NATIONAL HIV VACCINE PLAN

RESEARCH, DEVELOPMENT
AND EVALUATION

Ministry of Health

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FOREWORD

The present version of the National HIV Vaccine Plan introduces several changes in relation to the first plan prepared in 1992.

When the first studies were started it became clear that the four components of the original Plan were so closely interrelated that it would be impossible to treat them apart. Epidemiological, behavioural and clinical studies were carried out in close association, in a model which is still being refined. Laboratory studies have highlighted the monitoring of the epidemic according with recent advances in molecular epidemiology. Clinical studies have also incorporated new perspectives, influenced by the results from the epidemiological and behavioural studies carried out with volunteers from incidence cohorts studies. The seroconversions among the volunteers followed led to important developments. On one hand, there was the early isolation of HIV by the system of laboratories organised in a network associated with the National HIV Vaccine Plan; on the other hand, the study of the development of the infection (natural history of the disease) in these recent seroconverted individuals, without immediate therapeutic intervention or receiving early treatment with combinations of antiretroviral drugs. A single Phase I/II study (safety/immunogenicity) was carried out in this period, in 1995/96, using a synthetic peptide produced by an American Manufacturer (U.B.I.). Although the results were not satisfactory given the nature and length of the immune response, they have allowed some important conclusions. Among them, we would like to highlight that the teams that participated in the study in Belo Horizonte and Rio de Janeiro cities have acquired an experience that will be important in new clinical studies in the future.

We have taken an explicit and deliberate decision to consider the transdiciplinary nature of HIV vaccine trials in the following areas as indispensable:

a) Virological and immunological studies (HIV isolation and characterisation, with the creation of a national repository, and the implementation of techniques to assess humoral and cellular immunity);
b) Clinical and epidemiological trials (Setting up and maintaining cohorts [HIV-positive and HIV-negative individuals, perinatal], HIV incidence studies, risk factor studies, Phase I/II (safety and immunogenicity) studies, Phase III (effectiveness) studies);
c) Socio-behavioural studies (vulnerability studies, evaluation of non-vaccine preventive measures, study of the social dynamics of the epidemic);
d) Development and production of supplies and vaccines (product availability, intellectual property, transfer of technology)

In our opinion, in order to fulfil the proposals implicit in the new version of the Plan, it is essential to set targets to be met in short, medium and long term.

The elaboration of this new Plan was made possible by the efforts of the members of the National HIV Vaccine Committee, designated by the Minister of Health, in several meetings and through consultations by electronic means. I would like to highlight the fundamental and constant presence of Dr. Pedro Chequer, Coordinator of the National STD/AIDS Program; the competent contribution of the Committee's secretary, André Galvão; the invaluable help from other support staff of the National Coordinating Office, besides the high quality technical collaboration from Professor Mary Jane Paris Spink (behavioural studies) from *PUC/São Paulo* and Professor Carlos Maurício de Azevedo Antunes (Epidemiology) from Federal University of Minas Gerais.

José da Rocha Carvalheiro
President of the Committee

NATIONAL HIV VACCINE PLAN

RESEARCH, DEVELOPMENT AND EVALUATION

Summary

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1. BACKGROUND

1.1. The AIDS Epidemic in Brazil

The first AIDS cases in Brazil were described in 1982 in social groups presenting a similar profile to the initial groups in the USA. After an early period of low incidence, the epidemic became explosive in some high vulnerability groups, particularly men who have sex with men without condom protection and injecting drug users who shared syringes. Progressively it started to occur in situations initially considered of low vulnerability; today, heterosexual transmission accounts for a significant percentage of new HIV infections. Transmission by blood transfusions was very intense early in the epidemic, particularly among hemophiliacs, but at the present time it is under control. Similarly, the reports of perinatal transmission are decreasing steadily after the introduction of control measures that include serology in pregnancy and antiretroviral treatment of infected pregnant women. The table below summarizes data from the AIDS Epidemiological Bulletin of the National Program for STD and AIDS of the Ministry of Health (MOH).

AIDS Epidemiological Bulletin – data of February 1999

HIGHLIGHTS	DATA
Cases reported since 1980	155,590
Male:Female ratio, cumulative since 1998	3:1
Main type of exposure	sexual (52.76%)
Municipality with the highest number of reported cases	São Paulo, 35,570 cases
Municipality with the highest incidence rate (cases/100,000)	Itajaí, 845.7
Known educational level	Elementary education, 45%

The first AIDS cases were limited to the Southeast region. By 1999, all units of the federation have reported cases, but their distribution is uneven, with 76% concentrated in the states of São Paulo and Rio de Janeiro. The epidemic is no longer concentrated only in large urban centers, and there have been changes from the initial situations of risk.

The cumulative incidence of AIDS increased from 0.005/100,000 in 1982 to 3.1/100,000 population in February 1999, when 155,590 cases had been reported to the MOH. The modes of age groups are 25 to 34 years (men) and 20 to 29 years (women).

The sex ratio fell from 29M:1F in 1985 to 2M:1F in 1999. This decrease was mainly due to the transmission by heterosexual injecting drug users and heterosexual transmission to female partners of bisexual men, in addition to the increasing number of female injecting drug users. In the beginning, the epidemic was concentrated among men who have sex with men, with a high educational level and living in the country's larger metropolitan regions. Today, in addition to the process of "feminization", the epidemic is also spreading to smaller towns ("interiorization") and affecting the poorer strata of the population.

1.2. AIDS impact on development

The AIDS epidemic has had a negative impact on life expectancy in the past three decades, particularly in Sub-Saharan Africa. In the most severely affected countries, life expectancy can be as much as 20 years shorter than before the AIDS epidemic.

The demand for medical care related to HIV infection overburdens already fragile health systems, and AIDS exacerbates poverty in the poorest countries of the world. The disease affects mainly individuals in the most productive age group, reaping lives and leaving orphans to be cared for by relatives or by the State.

1.3. Prevention

Prevention activities in Brazil are coordinated by the National Program for STD and AIDS and epidemiologically oriented. Thus, eventual changes in the epidemic profile are translated into new prevention strategies and proposals.

The Program's prevention component is designed to promote health education activities, information campaigns in the media (radio, TV, magazines and newspapers) and behavioral interventions aiming at substantive changes in the sexual risk behaviors and practices in specific population segments. Other prevention strategies are the anonymous counseling and testing services, offered by the Centers for Testing and Counseling (CTA) and the national free telephone information service – AIDS/Health Hotline, which provides clarification about the transmission, prevention and treatment of HIV infection and AIDS and about specialized health services.

Assisted by the National AIDS Commission, the National Program for STD and AIDS has adopted the following main strategies:

- Encouragement of behavioural change through access to quality information about transmission routes and prevention as well as through changes in the perception of risk;

- Creation of intervention models allowing the consideration of the different population groups in terms of their self-assessment of their own vulnerability and risk, taking into account the epidemiological, cultural and gender aspects, the social context and the relative values of the groups involved. It includes the setting up of cohorts for socio-behavioural studies, assessment of the HIV infection incidence rate and future clinical trials with HIV vaccine candidates. Through the HIV Vaccine Committee, the National Program has defined regional centers for HIV vaccine research in Minas Gerais, Rio de Janeiro and São Paulo;

- Development of interventions based on peer education and outreach work, highlighting the changes in practices, attitudes, values and beliefs concerning STDs and AIDS;

- Strengthening of social networks, in order to achieve the objectives of the health promotion and protection activities, by providing social support to the groups involved, thus creating alternatives for dealing with the epidemic;

- Development of partnerships with non-governmental organizations, community associations, unions and class associations, broadening the scope of the prevention activities and the extended response to HIV infection;

- Creation of institutional mechanisms to increase the participation of the business sector, private companies and other social agents in the fight against AIDS;

- Development of partnerships with the business sector, encouraging joint activities with government agencies at the three levels of government (federal, state and municipal);

- Encouragement to the demand and promotion of access to prevention devices, such as condoms and disposable syringes;

- Training of human resources for the creation of multiplying agents of information on STDs and HIV/AIDS.

1.4. The ethics of the research of HIV vaccine candidates

The ethical debate: consensus and disagreement

At the present time, the ethical issues surrounding the HIV vaccine trials give rise to a great deal of international controversy. In Brazil, the issue must be analyzed in light of the recent process of organization of the ethical control procedures of scientific research involving human subjects. A National Commission of Ethics in Research (CONEP), subordinated to the National Health Council of the Ministry of Health, was created in 1996. Although several Institutional Committees of Ethics in Research already existed, this process became more expressive after the new regulation. At the present time, there are approximately 300 institutional committees (CEPs) in all states; among their attributions, they must submit all international multicentric trial protocols to the evaluation of CONEP.

The Brazilian position concerning the ethics of HIV vaccine trials in developing countries is very clear. There is a national consensus, particularly within CONEP, that the only changes which will be accepted are those that increase the capacity of the International Declarations and Resolutions to ensure the integrity of the human subjects of scientific research anywhere in the world. Thus, the agencies responsible for clinical trials with HIV

vaccine products in Brazil must provide the best treatment proved anywhere in the world to those volunteers who may eventually become infected by HIV.

It is worth highlighting that waiving this ethical principle on the treatment of individuals who have serological conversion has several risks. One is that subsequently waiving counseling becomes easier. In addition, once ethical requirements are lowered, it is very difficult to revert this process, and the eventual return to the original ethical requirements becomes extremely hard.

Thus, to ensure the safety and the protection of the human rights of the human subjects participating in research trials, all protocols pertaining to HIV vaccine research involving human subjects will be evaluated by an institutional Committee of Ethics in Research (CEP) duly accredited by the National Commission of Ethics in Research (CONEP). CEP will assess the project under the relevant CONEP recommendations, (Resolution #196/96). The National STD/AIDS Program , subsidized by a written position of the National Vaccine Committee, must approve all research projects receiving international support.

Whenever required, the project shall also be evaluated by the institutional review committees of the institution(s) the foreign researcher is affiliated with.

2. OBJECTIVES OF THE NATIONAL HIV VACCINE PLAN

The general objective of the Plan is to establish strategies for the development, the evaluation, the diffusion of information, the availability and the production of safe, effective and affordable vaccines to prevent HIV infection.

2.1. Specific objectives:

1. To determine the components required for the development of the different aspects (epidemiological, clinical, behavioural and virological) related to HIV vaccines;

2. To establish strategies to evaluate the safety, immunogenicity and effectiveness of preventive, immunotherapeutic and perinatal HIV vaccine candidate products;

3. To establish policies and processes for the planning, development and availability of safe, effective and affordable vaccines to prevent HIV infection (preventive vaccines). The development of other potential uses for HIV vaccines (therapeutic/perinatal) and/or specific immunotherapy will also be sought;

4. To implement, monitor and manage research activities related to HIV vaccine candidate products;

5. To identify national and international academic and research institutions and international agencies to collaborate with the efforts for developing and evaluating HIV vaccine candidate products;

6. To evaluate the current capacity of the national institutions to conduct the required research activities, including production;

7. To identify the needs and costs required to strengthen the infrastructure and to train personnel to carry out all research activities required for the trials of HIV vaccine candidate products in Brazil, and to define sources of funding, including for local production.

3. CHALLENGES INVOLVED IN DEVELOPING AN HIV VACCINE

The development of a safe and effective vaccine against HIV infection involves several challenges. The ideal vaccine should stimulate immunological responses capable of blocking the sexual, injecting and vertical infection. It must also be able to produce not only antibodies capable of neutralizing free viral particles but also immunological cell responses able to destroy infected cells. There is the additional challenge involved in our not knowing the correlates of immunity to enable us to define what to expect from an effective vaccine. In addition, based on our present knowledge, it is possible that several vaccines (or true "cocktails") are required to deal with the various HIV subtypes prevalent in the different countries affected by the epidemic.

In spite of these difficulties, the scientific community is reservedly optimistic concerning the possibility of developing one or more vaccines with varying levels of effectiveness against HIV. This optimism is based on several facts, including: a) the existence of individuals who are repeatedly exposed to HIV, do not become infected and develop immunological responses which might explain this resistance; others probably do not become infected because of the lack or changes in the receptors required for HIV entry in the cells; b) the existence of vaccine products that protect monkeys from the infection or from developing the disease; c) some vaccine products have triggered potent immunological reactions in human volunteers; d) the successful development of other vaccines against several viruses (e.g., hepatitis, poliomyelitis, mumps) even when the understanding of pathophysiology was smaller than in the case of HIV infection.

There are three different types (and purposes) of vaccine candidate products being developed and evaluated:

1. Preventive vaccines: to prevent HIV infection (sterilizing immunity) or the progress towards AIDS (partial immunity);

2. Therapeutic vaccines or active immunotherapy: to prevent or delay the progression of the disease, to decrease the viral load in HIV-infected individuals and to decrease the transmission of HIV infection from infected individuals to their contacts;

3. Perinatal vaccines: to prevent the progression of the disease in HIV-infected pregnant women and the transmission of the viral infection to their children.

There is a growing optimism in the international scientific community concerning the possibility of developing safe and effective preventive vaccines. However, despite the progress in recent years, the correlates of immunity associated with protection are still not well established. Indeed, the first vaccines developed favoured the "protective" humoral immune response, characterized by the presence of neutralizing antibodies targeted mainly to the V3 loop of the viral envelope. However, the difficulty to neutralize primary isolates of the virus was always a limiting factor of these vaccine protocols. Recent studies unveiling the molecular structure of gp120 have clarified this issue, showing that the conserved regions which bind to the cell receptors are hidden within the molecule, protected by loops with more variable and highly glycosilated sequences. Indeed, during the process of virus-cell interaction the binding site to the second receptor is only very briefly exposed after the interaction of gp120 with the CD4 molecule, which makes it a target of difficult access to antibodies. In addition, given this structural complexity, the incorporation of these epitopes in vaccine constructions continues to be limited.

A highly relevant factor described in recent years by many research groups was the association between the presence of cytotoxic CD8+ T-lymphocytes and the decrease of the plasma viral load after the acute phase of HIV infection. These findings have strengthened the importance of the cell-mediated immunity in the control of the viral infection and led to a redirection of the HIV vaccine protocols. The use of live vectors expressing viral antigens allows their presentation to the CD8+ T-lymphocytes expressed in the context of the class-I molecule of the main histocompatibility complex. It is therefore important to take into account the genetic background of the population to be vaccinated, strengthening the need to test different vaccine combinations in different populations.

Trials in animal models have been conducted with different vaccine protocols, both with attenuated or inactivated vaccines and using recombinant proteins, synthetic peptides and molecules expressed in live vectors, among others. Two primate models have been more widely used. First, in *Rhesus* monkeys, vaccine protocols have used the simian immunodeficiency virus (SIV) since this species does not become infected with HIV. The infection of *Rhesus* with SIV has a faster course, progressing to AIDS within one year, which limits the comparison between these two infections. The different protocols so far tested with this model, with the exception of those using a virus attenuated by genic deletion, have not been proven very encouraging in terms of the acquisition of immunity and subsequent protection. Second, studies in chimpanzees were more promising, and some protection was observed in some vaccine protocols. However, although

chimpanzees can acquire HIV-1 infection, it does not progress to AIDS, which limits the evaluation of the impact of the immunity triggered by the different vaccine products on the natural history of this viral infection. More recently, constructions of hypothetical SIV viruses containing genes from HIV-1 (SHIV) and other primate species have been used, trying to obtain conditions which better reproduce the human disease.

In spite of this big progress, HIV genetic variability continues to be one of the obstacles to vaccine development. Viruses isolated from different patients, and specially from different geographic regions, show considerable genetic and thus antigenic variations, which may be a limiting factor to the development of a universal vaccine. For instance, the differences in the aminoacid sequences of envelope glycoproteins from isolates from the United States and from Africa can be as high as 50%. At the present time, HIV-1 can be divided in 3 groups called M (majoritary), O (outlier) and N (new or non-M, non-O). While samples from groups O and N are limited to the African continent, with some isolated cases of group O in Europe and in the United States, group M variants are responsible for the AIDS pandemic. At the present time eight subtypes of the group M have been described (A, B, C, D, F, G, H and J), with approximately 30% of difference between them; in addition, there are four recombinant forms (A/E, A/G, A/B and AGI). It is therefore important to know whether the HIV-1 strains circulating in the country where the vaccine might be used in the future are sufficiently related to the vaccine prototype being tested. In order to obtain this type of information, it is necessary to keep an HIV molecular surveillance program in the country, systematically collecting blood samples for HIV isolation and its biological, genetic and antigenic characterization.

Concerning therapeutic vaccines, preliminary results from initial trials using inactivated virus with deletion of the gp120 glycoprotein from the viral envelope (*REMUNE*) in HIV-infected individuals have shown an enhanced immune response to the virus, with stabilization and even increase of the number of CD4+ T-lymphocytes in vaccine recipients. While these results are encouraging, the trials of immunotherapy or post-infection immunization must be expanded and deepened in order to allow a better assessment not only of the immunological response but also of the clinical and virological parameters, including the effect on HIV transmission, development of AIDS and time of survival. At the present time, with the advent of highly effective antiretroviral therapy (*HAART*), which leads to undetectable levels of circulating virus, immunotherapy may also be considered as a coadjuvant of treatment, in the sense of stimulating and maintaining the immunity to viral antigens.

4. VACCINE EVALUATION PROCESS

Before an HIV vaccine candidate product is evaluated in human subjects, trials to determine the vaccine safety, toxicity and immunogenicity are conducted in small animals and later in non-human primates. As previously mentioned, some trials have been carried out in primates, such as giving an HIV vaccine to chimpanzees and “challenging” them experimentally with HIV, or giving a SIV (an analogous of HIV) vaccine to monkeys and

challenging them experimentally with SIV. After these pre-clinical phases, and if the vaccine products are safe and capable of stimulating the immunological system, they can enter the human phase of clinical trials. Phase I and Phase II trials of safety and immunogenicity of vaccine candidate products are usually conducted in approximately 40 to 200 human volunteers, and the effectiveness in human subjects is determined in Phase III studies, randomized and with appropriate controls, carried out in thousands of volunteers. The following table presents a summary of the development of clinical trials with vaccine candidate products.

Development of Vaccine Candidate Products

Pre-clinical phase: The safety and immunogenicity of the vaccine product are evaluated in animal trials. This phase must always precede clinical trials in human subjects.

Clinical phase: Clinical trials will determine the safety, immunogenicity and eventually the effectiveness of the product tested. There are three mandatory phases before a vaccine is licensed by the relevant health authorities:

- **Phase I:**

Initial trials of safety (innocuity) and immunogenicity in a limited number of volunteers (10 to 30 individuals). These studies usually involve healthy adults at low risk for HIV infection, for periods varying between 6 months and one year;

- **Phase II:**

Continuation of the safety and immunogenicity trials

The vaccine capacity to stimulate certain immunological responses which might indicate possible protection is evaluated in a larger (around 200) number of individuals. Different doses and schedules are tested, as well as different adjuvants. This phase can last from 6 to 24 months;

- **Phase III:**

In the third and last phase before the possible license for marketing, the efficacy of the vaccine product is tested in a large number of volunteers (thousands of subjects). The number of volunteers will vary inversely to the incidence of infection and/or the expected efficacy of the vaccine product. The smaller the incidence of infection and/or the smaller the expected efficacy of the vaccine product, the larger the number of volunteers required. The efficacy is measured by comparing the rates of infection of individuals who received the product and those who received placebo. These trials last from 3 to 5 years and are very expensive.

A high level of efficacy in Phase III does not guarantee effectiveness in controlling the epidemic. This must be assessed under the normal working conditions of the health system, which are different from the special conditions in which the effectiveness trials (Phase III) are conducted, when healthy volunteers are selected and receive the vaccine product or the placebo under highly controlled conditions. Effectiveness depends on the coverage, which is associated with the price of the products and the level of organization of the health services.

The following table lists the types of experimental HIV vaccines that were or are being tested, involving over 3,000 human volunteers non-infected with HIV, in Phase I and

Phase II safety and immunogenicity trials in Australia, Belgium, Brazil, China, Cuba, England, France, Switzerland, Thailand, Uganda and the United States, until 1999.

Once demonstrated to be safe and capable to stimulate lasting immunological responses, some of these vaccines probably might be evaluated in large scale Phase III (efficacy) trials. Only two Phase III (efficacy) trials have been started so far, one in 1998 in the United States with 5,000 volunteers at risk of sexual transmission, and the other with 2,500 injecting drug users volunteers in Thailand (1999). The two experimental vaccines currently being tested are based on the gp120 (strains BB in the USA and BB/BE in Thailand). In addition, a therapeutic vaccine (inactivated virus with deletion of gp120) is also undergoing Phase III trials in the USA.

Since HIV strains vary and populations might differ in their capacity to respond to vaccination, vaccine candidate products must undergo the different testing phases in different population/countries, with the purpose of finding an effective and appropriate vaccine to be used in the prevention of HIV infection and AIDS.

Since there are several HIV subtypes circulating in Brazil, candidate vaccines to be tested must be antigenically related to them.

Vaccine products tested in Phases I/II in volunteers non-infected by HIV*
1999 Update

Experimental vaccine	Manufacturer	Site of clinical trial
Envelope subunits		
Rgp 160	**MicroGeneSys**	**USA**
	Immuno Ag	**USA**
	Pasteur-Merieux-Connaught	**France**
	University of Brussels	**Belgium**
Rgp 120	**Biocine**	**USA, Switzerland**
	SmithKline/Beecham	**England**
	VaxGen/Genentech**	**USA, Thailand**
	Biocine/Chiron	**USA/Thailand**
Synthetic peptides		
V3-MPAS	**United Biomedical Inc.**	**USA, Thailand, Brazil, Australia, China**
V3PPD conjugate	**Serum and Vaccines Institute**	**Switzerland, Israel**
HGP-30 (p17)	**Viral Technologies**	**USA, England**
V3, V3-p24	**Pasteur-Merieux-Connaught**	**France**
rV3 peptides	**Centro Ingineria Genetica Biotecnologia**	**Cuba**
Rp24	**Chiron**	**USA**
Particles		
Ty-p24 VLP	**British Biotechnology**	**England**
Live vector/combinations (prime-boost)		
Vaccinia-gp 160/rgp160	**Bristol-Myers-Squibb/MicroGeneSys**	**USA**
Vaccinia-env/gag/pol	**Therion Biologicals**	**USA**
Canarypox-gp160	**Pasteur-Merieux-Connaught**	**France, USA**
Canarypox-env/gag/pol/rgp120	**Pasteur-Merieux-Connaught/ Chiron**	**USA, Uganda**
Canary pox-env/gag/pol/ prot/rgp120	**Pasteur-Merieux-Connaught/ Chiron**	**France, USA**
"Naked" DNA		
Env/ver	**Apollon**	**USA**

* Adapted from Osmanov S & Esparza, 1998 (UNAIDS)

** Phase III trials started in the USA (1998) and in Thailand (1999)

5. GENERAL PRINCIPLES OF HIV VACCINE-RELATED TRIALS

1. All HIV vaccine candidate products to be tested must first be approved in safety and immunogenicity trials in animal models. An evaluation trial with human subjects must comply with the relevant National Health Council/CONEP resolutions;

2. Research of HIV vaccines may involve Phase I (safety), Phase II (immunogenicity) or Phase III (effectiveness) trials. If the study proposed is on safety or immunogenicity, the protocol should include a plan for future effectiveness studies;

3. Before starting the study, the laboratory markers to be used to distinguish between natural HIV infection and the immune response to the vaccine product should be determined;

4. If the candidate product was developed abroad, all the researchers, both from the country of origin and Brazil, should collaborate in all the stages of the study, from the development of protocols to the diffusion of data;

5. Studies aiming at assessing the safety, immunogenicity and effectiveness of HIV vaccine candidates in Brazil should have a broad national and international dissemination. This should take place early on to facilitate a visible and transparent debate among researchers and with the civil society about the project's ethical and scientific aspects.

6. The use of free and informed consent is of foremost importance. Consent should be obtained by a trained professional in an environment that respects the dignity of each individual. The wording of the consent should be understandable, taking into account the participants' language, culture and circumstances;

7. The study protocol should include written guarantees that the manufacturer will provide sufficient amounts of vaccine, free of charge, for the duration of the study. If the proposed study is on safety and/or immunogenicity, in addition to plans for efficacy studies there should be a written assurance that the manufacturer will provide sufficient amounts of the vaccine, free of charge, for all the studies proposed. If the candidate product is shown to be efficient, should must be an assurance of its free provision to all study participants, for as long as required to ensure its immunizing activity;

8. There should be a written guarantee that, if the vaccine candidate product under study proves to be efficient and adequate for large-scale public use, including strain-specific, if indicated, the manufacturer will provide this vaccine to Brazil at special prices within an appropriate period;

9. All involved partners should reach an *a priori* agreement on mechanisms to ensure the transfer of technology, including the local production in case of vaccines developed abroad, as well as the issues pertaining to intellectual property;

10. All volunteers in the study should receive appropriate counseling both at the time of recruitment and at the different stages of the trial. The study protocol should include the planning for the counseling process;

11 Study sponsors should ensure their full support to the institutions involved in the HIV vaccine trials to develop the research potential required by the trial, including training of personnel, logistic support and infrastructure;

12. All studies should be conducted by a team of researchers with multidisciplinary knowledge and experience. The Brazilian institution to which the main researcher is affiliated must be responsible for the trial;

13. There should be previous agreement that if the volunteers suffer any complication or injury secondary to the vaccine product the sponsor will be responsible for their treatment and rehabilitation. Volunteers must have guaranteed access to the best proven preventive and therapeutic care. There must be agreements with hospitals or health care institutions for the provision of the required medical and rehabilitation services;

14. A monitoring system for long-term side effects in the volunteers must be set up and volunteers must be followed for at least 5 years after the end of the trial;

15. All HIV/AIDS vaccine studies must be assessed and monitored by the National HIV Vaccine Committee;

The protocols submitted to evaluation must comply with Resolution #251/97 of the National Commission of Ethics in Research.

6. STRUCTURE AND ACTIVITIES OF THE NATIONAL HIV VACCINE PLAN

6. 1. General description

The National Plan includes virological and immunological studies, clinical and epidemiological trials, socio-behavioral studies and the development and production of supplies and vaccines. It has the following structure:

Ministry of Health National STD/AIDS Program National Vaccine Committee

- Identification of research priorities;
- Evaluation of research proposals;
- Adaptation of the infrastructure, including training; and
- Guarantee of compliance with the international ethical requirements.

Virological and immunological studies	**Clinical and epidemiological trials**	**Socio-behavioral studies**	**Development and production of supplies and vaccines**
. HIV isolation and characterization . TLC . Neutralizing antibodies	. Establishment of cohorts (HIV-positive and HIV-negative individuals, perinatal) . HIV incidence studies . Risk factors studies . Phase I/II (safety and immunogenicity) studies . Phase III studies (effectiveness) . Long-term follow-up of study participants.	. Vulnerability studies . Evaluation of non-vaccine preventive measures . Study of the social dynamics of the epidemic	. Product availability . Intellectual property . Transfer of technology

6. 2. Role of the MOH – National STD/AIDS Program (NAP)

According to the national multisectorial strategy for the prevention and control of STD and AIDS, the NAP is the key sector for the implementation of the proposed vaccine development plan. With the assistance of the National HIV Vaccine Committee, it is responsible for the planning and implementation of all activities related to the evaluation of HIV vaccines in the country.

6. 3. Role of the National HIV Vaccine Committee

The main responsibilities of the Committee are:

1. Coordination of the HIV vaccine-related activities, under the NAP;

2. Assistance to the NAP in identifying prioritary activities related to HIV vaccines, including virological and immunological studies, clinical and epidemiological trials, socio-behavioral studies and the development and production of supplies and vaccines;

3. Identification of institutional infrastructure and training needs;

4. Encouragement of agreements for the transfer of technology;

5. Evaluation of HIV vaccine-related research protocols and proposals.

7. EVALUATION OF PROPOSALS AND PROTOCOLS

7. 1. Technical evaluation

HIV vaccine-related research proposals and protocols must be submitted to the National Coordination Office for STD and AIDS before they are implemented. The National Coordinating Office, through the National Vaccine Committee, must verify that the vaccine protocols comply with the specifications of the appropriate Good Clinical and Laboratory Practices Codes and with the specifications of the National Health Council (National Commission of Ethics in Research - CONEP).

7. 2. Research activities required for the conduction of HIV vaccine-related studies

The National HIV Vaccine Committee will provide assistance to the NAP to:

- Identify research priorities in the different areas included in the Plan;
- Facilitate the collaboration among all the participating institutions, making optimal use of infrastructure, personnel and expertise;
- Review the research proposals submitted and try to identify funding possibilities, when pertinent;
- Ensure continuous quality during the implementation of the National HIV Plan;
- Interact with other ministries and national research agencies;
- Interact with international agencies and the pharmaceutical industry.

The MOH will support institutions and researchers conducting the HIV vaccine-related studies, through the maintenance and creation of new "Centers for the Development and Evaluation of HIV Vaccines". Each Center might include all the participating institutions active in the different priority areas defined in the National Plan.

These institutions must be able to work together in order to conduct comprehensive HIV vaccine studies. The feasibility of this joint work will depend on several factors, including geographical location, the institutions' administrative structures and a clear demonstration of their willingness to work together. It is also essential that they have a good work relationship with potential study population groups for future vaccine trials, with the media and with NGOs.

To conduct these research activities, the Brazilian institutions and their eventual international collaborators must have experience in or the potential capacity for:

7.2.1. Virological and immunological studies, including:

- Isolation and characterization of HIV strains;
- Staff trained in immunology and retrovirology;
- Experience in HIV virology research, immunology and molecular biology;
- Existing or implemented techniques: assessment of the humoral and cell response to HIV infection, flow cytometry, techniques for viral load determination, and evaluation of resistance to antiretroviral drugs;
- Appropriate contention equipment and facilities;
- Availability to work as a reference laboratory for the centers and institutions responsible for the conduction of the clinical/epidemiological/sociobehavioral trials.

7.2.2. Clinical and epidemiological trials

Clinical trials including:

- Staff trained in clinical research and provision of medical care to HIV/AIDS patients;
- Access to a clinical laboratory complying with good laboratory practices;
- Possibility of providing the required education and counseling;
- Access to appropriate populations for the Phase I/II clinical trials and eventual effectiveness trials;

Epidemiological trials and data management, including:

- Staff trained in epidemiology;
- Experience in conducting cohort studies/clinical trials;
- Access to populations with probable high HIV incidence rates;
- Provision of education and counseling to study populations;
- Experience in following cohorts and in data management and statistical analysis;
- Computer hardware and software appropriate for epidemiological studies.

7.2.3. Socio-behavioral studies, including:

- Sound knowledge on the technical and practical aspects of the social and behavioral issues of HIV infection;
- Staff trained in research methods, with good knowledge of quantitative and qualitative approaches;
- Sensitivity about ways to inform the public and interaction with the mass media;
- Active in the field of STD/AIDS prevention, with recognized capacity to relate and exchanges with NGOs.

7.2.4. Development and production of supplies and vaccines, including:

- Installed or potential capacity to produce the supplies required for conducting the trials and eventually produce or participate in the production of HIV vaccines;

7. 3. Guidelines for the submission of proposals and protocols

The Committee will receive all the proposals and protocols related to the different steps of the development of HIV vaccines for registration purposes and assessment as to priority ranking and relevance. Their technical, scientific and ethical aspects will be evaluated.

7.3.1. Data monitoring and safety commission (CMSD)

In each trial, the establishment of a monitoring and data safety commissions (CMSD) to evaluate data from HIV vaccine research studies conducted in Brazil is recommended. These commissions should be multidisciplinary, with the participation of individuals unrelated to the study, the researchers or the sponsors. For international multicentric trials, there is the additional recommendation to establish an international CMSD, with appropriate representation from research institutions and national and international regulatory agencies.

7.3.2. Multidisciplinary community follow-up committees (CCMA)

In each trial, the implementation of multidisplinary community follow-up committees (CCMA) is recommended. These committees should participate in the research process, especially in the ethical aspects and the human rights of the volunteers. They must be independent both from researchers and sponsors.

7.3.3. Selection of vaccine candidate products

The National Vaccine Committee, together with the NAP, will review all preclinical data and previous results of trials involving human subjects and recommend (or not) a vaccine product for evaluation, according to the previously defined General Principles of HIV Vaccine-Related Trials. The decision will be based on the research's relevance for the country, the evidence of safety and immunogenicity, on the report of the vaccine antigen with the HIV strains circulating in the country and on the potential effectiveness.

7.3.4. Setting up and maintaining cohorts

In order to assess the incidence of HIV infection, for behavioral studies, counseling and discussion about free and informed participation in vaccine candidate products trials, cohorts epidemiologically compatible with the research objectives should be set up.

7.3.5. Virological and immunological studies and the development and production of supplies and vaccines

Specific projects in the different areas involved should be formulated, not only for developing clinical trials but also particularly for the transfer of technology, with local research and production of supplies and of the vaccine candidates themselves.

8. EXECUTIVE SUMMARY

The position of the MINISTRY OF HEALTH is that:

1. All efforts should be combined to prevent the greater dissemination of HIV infection, to continue prevention activities, to propagate appeals for solidarity and non-discrimination, to provide treatment against the virus and opportunistic infections and to carry out research on new drugs and vaccines;

2. In international projects, all researchers involved must collaborate in all steps of the trials, from the planning of the protocols to the utilization of the results obtained;

3. The different Phase I/II trials conducted in the countries of origin shall be repeated in Brazil whenever deemed convenient. This is justified by possible differences in immunological responses and side effects due to factors such as nutritional status, different viral strains, and presence of other infections and/or genetic differences in the different populations. Repeated or parallel Phase I/II studies will also contribute to staff training and institutional strengthening;

4. Research benefits and difficulties should be equally divided. Brazil must have access to the drugs, prevention strategies, health care, vaccines and any other benefits resulting from the study;

5. Research projects must include training at all levels, not only related to the specific research. This includes support to infrastructure and improvement of research conditions;

6. The expansion of immunological, virological and clinico-epidemiological trials in Brazil is fundamental;

7. It is deemed timely to increase the scientific knowledge on the influence of the infecting agent’s and the host’s genetic variability on vaccine effectiveness, as well as the

assessment of other regional factors;

8. It must be emphasized which decisions on the types of vaccines to be evaluated, the final research planning, the identification of sites and respective institutions, and all other elements inherent to the conduction of clinical trials related to HIV vaccines in Brazil shall be based on strict internationally accepted ethical and scientific criteria.

The current revision of the National HIV Vaccine Plan expands the scope of its action within the national and international efforts for the development and availability of effective HIV vaccines. Its priorities are:

a) virological and immunological studies (HIV isolation and characterization, establishment of a national repository, and techniques for humoral and cellular immunity evaluation);

b) clinical and epidemiological trials (setting up and maintenance of cohorts (HIV-positive and HIV-negative individuals, perinatal), HIV incidence studies, risk factors studies, Phase I/II trials (safety and immunogenicity), Phase III trials (effectiveness);

c) socio-behavioral studies (vulnerability studies, evaluation of non-vaccine prevention measures, study of the social dynamics of the epidemic);

d) development and production of supplies and vaccines (product availability, intellectual property, transfer of technology).

Targets:

Short term:

- Establishment of forums of debate, including the MOH website, aiming at the dynamic development of the National HIV Vaccine Plan, deepening and expanding the relations with the scientific community and the civil society;
- International meeting to present the National Plan, for purposes of dissemination, networking, exchange of experiences and update;
- Meeting with funding agencies, manufacturers, Brazilian researchers and institutions and the civil society;
- Increase of the relationships of effective collaboration, not only South-North but principally South-South.

Short/medium term:

- Definition of research and development priorities in the different areas, with funding and collaboration from the Research Support Funds (FAP), FINEP, CNPq, MOH, UNAIDS, The World Bank and other international agencies;
- Encouragement of Phase I and Phase II studies of HIV/AIDS vaccine

candidates, strengthening the existing vaccine centers and promoting the creation of new ones.

Medium term:

- Preparation for Phase III trials (strengthening and expansion of the cohorts, including in new centers, adequation of infrastructure, training of personnel);
- Transfer of technology

Medium/long term

- Production of supplies and vaccines

ANNEX I – SPECIFIC ACTIVITIES

This Annex provides a transparent presentation of the main differences of this *Revision* in relation to the original 1992 Plan. For instance, at that time, the role of epidemiology was conceived exclusively as the background condition for cohort studies for efficacy trials; "laboratory" (bench) studies as pertaining only to the isolation and characterization of the HIV strains circulating in the country; clinical trials, for the testing of products or concepts in Phase I (safety/innocuity) and Phase II (immunogenicity) trials; and behaviour studies, for assessing the acceptance of effectiveness (Phase III) trials by recruited volunteers, the authorities and the public opinion.

However, when the first studies were started, it became very clear that the four components of the original Plan were so closely interwoven that it would be impossible to separate them. Dynamically, they influenced one another: epidemiological trials were conducted in close association with behavioural and clinical studies, in a model, still being refined, which changed the perspectives of the different stakeholders. This model demands a competent process of methodological triangulation that goes beyond the mere design of a matrix of empirical qualitative and quantitative data. In particular, the use of the category *vulnerability*, instead of the epidemiological concept of *risk*, generally obtained by statistical measurements (*odds ratio*), must be analyzed more in depth.

Bench studies stress the monitoring of the epidemic in line with the recent developments in molecular epidemiology. Virological, immunological and biochemical studies were carried out with the purpose of increasing the understanding of the process at the molecular, cellular and organic systems' levels. In addition, they have contributed to improve the virological (e.g., determination of the viral load, early diagnosis) and immunological evaluations.

Clinical trials have also incorporated new perspectives influenced by the results of the epidemiological and behavioral studies with volunteers from the incidence cohorts. Important developments resulted from seroconversions among the volunteered followed. On one hand, there was the early isolation of HIV by the system of laboratories organized in a network associated to the National HIV Vaccine Plan; on the other, the study of the development of the infection (natural history of the disease) in these recent seroconverted individuals, without immediate therapeutic intervention or receiving early treatment with combinations of antiretroviral drugs. In the latter, the clinical trials have contributed to the understanding of the intermediate outcomes of vaccine studies (*secondary end points*). A single Phase I/II trial (safety/immunogenicity) was carried out in this period, in 1995/96, using a synthetic peptide manufactured by an American laboratory (U.B.I.). The results, while non-satisfactory given the nature and length of the immune response, have allowed some important conclusions: (1) the product may be considered safe, without significant adverse effects; (2) the study triggered a broad debate on the technical and ethical aspects of vaccine candidate trials in Brazil; (3) participating teams in Belo Horizonte and in Rio de Janeiro have gained an experience which will be important in other future clinical trials.

In a design more appropriate to the current situation, the different axes of the new Plan (1999 Revision) are conceived as *components.* However, they will continue to be called s*tudies*, given the heavier concentration in one of the fields and to allow comparisons with the original 1992 Plan and with plans developed with the participation of UNAIDS/WHO in other developing countries. There was an explicit and deliberate decision to consider the transdisciplinary nature of the HIV/AIDS vaccine studies as indispensable. These studies have different virological, immunological, clinical, epidemiological and behavioural components, which can be identified in the following items:

Virological and immunological studies
Clinical and epidemiological trials
Socio-behavioural studies.

Clinical and epidemiological trials were grouped in a single item, given the near impossibility of splitting them in the three clinical trial phases, studies of the natural history of the disease and even studies of early treatment and of observation of the secondary end points. The socio-behavioural trials were kept separate, in spite of their interactions with the others, particularly epidemiological ones. A new chapter, "Development, Production and Availability of Supplies and Vaccines", not present in the 1992 Plan, was added, although some of its aspects already were addressed.

1. Virological and Immunological Studies

HIV-1 Isolation and Characterization

Given the importance of and the need to obtain information on the genetic and antigenic properties of the HIV strains causing the epidemic in Brazil, HIV isolation and characterization studies should receive a high priority in the National HIV Vaccine Plan. Their general objective is the establishment of a system to monitor the genetic and antigenic variation of HIV strains in Brazil, an information which is essential for the evaluation and development of HIV vaccines potentially effective in the country.

In order to obtain the data required to correlate the genetic, immunological and biological properties of HIV-1 isolates and to facilitate the development of appropriate vaccines, the NAP initially established the Collaborative Network for the Isolation and Characterization of HIV-1 in Brazil. The network was composed by primary sites, a national reference laboratory and secondary laboratories. The Primary Sites (the Federal University of Minas Gerais, in Belo Horizonte, the Banco da Providência Outpatient Clinic and the Hospital Evandro Chagas – Oswaldo Cruz Foundation, in Rio de Janeiro, and the AIDS Reference Center in Santos and Project Vela Vista in São Paulo), were responsible for the selection of volunteers and the collection and shipping of samples to the national reference laboratory. The Central Reference Laboratory (Advanced Public Health Laboratory of the Gonçalo Muniz Research Center – Oswaldo Cruz Foundation, in Salvador) was responsible for the viral isolation, expansion and storage, as well as for the distribution of samples to the network's secondary laboratories (Oswaldo Cruz AIDS and Immunology

Laboratories, LASP, CpqGM, FIOCRUZ; UFRJ Molecular Virology Laboratory; the Retrovirology Laboratory and the Microbiology Service of the Instituto Adolfo Lutz, in São Paulo, and the UFMG Virology Laboratory), which performed samples' genetic, biological and immunological characterization.

This network has carried out three projects: a) Genotypic, biological and immunological characterization of HIV-1 isolates (prevalent samples) from three vaccine evaluation sites (RJ, MG and SP); b) Genotypic, biological and immunological characterization of HIV-1 isolates (incidence samples) from three vaccine evaluation sites; c) Prevalence of HIV-1 subtypes in Brazil.

In April 1997, this network was restructured into collection sites, national repository, sequencing and serotyping laboratory, HMA laboratory and a technical advisory committee.

Given the recent progress of the studies on HIV-1 polymorphism in Brazil and aiming at reducing costs, a new polymorphism surveillance strategy was designed. The HMA screening and sample sequencing activities were transferred from the Advanced Public Health Laboratories/CPqGM and the AIDS and Molecular Immunology Laboratory/IOC to the national repository.

2. Clinical and epidemiological trials

Clinical trials

In order to conduct clinical Phase I/II (safety and immunogenicity) and Phase III (efficacy) trials with HIV/AIDS vaccine candidate products, experienced researchers and appropriate infrastructure are required. The careful and frequent monitoring of side effects, final clinical outcomes and laboratory results is of the utmost importance. Researchers must have access to specialized medical and laboratory services where they can refer volunteers who develop medical problems or complications.

The facilities for clinical trials must have room, equipment and personnel trained for the recruitment, interviewing and counseling of volunteers, physical examination, nursing tasks, data management, storage of the study records and supplies, and appropriate vaccine storage. Clinical tests required for the trials include the determination of CD4+ T lymphocytes and CD8+ levels and viral load, in addition to normal hematology exams, liver and renal function tests, blood sugar, pregnancy tests, urinalysis and STD diagnostic tests. These exams must be performed in laboratories that comply with the good laboratory practices required by the Data Safety and Monitoring Commission, vaccine manufacturers and national and international regulatory vaccine registration authorities.

Appropriate guidelines must be established so that there is consensus on how and when to break codes during the trials to monitor the research progress. Ethical considerations must be rigorously addressed and follow international standards. To provide appropriate follow-up, budgets must include items to facilitate volunteer participation, including accommodation (if required), food and transportation costs. Health information must be given both to the vaccine recipients and to the general population. Laboratories participating in clinical trials must meet international standards.

The selection and training of appropriate research personnel are considered immediate requirements. Selection must take into account the candidate's motivation, interest and dedication and training in research methodologies. Training includes a quick and rigorous course on counseling for staff at all levels, seminars and periodic individual training for in-service training and update, meetings of personnel or different trial centers, and the provision of journals and other relevant publications. Local training must be encouraged, but units or individuals may take the initiative to seek training for their staff in appropriate Brazilian or foreign institutions.

Research teams should be composed of: main researcher, physicians, nursing staff, social scientists and psychologists, counseling staff, laboratory personnel, pharmacists and data managers/biostatisticians. Other professional categories eventually required for an appropriate clinical trial in the clinic or local reference center should be included. The creation of community follow-up committees should be encouraged.

Epidemiological studies

It is unnecessary to stress the importance of the epidemiological component in this type of trial. The fundamental albeit not the exclusive issue is the design of the cohort studies to determine the baseline of the epidemic's behavior in certain population groups, how it is disseminated and what are the most relevant epidemiological characteristics when groups with different levels of vulnerability are selected for study. The characteristics one seeks to determine are the relative frequencies of HIV-positivity among the candidates to participate in the trial (erroneously called *prevalences*), profiles of behaviors and practices and, specially, the incidence of new infection among the volunteers selected. In order to do that, the research institutions must be able to carry out the usual procedures of epidemiological trials, which mandatory include those listed below.

As a preliminary condition for the conduction of Phase III effectiveness trials of preventive vaccines, institutions with the capacity to recruit, enroll and longitudinally follow-up HIV-negative individuals must be developed or strengthened. Their institutional characteristics, competencies and things offered to the cohort participants should include the following:

1. the cohort studied must have access to a medical institution where the volunteers can receive treatment for medical problems arising during a possible future vaccine trial;

2. the institutions must be capable of managing and analyzing data from all the

multidisciplinary trials conducted;

3. epidemiological studies on the types of viral transmission are required and the incidence of HIV infection in the seronegative cohorts must be determined and monitored;

4. counseling and interventions to prevent HIV infection must be provided to the cohort members and their effects on the incidence of HIV must be determined and monitored;

5. the cohort must have access to appropriate laboratory facilities for carrying out the required immunological, hematological and chemical tests;

6. one of the priorities of the cohort study should be the continuous behavioral and/or sociological investigation, aiming at understanding the social/behavioral/cultural factors that influence the cohort, including risk factors for HIV infection. This requirement makes epidemiological trials inevitable partners of socio-behavioral studies, which are analyzed separately.

Two other aspects of the original 1992 Plan should be mentioned. One concerns the feasibility of efficacy trials (Phase III) and involves the presumable incidence, which cannot be too small (at least around 2.0 per 100 persons-year of follow-up), and the proportion of participants lost to follow-up, which cannot be too big. Both these characteristics can only be estimated "a priori" after the required preliminary studies in incidence cohorts.

The other aspect, always valid in any circumstance, concerns the commitment of the funding agents ("sponsors"), since this type of trial must have a guaranteed, stable and long-term funding.

3. Socio-behavioral studies

There are three types of social studies: gathering of contextual information, understanding of the participants and community support. The gathering of contextual information precedes the beginning of the trial and is an essential background to the other activities. It incorporates four interrelated dimensions, which should be explored through specific studies or familiarization with existing studies. The first concerns the socio-demographic issues enabling the definition of recruiting strategies. The second addresses the understanding of the dynamics of the health services available in the region of the trial, to enable the design of strategies for recruitment and for monitoring intercurrent events. The third is the understanding of the system of beliefs and values and the mapping of the available information on vaccines in general and HIV vaccines specifically, aiming at making available the knowledge required to enable informed consent for participating in the vaccine trials. Finally, the fourth dimension refers to the identification of the essential counterparts, individuals representing the groups where volunteers will be recruited. A

range of institutions from the public sector and the organized civil society can be considered. The mapping of NGOs active in the fields of human rights and AIDS and a good dialogue with their leaders is essential to ensure the ethical conduction of vaccine trials. Obviously this stage includes the appropriation of the basic knowledge about the ethics of vaccine trials, which implies not only the information on the appropriate procedures to submit vaccine trial proposals but also the identification of the community's concerns in this area.

Two other aspects of the participants' perspective should be considered: recruitment per se and follow up for the duration of the trial. From the social studies perspective, the crucial issue in recruiting is understanding the motivations to participate in vaccine trials. Such motivations are partly anchored in the available repertories which give sense to vaccines, an aspect intrinsically linked to past experiences with vaccines – both past and current. The understanding of these aspects of the present world is essential for developing an information program appropriate to the participants' needs. This is the background that will provide the conditions required to deal appropriately with informed consent, an ethical assumption of research involving human subjects. The follow-up of participants during the trial involves two types of activities. The first refers to the different types of counseling which are mandatory: pre-enrollment counseling, aiming at ensuring the understanding of the information and the psicosocial readiness to participate in the trials; counseling in crises, generated by various factors including potential discrimination of participants, side effects and aspects related with risk practices for HIV infection; and continuous support, which includes the monitoring of social practices. Thus, the monitoring of social practices is a component of follow-up and is fundamental for the understanding of the chain of factors leading to a conclusion about the vaccine efficacy.

Community support concerns the continuous process of providing information ensuring the transparency of the research process and enabling the continuous population support to the conduction of vaccine trials. It involves the development of communication strategies which include the elaboration of specific materials to be distributed to the population, systematic press releases and the training of media professionals for the correct use of the technical terms involved therein. It also includes monitoring of public opinion, either through the media or by specific opinion surveys.

Socio-behavioural studies, thus, must be conducted before, during and after starting the vaccine trials. Before, in order to obtain the contextual information, understand the motivations to participate in the trials and develop appropriate information processes. During, to provide continuous counseling and monitor the social practices of the participants. After, to provide the required support given the possible social and health consequences of participation in trials.

4. Development and production of supplies and vaccines

In addition to the isolation and characterization of HIV strains transfer of technology will be necessary, including the training of personnel at the institution/manufacturer responsible for the development of the immunological/virological techniques and the vaccine candidate, as well as the adequation of the Brazilian institution's infrastructure, quality control procedures and production methods.

In summary, it is necessary to have a diagnosis of the Brazilian institutions with the installed capacity for production (adapting them according to the needs), facilities compatible with the good manufacturing practices (GMP) requirements and capacity of internal quality control of the final product, the production steps and the preliminary immunity tests, in the case of a vaccine, and reproducibility, in the case of supplies.

5. Availability and Advocacy

If an effective product is successfully developed, as expected, at prices compatible with the coverage needs for the control of the epidemic, the National HIV Vaccine Committee should participate actively in the debate on the availability of vaccines for the entire Brazilian population. This is the core of the controversy between the humanitarian character of the initiative of HIV vaccine production and the commercial interests of the big vaccine manufacturers in worldwide scale. It is necessary to participate in the so-called "advocacy" efforts for a greater commitment of these manufacturers in applying their own resources in the development of HIV vaccines. From a developing countries' perspective, one must always have present the issue of availability of the products generated by the international effort, refusing the exclusive and passive role of eventual field for the conduction of effectiveness (Phase III) trials of the vaccine candidate products. In this case, advocacy is expressed by a discussion of the availability of effective vaccines for the entire world population at risk. The issue is far more complex and is associated not only to the development of new types of vaccines but also to the transfer of production technology and to rediscussion of intellectual property in terms that are more appropriate to the urgency to combat this epidemic which strikes mankind at the threshold of the XXI century. This debate, which may be called "anthropology of position making" instead of "advocacy", is actually an incursion in macroethics, as relevant or more than the ethics usually concerned in the protection of human subjects participating in trials of vaccines and other products.

Through the National HIV Vaccine Committee, the NAP should include this discussion in the Brazilian public health *agenda*, becoming associated at the national level with the efforts to attain self-sufficiency in the production (or at least the availability) of vaccines in

general. At the international level, it should continue its close relationship with international agencies working towards the same objective, especially with UNAIDS, its privileged partner.

6. Data Management

The Ministry of Health's NAP/National HIV Vaccine Committee must evaluate the data management capacity and the needs of training and infrastructure for the multidisciplinary activities of HIV vaccine candidates research.

Research staff selected for the Phase I and Phase II trials must receive formal training for them, as well as for possible future Phase III trials. All data must be computerized and internal and external quality control must be guaranteed.

The participating institutions must ensure the storage and the safety of the data collected during the conduction of all trials. The main researcher must keep an appropriate back-up copy of the data. The main researcher and the CMSD will keep in contact to monitor the need and the timing of any eventual data analysis before the end of the trial. At the end of the trial, a copy of the full set of clean data files will be given to the Ministry of Health for storage. These confidential files will be available for any eventual analysis during the trial and for future review.

ANNEX II – HISTORICAL BACKGROUND

Brazilian participation in international trials of HIV vaccine candidates

In July 1991, a team from the Vaccine Development Unit (VDU) of the Global Programme on AIDS (GPA) of the World Health Organization (WHO) visited Brazil, meeting staff from the Ministry of Health, the coordinating officers of the National STD/AIDS Programme and several scientific institutions to discuss the feasibility of the Brazilian participation in the world effort for the development of HIV vaccines. After this visit and based on previously determined criteria, GPA/WHO selected Brazil and three other countries (Rwanda, Thailand and Uganda), among 14 developing countries assessed, as sites where trials with HIV vaccine candidates could be conducted in a first moment. It was recognized that the Brazilian scientific institutions had the technical potential that would allow the development of research protocols related to HIV vaccine research, with the required scientific competence and the adhesion to the ethical principles of research involving human subjects.

After this preliminary selection, a GPA/WHO team visited Brazil in December 1991 to start discussions on possible HIV/AIDS vaccine research in the country. These discussions were interrupted after the occurrence of misunderstandings with the then Minister of Health and contacts with WHO were only resumed in February 1992, when a new team took office in the MOH. Soon afterwards, by request of the Minister of Health, the National AIDS Commission, after consultating representatives from the Brazilian scientific community, prepared a document of intent, which was formally approved by the Minister in March 1992.

In July 1992, the Minister of Health created the National HIV Vaccine Committee, linked to the NAP. GPA/WHO was then invited to a second joint meeting with the National AIDS Commission. In this visit (as in the previous one) there was no discussion of a specific vaccine for evaluation in Brazil. The meetings focused on the state of the art of vaccine development, with presentation and discussion of available data on the 16 vaccines under evaluation (or already evaluated) in Phase I/II trials in industrialized countries, and the Brazilian responsibilities concerning the establishment of a site, with WHO support, to evaluate an HIV vaccine. It was agreed that the purpose of such a site would be the evaluation of preventive HIV vaccine candidates; in addition, it should be adequate for the future evaluation of therapeutic and perinatal vaccine candidates, if the Government decided later to do so. It was also agreed that it should provide a favourable environment where national scientists, international collaborators, including WHO, and vaccine manufacturers could work together towards the common purpose of HIV vaccine-related research, and that the quality of the data collected would meet the requirements for the registration of any vaccine proved to be effective.

As a result of this meeting, it was defined that the Brazilian government would set the criteria for defining and implementing one or more sites for the evaluation, following internationally accepted ethical and technical standards and with logistic and financial

support from WHO, in Phase I/II and eventually Phase III trials, of HIV vaccine candidates selected by the MOH. During this visit there was an agreement on strategies for the formulation of the first National HIV Vaccine Plan, which was prepared by the National Vaccine Committee and approved by the Ministry of Health in August 1992.

Since the implementation of the National HIV Vaccine Plan in 1992, several activities specifically related to the development of vaccines in Brazil have taken place, including:

a) Establishment of the National Network for the Isolation and Characterization of HIV strains circulating in Brazil, coordinated by the Gonçalo Moniz Research Center (Fiocruz, Salvador) and involving laboratories of institutions in Minas Gerais, Rio de Janeiro and São Paulo. This network collaborates with the international network for HIV isolation and characterization;

b) Establishment of three national HIV vaccine centers (in Belo Horizonte, Rio de Janeiro and São Paulo);

c) Phase I/II trials to evaluate the safety and immunogenicity of a HIV vaccine candidate using a synthetic peptide similar to the crown of the v3 loop of gp120, provided by United Biomedical Inc (USA). This was a double blind, placebo-controlled trial with HIV-negative volunteers at low risk of infection (six received placebo), between 1995 and 1996. The trial was approved by the ethics committees of the institutions involved and by the Ministry of Health and coordinated by Federal University of Minas Gerais (Belo Horizonte) and (Rio de Janeiro);

d) Establishment and follow-up of non-infected homosexual and bisexual males cohorts to evaluate the incidence of HIV infection, for socio-behavioral studies and discussion of possible participation in future trials of other HIV vaccine candidates. Four cohorts were set up since 1994, three funded by the Ministry of Health and UNAIDS (Belo Horizonte, Rio de Janeiro and São Paulo) and one, also in Rio de Janeiro, funded by the United States National Institutes of Health (NIH). More than 2,000 volunteers were recruited since 1994.