

HIV Vaccines: A Global Perspective

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Abstract: Twenty years after its recognition, HIV/AIDS has become the most important infectious disease globally and the leading cause of death in Africa. A preventive vaccine represents the best long-term hope for its control. The development of such a vaccine, however, has encountered a number of scientific challenges, including the lack of information on immune correlates of protection, the limitations in our understanding of the relevance of primate protection experiments in relation to vaccine-induced protection in humans, and the significance of genetic and immunologic variability of HIV strains for potential vaccine efficacy. Despite these uncertainties, the first phase I trial of an HIV vaccine was conducted in the United States in 1987. Since then more than 30 candidate vaccines have been tested in over 70 phase I/II clinical trials in both industrialized and developing countries. The first HIV vaccine trial in a developing country was conducted in 1993, six years after the first trial in the United States. Since then eighteen phase I/II trials and one phase III trials have been or are being conducted in developing countries, and additional phase II and III trials are planned to start in 2003. Most of these initial trials have been conducted in Thailand, but more recently trials have been initiated in Africa and Latin America and the Caribbean. Over the past years, the HIV vaccine development effort has followed three major overlapping paradigms. The first "wave" of candidate vaccines aimed at inducing neutralizing antibodies. The second wave focused on stimulation of CD8+ T-cell responses. The current "wave" of HIV vaccine research is aimed at optimizing both humoral and cell-mediated immune responses. The first generation of candidate vaccines (based on the HIV envelope protein) entered phase III efficacy evaluation in 1998, and definitive results from these trials will become available in 2003. Plans to ensure wide access to future HIV vaccines must be developed well in advance.

INTRODUCTION

In 2001 the AIDS pandemic reached the 20th anniversary of its recognition. During this time it has been recognized that humanity may be confronting one of the most devastating epidemics in its history, the impact of which is threatening the development and prosperity in major regions of the world [1]. It has also been recognized that the world is in a position to bring the epidemic under control provided that effective preventive and therapeutic interventions are scaled-up and made accessible worldwide. There is also a growing political attention and support to an intensified global response to HIV/AIDS, exemplified by the adoption of the Declaration of Commitment on HIV/AIDS by the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) in June 2001 [2] and by the establishment of the Global Fund to Fight AIDS, Tuberculosis & Malaria [3]. Article 70, of the UNGASS Declaration of Commitment requests to "increase and accelerate research on the development of HIV vaccines, while building national research capacity, especially in developing

countries". This call is a clear recognition of the need to ensure international collaboration and coordination in the development of an HIV vaccine which, in combination with other interventions, should constitute the best long-term hope for the control of the HIV/AIDS pandemic, especially in developing countries.

THE URGENT NEED FOR AN HIV VACCINE

Only twenty years after its recognition, HIV/AIDS has become the most important infectious disease, the leading cause of death in sub-Saharan Africa and the fourth most common worldwide. From approximately 60 million people who have been infected with HIV since the beginning of the epidemic, 20 million have already died of AIDS, 3 million in 2001 alone; this is more than the number of deaths from tuberculosis or malaria, the other two major killers of mankind. Today, 42 million people are living with HIV/AIDS, 95% of them in developing countries, especially in sub-Saharan Africa, which is home to more than 29 million of those infected (Table 1). The average HIV prevalence in the adult population in sub-Saharan Africa is 8.8%. There are seven countries, all in the southern cone of Africa (Botswana, Malawi, Namibia, South Africa, Swaziland, Zambia and Zimbabwe), where more than 20% of adults are already infected with HIV, and in

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Table 1. Regional HIV/AIDS statistics (end of 2002).

Region	Number of people living with HIV/AIDS	Adult prevalence rate (%)	New infections in 2002
Sub-Saharan Africa	29,400,000	8.8	3,500,000
North Africa & Middle East	550,000	0.3	83,000
South and South-East Asia	6,000,000	0.6	700,000
East Asia & Pacific	1,200,000	0.1	270,000
Latin America	1,500,000	0.6	150,000
Caribbean	440,000	2.4	60,000
Eastern Europe & Central Asia	1,200,000	0.6	250,000
Western Europe	570,000	0.3	30,000
North America	980,000	0.6	45,000
Australia & New Zealand	15,000	0.1	500
TOTAL	~ 42,000,000	1.2	~ 5,000,000

nine other African countries the adult HIV prevalence exceeds 10%. The second most affected region in the world is the Caribbean, with an average adult HIV prevalence of 2.4%. In Haiti, for instance, the HIV prevalence among pregnant women is estimated to be 3.8%.

The pandemic continues to progress at a rate of nearly 15,000 new HIV infections every day, 95% of them in developing countries. The devastation that HIV/AIDS is causing in Africa could extend to other continents. In some Asian countries HIV incidence is increasing at an alarming rate, although the overall HIV prevalence remains deceptively low due to the concentrated nature of the epidemic in countries with very large populations [4]. Recent baseline projections of the pandemic indicate that the number of new infections among adults between 2002 and 2010 could rise by a cumulative total of 45 million, although if by 2005 successful preventive interventions are expanded to a global scale, about 29 million of these new infections could be prevented [5]. The observed decline in HIV-1 prevalence in Uganda has largely been ascribed to the implementation of effective HIV/AIDS prevention interventions, which in one of its rural districts drove HIV-1 incidence down from 0.8% in 1990 to 0.52% in 1999 [6]. Nevertheless, as some observers have commented [7], the sustained high rates of transmission across sub-Saharan Africa, even in successful countries, such as Uganda, emphasize the need to develop additional biomedical preventive tools which are simple, affordable and effective, such as microbicides and preventive vaccines [8].

CHALLENGES IN THE DEVELOPMENT OF HIV VACCINES

The development of an HIV vaccine, however, is encountering a number of financial, logistic and scientific challenges.

The global public and private expenditure on research and development (R&D) related to HIV vaccines in 2002 was estimated in the order of US\$ 500 - 600 million, a large proportion of which was provided by the US National Institutes of Health (US-NIH). Although this amount may seem high, it represents only a fraction of the estimated US\$ 3 billion invested annually in HIV research, or an estimated US\$ 9.2 billion that will be required every year for an effective response to the epidemic [9]. Additional 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 improve this situation is to create, or increase, financial incentives to stimulate more active industry participation in the quest for an AIDS vaccine [10]. Financial mechanisms, such as the establishment of a vaccine purchase fund to increase the market potential for future HIV vaccines, or tax breaks for investments in HIV-vaccine R&D, could "pull" industry to make more investments in the field. But it is unlikely that these approaches alone will be sufficient, due to real or perceived limitations in the scientific knowledge, which dictates a need for complementary "push" mechanisms in support of more basic and clinical research [8,10].

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-evaluation sites in developing countries, with

appropriate epidemiological characteristics, will need to be identified and strengthened [11], giving careful consideration to related ethical issues [12,13]. 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 developing countries [14].

Although the above financial and logistic challenges are not negligible, the major obstacles for the development of an HIV vaccine are mostly of a scientific nature [15-19].

AIDS may differ 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 [20]. Despite these gaps in knowledge, experimental vaccines have provided different degrees of protection in immunized animals, which gives rise to a real hope that an effective preventive vaccine against HIV could be developed. Most of the animal experiments have been done in chimpanzees challenged with HIV-1, or in macaque monkeys challenged with either Simian Immunodeficiency Viruses (SIV) or with hybrid HIV/SIV viruses (SHIV). Although chimpanzees immunized with recombinant gp120 (rgp120) were protected against HIV-1 challenges under well-defined experimental conditions, in general, vaccine induced protection in macaque monkeys has been incomplete and difficult to achieve. Most experimental vaccines tested in the SIV/SHIV-macaque model failed to provide absolute protection ("sterilizing immunity") against virus challenges. Instead, vaccination usually resulted in an attenuation of the infection, with reduction of virus load levels and slower progression to disease in immunized animals who become infected after challenge. A major limitation of these experiments has been a failure to provide definitive information on immune correlates of protection. Also, it must be recognized that the relevance of these primate protection experiments in relation to potential vaccine-induced protection in humans remains to be established by future phase III efficacy trials [21].

Another potential obstacle for the development of broadly protective HIV vaccines is related to the extensive genetic variability of the virus [22,23]. Phylogenetic analysis of the nucleotide sequence of the envelope genes (*env*) of numerous HIV-1 strains from different parts of the world has resulted in their classification within a "major" or M group and two minor groups (O and N). HIV-1 strains belonging to the M group are subdivided into at least nine pure genetic subtypes or clades (A-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-subtype recombinational events, resulting in a variety of mosaic viruses. In areas where more than one HIV subtype co-circulate, it is frequent to observe a wide range of inter-subtype unique recombinant forms of the virus, resulting from numerous mixed infections in the community. The most successful mosaic viruses become established as Circulating Recombinant Forms (CRFs), which are associated with several well established or emerging epidemics in different parts of the world [24]. Group M strains are the main cause of the HIV pandemic, and different HIV subtypes and CRFs show distinct geographical differences on their distribution [25]. In 2000, it was estimated that most of the new HIV infections in the world, approximately 47% of them, were caused by subtype C viruses, which are mostly prevalent in Southern Africa, Ethiopia and India (Table 2). Subtype B viruses are prevalent in the Americas and Western Europe, while subtypes A and D are prevalent in Central and Eastern Africa. The epidemic in Thailand and other South East Asian countries is driven by the first identified CRF (CRF01_AE), frequently referred to as subtype E. The epidemic in West Africa is predominantly caused by CRF02_AG, a mosaic virus with a subtype A *env* gene. Other prevalent CRFs have been identified in Eastern Europe, China and South America. It is important, to emphasize, however, that HIV is constantly evolving, increasing the genetic distance between strains and generating new inter- and intra-subtype recombinant viruses [26].

Table 2. Geographical distribution of HIV-1 genetic subtypes.

Region	Predominant subtypes and CRFs
Southern Africa	C
West Africa	CRF02_AG
East Africa (excepting Ethiopia)	A, D, C
Ethiopia	C
Central Africa	A, D
North Africa and Middle East	B
Western Europe	B
Eastern Europe and Central Asia	B, A, CRF03_AB
East Asia and Pacific	B,C, CRF07/08_BC
South East Asia	CRF01_AE
South Asia (including India)	C
Latin America and the Caribbean	B, CRF12_BF
North America	B

The key questions are: What is the relation between the HIV genetic subtypes and a possible

existence of vaccine-relevant immunological types? 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?

This topic is too complex to be discussed here in greater detail, but it has been extensively reviewed elsewhere [27,28]. However a few general comments should be made in this regard. The *env* gene codes for gp120 and gp 41 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, although no clear correlation has been established between genetic subtypes and observed *in vitro* cross-neutralization patterns. 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.

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 [27, 29-31]. Other approaches addressing this problem include the use of cocktail vaccines containing antigens representative of several genetic subtypes [32,33], the design of candidate vaccines targeting at conserved HIV epitopes [34,35], or candidate vaccines based on consensus or ancestor sequences selected to minimize the genetic differences between vaccine strains and contemporary isolates [27, 36]. In any case, the clarification of this issue is of high importance for the development of broadly effective HIV vaccines for developing countries, where multiple subtypes and strains are driving the epidemic.

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 [28, 37]. 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 [38]. For that reason, new generations of envelope based vaccines are also including antigens derived from R5 viruses [32, 39-41].

EVOLUTION OF VACCINE CONCEPTS AND CLINICAL TRIALS

Despite the scientific uncertainties described above, a wide range of candidate vaccines has been developed and tested in animal models. The most promising products have already moved to clinical trials in humans [42]. Preventive vaccines are tested on healthy human volunteers through three sequential clinical trial phases. Phase I and II trials provide safety and immunogenicity data, and are conducted among small numbers of volunteers (20 to 50 for phase I trials, and in the low hundreds for phase II trials). 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 [43]. Phase III trials are usually controlled double-blind trials, involving thousands of volunteers at higher risk of HIV infection, and they present a number of scientific, logistic and ethical challenges (8,11).

The first phase I trial of an HIV candidate vaccine was conducted in the United States in 1987. Since then, more than 10,000 healthy human volunteers have participated in more than 70 different phase I/II trials of over 30 different candidate vaccines. Most of these trials have been conducted in the United States under the aegis of the US-NIH, and in France, sponsored by the Agence Nationale de Recherche sur le SIDA (ANRS), but trials have also been conducted in a number of developing countries (see below).

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 paradigms¹.

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, and received early support from chimpanzee protection experiments [44] and, more recently, from protection experiments using passive transfer of antibodies [45, 46]. Several candidate vaccines based on the envelope proteins of HIV-1 (gp120 or gp160), or on synthetic peptides representing the V3 loop of gp120, have been tested in human trials. In fact, the first human trial of

¹ This analysis derives from a presentation made by one of the authors (JE) at the 1st International AIDS Society Conference on HIV Pathogenesis and Treatment (Buenos Aires, July 2001) and from a Plenary Presentation by Dr. Lawrence Corey at the XIV International AIDS Conference (Barcelona, July 2002).

an HIV vaccine was conducted with a monomeric rgp160 produced in a baculovirus-insect cell system. Improved versions of the envelope approach have included rgp120 or rgp160 produced in mammalian cells, resulting in proteins with a more native glycosylation pattern. Mammalian-cell derived rgp120 candidate vaccines were found to be safe and capable of inducing binding antibodies in a large proportion of volunteers [47], although, as mentioned before, the neutralizing ability of these antibodies was mostly restricted to X4 strains from a homologous subtype [38, 48,49]. With the elucidation of the co-receptor use by different strains of HIV-1, novel envelope candidate vaccines have included R5 strains in their design, such as the two bivalent BB and BE rgp120 candidate vaccines from VaxGen that are being tested in phase III trials (see below) [32, 50,51].

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 [52]. 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 I 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 [53-57]. The best explored of these vectors is ALVAC vCP205 (a subtype B multigenic construct expressing gp120 from the MN strain, the gp41 transmembrane portion from the LAI strain, *gag* from LAI, and portions from the LAI *pol* gene coding for the protease). Subsequent ALVAC trials were conducted with an improved subtype B vector, vCP1452 (a multigenic construct expressing the same genes as vCP205, plus CTL epitopes from *nef* and *pol*, and two vaccinia virus sequences, E3L and K3L, which enhance gene expression), and with a novel vector expressing a subtype E envelope, vCP1521 (a multigenic construct similar to vCP205, in which the MN *env* gene has been replaced by that of 92TH023, a R5 *env* E strain from Thailand [58]). 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 [53-57, 59, 60]. A large body of data with this approach indicates that ALVAC-HIV vectors have been safe and able to elicit detectable CTL responses, but only in about 20-40% of vaccinees. These candidate vaccines, however, have been found to elicit cross-reactive CTL responses against different HIV subtypes, providing some encouragement regarding the possibility of developing broadly protective vaccines [61-63].

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 [31, 64-68], different types of DNA vaccines [69-72] and lipopeptide vaccines [73-75].

The third "wave" of HIV vaccines started with the new century, and it should see a large amount of work aiming at optimizing immune responses by 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 R5 and X4 strains from all HIV subtypes, and/or (2) high levels of long-lasting cross-reactive CTL responses. 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/macaque model induced high levels of CTLs, resulting in marked attenuation of infection after challenge [76]. Initial data from human trials with this candidate vaccine confirmed its ability to induce high levels of cross-subtype CTL reactivity in seronegative volunteers [77]. Other bacterial and viral vectors that are being explored include Fowlpox virus [78-81], Venezuelan Equine Encephalitis (VEE) replicons [82,83], Vesicular Stomatitis Virus vectors [84, 85], BCG [86-88] and *Salmonella* [89,90]. Other researchers are exploring the use of TAT and other regulatory proteins [91-95] or novel genetic vaccine designs, such as those being developed by the Vaccine Research Center of the US National Institutes of Health [35]. And, of course, research will continue into development of more effective prime-boost combinations, the use of novel cytokine adjuvants (IL-2, IL-12, IL-15 and GM-CSF) and different delivery systems. Results from clinical trials with these candidate vaccines will be eagerly awaited.

PHASE III EFFICACY TRIALS

The first phase III trials of an HIV vaccine were initiated in North America in June 1998 and in Thailand in March 1999, using two different versions of bivalent rgp120 candidate vaccines, based on locally prevalent genetic subtypes of HIV-1 (BB for the North American trial, and BE for the Thai trial), produced by VaxGen [32, 50, 51]. Both bivalent candidate vaccines include an X4/B subtype isolate (MN strain) plus an R5 isolate (either the B subtype GNE8 strain, or the E subtype A244 strain). The North American trial, which also involves sites in Canada and the Netherlands, enrolled 5,109 men who have sex with men and 309 heterosexual women at higher risk of HIV infection². The Thai trial enrolled 2,545 volunteers, all of them are injecting

² Harro, C., Judson, F., Brown, S., Coutinho, R., Popovic, V., Gurwith, M.; Vax004 Study Team. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract WeOrD1299.

drug users, and is being conducted in collaboration between the Bangkok Metropolitan Administration and the US Centers for Disease Control and Prevention [96]³. The North American/European trial was completed at the end of 2002, and the Thai trial will be completed by the end of 2003, but already it could be concluded that phase III can be properly conducted in industrialized and developing countries with the highest scientific and ethical standards.

The analysis of results of the above phase III trials will present scientific challenges of its own.⁴ As discussed before, experiments in macaques consistently failed to confer absolute protection against infection, resulting instead in attenuation of the infection. Although these results can not be extrapolated to humans, there is a distinct possibility that the same could happen at least with the first generation of HIV vaccines in humans. For that reason, the ongoing phase III trials have been designed to detect, as a primary endpoint, the acquisition of HIV infection (as determined by serological and nucleic acid tests) and as a secondary endpoint attenuation of the infection (determined by the plasma viral load "set point" and/or the drop of CD4 cell counts). The viral load secondary endpoint was proposed based on results from natural history studies showing a correlation between virus loads and progression to AIDS [97]. Moreover, low viral load levels seem to correlate with a decreased probability of heterosexual transmission of HIV-1 [98]. There is no guarantee, however, that natural history observations are equally applicable to vaccine-induced reduction in viral load levels. On the other hand, there is little doubt that a vaccine which "only" reduces virus load, and thus is able to prevent progression to AIDS and decrease HIV transmission, may have an enormous public health impact and should not be uncritically discarded. The challenge ahead will be to interpret primary and secondary endpoints data in a way that would make sense from both scientific and public health point of views.

The next phase III trial is to be conducted in Thailand, as a collaboration between the Thai Ministry of Public Health, the US Military HIV Research Programme, and the US-NIH. The trial is planned as a community-based trial, involving 16,000 volunteers, and is due to start in 2003⁵ [99]. This trial will assess the efficacy of a prime-boost

combination using ALVAC vCP1521 from Aventis Pasteur, and rgp120 BE (MN/A244) from VaxGen, with the final results expected to become available in 2007 or 2008.

In the meantime, it is important to increase efforts to move additional candidate vaccines to clinical trials, including phase III trials, with a special urgency to develop and test vaccines relevant for use in Africa and other heavily affected areas of the world.

CLINICAL TRIALS IN DEVELOPING COUNTRIES

Vaccine research and trials in developing countries are necessary because: (a) the large majority of infections are occurring in these countries, 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 more frequent in developing countries; (c) the variability of HIV may necessitate testing of candidate vaccines in different areas of the world where different strains are prevalent⁶; and (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 [100,101].

From 1990 to 1992 the former Global Programme on AIDS (GPA) of the World Health Organization (WHO) assessed a number of potential vaccine evaluation sites in developing countries and collaborated with Brazil, Thailand and Uganda in the initial development of their National AIDS Vaccine Plans [100, 102]. Today, the international community recognizes the importance of this partnership between industrialized and developing countries, and many more developing countries are getting engaged in different activities related to HIV vaccine research and evaluation [103-106].

The first HIV vaccine trial in a developing country was conducted in 1993, six years after the first trial in the United States (Table 3). Since then, eighteen phase I/II trials and one phase III trial have been or are being conducted in developing countries, and additional phase II and III trials will start in 2003.

The first trials were conducted in 1993 in China and in 1994 in two of the countries with WHO-sponsored National AIDS Vaccine Plans, Thailand and Brazil. [107-108]. These trials followed initial evaluation in industrialized countries of a prototype MN V3 loop based multibranching synthetic peptide candidate vaccine produced by United Biomedical

³ Choopanya, K., Tappero, J., Pitisuttithum, P., Vanichseni, S., Kitayaporn, D., Sangkum, U., Hiranrus, K., Francis, D. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract WeOrD1300.

⁴ Hudgens, M.G., Hoering, A., Self, S. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract WeOrD1298.

Gilbert P.B., Self S.G., De Gruttola V.G., Hudgens M.G., Hammer S.M. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract MoPeD3643.

⁵ Rerks-Ngarm, S., Pitisuttithum, P., Kitayaporn, D., Nitayaphan, S., Gurnathan, S., Heyward, W., Brown, A. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract LbOr24.

⁶ McCutchan, F.E., Carr, J.K., Harris, M., Dowling, W., Hoelscher, M., Robb, M., Birx, D.L. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract TuOrC1193.

Table 3. HIV Vaccine Trials in Developing Countries

Year	Candidate vaccine	Subtype	Country	Phase	Total number of participants
1993	MN V3 branched peptide	B	China	II	23
1994	MN V3 branched peptide	B	Thailand	II	24
1994	MN V3 branched peptide	B	Brazil	II	30
1995	rgp120 B (MN)	B	Thailand	I/II	30
1995	rgp120 B (SF2)	B	Thailand	I/II	52
1996	V3 multi-epitope polypeptide	B	Cuba	I	30
1997	rgp120 BE (SF2/CM235)	B,E,BE	Thailand	II	380
1998	rgp120 BE (MN/A244)	BE	Thailand	II	90
1999	ALVAC vCP205	B	Uganda	II	40
1999	rgp120 BE (MN/A244)	BE	Thailand	III	2,545
2000	ALVAC vCP1521 +/- rgp120 BE (SF2/CM235)	E	Thailand	I/II	60
2000	ALVAC vCP1521 +/- orgp 160 E (TH023)	E	Thailand	I/II	70
2000	ALVAC vCP1521 +/- rgp120 BE (MN/A244)	E	Thailand	I/II	125
2001	DNA-gag/multi-T-cell epitopes (HIVA)	A	Kenya	I	18
2001	ALVAC vCP1452 +/- rgp120 BB (MN/GNE8)	B	Haiti	II	40
2001	ALVAC vCP1452 +/- rgp120 BB (MN/GNE8)	B	Trinidad	II	40
2001	ALVAC vCP1452 +/- rgp120 BB (MN/GNE8)	B	Brazil	II	40
2002	ALVAC vCP1452 +/- rgp120 BB (MN/GNE8)	B	Peru	II	40
2002	MVA-gag / multi-T-cell epitopes (HIVA)	A	Kenya	I	18
2003*	DNA-HIVA + MVA-HIVA	A	Uganda	II	50
2003*	DNA-HIVA + MVA-HIVA	A	Kenya	II	120
2003*	ALVAC vCP1521 + rgp120 BE (MN/A244)	EB	Thailand	III	16,000

*Planned to start in 2003

Inc. (UBI), although its low immunogenicity did not justify further development.

The first generation of envelope based candidate vaccines that entered phase I/II trials in Thailand in 1995, were monovalent rgp120 based on B subtype X4 strains (MN or SF2) from Genentech and Chiron Biocine, which had been previously evaluated in the United States [109, 110]. These initial trials provided the necessary scientific background to allow Thailand start testing in 1997 a second generation of bivalent BE envelope candidate vaccines⁷. One of these rgp120 candidate vaccines, a bivalent candidate vaccine based on the B-MN and E-A244 strains, entered phase III clinical evaluation in 1999 [32,50]. In the meantime, other countries also

initiated phase I/II HIV vaccine trials. In 1996, a multi-epitope polypeptide V3-based subtype B candidate vaccine was tested in Cuba [111], although that approach is now being replaced by more immunogenic products [112].

The second "wave" of HIV vaccines reached the developing world in 1999, when Uganda, another country with a WHO-sponsored National AIDS Vaccine Plan, conducted its first (US-NIH-sponsored) clinical trial with the already well studied subtype B ALVAC vCP205, at the time when cross-subtype CTL reactivity had been recognized [62, 113,114]. Since then, two series of ALVAC-HIV prime-boost phase I/II trials have been conducted in Thailand and in the Americas. In Thailand, three trials were initiated in 2000 (in collaboration with the US Military HIV Research Programme), in which vCP1521 was given alone or in combination with bivalent rgp120 BE (SF2/CM235), bivalent rgp120 BE (MN/A244), or

⁷ Malia, J.A., Eamsila, C., Chanbancherd, P., Trichavaroj, R., Rungruengthanakit, K., Benenson, M., Gurunathan, S., Dullege, A.M. XIV International AIDS Conference, Barcelona, 7-12 July 2002, Abstract MoPeA3048.

oligomeric rgp160 E (TH023)⁸. One of these prime-boost combinations, vCP1521 and bivalent rgp120 BE (MN/A244), is the one selected for testing in the already mentioned planned phase III trial in Thailand [99,115]. In the meantime, another vaccine combination is being tested in phase I/II trials in the Americas (Brazil, Haiti, Peru, and Trinidad), priming with vCP1452 and boosting with a bivalent rgp120 BB (MN/GNE8) [116]. These trials, which are scientifically driven by the US-NIH-sponsored HIV Vaccine Trial Network (HVTN), were initially planned in anticipation of a future phase III efficacy trial in the Americas with that prime-boost combination. In February 2002, however, a decision was made not to proceed with the proposed phase III trial because it was felt that the relatively low level of CTL responses obtained in preliminary phase II trials conducted in the United States was not sufficient to identify immune correlates of protection, which was one of the major objectives of the trial. The ongoing phase II prime-boost trials in four countries in Latin America and the Caribbean are continuing because they should provide important information about the safety, immunogenicity and timing of the prime-boost combination in populations in these countries⁹.

The second HIV vaccine trial in Africa was conducted in Kenya in 2001, as a collaborative project between the University of Nairobi, the International AIDS Vaccine Initiative (IAVI), Oxford University and the Medical Research Council of the United Kingdom [31,68,117]. The candidate vaccine, which is a DNA construct containing a full *gag* (p17 and p24) plus twenty-five CTL epitopes from *gag*, *pol*, *nef* and *env* of a subtype A strain (this construct being referred to as HIVA), was tested simultaneously in the United Kingdom and Kenya. The second trial in Kenya started in 2002, and is testing an MVA vector containing the same genes as in the DNA product. These two trials will be followed by larger DNA/MVA prime-boost trials in the United Kingdom, Uganda and Kenya.

Other candidate vaccines are in the pipeline, some of which will be tested in developing countries, including novel DNA constructs (subtypes A/B/C), DNA microparticles, new ALVAC-HIV vectors, VEE replicons (subtype C), Adenovirus vectors (subtype

B), envelope and regulatory proteins in novel adjuvants, V2-deleted envelope proteins, and *Salmonella* vectors.

FUTURE ACCESS TO HIV VACCINES

The first opportunity to have an HIV vaccine is at the beginning of 2003, when definitive results of the ongoing phase III trial of rgp120 BB in North America and Europe will become available, although by the time this article is being written (January 2003) these results have not yet become available.

In any case, it is imperative to start planning now how a potential HIV vaccine will be used [8, 118]. Early planning is needed to ensure that, once a vaccine is discovered, it will be made widely accessible to all populations in need without unnecessary delays. 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 [119]. These policies and strategies must be based, among others, on different characteristics of a vaccine, including level of efficacy and cost, and different epidemiological situations of target populations. Of special importance would be to ensure that introduction of vaccination strategies is coordinated with and be complementary to the overall HIV/AIDS prevention effort.

CONCLUDING REMARKS

The development of a highly effective preventive HIV vaccine will not be easy, nor will it be fast. To accelerate its development, it is essential that additional resources are invested in basic research, product development and clinical trials. A major effort must be made to stimulate the development and evaluation of candidate vaccines for developing countries, where 95% of all HIV infections are occurring. Fortunately, major increases in funding of vaccine research have occurred over the last two years by institutions and organizations such as the US NIH, ANRS, IAVI and the HVTN, which have reinvigorated the overall effort. In addition, the WHO-UNAIDS HIV Vaccine Initiative recently launched the "African AIDS Vaccine Programme" (AAVP), a network of African scientists working to promote and facilitate HIV vaccine research and evaluation in Africa. However, it should be emphasized that a future vaccine would not replace other preventive interventions. These future vaccines would need to be delivered as part of comprehensive HIV prevention packages, including health promotion and other interventions. But a safe, highly effective and affordable preventive vaccine will be a major

⁸ Suriyanon, V., Thongcharoen, P., Kamboonruang, C., de Souza, M., Gurunathan, S., Kim-Ratto, S., Kim, J., Duliege, A.M., Brown, A.E. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract WePeB6051.

Thongcharoen, P.T., Suriyanon, V.S., Khamboonruang, C.K., Kim, J.K., Polonis, P., de Souza, M.D.S., Gurunathan, S.G., Brown, A.E.B. XIV International AIDS Conference, Barcelona, 7-12 July 2002. Abstract TuOrA1225.

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⁹ NIAID News, 25 February 2002. Available at: <http://www.niaid.nih.gov/newsroom/releases/phase3hiv.htm>

contribution to improve the global response to the HIV/AIDS pandemic.

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