the Tanzania population more than any other epidemic. Using prevalence figures among blood donors and the 2002 census data to estimate the year 2002 burden of HIV infection in Tanzania mainland, the following estimates are realized. A total of 1,894,160 individuals (791,318 males and 1,102,842 females) aged 15 years and above were living with HIV in Tanzania during the year 2002. Of these, 1,665,309 (672,825 males and 992,484 females) were aged between 15-49 years. Regarding youths aged 15-24 years who constitute 20% of the total Tanzania mainland population, a total of 566,129 of them were HIV infected. Of these, 214,918 were males and 351,211 were females.

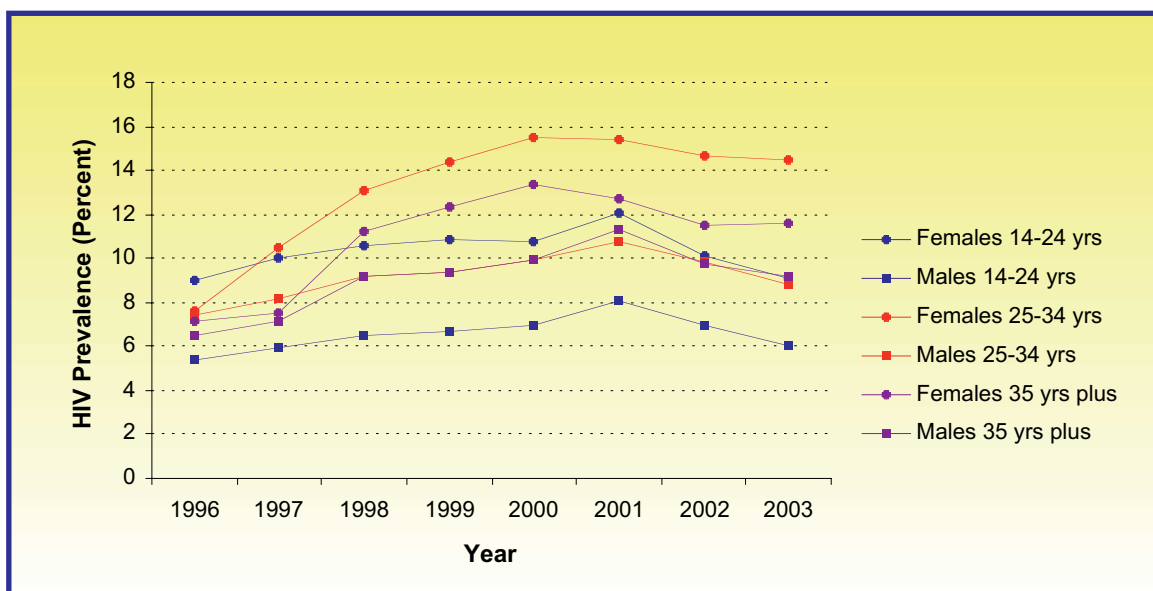


Fig1: Trends of HIV prevalence among blood donors in Tanzania 1996-2003

The potential role of an effective vaccine in control of the HIV epidemic

The current responses to the epidemic include preventive education and behavior change strategies as well as voluntary counseling and testing and treatment, care and support interventions, measures which have led to reduction in the prevalence and incidence of HIV in some populations in the country as

well as mitigating the impact of the epidemic. However, there is a need for more effective measures to further “control the epidemic.” An effective vaccine against HIV is one intervention that is likely to have the ultimate effect of controlling the epidemic.

Current efforts to develop a HIV Vaccine

Since the first Human HIV vaccine trial in 1987, more than 30 different HIV vaccine candidates have been tested in several phase I and II clinical trials globally. Only two HIV vaccine candidates (VAXGEN vaccine) has been through phase III trial both in the USA and in Thailand. Although safe, the candidate vaccine failed to confer protective efficacy among trial participants.

Most HIV vaccine trials have been done in the USA and Europe with very few conducted in Africa where HIV infection rates and the burden of disease are the highest. Only 4 countries have conducted phase I and II vaccine trials in Africa to date (Uganda, Kenya, S. Africa and Botswana). Other African countries (Cameroon, Cote d’Ivoire, Malawi, Nigeria, Rwanda and Tanzania) in collaboration with international partners are getting prepared to initiate HIV vaccine trials.

Various other African countries are at different levels of planning to conduct HIV vaccine trials such as Burkina Faso, Central African Republic, Ethiopia, Gabon, Ghana, Senegal, Zambia and Zimbabwe.

Role of the Government, Political Leaders and Policy Makers

Political support is important for the success of any HIV vaccine development. The Government will provide an enabling environment for the researchers, their collaborators and funding agencies. It is important for political leaders at all levels from the top down to the grassroot levels, cultural and religious leaders to be adequately informed and consulted at all stages of the vaccine development.

Political leaders play a critical role in communicating the relevant messages to the populations as well as in mobilizing the community for participation in national HIV vaccine development.

It is important to realize that early vaccines may not be 100% effective and must therefore, complement, not displace ongoing prevention, control, treatment, care and support programs. Also, vaccine development is a long-term goal which requires long-term financial, scientific, political and societal commitment and resources over many years. It is important to ensure that the public does not receive mixed messages in this regard. Emphasis need to be placed on the fact that prevention is still an integral part of the strategy of combating HIV/AIDS.

Role of Regional and Sub-regional Intergovernmental organizations in Tanzania’s

National AIDS Vaccine Strategic framework

Regional and sub-regional intergovernmental organizations in Africa such as the African Union (AU), East African Community (EAC), Southern Africa Development Community (SADC), and Economic Community of West African States (ECOWAS), Central African Community (CEMAC), may be able to provide the strength and support for the development of HIV vaccine/s through partnership and collaboration, and sharing of lessons learnt among different African countries. Other ways of collaboration is through sharing of resources, both material and human, as well as facilitation and support of multi-centre clinical trials. The use of existing centers of vaccine research and supporting them to become regional centers of excellence would be extremely beneficial to countries with vaccine programs.

The need for an HIV vaccine for Tanzania

The continuing high rates of new HIV infections in Tanzania even in regions such as Kagera and Mbeya where falling incidence and prevalence are occurring emphasize the need for additional biomedical tools such as preventive HIV vaccines and microbicides which are simple, affordable and effective to complement ongoing efforts. It is clear that development and availability of a safe and effective HIV vaccine offers the best and most cost-effective strategy for prevention of new HIV infections in the country and will contribute significantly to efforts in poverty alleviation.

An AIDS vaccine is urgently required for Africa for the following reasons:

- AIDS has serious and devastating social, economic, health and security consequences and is threatening our own existence in Africa.
- Treatment care and support for HIV/AIDS including access to HAART is not yet readily available to most affected individuals in Africa and will never suffice in HIV prevention and control.
- Private sector market driven HIV vaccine research and development is not attractive to making vaccine relevant to developing countries including Africa and special initiatives are needed to support vaccine development for use in developing countries.

Why Conduct vaccine Trials in Tanzania

It is important to conduct HIV vaccine trials in Tanzania for various reasons including the large number of new infections occurring in the country so that an effective vaccine would eventually have the most benefit. The high variability of HIV in the country necessitates testing of vaccine candidates in different areas of the country where different subtypes are prevalent. It is also necessary to evaluate how different routes of transmission and other cofactors as well as host genetic background influence vaccine-induced protection. In addition, licensing of HIV vaccines by the regulatory body will require prior trials in the country.

Other compelling reasons for Tanzania's participation are as follows:

- Discovery of an HIV vaccine in developed and other developing countries may not be generalized and is likely to take a long time to trickle down to Tanzania.
- HIV vaccine trials provide opportunities to study diverse population groups in highly endemic areas, against a multiplicity of HIV subtypes found in the country.
- Infrastructure and capacity developed for vaccine research would serve for other relevant interventions such as microbicide research, provision of HAART and for research in other priority infectious diseases in the country.

Need for a National HIV vaccine Plan/Strategic Framework

There are several reasons that can be advanced as to why Tanzania should have a vaccine strategic framework. Participation in vaccine trials involves collaboration between various national and international players and stakeholders. In addition the necessary research and related activities require multi-disciplinary team work with stringent regulatory guidelines and control. A national strategic framework provides a medium for expressing a consensus position on the country's strategies for development and evaluation of candidate vaccines. By providing clear rules on regulatory approval, scientific and ethical reviews, biosafety as well as monitoring guidelines, such a plan is likely to attract the vaccine industry, research collaborators and funding agencies who may wish to contribute in the form of candidate vaccine products, building local infrastructure or transferring knowledge and technology.

1.0 BACKGROUND

1.1 The HIV epidemic in Tanzania and the need for an HIV Vaccine

Only twenty-one years after its recognition, HIV/AIDS has become the most important infectious disease and the leading cause of death in Tanzania. Approximately 800,000 people have developed AIDS between 1983 and 2002 and more than 80% of these are estimated to have died during the period.

In sub-Saharan Africa, which is home to more than 28 million infected people, the average HIV prevalence in the adult population is 8.8%. There are seven countries, all in southern Africa (Botswana, Malawi, Namibia, South Africa, Swaziland, Zambia and Zimbabwe), in which more than 20% of the adults are already infected with HIV, and in nine other African countries including Tanzania the HIV prevalence is between 10% and 20%.

It is evident from recent data that current measures of HIV prevention and care have had a positive impact on HIV/AIDS incidence, prevalence and clinical presentation. However, despite recent positive trends of falling prevalence among young people, particularly young women in Kagera and Mbeya regions, overall about twice as many young women as men are infected in Tanzania. Although there are several factors contributing to this high HIV prevalence, it is clear that an HIV vaccine could be a major contribution to prevent HIV infections among young people in Tanzania.

The development of a safe and highly effective HIV vaccine will require the conduct of multiple clinical trials to assess the protective efficacy of different vaccine concepts, against different HIV subtypes, and in diverse populations which may differ in the routes of virus transmission, as well as in their genetic, nutritional or health backgrounds. To address these questions, multiple phase III trials will have to be conducted in both industrialized and developing countries and this will require intense international cooperation and collaboration.

Vaccine research and trials in Tanzania and in other developing countries are necessary because: (a) the large number of infections occurring in the country, where an effective vaccine would eventually have the most benefit; (b) phase III trials need to be conducted in populations with relatively high incidence of HIV infection which, unfortunately, are found in the country; (c) the variability of HIV may necessitate testing of candidate vaccines in different areas of the country where different strains are prevalent; (d) it may be necessary to evaluate how different routes and/or cofactors for HIV transmission and host genetic background could influence vaccine-induced protection; and (e) relevant research from different parts of the country with similar epidemiologic conditions may facilitate licensing and fulfillment of regulatory requirements.

1.2 Challenges and opportunities for development of an HIV vaccine

1.2.1 Scientific Challenges and opportunities for development of an HIV vaccine

Soon after the identification of HIV as the cause of AIDS, the search for an HIV vaccine began nearly twenty years ago with great optimism. This optimism was based partly on recognition that some individuals were resisting infection despite exposure and others who were infected were capable of remaining relatively healthy despite persistent infection (non-progressors). However, progress has not matched the initial hopes despite a large concerted effort. The development of an HIV vaccine has encountered a number of scientific, financial and logistical

challenges. Some of the scientific challenges 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 ideal animal 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 the immune defences to other microbes, and in the response to vaccines. AIDS differs from other vaccine-preventable diseases in that HIV infection may persist, and AIDS may develop, despite a broad range of immune responses from the host. Therefore, the major conceptual problem for HIV vaccine development is the lack of information on immune responses known to correlate with protection against HIV or AIDS.

Another potential obstacle for the development of broadly protective HIV vaccines is related to the extensive genetic variability of the virus which is further compounded by the high mutation rate in an infected individual. 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 sub-divided into at least nine pure genetic subtypes or clades (A-D, F-H, J and K). Strains belonging to the same subtype can differ by up to 20% in their *env* sequences, whereas the differences between subtypes can be up to 35%. The analysis of other HIV-1 genes demonstrated a higher degree of conservation, which for the gag gene, that codes for the HIV core proteins, is between 85-90%. Full-length genome sequence of HIV-1 has also revealed frequent inter and intra-sub-type 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.

In the year 2000, it was estimated that most of the new HIV infections in the world, approximately 47% of them, were caused by subtype C virus, which are mostly prevalent in Southern Africa, Ethiopia and India. Subtype B viruses are prevalent in the Americas and Western Europe, while sub-types A and D are prevalent in Central and Eastern Africa. It is important, to emphasize, however, that HIV is constantly evolving, increasing the genetic distance between strains and generating new inter and intra-sub-type recombinant viruses.

In Tanzania subtype C, A and D as well recombinants of these three are found. The key question is: Is there a need to develop candidate vaccines specific for each HIV subtype, or would it be possible to design immunogens capable of inducing broad cross-clade protective immunity?

The *env* gene codes for gp120 and gp41 which are responsible for the induction of 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 the induction of cytotoxic T lymphocytes (CTLs) against gag gene products and other relatively conserved HIV-1 proteins, are usually assumed to be more cross-reactive, offering a hope for the development of broadly protective vaccines. Immune responses to CTL epitopes, however, are restricted by the HLA makeup of the host, and this may require the design of specific candidate vaccines for use in different populations.

In addition, HIV strains also exhibit significant biological differences. The most relevant observation for HIV 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, and they were found to induce antibodies capable of neutralizing X4 viruses, with only negligible ability to neutralize R5 strains, which are considered to be more clinically and epidemiologically relevant. For that reason, new generations of envelope based vaccines are also including antigens derived from R5 viruses.

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 the use of cocktail vaccines containing antigens representative of several genetic subtypes, the design of candidate vaccines targeting at conserved HIV epitopes, or candidate vaccines based on consensus or ancestor sequences selected to minimize the genetic differences between vaccine strains and contemporary isolates.

1.2.2 Socio-cultural and political challenges to development of a HIV vaccine

Social challenges to HIV vaccine trials include seroconversion of study participants to a positive commercial HIV serological test as a result of the vaccine. This may have a negative impact on future health and life insurance, employment, immigration and marriage prospects. Vaccine study participants may be liable to increased risky sexual behavior as a result of a belief that the study vaccine has life long protective effects. This would have a considerably adverse effect on the current HIV preventive strategies.

Political issues regarding exploitation (guinea pig assertion) of the study populations, and future assurance to access to a successful vaccine candidate need to be addressed. There should be equal partnerships between the local investigators and the sponsoring or partner investigators. The research should promote collaboration between governments and institutions, including universities and research organizations in developing and industrialized countries. Of equal importance the need to involve women and men equally in HIV vaccine research and trials is paramount to ensure that both genders will benefit from a future vaccine.

1.3 Process of vaccine development and evaluation

Despite the scientific uncertainties described above, a wide range of candidate vaccines have been developed and tested in animal models and in humans. Before a candidate HIV vaccine is evaluated in humans, tests to assess the safety, toxicity, and immunogenicity of the vaccine are conducted in small animals, and or non-human primates. The efficacy of a vaccine can also generally be assessed to a limited degree in these non-human primates. This can be done by vaccinating chimpanzees with HIV vaccines and challenging them experimentally with HIV, or 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 SIV core).

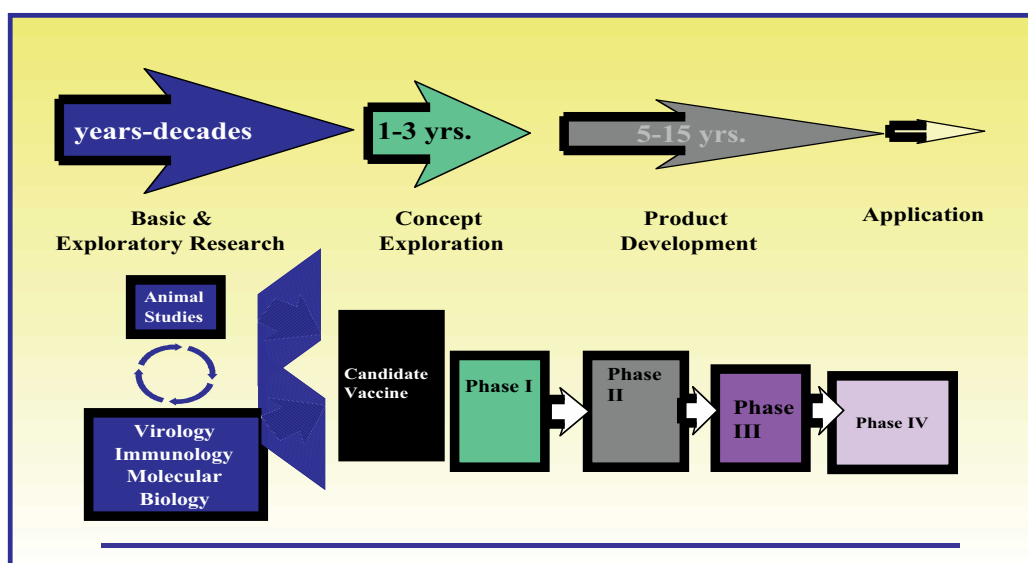
Several experimental vaccines have induced different degrees of protection in primate models. It is important to note that most experimental vaccines tested in macaques have failed to fully protect against infection (“sterilizing immunity”). Instead, such vaccines just mediate an attenuation of the infection, through reduction of virus load and consequent slower progression to disease in immunized animals which 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 animal results will be predictive of vaccine-induced protection in humans. Such information will only be obtained 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. Phase I trials primarily provide safety data (and occasionally preliminary immunogenicity data), and are conducted among small numbers of volunteers (20 to 50) at low risk of HIV infection. Phase II safety and immunogenicity trials are conducted in about 100-200 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 the results obtained, 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 challenges. Post marketing, phase IV, studies provide additional safety data and effectiveness data, and are especially important for identification of rare adverse events. Although the various phases of clinical trials are described above as distinct, in reality, the phases often overlap. The decision to progress through these phases of vaccine evaluation should be based on pre-established agreed criteria.

Table 1: Phases of HIV Vaccine Trials

Phase	Sample Size	Sample Characteristics	Endpoints	Duration
I	20-50	Healthy, HIV-uninfected at lower risk for HIV-infection; dose, regimen	<ul style="list-style-type: none"> • Safety • Preliminary Immunogenicity 	18-24 months
II	200-500	(Healthy), HIV-uninfected at lower to higher risk, dose; regimen	<ul style="list-style-type: none"> • Safety • Immunogenicity 	18-24 months
III	5000-10.000	HIV-uninfected, at risk (CSW, discordant couples, general population)	<ul style="list-style-type: none"> • Expanded safety • Efficacy • Correlates of protection 	3-5 years
IV				

Figure 1: HIV Vaccine Development and Evaluation Process



1.4 Key issues regarding evolution of vaccine concepts and approaches

A variety of HIV vaccine approaches (or vaccine concepts) have been tested in three successive overlapping “waves” which have been dominated by different vaccine development paradigms.

The first “wave” of candidate HIV 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. With the elucidation of the co-receptor use by different strains of HIV-1, novel envelope candidate vaccines also included in their design envelopes from primary isolates (R5 strains) of HIV.

Envelope-based candidate vaccines were found to be safe and immunogenic in diverse populations, inducing neutralizing antibodies in essentially 100% of the volunteers, but not cytotoxic T lymphocytes (CD8+ CTL's). 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. In addition, reflecting the variability of the gp120 molecules, those neutralizing antibodies are subtype-specific, with little cross-reactivity with other subtypes.

The second “wave” of HIV vaccine research and trials started in the mid-1990's with the recognition of the importance of CD8+ T-cell responses in the control of HIV infection. This paradigm led to the development (or refinement) of live recombinant viral vectors, especially poxvirus vectors, capable of delivering HIV-1 antigens in the context of the MHC class 1 pathway. Prime examples of this approach have been the development of different constructs using replication-defective canarypox-HIV recombinant vectors from Aventis Pasteur, collectively known as ALVAC-HIV.

Most trials with the above 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 paradigm include the use of the attenuated Modified Vaccinia Ankara (MVA) virus as a vector, usually in combination with DNA, different types of DNA vaccines and lipopeptide vaccines.

The third “wave” of HIV vaccines started at the beginning of the new century. It aims at optimizing immune responses to existing, or yet to be developed, candidate vaccines. The goals of this new “wave” of HIV vaccine research would be 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 of these novel candidate vaccines is represented by a recently described replication incompetent Adenovirus type 5 vector developed by Merck, which in a DNA-prime/Adenovirus-boost regimen in the SHIV/maaque model induced high levels of CTLs, resulting in marked attenuation of infection after challenge. Initial data from human trials with this candidate vaccine confirmed its ability to induce 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 of HIV or novel genetic vaccine designs.

1.5 International efforts in HIV vaccine evaluation

In many countries, development of candidate HIV vaccines are at an advanced stage, with some already evaluated in clinical trials. The first human trial of an HIV vaccine was conducted in the United States in 1987. Since then, more than 30 different HIV candidate vaccines have been tested in more than 80 phase I/II trials. The first phase I/II vaccine trial in a developing country was conducted in China in 1993. Since then, 20 phase I/II trials have been completed in developing countries, the majority in Thailand (9 trials), but also in Brazil, Cuba, Haiti, Kenya, Peru, Trinidad, and Uganda. (Table II). In other African countries, several efforts are being made to develop suitable HIV vaccines. These research activities are either being carried out in laboratories located within the continent, or are in collaboration with researchers working in laboratories outside the continent (Table III).

Table II: HIV 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, and Thailand
1997-1998	Envelope based candidate vaccines (gp120)	B, E	Thailand
1999-2002	Canarypox and Modified Vaccinia Ankara vectors, DNA constructs, and prime-boost combinations.	B, E, A	Brazil, Haiti, Kenya, Peru, Thailand, Trinidad and Uganda.
2003	Multiepitope DNA vaccine, Adenovirus vectored, VEE vectored, DNA/MVA.	Multi-clade, B, C	Several countries in Africa, Asia and the Americas

Only four phase I/II HIV vaccine trials have been conducted in Africa. The first one, conducted in Uganda in 1999, was sponsored by the National Institute of Health (NIH) of the United States. In this ALVAC-HIV preventative HIV vaccine study, a canary pox vector containing HIV-1 clade B antigens was used. Immunogenicity was low but the vaccine elicited CD8+T-cell responses with detectable cross-activity against clade A and D antigens in a significant proportion of vaccine-recipients. Three other trials were sponsored by the International AIDS Vaccine Initiative (IAVI) and were conducted in Kenya in 2001 and 2002, and an on-going one in Uganda. The vaccine concept being evaluated is

based on a prime-boost combination using DNA and MVA candidate vaccines expressing a number of genes from clade A HIV-1 strain.

In addition to IAVI, other agencies and institutions that are increasing their HIV vaccine preparedness activities in African countries include the NIH-sponsored HIV Vaccine Trials Network, the US Centers for Disease Control and Prevention, the US Military HIV Research Program, the French Agency for Research on AIDS (ANRS), the Harvard AIDS Institute, the European Union and others.

Table III African countries with ongoing HIV/AIDS vaccine research activities

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

The first phase III HIV 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. Preliminary results from the North American trial became available in February 2003, and they showed that the vaccine failed to confer protective efficacy in the majority of the population. A preliminary subset analysis of less than 10% of the enrolled volunteers, suggested vaccine efficacy among black volunteers, however the interpretation of those data are still being debated. The data also suggest that women produced higher levels of antibodies than men and that vaccinated volunteers preferentially excluded viruses resembling vaccine antigens (virus sieving). Those results are controversial and additional data are needed before a definitive conclusion can be reached. Preliminary results from the Thai trial indicate that the vaccine failed to confer protection. The next phase III trial, with a different vaccine regimen, is planned to start in Thailand in 2003, with definitive results expected in 2008.

2.0 NATIONAL HIV VACCINE PLANS/ FRAMEWORK

2.1 Vision

Availability of effective, safe, affordable and accessible HIV vaccines for the benefit of all Tanzanians.

2.2 Mission

To promote research, development, production and evaluation of suitable HIV vaccines and ensure sufficient availability of the vaccine in an equitable way for the entire needy population of the country, through national, regional and international collaboration.

2.3 Objectives of developing an HIV vaccine are:

2.3.1 Main objective

2.3.1.1 To prevent HIV infection in HIV-uninfected persons.

2.3.2 Secondary objectives (where infection still occurs after vaccinations)

2.3.2.1 To prevent or delay progression of disease.

2.3.2.2 To reduce the transmission of HIV infection from infected persons to their sexual contacts.

2.3.2.3 To reduce transmission of the infection from mother to the child.

2.4 National HIV strategic framework

Tanzania needs a National HIV Vaccine Strategic framework because. Apart from providing an opportunity to build consensus in the country, such a strategic framework could be presented to international partners and agencies for collaboration and support. By providing clear rules of the game, a National HIV Vaccine Strategic framework is likely to attract partners who will be assured that there are clear guidelines and no ad hoc decisions.

2.4.1 Objectives of the National HIV strategic framework:

2.4.1.1 To facilitate the development of a vaccine that either prevent HIV infection or delay progression of disease.

2.4.1.2 To build national consensus on a comprehensive, well co-ordinated, long-term strategy for the development and evaluation of safe, immunogenic, efficacious and affordable preventive, therapeutic and perinatal HIV vaccines.

2.4.1.3 To develop and provide legal framework for regulatory approval, manufacture and licensing of HIV vaccine products

2.4.1.4 To provide guidelines for scientific and ethical review of HIV vaccine trial proposals and protocols.

2.4.1.5 To provide guidelines for monitoring the conduct of HIV vaccine trials according to scientifically and ethically acceptable standards.

2.4.1.6 To propose ways and means of building local infrastructure, and transferring knowledge and technology.

2.4.1.7 To propose ways and means of ensuring availability and accessibility of an efficacious vaccine to the general population.

- 2.4.1.8 To ensure community awareness and participation in HIV vaccine trials
- 2.4.1.9 To develop post-HIV vaccine trial follow-up plan on care and support services

STRATEGIES

Strategies to achieve the above objectives include:

- Developing clear national policy and implementation guidelines regarding vaccine development, research, evaluation and utilization.
- Identifying national and international research institutions and other organisations, including vaccine manufacturers, that are willing to collaborate and have the capacity to participate in the conduct of HIV vaccine-related research and evaluation with the United Republic of Tanzania.
- Identifying potential population cohorts suitable for evaluation of promising HIV candidate vaccines.
- Mobilization of national resources.
- Evaluating national institutions for ability to conduct the relevant research and where necessary improve infrastructure/communication and provide training.
- Collaborating with relevant partners and donor agencies for technical, financial and logistic support (e.g. WHO-UNAIDS, IAVI, African AIDS Vaccine Program etc.)
- Periodically evaluating the progress of the Plan.
- Update stakeholders on the progress of vaccine development.
- Assessing 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 logistical support.

2.5 Essential elements of the National HIV Vaccine Strategic framework include:

- Political, Socio-cultural and Policy Issues in HIV Vaccine Development and Evaluation
- Regulatory Approval Process
- Scientific and Ethical Review According to National Guidelines
- Biosafety and environmental safety assurance
- Multi-disciplinary Research Activities in Preparation for HIV Vaccine Trials
- Implementation Issues in Phase I/II/III and IV Vaccine Trials
- Operational and Logistical Issues

3.0 POLITICAL, SOCIAL AND POLICY ISSUES ON HIV VACCINE DEVELOPMENT AND EVALUATION

3.1 Political commitment and involvement

Political support is both important and critical for the success of any HIV vaccine trial. It provides an enabling environment for the researchers and their collaborators or funding agencies as well as re-assurance for the potential study volunteers. Strong political commitment and involvement are, therefore, key to the success of HIV vaccine trials. The National Vaccine Strategic framework will solicit the commitment of various political, administrative and community leaders in the Country.

“Political” refers to levels of influence that cover not only politicians but all types of leaders. The National vaccine strategic framework will ensure that it has raised political awareness on the importance and process of HIV vaccine research; so that the politicians can be relied upon to communicate relevant messages to the people they lead. This is because there is limited ability of individuals or groups in the community to fully appreciate and understand the research process including the importance of the informed consent process, and all the other ethical issues involved. The leaders will be adequately informed and consulted at all stages before, during and after conducting any vaccine trial. The focus should be for their involvement in facilitating scientific progress, education and advocacy, and creating a supportive environment for Tanzania’s participation in HIV vaccine development. Specific target groups may include, but are not limited to, lawyers, activists, journalists, social scientists, health workers, religious and cultural leaders, people living with HIV/AIDS, epidemiologists, gender activists, youth, vaccine scientists, and political leaders at all levels of government (from lower level local leaders to heads of state), with active and equitable involvement of women, men and youths at all stages of vaccine development and among trial volunteers.

Building Political Support and Commitment for HIV Vaccine Research through:

- Identifying government bodies responsible for forming policies and giving advice on HIV/AIDS
- Identifying the key members in those bodies who have high level of awareness of issues related to research and HIV/AIDS
- Initiating open and honest discussions with key policy makers and other stakeholders and provide comprehensive information on the proposed research for their review prior to the meeting. This meeting could include members of the scientific community who act as advisors to policy makers
- Providing information covering all aspects of risk/benefit to individuals, communities, and the country.
- Developing a strategy for approaching gradually widening circles of opinion leaders and stakeholders, e.g., for politicians from Ministers and parliamentarians (through the Tanzania Parliamentary AIDS Coalition-TAPAC) to community leaders. Stakeholders include key members of scientific and medical community and can expand to NGO’s and health professionals.
- Providing regular relevant and timely updates to appropriate government bodies and stakeholders.
- Demonstrating sensitivity to national decision-making processes and policies.

- Developing media strategy to ensure that key policy makers and advisors are informed before the media rather than through the media.
- Advocating with national leadership for inclusion of HIV/AIDS vaccine development in the national priorities and overall national strategy for HIV/AIDS.
- Advocating with the national leadership for inclusion of the HIV/AIDS vaccine strategic framework as a priority in the national political agenda.

3.2 Social mobilization

3.2.1 Community support and participation

Communities have the right and responsibility to take decisions regarding the nature of their participation in HIV vaccine research. Strategies should therefore be developed to inform and educate communities from which participants for vaccine trials are to be drawn.

To ensure the ethical and scientific quality of the proposed research, its relevance to the affected community, and its acceptance, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research. PLWHA and Non-Government Organisations (NGO's) involved in AIDS work should be consulted during the planning and implementation phases of the trials. Bias against participation of women and youth must be addressed, with the ultimate goal of removing barriers to their participation. The rights and responsibilities of vaccine volunteers must also be formally addressed.

There will be established within the strategic framework, a continuing forum for communication, consensus building and problem-solving on all aspects of vaccine development from phase I through phase III and beyond, to the distribution of a safe and effective, licensed vaccine. This forum will address such issues as public and media misconceptions and reports. All participating parties should be able to define and understand this ongoing relationship.

For a vaccine trial to start, community members, policy makers, ethicists and investigators in the country should have determined that their residents are adequately protected from harm or exploitation, and that the vaccine development programme is necessary for and responsive to the health needs and priorities in their country.

Attention should be given to how a successful vaccine, and other benefits resulting from the research, will be made readily and affordably available to the communities and country where such a vaccine is tested, as well as to other communities and countries at high risk of HIV infection. This process of discussion and negotiation should start as soon as possible, before the trials start, and be carried out through the course of the research.

3.2.2. Role of a Community Advisory Board

As part of a process to facilitate dialogue between community members, study volunteers and researchers, a Community Advisory Board (CAB) should be created. There should be dialogue, to and from the CABs, in order to provide at least the following:

Information regarding health beliefs of the study population,

- Information about community concerns regarding vaccine research,
- Input into the design of the protocol including the appropriate informed consent process to ensure cultural sensitivity,
- Advice on effective methods for disseminating information about the trial and its outcomes,

- Information to the community at large on the proposed research,
- Create trust between community and researchers,
- Advice on equity in choice of participants.

CAB members should be identified by the community where the trial is expected to take place in consultation with the local investigator or principal investigator designee. Their role and expectations should be clearly stated in their term of references. The board can be made of 10 to 15 members and should include a study team member for coordination. The CAB should elect a chair and secretariat and should decide on ways to operate (frequency of meetings, termination of participation, etc.). The CAB should be assisted (venue, meals, transportation cost, correspondence) by study investigators to fulfill its role.

Community advisory board membership should include people who can understand the study, as well as those who know the local cultures and community perspectives.

Members could include:

- Human right activist
- People with understanding of laws and ethics of the community
- Gender advocacy group representative
- Youth group representative
- Role models
- Religious leaders
- People leaving with HIV/AIDS
- Representative of trial participants

3.2.3 Information dissemination to the media and the public

Lack of information to the media and/or the public inevitably leads to misinformation. It is essential to have an information strategy for the scientific community, the media, the public and the volunteers. Continuous education efforts should be directed at the media, providing them with regular updates on various aspects of the trial, including progress reports. The media should be actively involved throughout the vaccine research process, from planning to implementation, in order to accurately inform the population. A community advisory board will provide a very useful link between researchers and the public. Focus group discussions will provide an outlet for trial volunteers to report their problems and concerns and to receive information about other trials in the country. A strategy for advocacy, consensus seeking as well as information dissemination should therefore, be in place before trial initiation. In order to provide a unified and consistent message, an information desk to correct misinformation appearing in the electronic or printed media and to issue periodic bulletins should be set up either in the Ministry of Health or the Ministry of Information. Additionally, researchers should be trained and briefed to adequately prepare them to effectively and accurately interact with the media.

3.3 Policy Issues

3.3.1 Role of the Tanzania Government

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

- Assure political commitment to support the vaccine effort
- Develop and disseminate a policy statement regarding the critical importance of the development and evaluation of HIV vaccines

- Specifically address HIV vaccines as an integral part of the HIV/AIDS Multi-Sectoral Strategic Plans
- Provide a favorable environment conducive to collaborative research.
- Establish a legal framework protecting trial participants against exploitation and stigmatization by ensuring adequate compensation in case of injury and providing protection for vaccine trial volunteers against discrimination in insurance, employment and immigration.
- Empower the Foods and Drugs Authority for regulatory approval, registration of candidate vaccines and licensing of new vaccine products as well as inspection and certification of vaccine manufacturers. This body would develop criteria for selection of suitable HIV vaccine candidates for development and evaluation as well as guidelines for vetting vaccine manufacturing companies.
- Empower a designated government body responsible for policy planning, coordinating and overseeing HIV/AIDS vaccine related research activities, including the development of guidelines for scientific and ethical review of research proposals.
- Empower a Biosafety and Environmental Impact Assurance Body to process candidate HIV vaccines
- Participate in mobilization of communities to participate in trials.
- Provide appropriate legal framework regarding researcher liability and protection of research subjects.
- Develop or support means to cover researchers appropriately from exposure to litigation.
- Be willing to work with sponsors on long-term basis from phase I through phase IV studies.
- Ensure provision of infrastructure and personnel required for the successful transfer of technology.
- Promote regulations that ensure the transfer of technology in HIV vaccine research.
- Interact with vaccine manufacturers or vaccine trial sponsors to:
 - Ensure study participants' insurance and liability coverage
 - Ensure provision of suitable candidate vaccines for trials
 - Ensure availability and affordability of safe and effective vaccines

3.3.2 Involvement of Regional and Sub-regional Inter-governmental Organizations (e.g., EA Community, SADC, ECOWAS, AU, CEMAC)

- Facilitate partnership and collaboration
- Share lessons learnt
- Share resources, both material and human
- Facilitate and support multi-center studies
- Promote the development of centers of excellence for vaccine research within the region

3.3.3 The role of WHO and UNAIDS

Since 1990, the WHO and UNAIDS have been playing a key role in facilitation of international HIV vaccine activities, focusing on collaboration with developing countries, to ensure that trials are conducted with the highest scientific and ethical standards. Key to this role was the collaboration that led to the early development (1992) of “National AIDS Vaccine Plans” in Thailand, Uganda and Brazil, 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 vaccine programmes in industrialized and developing countries. The WHO-UNAIDS HIV Vaccine Initiative implements activities in the following four areas:

- Advocacy, guidance and coordination of the international HIV vaccine effort with equitable participation of multiple partners, from the public and private sector.
- Promotion of simultaneous 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,
- Assisting and advising governments regarding intellectual property issues, and rights
- Access to future HIV vaccines.

3.3.4 Role of the African AIDS Vaccine Programme (AAVP)

The African AIDS Vaccine Programme (AAVP) was conceived in 2000 as a network of African experts, working together to promote and facilitate HIV vaccine research and evaluation in Africa through capacity building and regional and international collaboration. The AAVP advocates and supports a coordinated effort to contribute to the global HIV vaccine effort, ensuring that appropriate vaccines are developed and made accessible in Africa within the shortest possible timeframe.

Organisation

The Secretariat of the AAVP is hosted by the WHO-UNAIDS HIV Vaccine Initiative, **in Geneva and Harare where** technical, financial and administrative support **is provided** to the AAVP.

The AAVP has a Steering Committee which acts as the advisory body of the AAVP and provides strategic direction and oversight for the Programme. The Steering Committee also coordinates the work of the Thematic Working Groups (TWGs), which implement the activities of the AAVP in collaboration with countries in the region with support from international and national partners and organizations.

The Thematic Working Groups are established for each one of the activity areas. The groups are composed of a small number of African scientists and experts (5-8), responsible for planning, implementation and coordination of thematic activities which include:-

- Advocacy, Information/Education and Resource Mobilization (ARM).
- Biomedical Sciences (BMS).
- Population-based Studies (PBS).
- Ethics, Law and Human Rights (ELH).
- National Strategic Planning (NSP).
- Community Preparedness Working Group

The core activities of the AAVP, are aimed at:

- Serving as a forum for collaboration and co-ordination.
- Strengthening sites and infrastructures for promoting the 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 by facilitating networking.
- Providing an advisory and advocacy role to government and inter-governmental bodies.

Since the AAVP is not directly involved in the development of any specific candidate vaccines, it will facilitate the testing of the best candidate vaccines at the most appropriate sites. To that effect, the AAVP has established close working relationships with all agencies and parties working on HIV vaccine research and development in Africa.

3.3.5 Role of Vaccine Manufacturers

In some situations the manufacturer of the candidate vaccine also provides the funding for the study. In that case the issues stated under 3.3.6 would apply to the manufacturer as well. The responsibilities and expectations of the manufacturer of the vaccine should be specified in written agreement as early as possible in the protocol development process, but certainly prior to protocol implementation. The issues to consider include, but are not restricted to:

- Provision of GMP study product
- Archival of vaccine samples from each batch produced
- Ensure registration of product in country of manufacture and of trial(s)
- Assurance of care of research-related injury
- Intellectual property rights
- Publication policies
- Use and disclosure of study data
- Use of study samples
- Assurance of affordable accessibility to vaccine if licensed
- Confidentiality of data and proprietary information

The manufacturer, the funding organization and the collaborating academic institutions should be linked through a MOU and should meet regularly in a study steering committee meeting. This meeting is sometimes held face to face or through conference calls.

3.3.6 Role of Funding Organizations

Funding organizations play a central role in assuring that prior to protocol implementation, formal agreements are reached on the responsibilities and expectations of the various parties. These organizations are usually referred to as the “sponsor.”

They also:

- Provide oversight to assure that trials are conducted according to GCP and GLP.
- Support local capacity building (training and infrastructure)
- Support archival of samples from research participants
- Ensure that adequate data and record keeping is maintained

3.3.7 Role of investigators and collaborating Academic and other Institutions

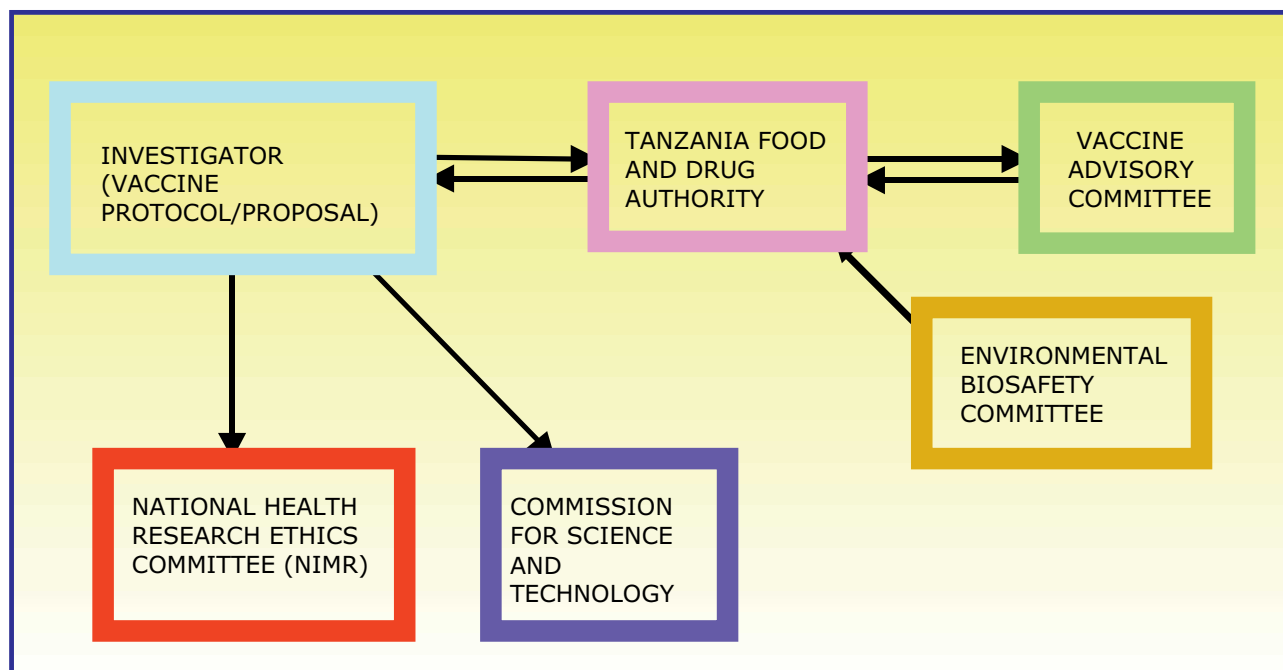
Written agreements should spell out the contributions to the project of the different investigators and collaborators. The institutions usually include local and international Universities and Scientific organizations that are neither sponsors nor manufacturers but are partners in the research. Contributions of these institutions and investigators include but are not restricted to:

- Assuring in-country regulatory approval
- Submitting the proposal to and responding to comments from the scientific and ethics review committee
- Providing the key investigators
- Providing technical assistance
- Recruiting, training and supervising study personnel
- Providing infrastructure and space
- Convening the study steering committee meetings (face to face or through conference calls)
- Taking full responsibility for the study at the site and being answerable to the national authorities
- Providing regular study monitoring reports to the scientific and ethics review committee
- Assuring confidentiality of data and proprietary information
- Ensuring equal partnership and ownership of data, samples and, publication with collaboration units
- Ensure independent monitoring of trial
- Collaborating with sponsors and manufacturers to ensure that there is a Data and Safety Monitoring Board
- Ensuring indemnity cover for investigators

4.0 REGULATORY APPROVAL PROCESS

Figure 2, summaries the regulatory approval process for a candidate vaccine before it can be tested in human subjects. It also outlines the pathway for ethical review of clinical trial protocols

Figure 2: Regulatory, Scientific and Ethical Approval Process



4.1 Tanzania Food and Drugs Authority

No vaccine should be tested in humans without regulatory oversight to assess safety, immunogenicity, potential efficacy and environmental biosafety (when applicable). For this purpose, it is important that regulatory bodies are established to develop guidelines and procedures for:

- Selection of HIV candidate vaccines
- Inspection and certification of manufacturers
- Registration and licensing of products.

This overseeing should cover all aspects from the earliest development stages, consistent with Good Manufacturing Practices (GMP), and continuous surveillance for rare and late adverse events following vaccination. WHO defines GMP as “that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.” The guiding principle of GMP is that quality is built into a product and not just tested into a finished product. Therefore, the assurance is that the product not only meets the final specifications, but that it has been made by the same procedures under the same conditions each and every time it is made.

WHO-UNAIDS HIV Vaccine Initiative should facilitate discussions among national regulatory authorities to reach consensus on scientific criteria for assessing the immunogenicity, safety and efficacy of HIV candidate vaccines. This role should be spearheaded by the Tanzania Foods and Drugs Authority.

Tanzania Foods and Drugs Authority (TFDA) has:-

- A legal mandate for its functions. The authority was established by Parliamentary act no1 of 2003 and is mandated to provide for the efficient and comprehensive regulation and control of food drugs, medical devices, cosmetics, herbal drugs and poisons.
- A standard set of clear guidelines for registration and testing of candidate vaccines and licensing of products or manufacturers
- Sufficient human and financial resources
- Access to appropriate scientific expertise
- Access to a quality control laboratory

The main functions of the Foods and Drug Regulatory Authority include:

- Registration and licensing of new drugs and vaccine products
- Ensure products are produced according to GMP, and, if necessary, inspect manufacturing facilities
- Evaluate the adequacy of quality control tests performed on all candidate vaccines intended for clinical trials in Tanzania
- Inspection and licensing of dealers
- Post marketing surveillance – quality, adverse reactions
- Authorisation of use of candidate products in clinical trials
- Enforcing compliance with Tanzania’s regulations
- Overseeing compliance with international regulations (e.g., WHO Guidelines)

4.2 National HIV Vaccine Advisory Committee

There shall be established a Vaccine Advisory Committee (VAC) which will be housed under the umbrella of the Tanzania Foods and Drugs Authority. The committee will be consulted during the evaluation of the credibility of the Vaccine Manufacturing Company as well as the suitability of any potential candidate vaccine with emphasis on pre-clinical data and safety and immunogenicity in humans, as well obtain and evaluate information on any environmental safety concerns. This committee would give its report and recommendation to the TFDA and other relevant organizations before a protocol is prepared.

In the case of a new HIV vaccine product that an investigator wants to evaluate in the country, the following steps should be taken:

- The in-country principal investigator (PI), alone or together with his/her collaborative counterpart or a representative of the sponsor or manufacturer will submit the relevant information concerning the product to TFDA who will consult the Vaccine Advisory Committee (VAC).
- This committee will carry out the necessary investigative work as well as seek advice of the National Biosafety Committee wherever necessary and advise the Tanzania Food and Drugs Authority.
- Communication will be sent to the interested parties giving clearance to go ahead and prepare a full proposal, or that the country is not ready to go ahead with further evaluation of the product.
- The VAC report will also be availed to all relevant stakeholders.

4.2.1 Terms of Reference of a National Vaccine Advisory Committee

- Advise on suitable candidate HIV/AIDS vaccines appropriate for further evaluation in the country.
- Receive from the Sponsor and review evidence of Good Manufacturing Practice for the proposed candidate Vaccine.
- Receive and review evidence of Good Clinical Practice, when necessary, concerning the proposed vaccine.
- Review all pre-clinical data and results of previous trials in human volunteers (safety and immunogenicity) or efficacy.
- Review academic and professional credentials of the researchers involved in these trials.
- Where necessary, solicit, receive and consider comments and/or recommendations from other National and/or International drug regulatory authorities regarding the proposed vaccine.
- Consult with the WHO-UNAIDS Vaccine Advisory Committee, IAVI, AAVP or other partners
- Work closely with other National Regulatory bodies and the local Ethics and Science Committees.

The committee's membership should include a person from civil society plus individuals with the necessary scientific expertise particularly in virology, vaccinology, immunology and molecular biology.

4.2.2 Criteria for selecting a Candidate Vaccine for evaluation

- Should be manufactured under GMP
- For repeat Phase I and or II human trials the prerequisite is safety data in small animals and Phase I and or II trials result in humans in the country of origin.
- for phase III trials the prerequisite is safety data in small animals, and human phase I and or II trials from country of origin/sponsor as well as product dossier from the manufacturer.
- Relevance to Tanzania in terms of virus clade/subtype or circulating HIV strains i.e. antigenic relatedness of vaccine immunogens to the HIV strains among recent seroconverters in the country.
- Relevance to country in terms of HLA types, nutritional status and prevalent parasitic and other diseases.
- Results of regulatory evaluation in the country of origin and or elsewhere should be made available.

Other important considerations:

- Results of studies involving minors; pregnant women, breast feeding women where these are relevant and indicated.
- Immunogenicity, both humoral and cellular, using various routes of administration such as: intra-muscular (IM), intra-dermal (ID), intra-vaginal, -intra-rectal or oral-mucosal.
- Protection in challenge experiments against infections acquired via the intravenous (IV), genital or anorectal routes.
- Robustness of immune response (IR) generated, including duration and rate of decay of antibodies, T cell or other factors.
- Prevention of mother to child transmission.
- Ability to distinguish HIV infection from vaccine immune responses.
- Flexibility of routes of administration such as orally, intra-nasally, IM and ID.
- Schedule of administration: ease of implementation (single or multiple doses of vaccine).
- Feasibility of combining with other vaccines in Expanded Programme of Immunisation (EPI).

- Storage: need for cold chain, and potency at room temperature.
- Stability in adverse conditions: transport on rough roads for long distances with retained stability and potency in tropical conditions.

4.2.3 Essential Information required for evaluating a Vaccine Manufacturer and/or Sponsor:

- Commitment to Good manufacturing practices (GMP) plans for production.
- Commitment to provide sufficient free vaccine for the study.
- Provision of assurance of treating all vaccine-related adverse events and injuries.
- Willingness to discuss provision of HAART to volunteers who seroconvert during the trial.
- Commitment to capacity building and transfer of technology to R and D institutions
- Readiness and willingness to agree on intellectual property issues regarding a given vaccine.
- Commitment to provide free vaccine for Phase III Trial where indicated.
- Readiness and willingness to provide free of charge to Phase III participants any preventive vaccine found to be safe and efficacious.
- Willingness to allow bulk purchases of efficacious vaccine at affordable price for participating country.
- Willingness to make available and at affordable prices such a vaccine to other individuals at high risk of HIV infection in the country.
- Assistance to governments to develop and implement vaccine distribution plans
- Willingness to discuss post study surveillance for long term side effects
- Any other matters relevant to the vaccine under consideration.

5.0 GUIDELINES FOR SCIENTIFIC AND ETHICAL REVIEW OF PROPOSALS AND PROTOCOLS

The mandate for reviewing the ethical and scientific content of all research in Tanzania lies with the Medical Research Coordinating Committee of the National Institute for Medical Research. The National Institute for Medical Research formed by Act of parliament No. 29 of 1979 to carry out, coordinate, control, register, monitor and promote all Health Research in Tanzania. There may however be the need to establish a separate subcommittee of the MRCC to deal with HIV vaccine trials with a view to it becoming the main subcommittee overseeing clinical trials.

All international guidelines require the ethical and scientific review of biomedical research alongside informed consent and the appropriate protection of those unable to consent as essential measures to protect the individual person and the communities who participate in research.

The guidelines for Scientific and Ethical review for HIV Vaccine Trials clearly describe:

- Essential documents required for review
- The review process
- Information which must regularly be communicated to the Review Committee.
- The authority and process for appointing scientific and ethics committee members

5.1 The Mission of the Medical Research Coordinating Committee in relation to HIV Vaccine Trials is:

- To safeguard the dignity, rights, safety and well being of all research participants through the review of research proposals and their supporting documents.
- To ensure that research is carried out according to the highest ethical and scientific standards.
- To oversee the ownership of research results in accordance with agreed national and institutional Intellectual Property Rights policies.

The Health Research Ethics Subcommittee of the Medical Research Coordinating Committee has developed and adopted Standard Operating Procedures (SOPs) using guidelines such as the “WHO Operational Guidelines for Ethics Committees that Review Biomedical Research (Geneva, 2000)”. **All IRB’s in Tanzania will be encouraged to do the same following the dissemination of these SOPs.** The following elements should be included in the SOPs:

- Membership
- Quorum requirements
- Education of Members
- Requirements for submission of proposals
- Time line for the review process
- Fees for review of research protocols if applicable
- Required documentation
 - Synopsis of protocol including Ethical considerations
 - Case Report Forms and other questionnaires
 - Brochures on investigator product- Clinical investigators Brochure
 - Material for recruitment including advertisements
 - Process to obtain and document consent and attached informed consent forms
 - Information about: Compensation
 Indemnity
 Insurance

5.2 Terms of reference for the National Science and Ethics Committee (NRB) for HIV Vaccine Trials

- Provide independent, competent, and timely review of the science and ethics of proposed studies, in accordance with national guidelines
- Verify Ethical Integrity of HIV Vaccine Trial Protocols in accordance with internationally and nationally accepted ethical guidelines, such as:-
 - Declaration of Helsinki
 - Council for International Organization of Medical Sciences (CIOMS) 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 (ICH) Guidelines for GCP, GMP, GLP
 - UNAIDS guidance document – Ethical considerations in HIV preventive vaccine research.
 - Tanzania Health Research Ethics Guidelines

Guidelines for the committee

- To safeguard the dignity, rights, safety and well being of all research parties
- Review research proposals and their supporting documents with emphasis on
 - Scientific design/objectives/statistics and methodology
 - Recruitments of participants
 - Care and protection of participants
 - Protection of Research participants confidentiality
 - Informed Consent Process
 - Community Consideration and cultural sensitivity
- Monitor Ethical Adherence to approved protocol, and other Aspects of the implementation of HIV Vaccine Trials.
- Minimize risk to volunteers by enforcing reporting of and review of the following:-
 - Protocol amendments, deviations and violations
 - Serious and unexpected adverse events
 - Periodic and final reports
 - New information which may affect risk/benefit ratio
- Where necessary, make recommendations to the Data and Safety Monitoring Board.
- Receive and consider recommendations from the Data and Safety Monitoring Board.
- Work closely with the WHO Ethical Review Committee OR WHO-UNAIDS Steering Committee on HIV Vaccine Development.

The Science and Ethics Committee is multidisciplinary, multisectorial and pluralistic with balanced age and gender distribution. Membership includes a social/behavioural scientist, PLWHA, clinicians, lawyer, ethicist, community representatives and an advocate or representative of children or youth with assurance of gender balance. Members should have independence from political, institutional, professional and market influences. Reviewers must however abide by existing national Legal and Regulatory Requirements (laws and regulations).

5.3 Essential Elements of the Review

- **Scientific Design and Conduct of the Study**
 - Appropriateness and relevance of:
 - Objectives
 - Study population
 - Statistical methods
 - Site/staff

- 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 to potential participants
 - Inclusion/Exclusion criteria
- **Care and Protection of Research Participants**
 - Qualification/Experience of investigators
 - Medical care during and after research
 - Care and support of participants who become infected with HIV during study participation
 - Compensation to participants who become infected with HIV during study participation.
 - Product availability to participants
 - Justification for withholding standard treatment for purpose of research.
 - Description of any financial costs to participation.
 - Rewards/Compensation for participation without coercion (undue inducement).
 - Provision for compensation/ treatment in case of injury.
 - Insurance and indemnity arrangements.
 - Referral to psychosocial and legal support if necessary.
 - Safety monitoring.
- **Protection of Research Participant Confidentiality**
 - Who will have access to personal data or samples
 - Measures to ensure confidentiality and security of personal information
- **Informed Consent Process**
 - Description of process for obtaining consent
 - Cultural sensitivity of the informed consent process.
 - Adequacy, completeness and understandability of written and oral information to participants or legally acceptable representative
 - Justification for and desirability of inclusion of minors and socially/legally vulnerable groups, such as refugees, prisoners and soldiers
 - Steps to protect the dignity, safety and welfare of above vulnerable groups from exploitation
 - Strategy for informing participants of new information during study concerning their rights, safety
 - Provision for receiving and responding to questions and complaints from participants
- **Community considerations**
 - Impact/Relevance of the research to the local community or study population.
 - Consultations with concerned communities while designing the research, and during the research to assess acceptability.
 - Contribution of the research to the community.
 - Availability and affordability of any successful study product to the concerned community.
 - Dissemination of research findings to study participants and to the concerned communities.

6.0 RESEARCH ACTIVITIES IN PREPARATION FOR HIV VACCINE TRIALS

The conduct of virological, immunological, epidemiological, clinical and socio-behavioural studies is an essential component in preparation for HIV vaccine trial implementation. The preparatory activities have to be carried out using a multi-disciplinary approach.

6.1 Virological and immunological studies

In preparation for HIV vaccine trials there is need to carry out virological studies on HIV including isolation and characterization.

There are different subtypes of HIV prevalent in different parts of the world. Within an individual, and within a population, there is a high viral mutation rate, with antigenic variations of HIV strains within the country. There is thus need to have on going HIV isolation and characterisation studies to monitor the genetic, biological and antigenic variation of these HIV strains.

In collaboration with the “WHO Network for HIV Isolation and Characterisation,” HIV isolation and characterisation 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 e.g. from mother-infant pairs.

Virological and immunological studies among HIV seronegative exposed individuals, sero-discordant couples and long-term non progressors can provide valuable information for vaccine design. Humoral (neutralizing antibodies) and cellular immune responses (CTL responses) studies among HIV infected individuals could 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, with freezers and storage capabilities including electricity generators as well as trained technical staff and data management and communication infrastructure to support these activities.

6.2 Epidemiological studies

Base-line epidemiological studies are required to characterise HIV infection in potential populations for HIV vaccine trials. Such studies should include HIV sero-incidence and sero-prevalence, routes of transmission and associated risk-behaviours or risk factors for HIV transmission. For phase III trials identification and access to populations with high HIV sero-prevalence and incidence are important. Continual HIV prevalence and incidence surveillance studies including those conducted at community level should also be carried out during vaccine trials. This would contribute to the knowledge of the dynamics of the epidemic and prevalent and incident HIV subtypes and/or immunotypes.

6.3 Socio-behavioural Studies

Before vaccine trials are initiated, it is important to gather data on public knowledge, attitudes, perceptions and practices particularly in the sex and age-groups at greatest risk in the study population. Such information will help in:

- Understanding how to obtain informed consent

- Identifying factors that may influence participation in trials
- Assessing feasibility of conducting placebo-controlled trials
- Assessing acceptability of the vaccine or placebo in a trial
- Designing public information counselling and education messages in vaccine trials

Studies on acceptance of VCT among targeted populations, myths and misconceptions and willingness to participate in vaccine trials should be carried out. Vaccine preparedness studies should identify recruitment and retention strategies for targeted populations. Lessons learnt from community mobilization for other HIV/AIDS intervention programs should be used to prepare populations for vaccine trials. Additional socio-behavioral studies would include: evaluation of non-vaccine preventive measures, vulnerability studies and studies of the social dynamics of the epidemic.

The investigators and other study personnel must understand and be fully aware of the local social and behavioural attitudes to HIV in general, and to vaccines in particular among the study population. People's knowledge of vaccines, and their attitudes to vaccines should be studied. Feelings and fears that vaccines could lead to disease should be examined. Beliefs in the community that the vaccine will provide adequate protection against HIV and thus negate the need for condom use, abstinence or other preventive measures are also important factors that need to be explored. Information should be obtained on the population's knowledge of, and attitudes to placebo controlled trials and their acceptability. The concept of counselling and testing may be new in many communities and researchers need to explore ways of initiating the practice.

It is also important to get the local views of PLWH/A on vaccine trials. Some of the concerns of PLWHA include whether the vaccine would be beneficial for PLWHA or would they be left out from the research work, as most efforts would seem to be on preventive vaccines. PLWHA may feel that priority efforts should also be put into looking for therapeutic vaccines.

6.4 Studies on expected community benefits from participation in vaccine trials

Such studies should solicit community views on:

- Impact and relevance of the research to the local community or study population.
- Contribution of the research to the community.
- Availability and affordability of any successful study product to the concerned community.

6.5 Studies of Normal Values in Healthy Subjects

Before initiation of a HIV vaccine trial, determination of laboratory normal ranges (hematology, biochemistry, CD4 count, etc...) should be undertaken.

7.0 IMPLEMENTATION ISSUES IN VACCINE TRIALS

7.1 Establishment of trial cohorts and sites

Establishment of cohorts of HIV un-infected volunteers including perinatal and paediatric subjects at a community level, and at risk of HIV infection, are required to prospectively determine HIV incidence, assess the effect of other preventive interventions on HIV incidence, as well as to explore the feasibility of recruiting the necessary number of volunteers and following them up for several years. For therapeutic vaccines, cohorts of HIV positive individuals are required.

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

- The study population should have access to an appropriate medical facility where they can receive treatment for medical problems that arise during a vaccine trial.
- The sites should have capacity to manage and analyse data from all the multidisciplinary studies performed.
- Counseling and interventions to prevent HIV infection should be provided to study populations. The effect of these measures on the HIV incidence should be determined and monitored.
- The incidence of HIV infection should be sufficiently high to ensure being able to select a manageable sample size (possibly between 1-2 % for phase III trials).
- The cohort should have moderate stability, with limited mobility.
- Funding for the cohort should be stable and long-term.
- The cohort should have on-going socio-behavioral investigations as a priority, in order to understand the social/behavioral/cultural factors influencing the population.
- Community representatives should be involved early in the planning process.

Sub-cohorts of high incidence population groups should be identified within existing larger cohorts to achieve smaller sizes in vaccine trials.

7.2 Conducting Phase I/II Clinical Trials

A country should engage in vaccine trials using vaccine candidates that have satisfied the selection criteria. Potential candidate vaccines should meticulously and independently be evaluated by the potential principal investigator (PI) and the HIV Vaccine Advisory Committee (HVAC), before they could be considered for trials in the country.

Phases I, II, and III trials of a preventive vaccine all have their own particular scientific requirements and specific ethical challenges. The choice of study populations for each trial phase should be justified in advance in scientific and ethical terms, regardless of where the study population is found.

Generally, early clinical phases of HIV vaccine research should be conducted in communities that are less vulnerable to harm or exploitation, usually within the sponsor country. Because HIV strains vary and populations can differ in their response to vaccination, participating countries should be prepared to carry-out/repeat Phase I/II trials and eventually Phase III efficacy

trials of promising HIV/AIDS vaccines. However, countries may choose, for valid scientific and public health reasons, to initiate conduct of any phase within their populations, provided there is sufficient scientific infrastructure and sufficient ethical safeguards.

Evaluation of potential vaccine candidates requires well-trained and experienced personnel at all levels of HIV vaccine trials, together with adequate and appropriate laboratory facilities. These are required for screening for HIV status and other inclusion/exclusion criteria as well as monitoring of side effects and assessment of laboratory end points.

Safety end points that should be monitored during phase I and II vaccine trials include:

- Physical examination and medical history to look for any evidence of local or systemic reactogenicity
- Full blood count (Hb, WBC total and differential)
- Biochemistry (creatinine, ALT, AST, total and direct bilirubin)
- Urinalysis (Proteins, Sugar, Microscopy)
- Urine pregnancy test
- HIV antibody ELISA, P24 antigen assay and PCR.
- Any other testing as needed to diagnose/follow up an adverse event

Immunological

studies and immunogenicity *endpoints*

Vaccine induced humoral (neutralising antibodies) and cellular (CTL) responses of the immune system to HIV-1 play an important role in HIV vaccinology. An ideal candidate vaccine should induce adequate, effective and durable immune responses that cross-react with isolates from the country where the trials are conducted. Studies should be conducted during the course of the trials to determine CTL killing activity, neutralising antibody responses, antiviral factor secretion of cytokines or beta chemokines, and other CD8+ T cell antiviral factors. Emphasis should also be placed on the induction of a mucosal immune response; both secretory IgA and mucosal CTL response, which could constitute local defence mechanisms in the vaccinated host, and protect against sexual transmission of HIV.

Clinical monitoring and site facilities

There should be adequate provision for monitoring and management of medical, social and psychological problems among the study populations. Personnel well-trained in trial implementation, monitoring and participant follow-up are crucial for new phase I/II/III trials. They include doctors, nurses, counsellors, laboratory staff, and administrative/fiscal support staff as well as radiation safety officers where necessary. Trial sites require the following minimum infrastructure: adequate and appropriate reception and waiting areas, health education and seminar rooms, counselling rooms that ensure confidentiality, physician's examination rooms, phlebotomy rooms, vital sign assessment areas, laboratory space, data processing and storage and filing areas. There should be immediate access on-site to emergency cardiac/respiratory care.

Trial sites should also have provisions for biosafety facilities and expertise. Other considerations include reliable utilities including power, water, telephone and IT/Internet. In addition, trial sites should have access to out patient facilities, in-patient wards and pharmacy, as well as roentgenogram (X-ray) facilities.

Site Initiation Checklist

Before a research site commences recruitment/screening/enrolment activities, the site must prove to the study sponsors and the study monitor that the following elements are in place:

- Protocol with full regulatory approval and approval by TFDA, NIMR (NRB) and IRB(s) as per the country requirements
- Full approval to import Candidate Vaccine
- All infrastructure needs as listed above
- Staff fully recruited, hired and trained in all relevant areas i.e. technical training, GCP, GCLP, counseling, confidentiality
- All laboratory and clinical SOP's developed and in place
- Site Master File in place (including roles and responsibilities of study team)
- Study monitoring in place
- Recruitment strategies in place
- Well understood plans for use of outside laboratories and medical facilities
- Data collection forms, case report forms and for laboratory requisitions developed

7.3 Conducting Phase III Efficacy Trials

In order to accelerate the 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 inter-country collaboration in multi-centre studies.

Possible outcomes that might be observed in an HIV vaccine Phase III efficacy trial should be documented. These outcomes include:

- i) Prevention of infection;
- ii) Prevention of chronic infection (i.e. limited to a transient infection);
- iii) Occurrence of infection, but AIDS is prevented or delayed (assessed by candidate surrogate markers such as virus loads, or by clinical findings such as AIDS or mortality);
- iv) Occurrence of infection but vaccinee is less infectious; and
- v) Combinations of above.

Because of the concerns about testing HIV antibody positive as a result of vaccination, thus leading to discrimination in insurance, employment or immigration, researchers must put in place mechanisms for protecting volunteers such as identity (ID) cards for participants, and tests relevant to the circulating HIV subtypes, capable of differentiating vaccine-induced seropositivity from true infection.

7.3.1 Criteria for conducting Phase III Efficacy Trials

There is urgency to conduct Phase III efficacy trials on vaccines relevant for use in Tanzania (Africa) and other heavily affected areas of the world. There are however, certain prerequisites for the conduct of such trials. These include:

- Political support, commitment and involvement
- Community support and participation
- Stable, well-defined population with sufficiently high HIV incidence rates

- Capability and feasibility to collect and characterize HIV strains prevalent in the potential study population or region
- Availability of candidate vaccines that have successfully completed toxicity/safety studies in animals, are safe and have promising immunogenicity profile in Phase II human trials.
- Arrangements to monitor side effects during and after the trial.
- A manufacturing company that has a favourable and acceptable profile
- Scientifically competent and ethically acceptable investigators, from reputable institutions or organizations with sound collaborative linkages
- Access to a medical facility to treat inter-current illness
- Provision of counseling and interventions to prevent HIV infection among the study population
- Ability to respond to psychological and medical needs of those people who either test HIV positive at screening OR who become positive in the course of the trial
- Capability to manage and analyze relevant data.
- Strategies in place to address inequalities in gender participation in vaccine trials.

7.4 Socio-behavioural Issues

7.4.1 Counselling for HIV Vaccine Trials

Participants in HIV vaccine research need to be counselled regarding their sero-status, avoiding risky behaviour, use of HIV prevention methods, importance of treating sexually transmitted infections (STI) and provision of support to self 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 vaccine trials will specifically be counselled regarding risk reduction. Counselling to HIV infected individuals should stress the need to avoid transmission of HIV to others.

During HIV vaccine trials, some participants will develop antibodies to some HIV antigens and hence test antibody positive. Some may attempt to un-blind themselves in the hope that if they were antibody positive they would consider themselves protected. There is need to be counselled about these results that mean response to antigens in the vaccine and not necessarily protection from natural infection.

7.4.2 Informed Consent Process

- Consent from a study participant to join any study should be free and informed.
- Informed Consent must be based on complete, accurate and appropriately conveyed and understood information.
- There must be a plan for monitoring the adequacy of the informed consent process and risk reduction interventions including access to prevention methods throughout the trial period.
- For legal minors, consent should be obtained from parents/guardians according to existing legal provisions.

7.5 Guidelines for monitoring of HIV Vaccine Trial Research Activities

7.5.1 Data and Safety Monitoring Board (DSMB)

Vaccine trials may have DSMB composed of experts appointed by sponsors, **in consultation with** collaborating national and international scientists. DSMB is an independent body which should provide reports to **the sponsor and** investigators and through them to the Scientific and Ethics Committee (SEC). Members must not have conflict of interest and should be independent of trial researchers, sponsors and vaccine developers or manufacturer.

Monitoring must be performed to ensure the safety of participants and the validity and integrity of the data, and, although not strictly necessary for all **trials**, external monitoring by a DSMB should always be considered. Monitoring should be commensurate with the level of risk of the study, which is often related to the size and complexity of the study, not just the absolute risk of the study intervention itself. For phase III trials, the size and complexity will invariably dictate need for a DSMB. Phase I and II studies will often require monitoring by a DSMB, particularly those that are complex, relatively large, and multi-site.

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

- Clinical trial experts
- Biostatisticians
- Bioethicists, and
- Clinicians knowledgeable about the disease and treatment under study
- Physicians
- Epidemiologists
- Virologists
- Immunologists,
- Social/behavioral scientists and;
- Community representative
- Representative of PLWA

7.5.2 Terms of Reference for Data and Safety Monitoring Board

The DSMB would:

- Review the research protocol and plans for data and safety monitoring.
- Receive and review regular periodic progress reports from the investigators
- Have access to all data generated from the trial and review for signs of quality and integrity.
- Monitor data regarding safety (adverse reaction), immunogenicity and efficacy.
- Receive and review results of interim analysis for outcomes especially as end points are approached (stopping rules)
- Evaluate the trial progress, including:
 - periodic assessments of data quality and timeliness,
 - participant recruitment, accrual and retention,
 - participant risk versus benefit,
 - performance of trial sites, and
 - 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, Science and Ethics Committee (SEC), and investigators concerning continuation or conclusion of the trial(s).
- Ensure protection of the confidentiality of the trial data and the results of monitoring.

7.5.3 Other monitoring agencies

Scientific and ethical monitoring by sponsor, manufacturer and collaborating institution is recommended. This is better done as a team, because different groups may have different interests. This monitoring 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. However, all this needs to be agreed upon before the research starts.

7.6 Issues on HIV Vaccine Availability and Affordability

In the development of an HIV vaccine there are challenges being encountered which include financial and logistical problems. An additional challenge is to identify and address potential regulatory obstacles to ensure the timely and valid evaluation and future use of HIV vaccines in Tanzania.

Logistics should be put in place to implement a successful HIV vaccination programme, working out obstacles “from research to programmatic implementation”. Information regarding the constraints of using HBV vaccines for older children and adults may assist in coming up with a workable programme.

Early planning is essential to ensure that future effective HIV vaccines are made available to all populations in need without unnecessary delay. For this purpose a number of actions must take place including the identification of policies and strategies for vaccine introduction and use in different communities, countries and regions, as well as the development of estimates of needs and probable vaccine uptake according to different estimates of vaccine efficacy. Of special importance would be to ensure that the introduction of a future vaccine is coordinated with, and be complementary to, the overall HIV/AIDS prevention packages, including behavioural and health promotion interventions.

Financial support is necessary, not only to develop new candidate vaccines, but also to strengthen appropriate infrastructures in developing countries where many vaccine trials will 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 AIDS vaccine. Financial mechanisms, such as tax breaks for investments in HIV-vaccine R&D, could “pull” industry to make more investments in the field. A new purchase fund for buying the vaccines for adults on a world scale may have to be created with the assistance of the World Bank, other UN agencies and other interested private organisations.

User fees may have to be introduced: or a special tax may have to be levied for the sole purpose of making these vaccines available and accessible. However, in Tanzania and in other developing countries the tax base is narrow and overburdened making it a problem as to when to start and as to how much to levy for HIV vaccines.

Technology transfer to the country and to other resource-constrained countries if accomplished, may provide the long lasting solution. However, this needs the agreement of the company manufacturing the vaccine and the political support of the country in which the company is situated. It also depends on whether the relevant country manufacturing the vaccine can satisfy the technology transfer package. Where technology transfer is not possible,

negotiations towards bulk purchases from the manufacturing company and repackaging locally will have to be considered.

Early negotiations with potential vaccine manufacturers, funding agencies and collaborators should be undertaken to ensure availability, accessibility and affordability of relevant vaccines to individuals at risk of HIV in Tanzania as soon as possibilities of a candidate vaccine proving effective begin to appear.

Phase IV trials should be carried 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.

8.0 OPERATIONAL AND LOGISTICAL ISSUES

8.1 Laboratory Support

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

- Staff fully oriented to GCLP and provided with training and regular updates
- Comprehensive SOP's for all aspects of the research laboratory functions
- Standardization and validation of assays for use in the participating country
- Establishment of laboratory normal values for the study population
- Establishment of an appropriate HIV testing algorithm
- Reliable computer network for storing and transmitting data
- Capacity to generate relevant immunological data both cellular and humoral.
- Availability of laboratory facilities to perform all assays required for screening and follow up of volunteers (safety lab tests)
- Availability of either regional or international reference laboratory
- Ability to monitor disease progression as required by protocol
- Adequate facilities to ensure cold chain for specimens and reagents
- Availability of qualified 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

8.2 Laboratory Network

- The primary laboratories at the vaccine trial site may not necessarily need to perform all laboratory assays, but should ensure that there is adequate quality control and quality assurance. Depending on the resources available the primary laboratory may collect biological samples with the ability to process the specimens and send samples out to partner laboratories for purposes of serology, microbiology, hematology, biochemistry and any other required tests.
- Secondary laboratories are expected to uphold standards of GCLP with well understood agreements between laboratories which outline the need to provide credible data obtained through the practice of GCLP.

8.3 Clinic Support

- Qualified medical staff with appropriate credentials and previous clinical experience.
- Clinic staff fully trained in all aspects of GCP with regular updates provided.
- Clinic staff well trained in counselling and in all aspects of participant tracing and follow up
- Sufficient numbers of qualified counsellors on staff

- Well developed SOP's for all aspects of the vaccine trials clinic
- Clear description of Severe Adverse Events management procedure
- Access to reliable transportation for volunteer tracing or follow up or emergency transport
- Resuscitation/emergency equipment present at vaccine trial site
- Access to emergency care and referral
- Ensure cold chain for vaccine handling and storage
- Ensure proper and timely submission of biological specimens according to SOP's
- Access to reliable means of communication (telephone/e-mail/fax)

8.4 Data management

- Data collected and stored according to GCP with appropriate source documents
- Ensure confidentiality of data as dictated by GCP by providing adequate security and limited access
- Well developed SOP's related to data management
- Adequate backup facilities for storing both electronic and paper documents/data
- Data QA/QC
- Adequate facilities for transmitting data (appropriate IT)

8.5 Administrative Issues

In order to ensure that infrastructure is adequately developed the study sponsor and investigators should take into consideration the logistical challenges inherent in performing high tech research in a setting that is not highly developed technologically.

- Ensure adequate facilities to site including back up power, a reliable water supply and other utilities including telephone and IT.
- Policies in place that ensure entire staff is given appropriate training in confidentiality
- Adequate system in place for managing transport issues
- 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 employee retention
- Adequate provisions for employee orientation and technical training
- Ensure adequate and appropriate communications between study team and outside partners
- Establish regular meetings between team and ensure regular meetings of a trials management committee

Appendix I

PERSONNEL/TRAINING

HIV/AIDS vaccine-related research is multifaceted and therefore requires personnel trained in multiple disciplines in order to address the various needs. Training is a continuous process. The training may be formal leading to degree courses or could be in house short courses, to strengthen specified capabilities at research sites. Below are key areas where training is required in order to build capacity for continued HIV vaccine trials.

All staff in the research unit need to have initial and ongoing training. Public relations training is important for all members of the team for efficiency.

Specific research training

GCP training should be provided for all clinical/health care staff before patient activities start. This should be followed by regular (annual or other agreed frequency) updates.

Should also be trained on:

- Protocol specific guidelines
- (handling of) source documents, CSF's
- Confidentiality
- SOP's
- Communication skills, emails, speakerphones, teleconferences
- Data handling

Training for all staff

- Adherence to:
 - Good Clinical Practices (GCP) guidelines
 - Protocol-specific guidelines and CRFs
 - Data Fax requirements
 - Protection of human subjects
 - Risk reduction counseling
 - Ethical Issues
 - Handling, storage, shipment of hazardous materials
 - Confidentiality issues
 - OHRP requirements
- Requires ongoing training with annual updates

Basic Science research

- Cell and Molecular Biology
- Virology
- Immunology/Vaccinology
- Specialized training of laboratory technologists in various techniques

Social/Behavioural

- Social Science
- Bioethics
- Counselling- HIV vaccine counsellors
- Anthropology

Epidemiology

- Formal training in Epidemiology and Biostatistics at degree level
- Short courses for doctors and nurses in Epidemiology, relevant to efficacy trials of HIV/AIDS vaccines
- Clinical research methodologies specifically for HIV/AIDS vaccine evaluation

Data management and computer technology

- Statistician and Biostatistician for overall supervision of data collection and entry and analysis of study results, as well as regular compiling of progress reports. Specialized training in analyzing data from HIV vaccine trials both clinical, laboratory and in particular, immune responses is important.
- Data Entry Clerks for data entry, cleaning and checking inconsistencies using appropriate software
- Records Officers for proper filing and archiving of clinical and laboratory data

Administration

- Short Management courses
- Social Administration
- Radiation safety

Public Relations courses

For all staff in the research unit.

- This training is necessary for efficient interactions with volunteers, spouses of participants and communities in which phase III trials may be held. This may also assist in recruitment.

Quality Management

For all staff in the research unit

- Quality Assurance
- Periodic review of various components of research process
- Ensuring adherence to policies, protocols, SOP
- Determining accuracy of records and their transmission
 - Overall plan, partial/complete record review
 - Timely response to periodic monitoring visits
- Quality Control
 - Daily process of ensuring accuracy and timely transmission of forms
 - Includes all records
 - Timely response to regular reports from Statistical Center

Appendix II

LABORATORY SUPPORT

For proper functioning, all the laboratories require well-trained staff in haematology, immunology, clinical chemistry and virology, as well as adequate equipment including refrigerators and freezers with generator back up. Training in good laboratory practices is essential, as is quality assurance and control measures with proper documentation and regular laboratory monitoring visits from international bodies with the expertise. To gain confidence of international collaborators, Clinical Laboratory Inspection Act 1998 (CLIA), College of American Pathologists (CAP) or other comparable certification is desirable especially for secondary laboratories.

Laboratories should be facilitated with a computer network that allows for entry of laboratory test results, as well as easy communication with different centres. Data management systems to link all information from the primary and secondary laboratories for ease of communication and retrieval of results would be beneficial. Accountability for samples for all participants and identification of appropriate freezer rack, box, position, accession number, sample type, study number, collection and storage date for each stored sample, identifying missing or pending results and generation of shipping records are crucial functions.

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

Appendix III

DATA MANAGEMENT

The research site must have a central computerised data management system with computers, pertinent software and peripherals as well as trained data management staff. The computers should be of sufficient capacity to hold a lot of data, with high quality printers, as well as adequate data saving/backup systems on site in case of power failure, fire or other catastrophe. There must be reliable generator power back up and uninterrupted power supply (UPS) for the computer systems.

Data needs to be managed by individuals well trained in this aspect of research. The raw data must be kept by the principal investigator (PI) with a set of back ups stored at the collaborating and co-ordinating centres.

Policy regarding who retrieves data, who can access the data entry room, when to export data, when back ups are made, duration of storage before destruction and use of secondary data need to be in place before the research starts. Data belongs to the Government. The principal investigator, on behalf of the Government, and in conjunction with co-sponsors and collaborators will decide on who and where data will be analysed and published.

Sites must have telephones/faxes, e-mail and internet access for communication purposes as well as project - dedicated transport facilities.

Appendix IV

SOCIO-BEHAVIOURAL AND CULTURAL ISSUES

- Counselling in Africa as a whole is compounded by socio-cultural factors.
- The health-care recipient tends to be wholly agreeable to any suggestion made by the health-care provider. Patients usually do not openly question a suggestion made by a health care provider, 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 the spouse in decision making should also be considered, in relation to the local socio-cultural norms. Stakeholders such as spouses and other family members should, if agreeable to the volunteer, be involved in the informed consent process to avoid future misunderstanding and conflicts.

Couples intending to participate in HIV vaccine research are welcome but should be aware of their responsibility to each other. It is desirable that they are counselled as couples and obtain their HIV results as such. Should this not be feasible, each member of the couple has the moral obligation to disclose his/her sero-status to her partner, if it is not a requirement of the physician or investigator to disclose the sero-status to the partner.

Issues in the consent form Process

- Often, the counselled person does not take the time or bother to read a lengthy consent form, required by the regulatory bodies, which even when translated into the native tongue, may make “heavy reading”.
- Worse still, 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 willing participant who opts not to read the consent form, hardly listens to the counsellor and is over eager to sign and enter the study is actually not a prepared HIV vaccine trial participant.
- In some cases the participants may read but not clearly understand.

Recommendations:

- The person being counselled for inclusion in an HIV vaccine trial should be appropriately and effectively counselled, with all aspects of the study discussed in detail during at least 2-3 sessions.
- The potential study participant must then be given time, not less than 48 hours, in between at least 2 counselling sessions to think (and consult) about participation in the study.
- After signing the consent form, there should be at least 2 counselling sessions before the potential volunteer participant is enrolled into the study. This lag period would also serve as a “cooling off period” that gives the person time to decide and change his/her mind if they so wish.
- Similarly a person who searches out the study team to enroll should be cautiously counselled to look for any other motives for the desire to join the study.

Some counselling issues

Study participants will have to realise that the HIV vaccine being tested is not protective so that they do not relax or refrain from whatever behaviour that has kept them free of HIV such as sticking to one sexual partner, preferably one who is HIV negative, using condoms at all times and avoiding circumstances such as alcohol ingestion that might impair one's judgement regarding taking risky behaviour.

Those found to be HIV positive, whether symptomatic or still asymptomatic, will be counselled to live positively, adhere to reasonable self health care i.e. minimise alcohol, commence TB prophylaxis, practice health seeking behaviour such as prompt treatment of opportunistic infections, avoid contracting new viruses from sexual partners by using condoms or abstaining from sex altogether, avoiding circumstances that could accelerate the course of HIV infection such as pregnancy and if circumstances allow consider starting ARV therapy.

Some technical aspects of the consenting process

- The counsellor must point out issues that the lay person does 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 would have an advantage over those in the placebo arm.
- The vaccine being tested will not as yet have been proven to prevent HIV infection, so the participant must be counselled about continued efforts to avoid HIV infection, such as abstinence and condom use.
- Short and long term planning for future pregnancies should be discussed in detail with female participants.
- End points of the vaccine trial should be clearly explained. If the endpoint is immunogenicity, the participant should not assume this means "protection" and thus the safety of risky sexual practices.
- The counsellor must not over-equate the HIV vaccine being tested to proven vaccines such as smallpox and polio vaccine which may confuse the participant, making them over confident of the vaccines efficacy and safety.
- The issue of compensation should be clearly discussed at the beginning of the counselling sessions. Monetary benefits could be an actual inducement for participation in a trial negating free consent, and this is usually discouraged. The potential participant should therefore understand that the studies do not carry monetary benefits, and the reasons behind this policy.
- Issues such as transport re-refund, compensation for work hours lost or for injuries from the study, medical treatment/benefits for self as well as nuclear and extended family should all be clearly discussed at the beginning of the study.
- Sensitivity of the participants need to privacy both at home and at work is an important factor. A participant who sees a car labelled "HIV vaccine trial" in his/her locality may opt to hide when visited, as may a wife whose husband has no idea she enrolled in a vaccine trial.
- Effect on loss of work time while attending the clinic for frequent follow-up visits, or the effect on a housewife's need to spend time at the daily home and garden chores should be borne in mind.
- Also determination of times for follow-up visits should be flexible, for example with consideration for the taxi driver or market vendor who cannot attend early morning or late evening clinics when business is at its peak, but can attend in the early afternoon.

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 cell 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 immunosorbent 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-surface 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.
Tat 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.



Participants at WHO/UNAIDS Network Workshop for HIV Isolation and Characterization important in HIV Vaccine Development held in Dar es Salaam, 1997.



Participants at the National HIV Vaccine Strategic Framework Development Workshop, Bagamoyo September 15 - 17, 2004.