CONDUCTING HIV VACCINE TRIALS — CHALLENGES FOR SOUTH AFRICA

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South Africa is experiencing a severe HIV/AIDS epidemic. It is estimated that at least 1 in 10 South Africans are HIV-infected, and data from the 2001 antenatal seroprevalence survey suggest that at least 1 in 4 pregnant women are HIV-infected (South African Department of Health). To date, despite the introduction of national prevention programmes there is no sound evidence that the epidemic is reaching a plateau. It has been estimated that HIV infection rates will peak at almost 17% by 2006 for the population as a whole. AIDS-related deaths will peak in 2010, at 256 AIDS deaths per 100 non-AIDS-related deaths.[1]

Several risk factors in South Africa predispose it to a severe epidemic. These include a disrupted family and communal life, due in particular to apartheid and migrant labour; good transport infrastructure and high mobility; high levels of poverty and income disparity; evidence of high levels of sexually transmitted diseases; poor condom use; the low status of women in society and relationships; and social norms that accept large numbers of sexual partners. As mass awareness programmes and prevention strategies that focus on behaviour change have not curbed the epidemic, there is an urgent need to investigate biomedical approaches to HIV prevention. The initiation of an HIV-vaccine-related research programme in South Africa presents many challenges to scientists working in this field.

CHALLENGES FACING HIV VACCINE RESEARCH

As yet, South Africa has not been involved in HIV vaccine clinical trials. The challenges facing researchers in South Africa are not unique, but are barriers similar to those seen in other developing world settings.

These include:

REGULATORY ISSUES

There is an urgent need to build local regulatory capacity to review vaccine trials. At present swift in-country review and the approval process appears to be hampered by inexperience. Between December 2001 and November 2002, three phase I/II trials were submitted for regulatory approval to the South African Medicines Control Council (MCC). Despite discussions between the MCC, investigators, sponsors and the South African AIDS Vaccine Initiative (SAAVI), no trial had been approved during this time. After submission of the first HIV vaccine trial, the MCC mandated a new committee to deal with HIV vaccine trials, the HIV Vaccines and Clinical Trials Committee, which has to report to the MCC meeting before final approval. Initial questions and responses from the MCC to vaccine trial investigators have taken between 3 and 18 months. The review by the HIV Vaccine and Clinical Trials Committee was not only scientific and regulatory, but also included review of biomedical ethical issues and the commitment of researchers to capacity development of previously disadvantaged communities. The HIV Vaccine and Clinical Trials Committee wanted assurances of access to lifelong highly active antiretroviral therapy (HAART) before approval could be given for the first HIV vaccine trial, submitted in December 2001. Although the time between submission and review was lengthy, investigators were often expected to respond within the standard 7 days of receipt of the review, often without being able to access committee members via phone or fax for clarifications. In the first quarter of 2003, the MCC together with the National Department of Health convened a meeting with the National Ethics Committee to gain consensus on appropriate standard of care for volunteers who become infected on HIV vaccine trials. There was overwhelming agreement that access to antiretrovirals was an important component to the standard of care for trial participants who became infected on these trials.

ETHICAL REVIEW

The government has not made HAART available in the state or private sector for the management of HIV-infected individuals who meet treatment criteria. Because of the lack of access to HAART in the public sector, there was no consensus in this country regarding the treatment and management of participants who may have 'breakthrough' infections while on vaccine trials. While investigators subscribe to the UNAIDS ethical considerations in HIV preventive vaccine research (2000) (guidance point 16:

where care and treatment for HIV/AIDS should be provided to participants in HIV vaccine trials, with the ideal to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country), there is lack of clarity regarding who is responsible for this care.

Attempts to obtain a consensus on the use of antiretroviral therapy for 'breakthrough' infections held up ethical clearance of HIV vaccine trials. Since the national meeting where it was determined that there will be access to antiretroviral therapy for trial participants who have 'breakthrough' infections while on the trial, the universities have now given approval for the phase I/II HIV vaccine trials that have been submitted to them.

CROSS-CLADE HIV VACCINE TRIALS

The variability of HIV-1 poses a major challenge to the development of an HIV vaccine. There is controversy among scientists in this country regarding the value or importance of cross-clade vaccine research. Trials should be designed to evaluate whether candidate vaccines are capable of inducing potent and broad cellular immune responses to HIV. Because of the increasing diversity of the HIV epidemic globally, with increasing frequency of recombinant forms, the development and testing of clade-specific vaccines in regions may not be the appropriate route to take. In South Africa, approximately 94% of the predominantly heterosexual epidemic is due to clade C, while 85% of the minority homosexual epidemic is attributed to clade B.[2] There are as yet limited data regarding recombinant forms in South Africa, but as the epidemic evolves, more mixing of clades can be expected, resulting in recombinant forms of HIV-1. There are published reports suggesting that cross-clade reactivity can be induced by natural infection, but homologous responses are frequently greater than heterologous responses.[3-6]

Other ways of addressing diversity issues can include multivalent cocktails of proteins that comprise a spectrum of regional variants with the assumption that the immune responses elicited by any one of the circulating strain will be of sufficient cross-reactivity to protect against other strains from the same subtype.[7]

ADOLESCENT INVOLVEMENT

One of the most effective ways to curb the epidemic will be to vaccinate older children and adolescents prior to their sexual debut, particularly in South Africa where 50% of 15-year-olds and almost 10% of under-12-year-olds are sexually experienced. The use of an HIV vaccine in this population will require clinical trials in adolescents to determine the vaccine's safety and immunogenicity as the Food and Drug Administration (FDA) and international licensing agencies will probably only license the vaccine for use in age groups in which it has been tested. Generally, candidate HIV vaccines have been studied in phase I/II trials in healthy adult volunteers. To date, no HIV vaccines have been evaluated in adolescents.

There are challenges researchers need to overcome to successfully complete HIV vaccine trials in adolescents, and because of this, adolescents are often excluded from clinical research. Treatments and interventions used in this group are usually extrapolated from studies performed in children or adults.[8] Many national committees and panels have recognised the lack of research involving adolescents, and have urged that more research be conducted in this age group.

South Africa needs a clear strategy to involve adolescents in vaccine trials. Ethical issues regarding informed consent, consultation with parents and HIV testing of minors need to be addressed in an expedient manner.

ESTABLISHMENT OF HIV VACCINE CLINICAL SITES

Disparities exist between urban and rural health care and 'local standards of care' differ dramatically. In rural areas, the doctor/patient ratio is lower than in urban areas, where patients may only access rotating medical doctors at a primary health care level once a week. Access to drugs on the essential drug list may be sporadic, and there are concerns that in rural areas where trial sites are being developed, better access to medical care may act as a perverse incentive for clinical trial participation. In a survey conducted in Soweto, an urban African setting on the outskirts of Johannesburg, almost 70% of participants stated that they would definitely participate in HIV vaccine research. Access to HIV testing, risk reduction counselling and condoms, and treatment of sexually transmitted diseases were cited as reasons to be involved in HIV vaccine clinical trials. In this survey, only 36% of participants believed that HAART should be provided to trial volunteers who had breakthrough infections.

TRAINING OF RESEARCHERS

Clinical researchers need to be trained adequately so that all trials conducted in South Africa are in accordance with the International Conference on Harmonisation of Good Clinical Practice (ICH GCP) and the highest ethical standards. In South Africa there are currently few researchers trained in ICH GCP and able to conduct trials under Federal Drug Administration (FDA) scrutiny. In addition, there are no concrete plans in South Africa to develop sufficient phase III capability to allow the testing of suitable vaccine candidates in phase III clinical trials. There is a paucity of black African scientists involved in HIV research, and in particular HIV vaccine research, in South Africa. To this end, the academic institutions involved in HIV vaccine research have committed themselves to the

development of scientists from previously disadvantaged communities and prioritised the training of both clinical and laboratory scientists.

PROTECTING TRIAL PARTICIPANTS

South Africa is uncharted territory in terms of HIV vaccine clinical research. HIV vaccine trials to be conducted in South Africa will largely involve people from populations which, through limited knowledge about science and research, advanced poverty, unemployment and gender inequality, may be vulnerable to exploitation and manipulation by research programmes. Trial participants deserve protection from social harm or any form of discrimination that may arise from their participation in HIV vaccine research.

It is therefore apparent that South Africa needs to work on legislation that will ensure the protection of trial participants from any form of harm arising from participating in HIV vaccine research. Some units within South Africa have built up considerable skills, infrastructure and approaches to HIV clinical trials. These will be fundamental to designing and carrying out successful vaccine trials in communities, which in the process will be enabled to become research-literate and empowered partners.

INVOLVING COMMUNITIES

Public dialogue, education and outreach are essential for successful HIV vaccine research and this process has not been systematic in South Africa. There is a need to embrace communities involved in research in a meaningful and constructive way. One way of achieving this is by the establishment of democratically elected and truly respresentative community advisory boards (CABs). Regular contact and communication between the CAB and researchers will open up channels of dialogue necessary to facilitate the successful execution of clinical trials.

VACCINE ACCESS

Strategies must be developed now to ensure that after being licensed the HIV vaccine is readily available to all sectors of the population.

SUMMARY

Although many steps are necessary for the successful implementation of HIV vaccine clinical research, most of the infrastructure and expertise exists in this country. To expedite the approval and initiation of the first phase I/II trials in South Africa, it is apparent that local regulatory capacity necessary for research and licensure needs to be developed as a matter of urgency. An important issue that threatened the initiation of HIV vaccine research pertained to 'standards of care', and what this constitutes in a country with no provision of HAART in the public sector. Although this has been resolved at a policy level, it is apparent that clinical researchers, together with local institutional review boards and the national Department of Health, will need to develop a model of care for participants who acquire 'breakthrough' infections while participating in vaccine trials. This model will need to encompass the challenges of long-term follow-up, monitoring and care, including expertise in treating with HAART and ensuring an uninterrupted supply of antiretroviral drugs. The national Department of Health will need to take the lead in establishing the national guidelines on 'standards of care' and to provide the infrastructure and treatment necessary for long-term follow-up and care for trial participants who seroconvert on trials. SAAVI must continue to identify and develop phase III clinical trial sites both in rural and urban areas, preferably as soon as the phase I/II trials commence. As the appropriate target group for vaccination will be adolescents before their sexual debut, a strategy for testing of HIV vaccines in adolescents needs to be fast-tracked in the region. Finally, once an efficacious vaccine has been tested, a plan for the urgent procurement and distribution is needed to make this vaccine available to all South Africans as quickly as possible.

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