

HIV Vaccine Development

Professor J.A. Idoko and Dr. S.O. Isa

*Infectious Diseases Programme, Department of Medicine,
Jos University Teaching Hospital, Jos, Plateau State.*

INTRODUCTION TO VACCINES

Vaccines save millions of lives each year and protect many more people from getting sick from a number of diseases including measles, chicken pox, influenza, hepatitis A and B, mumps, pertussis and rubella. They are one of the most powerful and cost-effective public health interventions available today. For example, extensive use of the smallpox vaccine eradicated the disease from the world. Similarly, widespread vaccination against polio has reduced the number of cases of the disease dramatically. Today, the Western Hemisphere, Europe, and many parts of Asia are free from polio. Unfortunately, however, there are a number of important diseases for which we have yet to develop an effective vaccine, including HIV/AIDS, malaria and tuberculosis.

WHAT IS A VACCINE?

The term vaccine is usually used to describe products that are designed to prevent individuals from getting a disease. All of today's licensed vaccines are preventive vaccines. In other words they are not cures and are not designed to help people who are sick or who already have a disease to recover. Scientists, however, are also trying to develop what are called "therapeutic vaccines". Therapeutic vaccines are designed to treat disease, not to prevent it, and could be used by people who are already infected.

All Correspondence to Professor J.A. Idoko

Infectious Diseases Programme,
Department of Medicine,
Jos University Teaching Hospital,
Jos, Plateau State, Nigeria.
E-Mail: jjidoko@yahoo.com

COMMON VACCINE PREVENTABLE DISEASES:

- Chicken pox
- Hepatitis A
- Hepatitis B
- Influenza
- Measles
- Mumps
- Pertussis
- Meningococcal meningitis
- Pneumococcal pneumonia
- Polio

Scientists are currently trying to develop therapeutic vaccines that will help the immune systems of people with HIV, cancer, hepatitis C and a number of other conditions. Therapeutic vaccines for HIV, however, are still very much in the early stages of development and no product has been licensed for use.

HOW DO VACCINES WORK?

Preventive vaccines work by provoking a response from a person's immune system, their body's mechanism for fighting disease. When an individual is given a vaccine against disease X, the vaccine stimulates the body's immune system and teaches it to recognize that disease. This response is then stored in the immune system's memory so that if he or she is exposed to disease X at a later stage the immune system is ready to respond rapidly and to fight off the potential infection. Given the rate of spread of HIV worldwide, even a less-than-ideal vaccine would provide substantial public health benefit and help contain the epidemic.

AN IDEAL HIV AIDS VACCINE WOULD:

- Be effective regardless of the nutritional and health status or ethnicity of the population
- Protect individuals against all subtypes of HIV

- Protect against any route of HIV infection
- Be inexpensive to manufacture and cheaply available to the population
- Be easy to transport and administer
- Be stable under field conditions
- Provide long lasting protection - i.e., require few (if any) follow-up inoculations.

Why Do we Need an HIV Vaccine?

The human toll of AIDS is staggering. Over 20 million men, women and children have died from AIDS. More than 40 million people are living with HIV. Each day another 15,000 people are infected globally[1], out of which 1,500 occur in Nigeria[2].

AIDS is overwhelming the health care systems and national economies particularly in sub-Saharan Africa. More than 95% of all new infections are in developing countries, making HIV / AIDS a serious threat not only to global health, but also to global development. According to the United Nations, medical and human costs of AIDS have actually reversed economic and social development in several countries[3].

Current prevention efforts - including condom education, clean needle distribution, peer education and counseling, providing HIV treatments to reduce mother to child transmission, and making blood supplies safer - have slowed the spread of HIV, but have not stopped it. Current treatments are inadequate because they do not lead to a cure, at best, they slow disease progression. They are complicated to administer, require close medical monitoring, and can cause significant side effects. They are also very costly and as a result, are inaccessible to the majority of people living with HIV/AIDS.

The best long-term hope for controlling AIDS is the development and widespread distribution of a safe, effective and affordable preventive vaccine. The world community eight years ago embraced the goal of developing a safe and effective vaccine by 2007 but we now know that this is not realizable even after 20 years of research. This will require both scientific breakthroughs and increased financial and political support from governments, pharmaceutical companies, international agencies, communities and individuals.

Potential HIV/AIDS Vaccines

There are two different types of vaccines:

Preventive vaccines, which are given to non-infected individuals with the goal of preventing infection and/or disease. Preventive vaccines are known to be the most cost effective for the control and potential eradication of the epidemic.

Therapeutic vaccines are given to infected individuals with the aim of modulating the host immune responses that would allow for better control of the infection and would prevent the development of disease. Therapeutic vaccines could produce secondary preventive effects by decreasing the viral load levels in infected individuals and thus rendering them less infectious.

HIV Vaccine Strategies

An important aspect of vaccine design is deciding which parts of HIV (antigens) the vaccine can induce immune responses against. HIV contains a total of 9 genes (env, gag, pol, nef, tat, rev, vpr, vif, vpu), all of which encode proteins that are potential targets for the immune system. Specialized immune system cells called antigen-presenting cells (APCs) break down proteins into small slices and with the help of the HLA system in the body present them as "epitopes", which can be recognized by individual T cells. Some vaccines include known epitopes from particular HIV proteins rather than (or in addition) using the whole protein. A diverse array of HIV antigens are being employed in current HIV vaccine trials. These antigens could be derived from the envelope proteins, as recombinant proteins, DNA, or introduced by various vectors such as non disease causing viruses or bacteria. For example in their Ad5 vaccine candidate, Merck has selected the gag, pol, and nef genes. This decision is based on extensive studies of HIV specific T cell responses in infected individuals, which shows that the proteins encoded by these genes are the most frequently targeted [4]. Other factors considered include the relative conservation of these genes across different HIV clades or subtypes. Clades are system for classifying HIV based on genetic make up of the virus; for example most viruses from North America and Europe are genetically related and belong to clade

B. Many viruses found in Africa are also similar in their genetic make up, but show distinct genetic differences from HIV clade B and have therefore been classified to different clades. Clades A, C, D and G are the most common in Africa, with A and G being the most prevalent in West Africa. Mixes between different clades are called circulating recombinant forms (CRFs). The most prevalent HIV in Nigeria is a mix between A and G [5] and is called CRF02_AG. The genetic variability of HIV globally presents a major challenge for vaccine development because immune responses that recognize HIV from one clade may fail to recognize viruses from other clades or recombinants. This underlies the focus on genes from HIV that are very similar from one clade to the other. In general, HIV's env gene varies the most while gag is the most conserved[6]. Initially most vaccine candidates were produced from clade B, an increasing number are now including HIV components from other and multiple clades.

Preventive Vaccines

In the last 5 years more vaccine candidates have been developed. The upsurge has been traced to improvement in techniques in inducing T cells (cell mediated) immune responses. Initial efforts to develop an HIV vaccine concentrated on the production of candidates designed to induce neutralizing antibodies against HIV. However, these efforts were thwarted by the discovery that while neutralizing antibodies can neutralize HIV grown in the laboratory, viruses taken from infected people (primary isolates) are highly resistant to antibody mediated neutralization. These observations were confirmed by the failure of AIDSVAX, an antibody vaccine candidate to protect against HIV infection in two large efficacy trials[7].

While research efforts continue to search for vaccine candidates capable of inducing neutralizing antibodies, only few of the current candidates are antibody based. Most of the leading candidates now are T cell based. This has arisen as a result of evidence that T cells play an important role in controlling HIV infection[8]. T cell responses comprise of both CD4+ (helper T) and CD8 (killer T) cells. Improved scientific technologies have made it possible for the evaluation of the numbers and

specificity (pathogen being targeted) and the functional properties of CD4 and CD8 T cells. Most AIDS vaccinologists believe that it is unlikely that a T cell based vaccine will lead to complete protection against HIV infection, but there is some optimism that it could slow or prevent disease progression in an immunized individual who is subsequently infected with the virus. Further more, if vaccination can lead to a reduction in viral load in the post infection period, then this might result in the risk of transmission of the virus.

The leading vaccine candidates for inducing HIV-specific T-cell responses involve the use of naked DNA and viral vectors. DNA is the genetic code engineered to produce selected HIV proteins when delivered into the body while viral vectors are harmless viruses altered so that they carry the genetic code for making selected HIV proteins when delivered into the body. Other approaches for producing vaccine candidates include the use of recombinant HIV proteins, lipopeptides and protein subunits and whole protein vaccines.

International and African Preventive HIV Vaccine Trials

During the past 17 years, most HIV vaccine development and assessment have taken place in developed, western countries. Early candidate HIV vaccines were based on the HIV -1 subtype B strains[9] prevalent in western nations, and most human clinical trials were done in the USA and Europe. Globally, there have been more than 80 phase I and II trials, and only one bivalent recombinant gp120 vaccine (AIDSVAX, VaxGen) has reached large scale phase III efficacy testing in North America, Netherlands and Thailand. The results of the first two phase III studies were reported [7]. Both showed clearly a lack of efficacy of the recombinant monomeric gp120 vaccine (AIDS VAX; VaxGen Inc, Brisbane, CA, USA) tested.

In anticipation of new vaccine candidates, preparations for HIV vaccine trials are being made in several African nations: The HIV Vaccine Trials Network (HVTN, sponsored by the US NIH) supports institutions and investigations in South Africa, Botswana and Malawi. CDC is strengthening research sites in Cote d'Ivoire and Kenya. The US

military HIV research program is developing epidemiological, clinical and laboratory infrastructure in Uganda, Kenya, Tanzania and Cameroon. The French research agency (ANRS) is working with Senegal and Cote d'Ivoire while the Harvard AIDS Institute is preparing sites in Botswana, Tanzania and Nigeria.

Three small scale phase I trials in Uganda and Kenya were very important in showing that such trials could be successfully undertaken in Africa, and have served to identify issues that need to be addressed in planning future trials in the continent. These trials provided several lessons on how to address public misunderstanding and mechanisms, and the importance of involving communities and media in preparations for such trials.

Therapeutic Vaccines

The availability of potent HAART regimens has led to a resurgence of interest in therapeutic immunization, based on the idea that viral suppression and the attendant immune reconstitution may provide an opportunity to induce new and more effective T-cell responses targeting HIV. Similar to preventive vaccines, the development of new and more reliable assays have improved the study of therapeutic vaccines. These tools have identified a number of properties that are associated with control of HIV viral load such as IL-2 production and proliferation. However, it remains to be seen whether the induction of these T-cell responses by vaccination will be of any benefit. The primary goal of therapeutic vaccines is to maintain a good control of viral replication during interruptions of HAART. This will therefore reduce the dependency on drug over the long term and possibly provide intermittent drug holidays. Although this is certainly a desirable outcome, there are currently no convincing human data showing that this is achievable. Researchers are divided about this, while some are optimistic, others remain profoundly skeptical.

Therapeutic Vaccine Trials

Extensive overlap exists between the therapeutic and preventive vaccine fields, with many of the same vaccine candidates being involved in studies in both fields. The ALVAC study is one of the prominent

therapeutic vaccine studies despite the poor immunogenicity of the candidate vaccine. In a recent ANRS study, a statistically significant difference was observed in post-treatment interruption control of viral load among recipients of a regimen that included ALVAC, lipopeptides, and IL-2 compared to participants receiving HAART alone. The numbers were however small and the difference in the interruption time (before commencing HAART) was small [10].

Jonas Salk's remune became more prominent after the advent of HAART because of the potential to induce HIV-specific CD4 T-cell responses capable of proliferating and producing IL-2 [11]. A small pilot study has also observed that these responses may also improve HIV-specific CD8 T-cell proliferation [12]. This has led to trials of remune in various treatment interruption studies, even though recent results from a study in acute HIV infection failed to show an effect of immunization on viral load [13].

A new strategy employed in therapeutic immunization involves the use of dendritic cells (DCs). The function of DCs is to process and present small protein slices called epitopes of pathogens to T cells, thereby initiating an immune response. This function is known as antigen presentation. A number of studies have taken DCs from an individual's blood, mixed with HIV proteins or epitopes and then reinjected it back to the individual to act as a vaccine. A recent small study using this method claimed an immunologic and virologic benefit in participants with early HIV infection who had not started HAART [14]. However, these need confirmation from larger controlled studies.

HOW CLOSE ARE WE TO HAVING AN HIV/AIDS VACCINE?

Since HIV was identified as the virus that causes AIDS in 1984, over 30 preventive vaccine candidates have been tested in Phase I trials. Only one vaccine candidate, however, has progressed to Phase III efficacy trials and only two other concepts have reached the stage of Phase II trials. The vaccine that entered in Phase III trials was developed

by VaxGen and is a recombinant subunit vaccine. Two Phase III trials of this product have been conducted. One trial was conducted in the United States, Canada and the Netherlands primarily in men who have sex with men, using a vaccine based on HIV subtype B. The other trial was conducted among intravenous drug users in Bangkok, Thailand, using a vaccine based on HIV subtypes B and E. Results from these trials was made known in late 2002 and 2003 [10]. To date, the vast majority of the clinical trials have been conducted in developed countries, and most of these vaccines have been based on HIV subtype B, the subtype of HIV that predominates in North America, Europe, Latin America, Australia and New Zealand. Subtype B, however, accounts for only a small percentage of new infections. So far, only two HIV vaccines have been tested that are based on the two most prevalent subtypes of HIV in Africa - A and C -, which together account for about two-thirds of all HIV infections worldwide. Both of these vaccines are based on subtype A and are currently in phase I trials in Kenya. A number of products based on subtype C and CFRO2_AG, however, are in pre-clinical development and hopefully will be ready to start clinical trials shortly. At this time, it is not clear how important HIV subtypes are in the development of HIV vaccine.

Prospects for an AIDS Vaccine: Three Big Questions, No Easy Answer

Although formidable practical, political, economic, social and ethical challenges face the AIDS vaccine development effort, the most fundamental challenges now reside at the level of the basic biology of HIV - I infection and pathogenesis. Of these biological considerations, three questions loom especially large;

- (i) Can we design immunogens that will elicit the immune responses (neutralizing antibodies and cytotoxic T cells) that are necessary for immune protection against a wide variety of primary HIV isolates;
- (ii) What is the specific constitution of HIV antigens necessary to confer protective immunity
- (iii) and to what extent will the tremendous genetic diversity of HIV -I affect the breadth

of vaccine elicited protective immunity and the overall effectiveness of an AIDS vaccine? Although these are exceptionally challenging questions, they are now being confronted with clear hypothesis whose testing is being facilitated by an ever-improving array of technologies for vaccine design and immunological characterization. The extent to which the AIDS vaccine research community can come together to answer these questions in the best coordinated, most efficient manner will probably determine how and when an effective AIDS vaccine will be developed.

Vaccine Research Efforts in Nigeria

The HIV epidemic has reached exponential levels in Nigeria with a national seroprevalence of 5.0%, with rates of over 10% in more than 2 states of the country [15] and with a rapidly expanding epidemic of HIV -1 subtypes A, G and A/G recombinants [16]. To date, the progress in the development of HIV vaccines has reached an important milestone, dictating the need to initiate phases I, II and III trials of different vaccine constructs (candidates). Vaccine efficacy trials under field conditions in different populations have very specific objectives, which cannot be achieved by other types of research. The question that should be addressed is related to vaccine efficacy against infection, or against the disease, and measurement of these protection end points. However, answering these questions require large and very complex efficacy trials in different settings dictated by several factors.

Active and full participation of developing countries like Nigeria as equal partners in the global process of HIV vaccine development requires advanced planning and preparation (vaccine preparedness) for both small (phase I and II trials) and large scale efficacy (phase III) trials.

Vaccine preparedness programmes should include the following:

1. Establishment of infrastructures and national capacity allowing for different types of trials
2. Conduct of preliminary epidemiological, virological, socio-behavioural and clinical research
3. Development of a national consensus and a national vaccine plan
4. Development of a framework that would

ensure high scientific and ethical standards in the conduct of trials in these countries with active participation of communities

Already a number of institutions in Nigeria have commenced vaccine preparedness programs in collaboration with international institution. They are developing their infrastructural and human capacity for research including good laboratory and clinical practice. Many are already carrying out studies in virology, immunology and molecular biology of HIV and cohorts are being established. These institutions include the Universities of Jos, Maiduguri, Ibadan, Lagos and the Nigerian Institute of Medical Research (NIMR) – all supported by AIDS prevention Initiative in Nigeria (APIN) Programme, National Institute for Pharmaceutical Research and Development (NIPRD) and Gede Foundation in Abuja.

In addition, other relevant vaccine related activities include the National Antiretroviral therapy programme sponsored by the Federal Ministry of Health which has over 20,000 HIV infected individuals on antiretroviral therapy across several centres nation wide. In addition, the Government has launched a pilot Prevention of Mother to Child Transmission (PMTCT) of HIV scheme in six (6) sites in the Federation in addition to 5 other APIN sites and 4 CDC sites.

CONCLUSION

The brunt of the HIV / AIDS pandemic is felt in developing nations, and is not only being measured in personal, family and community struggles but also gravely threatens the economic and political stability of whole regions of the world. There has been recent progress in making antiretroviral (ARV) drugs available in these regions, with sweeping pledges made to improve global access to these powerful drugs that can greatly improve the quality of life of HIV -infected people. When these drugs do become more widely available it will be a great stride forward that will alleviate much human suffering.

But ARV drugs will never be the whole answer; people will continue to become infected with HIV. The history of public health shows us that there is one crucial facet of an effective response to a pan-

demic like AIDS: a preventive vaccine. Scientists alone cannot find an AIDS vaccine. Communities, policymakers, government leaders, and AIDS activists all have important roles to play in this urgent mission.

REFERENCES

1. UNAIDS, Report of the Global HIV/AIDS epidemic, Geneva. 2004.
2. UNAIDS and WHO, AIDS Epidemic update, Geneva 2004.
3. UNDP. Human Development Report. 2003
4. Coplan G, Gupta SB, Dubey SA, *et al.* Cross-reactivity of anti-HIV-1 T cell immune response among the major HIV-1 clades in HIV-1 positive individuals from 4 continents. *J infect Dis* 2005; 191: 9, 1427-1434.
5. Peters M, Esu-Williams E, Vergne L, *et al.* "Predominance of subtype A and G HIV type 1 in Nigeria with geographical differences in their distribution". *AIDS Research and Human Retroviruses* 2000; 16 (4): 315-325.
6. McMichael AJ and Hanke T. HIV vaccines 1983-2003. *Nature Med* 2003; 9: 7, 874-880.
7. Flynn NM, Forthal DN, Harro CD *et al.* The rgp120 HIV Vaccine Study Group. Placebo controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *J Infect Dis* 2005; 191: 5, 654-665.
8. Pantelo G and Koup RA. Correlates of immune protection in HIV-1 infection: what we know, what we don't know, what we should know. *Nat Med* 2004; 10: 8, 806-810.
9. Robinsone HL. New hope for an AIDS vaccine. *Nat Rev Immunol* 2002; 2: 239-250.
10. Levy Y, Gahery-Segard H, Durier C, *et al.* Immunological and virological efficacy of a therapeutic immunization combined with interleukin-2 in chronically HIV-1 infected patients. *AIDS* 2005; 19: 3, 279-286.
11. Maino VC, Suni MA, Wormsley SB, Carlo DJ, *et al.* Enhancement of HIV type 1 Antigen-specific CD4 + Tcell memory in subjects with chronic HIV type 1 infection receiving an HIV type 1 immunogen. *AIDS Res Hm Retroviruses* 2000; 16: 18, 2065-2066

12. Lichterfeld M, Kaufmann DE, Yu XG, *et al.* Loss of HIV-1 specific CD8+ T cell proliferation after acute HIV-1 infection and restoration by vaccine induced HIV-1 specific CD4+ T cells. *J Exp Med* 2004; 200: 6, 701-712.
13. Perrin L. Data on Quest Therapeutic vaccination. Abstract 31, AIDS vaccine 04, Lausanne, Switzerland, August 30-September 1, 2004.
14. Lu W, Arraes LC, Ferreira WT, *et al.* Therapeutic dendritic cell vaccine for chronic HIV-1 infection. *Nat Med* 2004; 10: 12, 1359-1365.
15. Federal Ministry of Health. HIV/Syphilis sentinel survey. 2003.
16. Njoku M, Idoko JA, Edubio A *et al.* "Molecular Epidemiology of HIV-1 in North Central Nigeria", Abstract, 13th ICASA, Nairobi, Kenya, September 2003