THE INFRASTRUCTURE SUPPORTING HIV VACCINE CLINICAL TRIALS

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BACKGROUND

History has shown that vaccines have provided the key to epidemic disease control. It is imperative, however, that vaccination is integrated into effective public health programmes. These include life skills education, sanitation, potable water supply, environmental and other health care and service provision.

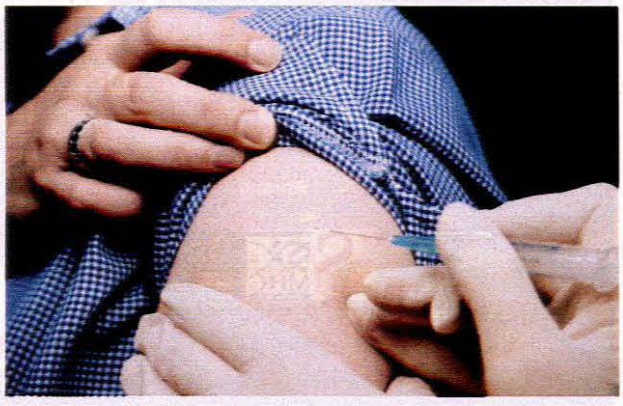
Current interventions have failed to sustain control in the spread of the HIV epidemic. A preventive HIV vaccine is considered the best hope of curbing the epidemic, and considerable international and national resources are being directed to this end. This has resulted in an alignment of these resources into two main coherent international networks, namely the HIV Vaccine Trials Network (HVTN – **www.hvtn.org**) and the International AIDS Vaccine Initiative (IAVI – **www.iavi.org**). Their core aim is to accelerate the production of a safe, effective and affordable preventive HIV vaccine. The South African AIDS Vaccine Initiative (SAAVI – **www.saavi.org**) is a vital contributor to and partner in both these collaborations.

The infrastructure developed in this quest so far is both impressive and complex. It is structured to harness the considerable intellectual input and investments required to achieve the goal of an effective HIV vaccine in the shortest possible time.

This article describes the infrastructure in global, national and site or regional levels. It concentrates mainly on the HVTN network at an international level and on SAAVI at a national level. Information on IAVI can be accessed via the Internet address given above.

GLOBAL

The HVTN is based in Seattle in Washington, USA. Its operations comprise a core operations centre, a statistical and data management centre, central laboratories, a community advisory board co-ordinating directorate, and HIV vaccine clinical trial units. Linkages have been established at various levels including the National Institutes of Health (NIH), the National Institute of Allergy



and Infectious Diseases (NIAID), the Division of AIDS (DAIDS), the US Food and Drug Administration (FDA), the Office of Human Research and Protection (OHRP), the US Walter Reid Army Institute for Research, vaccine developers, biotechnology companies, the pharmaceutical industry, universities and research institutions.

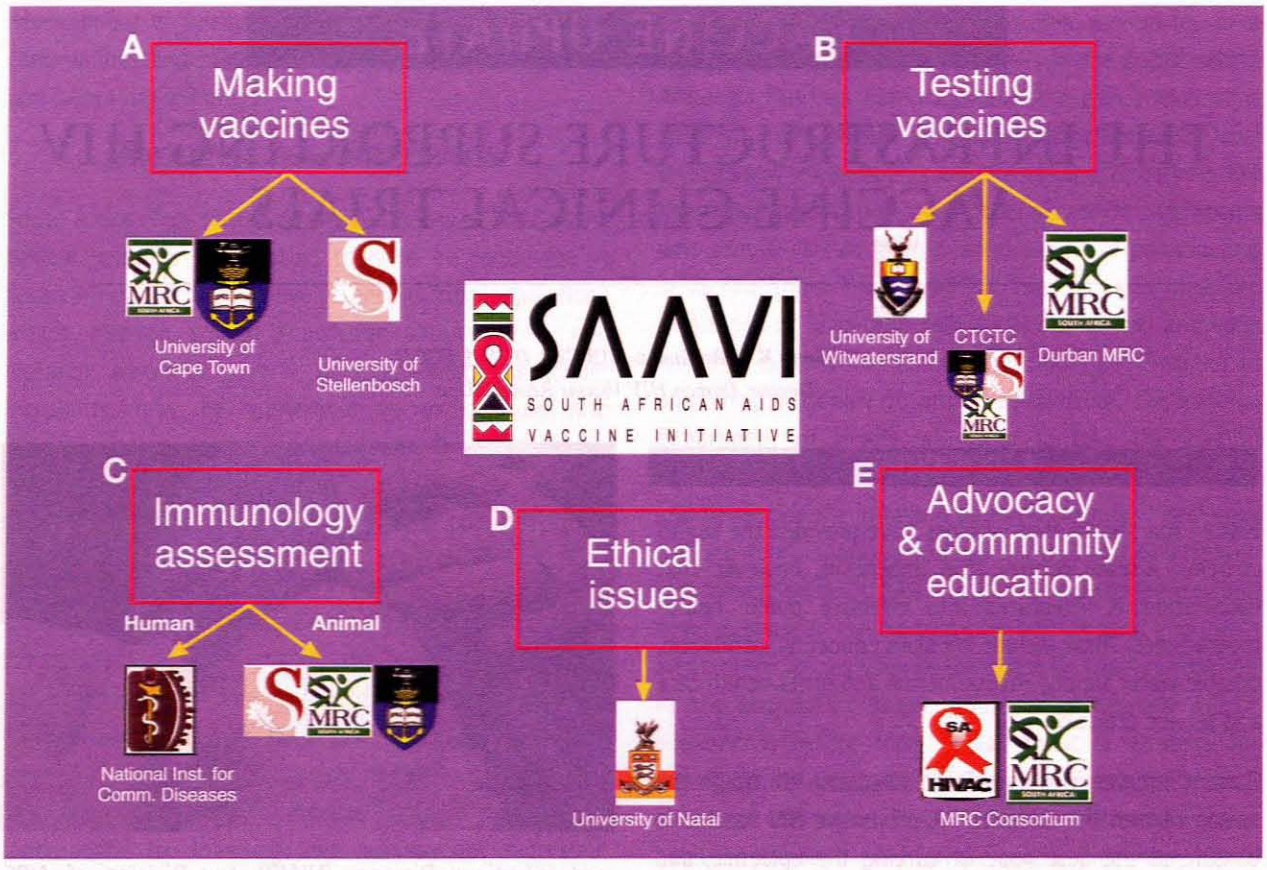
The HVTN co-ordinates its activities through a number of committees and task teams including a scientific steering committee, scientific committees covering the various phases of clinical trials (phases I, II and III) and laboratory sciences. Working groups or teams address development, protocols, primary infections, paediatrics and adolescents, and non-human primates.

This operation is co-ordinated by various mechanisms such as biannual HVTN full group meetings, conference calls, etc. in a standardised manner guided by the HVTN's Manual of Operations (MOP).

NATIONAL

The South African AIDS Vaccine Initiative (SAAVI) was formed by Cabinet in 1999 to co-ordinate the research, development and testing of HIV vaccines in South Africa. SAAVI is based at the South African Medical Research Council (MRC) and is an integral player in the international networks. It is funded by the South African Government and Eskom, and also by the NIH, the European Union and other international organisations.

SAAVI is a broad-based community research entity which co-ordinates vaccine research and development work at



various South African academic institutes such as

- the National Institute of Communicable Diseases (NICD), which will examine and track the immune responses to HIV/AIDS test vaccines
- research teams based at the universities of Cape Town and Stellenbosch that are aiming to develop new test vaccines and track the prevalence of circulating HIV strains
- an HIV/AIDS Vaccines Ethics Group (HAVEG) at the University of Natal
- the South African HIV Vaccine Action Campaign (SA HIVAC), which is a consortium focusing on community education, legal and human rights, as well as media and communications
- a behavioural sciences group
- a primate research centre, and
- established clinical trial sites at the Perinatal HIV Research Unit at Chris Hani-Baragwanath Hospital in Soweto and at the MRC in Durban, as well as two additional sites to be developed in Cape Town and Orkney.

REGIONAL CLINICAL TRIAL UNITS

This vast infrastructure is geared to enable the clinical trial sites to timeously enrol volunteer participants and undertake clinical trials of suitable candidate HIV vaccines. These units are geared to generate data of high quality to answer the necessary research questions in the quest for a safe, affordable and effective vaccine.

These sites have many similarities with other clinical research facilities. They require staffing, facilities and equipment necessary to meet the exacting internationally accepted requirements demanded of HIV vaccine research, the ethical care and management of volunteer participants, and meaningful community integration in all these processes.

STAFF

The staff complement at these sites consists of the principal investigator (PI), co-investigators, research clinicians, pharmacists, laboratory technicians, nurses, data managers, administrators, HIV/AIDS counsellors, social scientists, community outreach personnel such as educators, liaison officers and recruiters, and quality assurance personnel. These units are usually supported by information technology, financial, security and cleaning staff. The staffing operation must be aligned to real capacity building with the aim of meeting employment equity legislative requirements.

All personnel need to have training, or be trained and continually updated in the various aspects of clinical research such as good clinical practice (GCP), the numerous (50+) standard operating procedures (SOPs), MOPs and protocol-specific requirements. Ongoing training aims to enable them to meet their varied responsibilities within the highly complex, sensitive arena of HIV clinical research. In addition, frontline staff require media training to ensure that a coherent, clear and co-ordinated message necessary for such an undertaking is communicated to the public.

The PIs are responsible for the quality and integrity of the conduct of vaccine clinical trials, the medical care of participants to the highest ethical standards, protocol conduct with the agreed approvals by the Medicines Control Council (MCC) and the various ethics committees, and also the provision of quality staffing, facilities and equipment.

The PI's responsibilities to this end encompass submission of protocol and amendments to the regulatory authorities and adherence to the requirements of these regulatory authorities with confidential data management and transmission, and document storage. They are also responsible for the education, recruitment, enrolment and retention of participants, which encompasses a functional community advisory board (CAB) and other community mobilisation and education activities. Units also typically establish in-house voluntary counselling and testing (VCT) services which add to the recruitment process. The PIs ensure compliance with the International Committee of Harmonisation (ICH) GCP guidelines for the medical management and monitoring of participants, vaccine management such as cold-chain maintenance, storage, reconstitution and administration, and specimen collection in adherence to protocol, and sponsor policy and procedures. They must also ensure that specimen collection processing and shipment meets the requirements of the International Air Transport Association (IATA).

The PI is also responsible for the establishment, facilitation and maintenance of CABs, which are required to reduce the perceived power imbalance between researchers, participants and communities. These CABs comprise community representatives, and usually include representation from community-based organisations (CBOs), non-governmental organisations (NGOs), traditional leaders and practitioners, faith-based organisations, trade unions and governmental departments, among others. CABs require training to enable them to input meaningfully to the clinical trial process such as the informed consent process, inclusion/exclusion criteria, participant care, and recruitment and retention issues.

These CABs are organised and co-ordinated internationally in a highly structured way and exert a powerful influence in ensuring appropriate, expedited HIV vaccine research.

FACILITIES AND EQUIPMENT

Vaccine trial sites typically comprise examination rooms supported by an emergency care facility, pharmacy and laboratory, waiting and counselling areas, offices, secure document storage rooms and freezer repositories.

Standard equipment includes IT equipment and networking, telephones and fax, photocopiers, scanners, etc., as in most clinical trial units. In addition a pharmacy equipped with fume extraction cupboards for safe vaccine reconstitution, and -40°C freezers with temperature controls, alarms, and logs to ensure continual temperature controls is also required. An electrical back-up generator is required to ensure uninterrupted power to run the freezers. This is linked to a service company to ensure 24-hour functionality.

The site laboratories are equipped and staffed mainly for specimen preparation such as serum separation, peripheral blood mononuclear cell (PBMC) isolation, specimen shipment and tracking, test result management, and on-site rapid testing such as pregnancy and HIV tests.

LINKAGES

Clinical trial units, apart from their links with international and national HIV vaccine groups, communicate with many organisations, institutions and people within the region in which they operate. These include the government Departments of Health at central, provincial and local spheres, ethics committees, hospitals (both private and state), clinics and GPs, CBOs, NGOs, faith-based organisations, the media and trade unions.

CONCLUSION

This is an overview rather than an exhaustive description of the fine detail which, of necessity, exists right down to the needle tip or device delivering the HIV vaccine. These minutiae, however, are all essential to ensure that the correctly modified HIV antigenic fragments are delivered safely and expeditiously into volunteer participants and that all outcomes are managed appropriately.

Never before has a global endeavour of this magnitude and intricacy been mounted in the search for a vaccine. The development of the polio and smallpox vaccines was not supported by a mustering of this intensity. We should remind ourselves of the time it took to control smallpox – from Dr Jenner's inoculation of Master James Phipps in the 1760s to its eventual eradication in the 1970s – not forgetting the vaccination activities predating this. By contrast, some modern vaccines have been developed in only a few decades.

Is this complicated infrastructure sufficient in terms of quality, magnitude, courage and will to produce a safe, effective and affordable preventive HIV vaccine within the next decade? We hope so – but until such time, the public health education, care and treatment programmes must rise to meet the need.