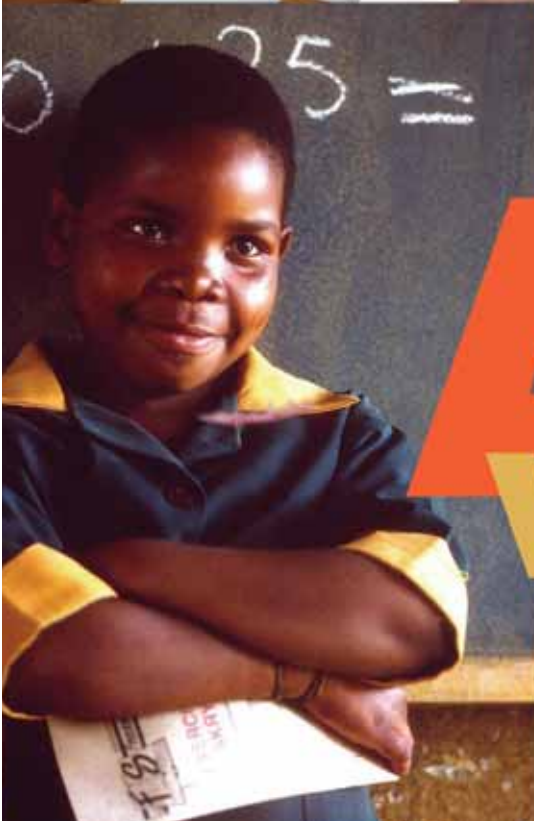
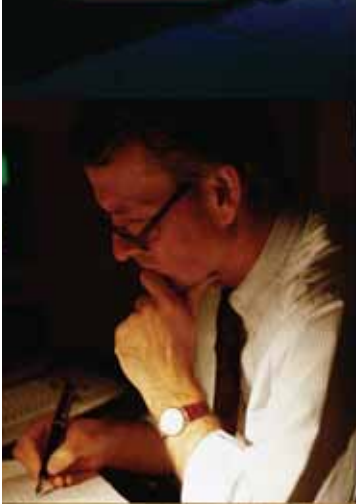


**SAAVI**  
SOUTH AFRICAN AIDS  
VACCINE INITIATIVE



South African  
**AIDS**  
vaccine  
initiative

2004/2005 Annual Report

# Contents

Report from the SAAVI Directorate	1
Scientific summaries	5
Laboratory development of vaccines	
University of Cape Town	5
University of Stellenbosch	6
Immunology	
National Institute for Communicable Diseases	8
Clinical sites	
Perinatal HIV Research Unit, Chris Hani-Baragwanath Hospital	10
HIV Vaccine Research Unit, Medical Research Council	11
Cape Town Clinical Trials Consortium	11
Aurum Health Research	11
Ethics	
HIV/AIDS Vaccine Ethics Group (HAVEG), University of KwaZulu-Natal	12
Community involvement	
Masikhulisane – SAAVI Community Involvement Programme, Medical Research Council	13
Socio-behavioural research	
Human Sciences Research Council and University of Stellenbosch	15
Actuarial assessments	
University of Cape Town	16
Bioinformatics and data management	
Medical Research Council and University of the Western Cape	16
Finances	17
Publications and conference presentations by SAAVI partners in 2004	19

## SOUTH AFRICAN AIDS VACCINE INITIATIVE (SAAVI)

Tel: +27 (0) 21 938 0262, E-mail: [saavi@mrc.ac.za](mailto:saavi@mrc.ac.za)  
SAAVI Vaccine Info-line 080 VACCINE  
[www.saavi.org.za](http://www.saavi.org.za)

SAAVI is proudly sponsored by:



# Report from the SAAVI Directorate

It has been another busy year for the SAAVI consortium with substantial developments in all areas of endeavour. Following the huge excitement in South Africa at the start of two phase I trials at the end of 2003, attention has been focused on the running of those trials and the recruitment of volunteers. In addition, SAAVI's own products have been submitted for manufacture and registration with regulatory bodies, and our research agenda has expanded into new and important areas.

## Increased international collaboration

SAAVI has emerged as a continental and international leader in HIV vaccine development. It has established new relationships with important partners both within the country (such as the Nelson Mandela Foundation) and with substantial new international endeavours including the Bill and Melinda Gates' Foundation 'HIV Vaccine Enterprise' (their HIV/AIDS vaccine research and development wing) where SAAVI directorate and consortium members are actively involved, and the European and Developing Countries Clinical Trials Platform (EDCTP) which is the European Community response to Malaria, Tuberculosis and HIV/AIDS in developing countries.

Co-operation and collaboration was further enhanced through exposure at international events including the International AIDS Conference in Bangkok in July and the AIDS Vaccine Conference in Lausanne in September. Ongoing work has been done with the HIV Vaccine Trials Network (HVTN) by many of the 220 members of the SAAVI consortium. Also the community involvement programme has facilitated an intensifying of relationships with study tours to other African countries involved in vaccine community involvement work – specifically Kenya, Nigeria and Uganda.

Although some of the vaccine science reported on at the Bangkok and Lausanne conferences was, to some extent, disappointing and certain of the HIV vaccine products developed internationally are not proving to illicit a vigorous immune response in early clinical trials, there was a strong international emphasis on the need to invest further funding in vaccine development at an international level and also to give vaccines and other prevention research (such as that on microbicides) the same kind of advocacy profile as treatment has had to date. It is evident that a concerted, co-ordinated international movement is needed to advocate for HIV vaccine and other prevention methods, and prevention should learn from advocacy work already done for treatment. This is an important step forward that was facilitated through meetings in Bangkok and further inter-country, SAAVI-supported meetings in South Africa (involving representatives from India and Brazil).

The SAAVI directorate and its consortium partners continue to hold a high profile in all the international bodies involved in vaccine development. This is an expression of the fact that SAAVI is a global leader in the field.

## Increased international funding

SAAVI is in the final stages of negotiating ongoing collaboration with the US National Institutes of Health's HIV Vaccine Trials Network (HVTN) for the purpose of collaborating on HIV vaccine human trials. In addition, the NIH has awarded an additional R6 million support for further SAAVI DNA vaccine manufacture and there has been increased investment by the HVTN in the SAAVI clinical sites – particularly the newer ones in Cape Town and Orkney. Three SAAVI trial sites have also received support from the International AIDS Vaccine Initiative (IAVI) to conduct another clinical trial in South Africa.

The European Commission has given the SAAVI Community Involvement Programme an additional grant to build on and expand its activities.

## SAAVI product development

The following table summarises progress in terms of developing our own candidate vaccines.

Product	Development group	Status
DNA-gag-rt-tat-nef // env	SAAVI/UCT	Pre-trial manufacture completed, almost completed preclinical toxicity testing in animals, regulatory review in 2005.
MVA-gag-rt-env-nef-tat	SAAVI/UCT	Pre-trial manufacture nearing completion. Then preclinical toxicity in animals, regulatory review in 2005.
Plant-based VLPs	SAAVI/UCT	Preclinical laboratory development phase.
BCG	SAAVI/UCT	Preclinical laboratory development phase.
Salmonella	SAAVI/UCT	Preclinical student project.



at the University of Cape Town – are being manufactured for trials and are going through the regulatory processes preceding phase I human trials. These will be tested both singly and in combination in a prime-boost approach. These are planned to enter trials in 2005/6.

The SAAVI directorate has positioned itself as a regional consortium with a global presence, and as such, SAAVI plans to be testing these products within South Africa and abroad, in collaboration with the NIH and HVTN. This would mean we would be running multiple, concurrent phase I trials of different products at different trials sites in the country, as well as abroad. It would also mean that SAAVI would be the first developing country HIV vaccine initiative ever to make and test its own products in developing and developed countries.

## New consortium partners

In this period our newer research areas such as the socio-behavioural work have been formalised and funded. The socio-behavioural group led by researchers from the Human Sciences Research Council and the University of Stellenbosch, has formulated its research agenda in more detail and started to facilitate collaborative work with the other groups. The socio-behavioural group has formed a national working group comprising other SAAVI researchers as well as leading experts in the field from other institutions in the country.

Our SAAVI data management group, run by the MRC and the University of the Western Cape, has also formally come on board and commenced work at both the trial sites and nationally. They have also been positioned by SAAVI as a regional force, and global agencies are in discussion with them about this group becoming the regional data management facility for many international trials.

## New areas of interest

We have also embarked on very early research on new and important areas such as the involvement of adolescents in HIV/AIDS vaccine research. Globally, approximately 60% of new infections occur in people under 24 years old. A recent SAAVI study among high school students, confirmed that these youth are at very high risk for HIV infection. SAAVI is an international leader in this area – having recognised very early the need to prepare intensively for testing vaccines in adolescents at a later stage and to ensure that we have a vaccine that works in, and can be licensed for eventual use in this group. The work on preparing adolescents will encompass detailed analysis and understanding of all the ethical and human rights issues as well as the scientific and clinical necessity for undertaking research work in minors and is an important future area of development.

The SAAVI Directorate has agreed that it is one of the focus areas in which we will collaborate closely with the Nelson Mandela Foundation which has a strong interest in this arena as well. SAAVI has recognised the need to educate, equip and mobilise adolescents as advocates in the debate about adolescent involvement in HIV vaccine trials as well as in other areas of preventative research. Again a national SAAVI adolescent working group encompassing leading experts in the field, and a broad and multidisciplinary range of skills has been established. This group is providing input to the Children's Bill which will come before the South African Parliament in 2005 and, along with the recently signed Health Act, has important implications for the regulation of research in minors. SAAVI researchers are also leading protocol development for the first international trial specifically aimed at adolescents, which is planned to be undertaken in collaboration with the HVTN and EuroVac. SAAVI was also well represented at a World Health Organisation meeting on adolescents and women.

## Clinical trials

### Current trials with products from other agencies:

The first two phase I trials (currently ongoing), which are sponsored by the HVTN and IAVI, are proceeding well, in that there have been no safety concerns, and results should be available during 2005. However, the IAVI-based product clinical trial was terminated early, based on a global decision by IAVI not to pursue this product further. Volunteers will be followed up normally, but no further volunteers will be recruited. We anticipate an additional two products developed outside South Africa going into phase I trials shortly – namely an 'adenovirus-based' product being developed and tested by Merck and an 'adeno-associated virus' product developed by IAVI. These products are undergoing review processes in preparation for phase I trials.

### Trials with SAAVI products:

Three South African developed products – two DNA-based and one MVA-based (see table) – developed by the SAAVI-funded group

## Annual review meeting

In March 2004 SAAVI held its formal review meeting which involved the full consortium team as well as the Scientific Advisory Committee and the SAAVI Steering Committee (comprising the primary funders). The meeting offered an opportunity for all the groups and individuals involved in the initiative to attain a broader understanding of the scope and depth of the work being undertaken and the progress. The meeting also allowed a scientific review of the work being done and feedback from the local and international reviewers. The initiative received very substantial praise from the international panel of experts on the Scientific Advisory Committee for what it has achieved in a short space of time and also for the multidisciplinary depth and breadth of its activities. Some recommendations were made for increased focus on certain areas and the streamlining of work in areas that do not show promise. These recommendations have or are being implemented. The international reviewers generally praised SAAVI for its unique character and depth of vision in this area.

## Human resources

The Directorate also acquired additional personnel during 2004 in the form of a Deputy Director (Scientific Affairs), a new Manager for the SAAVI Community Involvement Programme and a Medical and Regulatory Affairs Manager. Women still predominate in the Directorate as well as within the broader consortium. The personnel reflect a healthy demographic mix.

## Business issues

The SAAVI Directorate participated in a conference on Financing Neglected Product Development organised by the Initiative on Public-Private Partnerships for Health (IPPPH) which is focusing on developing products for so-called 'neglected diseases' like HIV and TB – diseases which the pharmaceutical industry is not keen to develop vaccines for because of the perceived lack of a market. The workshop brought together product development PPPs and major international funders like the Bill and Melinda Gates Foundation. Issues discussed included product pipelines as well as future funding needs. A detailed report on the need for vaccines was produced after the meeting which is available via the IPPPH website (<http://www.ippph.org>).

In November the SAAVI Business Manager attended a second IPPPH meeting arranged by the Center for the Management of Intellectual Property in Health R&D which focused on deal making and intellectual property management for public interest. Discussions centred around product development and securing the desired supply/access conditions.

SAAVI was also represented at a WHO meeting on intellectual property rights and vaccine development and the Business Manager was also an invited participant at the Forum 8 Summit on Health Research – in particular to sessions on product development partnerships to develop new tools to combat disease to achieve the Millennium Development Goals, and to be a panellist in a session on the operations of not-for-profit product development.

SAAVI is also undergoing an 'enterprise wide' liability assessment at the request of the MRC Board. This was conducted by Alexander Forbes, and the recommendations are currently being assessed by Marsh. It included looking at issues such as clinical trial and key person liability. The final results of the assessment have been made available, but the actions to be taken are still in development.

SAAVI's relationship with the Life Offices' Association was also strengthened and formalised. This relationship concerns formulating and implementing policies and practices in the insurance industry to ensure that vaccine trial volunteers are treated appropriately and have access to appropriate testing when applying for insurance.

## Media and Communications

SAAVI's media presence continues to be high in both local and international media with a steady stream of articles and input to electronic media over the course of the year. Four press releases were sent out and there was ongoing contact with journalists covering the story, in particular those who have attended our media workshops. The partnership with the Nelson Mandela Foundation was announced at a media preview of the AIDS film 'Yesterday' in August.

About a dozen radio interviews were done. SAAVI also participated in a TV documentary on HIV/AIDS in South Africa made by a US Production Company Persistent Productions.

SAAVI featured in as diverse publications as *Engineering News and Opportunity*, and an advert was placed in the *Mail & Guardian World AIDS Day Supplement*. Media interest and coverage intensified around events on World AIDS Vaccine Day in May and World AIDS Day in December.

The Media and Communications Manager was invited to be Managing Editor of the official daily newspaper of the Bangkok AIDS Conference in July 2004 and is on the Editorial Advisory Board of a new commercial AIDS publication – *Leadership in HIV/AIDS* which is aimed at the business sector.

An updated SAAVI website was launched early in the year, a corporate



**Actor Brad Pitt visited the Perinatal HIV/AIDS Unit at Chris Baragwanath Hospital. He is seen here with Unit Co-Directors James McIntyre and Glenda Gray.**

video was produced (at the end of 2003), and an Annual Report for 2003/4, updated brochures, fact sheets and an information pack for volunteers were also published.

Communications guidelines for volunteers who decide to go public in the media were formulated and there was ongoing training of SAAVI staff and consortium partner staff in dealing effectively and successfully with the media.

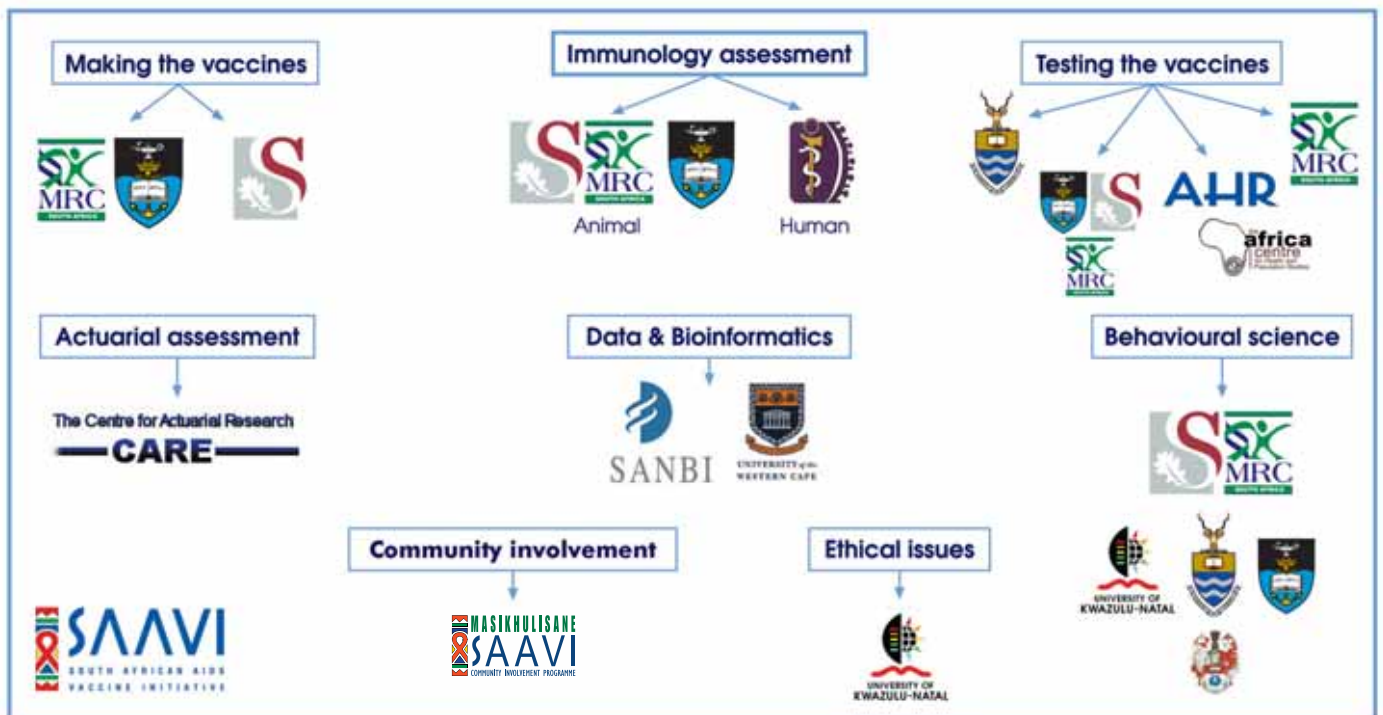
## Regulatory issues

There was increased contact and collaboration with the Medicines Control Council (MCC). However, the formulation of more effective procedures for working together is still required. SAAVI presented the DNA vaccine trial concept to the MCC's HIV vaccine committee as part of pre-submission meetings. This relationship will be further concretised and expanded with the appointment of the Medical and Regulatory Affairs Manager.



# SAAVI Groups

The core activities of SAAVI fall within the following categories:



# Scientific summaries



## Laboratory development of vaccines

### University of Cape Town

#### Development of candidate HIV-1 subtype C vaccines for southern Africa

**PROJECT DIRECTOR:** Associate Professor Anna-Lise Williamson, Institute of Infectious Disease and Molecular Medicine and NHLS, Faculty of Health Sciences, University of Cape Town. E-mail: [annalise@curie.uct.ac.za](mailto:annalise@curie.uct.ac.za)  
Tel: +27 (0) 21 406 6124.

The UCT group is investigating a number of different strategies to make vaccines, based on the HIV-1 subtype C viruses, the dominant strain circulating in southern Africa. The group's mission is to develop HIV-1C vaccines that are effective and affordable, and, through a comparative strategy, to advance the most promising vaccines or combinations of vaccines to clinical trials. The group consists of a multidisciplinary team with Professor Anna-Lise Williamson as Research Director, and Professors Carolyn Williamson, Enid Shephard, Ed Rybicki and Dr William Bourn as Principal Investigators. A competent team of over 30 people backs them up.

The DNA vaccines and a recombinant modified vaccinia virus Ankara vaccine (rMVA) have been selected to move forward to clinical trials. These will be used in combination in a DNA prime-rMVA boost inoculation regimen. Initial priming of the immune system with a DNA vaccine followed by a rMVA boost is widely regarded as one of the most promising vaccine strategies. A highlight of the 2004 UCT programme has been the commercial manufacture of two DNA vaccines constructed in the laboratory: one expresses a polyprotein comprising modified gag, reverse transcriptase, tat and nef (pTHr.grttnC), and the other expresses a truncated gp160 (pTHr.gp150CT). Cobra Therapeutics, in the United Kingdom, has manufactured these vaccines for clinical trials which are planned for 2005. The UCT SAAVI development team is working in partnership with the National Institute for Allergy and Infectious Diseases (National Institutes of Health, USA); the HIV Vaccine Trials Network (HVTN) of the National Institutes of Health (NIH), the National Institute for Communicable Diseases (NICD) in Johannesburg, Chris Hani-Baragwanath Hospital in Soweto and SAAVI.

The two DNA vaccines will be given to volunteers as a pre-prepared mixture which we have named SAAVI DNA C. This mixture has been shown to induce identical immunogenicity as the individual vaccines when injected into mice. The NIH is funding the rMVA manufacturing contract awarded to Therion Biologics Corporation Boston, USA. The rMVA-based vaccine, SAAVI MVA C, contains both grttnC and gp150CT and is thus designed specifically to boost the DNA vaccine prime. The research lot of SAAVI MVA C vaccine has been manufactured and initial immunogenicity tests in mice at UCT look very promising.

Senior scientist Ann Jaffray and helpers in Ed Rybicki's subunit vaccine group have made excellent progress with the development of candidate



vaccines using baculovirus and tobacco expression systems. The next most promising vaccine is the virus-like particle (VLP) vaccine based on an HIV-1 subtype C Pr55 gag protein, which is produced in insect cells via recombinant baculovirus. This vaccine induces an excellent immune response in mice. Production of the vaccine has been scaled up to do experiments in non-human primates. Initial studies show good immune responses in baboons primed with DNA gag C vaccine and boosted with gag C VLPs. This study has been extended to a larger number of baboons. The gag VLPs have also been successfully produced in tobacco via recombinant Tobacco mosaic virus (TMV), and development of methodologies for scaled-up production in plants is ongoing. If successful, this will be a cheap and effective production system for the subunit vaccines.

Longer-term projects involve optimising bacterial vectors as vaccine delivery vehicles. BCG – which is better known as the TB vaccine – would have many advantages as a vaccine vector, as production capacity is available at a local vaccine factory, the Biovac Institute. Production costs are also very low in comparison to other vaccine production strategies. Although rBCG expressing HIV-1 proteins induces an immune response in mice and baboons, it is not yet optimal for use as a vaccine, as expression of the HIV antigens is low and unstable. Significant improvements in expression and stability have been achieved. Preliminary studies in a few baboons show that a combination of a rBCG expressing gag C as a prime with gag VLPs as a boost gives a response similar to the DNA prime–VLP boost combination. The common gut bacterium *Salmonella* is also being investigated as a vaccine vector. Lastly, Ed Rybicki and Fiona Tanzer are investigating a novel DNA vaccine vector.

### **Monitoring HIV-1 diversity in preparation for phase III vaccine trials**

**PRINCIPAL INVESTIGATOR:** Carolyn Williamson, Institute for Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town. E-mail: [cwilliam@curie.uct.ac.za](mailto:cwilliam@curie.uct.ac.za), Tel: +27 (0) 21 406 6683.

### **UCT/SAAVI HIV diversity study**

HIV diversity remains one of the greatest challenges for developing an effective HIV vaccine: viruses belonging to the same subtype can vary up to 15% in certain regions of the genome, compared with 35% variation seen between subtypes. It is not yet understood how viral diversity will impact on vaccine efficacy. The purpose of the UCT/SAAVI HIV diversity study is to provide a comprehensive analysis of subtype distribution and genetic diversity in proposed phase III vaccine trial sites in South Africa. The study aims to define regions under selection in natural infection and will contribute data to future investigations on the impact of vaccine immune pressure on sequence diversity in vaccine trial 'breakthrough' infections. Lastly, it aims to investigate the relevance of viral diversity in vaccine design by integration of sequence data with immunological and host data generated by the National Institutes for Infectious Diseases Laboratories (NICD). This work forms part of the SAAVI SHIELD study.

The project was initiated in January 2003. A rapid method for HIV subtyping has been established based on subtype-specific probes (multi-region hybridisation assay, MHA). This assay utilises probes labelled with a fluorescent dye and a quencher, combined with real-time PCR. Probes were designed to subtype HIV in the gag, pol, gp120, gp41 and vpu region of the genome to enable easy identification of recombinants. These probes were 100% specific in all regions with sensitivity of 57, 90, 62, 100 and 96 % for gag, pol, gp120, gp41 and vpu regions respectively. Characterisation of viruses from the Cape Town clinical trial site, Masiphumelele, have shown a predominantly 'pure' subtype C epidemic with 131/132 viruses classified as

subtype C across the genome. One subtype B virus was identified. The assay is currently being modified to improve sensitivity in gag and gp120. Of these samples, fifty-five have been sequenced in partial env and gag. Sequence analysis showed two phylogenetically supported clusters, comprising four and three sequences each, suggesting transmission within this community. This study is now being extended to include samples from other vaccine trial sites in South Africa.

In addition, we have been involved in infrastructure development including moving to new laboratories; establishing laboratory and bioinformatics management systems; research laboratory support for the Cape Town Clinical Trials Consortium; protocol development as part of the SHIELD study, (currently undergoing ethical review); assay development including full-length genome sequencing; and, assessment of the relationship between genetic diversity and CTL responses (in collaboration with NICD).

## **University of Stellenbosch Immunology component**

**PRINCIPAL INVESTIGATOR:** Richard Glasshof, Department of Medical Virology, Stellenbosch University & National Health Laboratory Services. E-mail: [RGLAS@sun.ac.za](mailto:RGLAS@sun.ac.za), <http://www.sun.ac.za/virology/dept/default.htm>

Since the reportback in March 2004 for the SAAVI meeting in Johannesburg the experimental work in the laboratory has been focused on completion of the baboon primate study. This has involved assessment of both cellular and humoral (antibody) immune responses following vaccination of baboons with a DNA plus recombinant protein combination vaccine regimen. Briefly, 12 animals have been used in the study, divided into three groups of four animals each. Experimental groups (two of the three) received three priming vaccinations at four-week intervals with either naked or PLG microparticle-formulated plasmid DNA constructs (pCMVKm2GagPolBW and pCMVLinkgp140dv2TV1). The control group received no DNA priming. A combination vaccination (DNA/PLG-DNA plus MF59 adjuvanted recombinant gp140dv2) was given to the two experimental groups 40 weeks after the last prime. At this point the control group received adjuvanted recombinant protein alone. A second boost (MF59 adjuvanted recombinant gp140dv2) was given to all groups 13 weeks after the first boost.

Immune responses have been monitored throughout the study. Antigen-specific cellular immune responses have been assessed using both intracellular IFN- $\gamma$  detection by flow cytometry (ICS) following *in vitro* re-stimulation with superpools of peptides covering the whole of gag, pol and env. IFN- $\gamma$  ELISPOT using multiple pools of peptides for each gene was also performed. A detailed analysis of the responses was presented in previous reports. The responses after the second boost indicate an expansion of cellular responses in certain animals – predominantly to env peptides. These responses were not significantly enhanced compared to those after the first boost vaccination. Since the second boost was protein alone it is not surprising that responses to antigens other than env were minimal. Proliferative responses of baboon PBMCs have also been monitored for the duration of the study. These responses were variable. However, they do indicate that PLG-coupled plasmid DNA is better at inducing a functional memory T cell response than naked DNA. The PLG group consistently displayed better stimulation indices to more antigens than the DNA group. These data correlate with gag-specific IgG responses, but not with gp140-specific IgG responses.

Antibody responses (total IgG and neutralising titres) have been determined at various points throughout the study. After the second boost there was an additional enhancement of antibody responses to peak levels. The control group IgG titres equalised with those of the primed groups at this



point indicating that multiple boosting overcomes the advantage acquired by DNA priming. In addition to gp140-specific IgG responses, Gag-specific IgG levels have also been monitored. A clear distinction between the DNA and PLG-DNA groups was observed here. Only the PLG-DNA group displayed gag-specific responses. The antigen-specific serum IgA levels (anti-gp140) in certain animals have also been examined and indicate a similar pattern of development to the gp140-specific IgG responses. Neutralising antibody responses were determined against SF162 and TV1. TV1 is extremely resistant to neutralisation and responses to this isolate were detectable but weak. No clear distinction in neutralising potential of sera from the DNA, PLG-DNA and control groups was observed. Interestingly, neutralisation of SF162 was much better than TV1 – with the PLG-DNA vaccinated group displaying a consistently better neutralising response than the naked DNA or control groups.

In summary, this study has indicated that DNA priming (gag, pol, gp140) followed by recombinant gp140 protein boosting results in induction of antigen-specific cellular immunity as evidenced by IFN- $\gamma$  ELISPOT and ICS data. Importantly, antigen-specific memory was induced – most effectively in the PLG-DNA primed group. The PLG-DNA primed group also developed a strong gag-specific IgG response, which was not observed in the DNA or control groups. Good anti-gp140 specific IgG and IgA titres were observed in all vaccinated animals with primed animals displaying a better response after the first boost. Interestingly the advantage conferred by PLG-coupling the DNA that was observed with gag-specific antibody responses was not mirrored here, possibly indicating plasmid construct differences. Neutralising antibodies against SF162 and TV1 were observed, however, an additional boost is planned to try and enhance neutralising antibodies.

Planned work includes the additional boost and evaluation of both cellular immune responses and antibody responses. Neutralising antibody titres will be determined using both TV1 and TV2 (a more neutralisation sensitive strain). Ongoing work on functional CTL activity (B-LCL culture and determination of Ag-specific chromium release at various time points) will continue. Due to cessation of research-based funding from SAAVI, we will not be able to continue the work on the lines of additional cellular-specific boosting (e.g. alphavirus particles) and/or more detailed assessment of functional immunity (flow cytometric analysis of memory and CTL degranulation) originally envisaged. In addition, the immunogenicity of the mutated tat, rev and nef plasmid DNA vaccines in primates will no longer be feasible. This also applies to the planned work on novel strain-based env constructs.

## **Molecular epidemiology and vaccine design component**

**PRINCIPAL INVESTIGATOR:** Susan Engelbrecht, Department of Medical Virology, Stellenbosch University & NHLS. E-mail: [susanen@sun.ac.za](mailto:susanen@sun.ac.za), <http://www.sun.ac.za/virology/dept/default.htm>

We have previously reported on the full-length genome sequencing of subtypes A, B, C, D and G in the country and the detection of three AC recombinant viruses. Since March 2004 investigations have continued into the molecular epidemiology and diversity of HIV-1 subtypes circulating in the country. The background monitoring of circulating viruses goes hand in hand with vaccine development and it is important to keep track of the diversification of HIV strains in circulation.

During the past six months 128 positive patients from the Matthew Goniwe clinic in Khayelitsha, an informal settlement in the Cape Town Metropole were genotyped. Although the majority of the patients were infected with HIV-1 subtype C, two AC recombinants and one BC recombinant were also detected. Samples obtained from various other clinics in the Cape Metropole were also genotyped. These 127 samples showed more diversity than in Khayelitsha and a subtype G, and four subtype B strains were detected. We also saw an increase in recombinant viruses in these samples and detected



one AC recombinant, nine BC recombinants and two CD recombinants. The complete genome sequences of these recombinant viruses are being investigated. About 10% of the viruses genotyped were therefore not subtype C viruses.

To evaluate the efficacy of our HIV-1 envelope-based vaccines, the objective of this study is to construct an infectious and pathogenic subtype C SHIV that can be used in Macaque challenge studies. The production of a pathogenic SHIV is difficult and we have always perceived this as a high-risk project. SHIVs are chimeric simian/human immunodeficiency viruses composed of SIVmac239 modified to include the HIV-1 membrane (env) gene. The complete proviral DNA is divided into two halves. The 5' half plasmid construct contains SIV genes and the 3' half construct encodes the HIV-1 portions of the chimeric virus. Our approach in the construction of a subtype C SHIV was to clone the env region of TV001 directly into the pSHIV-89.6p (KB9 molecular clone, subtype B, obtained from the NIH AIDS Research Reference Reagent Program) with newly designed primers. The 2,1 kb env fragment of TV001 was amplified from a functional env plasmid and cloned into the pSHIV-89.6p. To obtain infectious virus we have ligated the 5' and 3' half constructs and transfected mammalian cells with the resulting full-length construct. We are currently screening transfected cell cultures for infectious virus using p27 SIV antigen ELISA and real-time PCR assays. During the last six months we have also set up baboon and Chinese rhesus macaque primary lymphocyte cultures and were able to infect these with SIV and monitor virus growth.

# Immunology

## National Institute for Communicable Diseases (NICD)

### Cellular Immunology Core

**PRINCIPAL INVESTIGATOR:** Clive Gray, NICD, E-mail: cgray@nicd.ac.za, Tel: + 27 11 386 6000, <http://www.nicd.ac.za>.

#### CTL Laboratory

**Milestone: Establishing an MHC/Tetramer Core Facility**

**PRINCIPAL INVESTIGATOR:** Agatha Masemola

Inclusion bodies containing the A3002 heavy chain or  $\beta 2$  microglobulin were purified for synthesis of the first tetramer using one of the novel gag epitopes: LVWASRELERF (LY11) recognised by subtype-C infected individuals. Monomers were synthesised, biotinylated and purified by gel filtration. Biotinylation was confirmed by mixing the purified fractions with streptavidin and proteins fractionated by gel electrophoresis. The positive monomer fraction, verified by the band shifts in the presence of streptavidin, was then used to make a tetramer using streptavidin-Phycoerythrin (PE). The tetramer (5, 10 and 50 $\mu$ l) was used to stain PBMC from an individual previously shown to recognise this epitope; the staining panel also included anti-CD3-APC and anti-CD8-PerCP. With a gate set on CD3+ lymphocytes, about 140 000 events were collected with a FACSCalibur and the frequency of tetramer-positive cells was determined by using Flowjo software. By using increasing concentrations of the tetramer in the staining mix, we were able to show an increase in the frequency of tetramer-positive CD8+ T cells. At present, we are in the process of synthesising monomers using an A2902 heavy chain construct and a novel epitope that we have identified in gag: LYNVATLY (LY9).

#### T Helper Laboratory

**Milestone: Evaluation and optimisation of Intracytoplasmic Cytokine (ICC) assay for the detection of CD4 T cell responses**

**PRINCIPAL INVESTIGATOR:** Dr Caroline Tiemessen

The purpose of the work thus far has been to establish the frequency, breadth and magnitude of CD4 T cell responses by ICC (IFN-gamma plus IL-2 detection) across the HIV-1 genome in comparison to CD8 T cell responses. We have used large pools of peptides corresponding to gag, pol, env, nef and the combined regulatory regions (reg). Thirty HIV-1 infected individuals and six HIV-uninfected controls have been recruited from Chris Hani-Baragwanath Hospital as part of a mother-to-child study. HIV-uninfected controls showed no detectable responses to any of the pools of HIV-1 peptides. Four HIV-1 infected mothers were tested for their responsiveness to peptide pools on follow-up, six weeks after the first analysis, and good concordance and reproducibility with the first sample was attained. CD4 T cell responses were detected to at least one expressed gene region in 80% of HIV-infected individuals, whereas CD8 T cell responses were detected to at least one expressed gene region in 100% of individuals. The regions most frequently targeted by CD8 T cells included nef (83%), followed by gag and env (80%), and with CD4 T cells. Gag and env were most frequently targeted (45%) followed by the reg regions (33%). The most striking difference between CD4 and CD8 T cell analysis using ICC was in the higher magnitude of responses found for CD8+ T cells. Twenty to fifty per cent of CD8+ T cell responses were >0,5% IFNg+IL-2+ to any gene region and only 16,7% of CD4+ T cell responses were >0,5% against the env pool and 4,2% against the reg pool. Overall, our preliminary findings show how detection of CD4 T cell responses compares to CD8 T cells in different HIV protein regions, and this begins to provide a basis for the more detailed mapping of HIV-1 subtype C CD4 T-helper cell epitopes across the genome. Once optimisation using superpools of peptides is completed in whole blood, and more detailed epitope mapping is under way, cryopreserved cells from HIV-infected adults will be tested, and the assay then applied to the testing of cryopreserved samples from the SHIELD study.

#### HLA Laboratory

**Milestones: (1) Continued participation in external quality assurance (EQA) scheme; (2) HLA typing for Class I and II at high resolution in South Africa populations**

**PRINCIPAL INVESTIGATOR:** Adrian Puren

We have continued to participate in the NEQAS UK external quality assurance programme for HLA typing for both high and low resolution with 100% concordance achieved so far this year. We have also recently undergone an internal audit and are in preparation for the upcoming South Africa National Accreditation Schemes (SANAS) audit that includes review of the HLA-A\* and HLA-B\* sequenced-based typing (SBT) method (high resolution).

We have completed the high-resolution (four-digit) typing for the HLA-Cw\* allele in 200 black South Africans and are completing the high-resolution typing of the Caucasian population including the HLA-A\*, HLA-B\*, HLA-Cw\* and HLA-DRB1\* alleles. This will signify the completion of the HLA data for the Eskom cohort, and after the relevant population genetics and statistical analysis, the data will be submitted for publication.

New South African Class I HLA-A\* and HLA-B\* alleles have been identified and we have completed sequencing of six alleles that were cloned into the pCR@4-TOPO® cloning vector. Sequences were subsequently submitted to the GenBank database as well as to the official HLA Informatics Group



(Anthony Nolan Research Institute) for the application for official acceptance and assignment of a new allele by the WHO Nomenclature Committee. Five out of the six submitted alleles were accepted as 'new' alleles and designated the following names: A\*300102; A\*300202; A\*6827; B\*4206 and B\*4507. The sixth allele has been accepted as a confirmatory report of an allele already described in December 2003, namely A\*2911. All six alleles will be listed in the next Full Nomenclature Report and will be published in *Tissue Antigens*, *Human Immunology* and the *European Journal of Immunogenetics*.

## Humoral Immunity Core

**PRINCIPAL INVESTIGATOR:** Prof. Lynn Morris, NICD, E-mail: lynnm@nicd.ac.za, Tel: + 27 11 386 6000, <http://www.nicd.ac.za>

The Humoral Immunity Core is tasked with providing laboratory support for preclinical studies and HIV vaccine clinical trials as well as conducting relevant research into the humoral immune responses to HIV antigens.

## Measuring antibody neutralisation

One of the major projects has been to determine the magnitude and breadth of neutralising antibody responses among HIV-1 subtype C infected Africans in preparation for HIV vaccine trials (HIVNET 028). This study has now been completed and data have been analysed by SCHARP. Results indicate a small but significant effect of neutralisation of subtype C isolates by country-matched sera. However, subtype C sera were as likely to neutralise subtype C viruses as subtype B isolates. These data were presented at a plenary session of the HIV Vaccine Trials Network (HVTN) full group meeting in Seattle in October 2004 and are being prepared for publication.

In collaboration with Dr David Montefiori we have been evaluating the TZM-bl cell line for use in neutralisation assays. TZM-bl cells (also called JC57BL-13) were obtained from the NIH AIDS Research and Reference Reagent Program. This is a HeLa cell clone that is engineered to express CD4 and CCR5 and contains integrated reporter genes for firefly luciferase and *E. coli*  $\beta$ -galactosidase under control of an HIV-1 LTR, permitting sensitive and accurate measurements of infection. These cells are highly permissive to infection by most strains of HIV, SIV and SHIV, including primary HIV-1 isolates and molecularly cloned pseudoviruses. We have found that this cell line is infected by all viruses tested so far. However, the assay is not very sensitive when uncloned PBMC-grown isolates are used and Dr Montefiori strongly recommended the use of molecularly cloned pseudoviruses produced by transfection in 293T cells.

There have been considerable discussions around the utility and standardisation of assays for measuring antibody responses with a shift towards the use of molecular assays. We have begun expanding plasmid DNA from the SG3 $\Delta$ Env backbone and gp160 molecular clones for use in the pseudovirion assay. Transformation experiments were performed on seed stocks of SG3 $\Delta$ Env backbone plasmid as well as molecular clones of a number of gp160 genes. This was done by incubating chemically competent *E. coli* cells with the pDNA provided, heat-shocking the cells and growing them in LB broth overnight. Ampicillin was used for selection and the Genelute HP Plasmid Maxiprep kit (Sigma) used to purify plasmid DNA. Exponentially dividing 293T cells will be cotransfected with the gp160 expressing plasmid and the backbone vector SG3 $\Delta$ Env to construct (produce) pseudoviruses that will be used in neutralising antibody assays.

## Peptide ELISAs

We have been identifying linear epitopes in the gp160 region from HIV-1 subtype C infected individuals. Briefly, 114 overlapping peptides spanning the

gp160 region of an HIV-1 subtype C virus, Du179, were coated onto an ELISA plate, and plasma samples were assayed against these individual peptides. To date 44 subtype C, 13 subtype B and 13 negative individuals have been screened against these overlapping peptides of gp160. Data show limited reactivity of linear peptides in gp160 with only a few regions being targeted. However, 98% of samples reacted with the peptide from gp41 used in the bed ELISA while immunoreactivity of A1ERY (equivalent to the AVERY in subtype B) was lost. Results obtained have been sent through to the Centers for Disease Control for further analysis and interpretation.

## New anti-envelope monoclonal antibodies

In collaboration with Dr James Robinson we have been characterising four anti-HIV envelope monoclonal antibodies derived from HIV-1 subtype C infected patients. All antibodies appear to be A32-like but do not directly compete with A32. They recognise discontinuous epitopes in the C2-C5 region of gp120. They show weak neutralisation of a few isolates and further studies are under way to determine the extent of this activity.

## Modified envelope immunogens

Du151 gp150 and gp140GCN4 were expressed in 293T cells and purified using a *Galanthus nivalis* column. The Du151 gp150 was purified to 4.8 mg/ml in 5 ml and shown to bind to conformational sensitive monoclonal antibodies including b12, A32, C11, 17b and 7b2 and to the sera from HIV-1 subtype C and subtype B infected individuals. The purified Du151 gp140 GCN4 was shown to be a trimer on the native gel and it bound to conformational sensitive monoclonal antibodies. The trimeric Du141gp140GCN4 was mutated by removing glycans at specific positions with the aim of increasing the exposure of conserved neutralisation epitopes. Site-directed mutagenesis was performed on Du151 gp140 GCN4 to remove carbohydrates at positions 289 and 331. Sequencing was performed to confirm the presence of desired mutation on the mutants. The mutants expressed the proteins at the same level as the wild type and the proteins were purified using *Galanthus nivalis*. The purified mutant proteins were shown to bind to conformational sensitive monoclonal antibodies at the same level as the wild type. This observation indicates that the conserved neutralisation epitopes were not exposed by removing glycans at position 289 and 331. The double mutant carrying 289 and 331 will be created and other glycosylation site will be deleted. The mutants will be characterised for the exposure of conserved neutralisation epitopes compared to the wild type.

## Preparations for the HVTN040 vaccine trial

The humoral immunity core will perform the binding antibody assays on the 040 vaccine trial. In preparation we have been in regular communication with the Duke Medical Centre who will be performing the same assays on the US arm of this trial. Two staff members from this laboratory visited the NICD in August 2004 and worked with South African researchers to standardise the HIV gag ELISA which is to be used to measure antibody responses among recipients of a candidate HIV vaccine (040 VEE vaccine trial). A number of experiments were performed to determine cut-offs, repeatability and variability assessments, and to finalise the SOP between the two laboratories. In discussion with SCHARP a margin of 20% variability on titers was deemed acceptable. A proficiency panel will be conducted in both laboratories and data submitted to SCHARP for assessment. Once this is reviewed and found to be acceptable, vaccine samples will be tested. A study plan for the vaccine trial has already been written.



## SHIELD study

We plan to monitor the evolving binding and neutralising antibody responses as well as the numbers and specificity of antigen-specific B cells from HIV-infected individuals residing in four vaccine trial sites. Sequential samples during the first two years of infection will be used. Antibody titers and numbers of B cells specific for the p24 and gp120 antigens by ELISA and ELISPOT respectively. The ELISPOT assay is a new assay that will be established in the laboratory but has been used in a previous study. Neutralising antibody response will be monitored initially using a subtype C T cell line adapted assay (TCLA). Those sera with the most potent activity will be used assayed in a primary virus neutralisation assay against a panel of viruses of different subtypes. The proposed panel will include viruses isolated locally from individuals infected with subtypes A, B, C and D to fully assess the extent of intra- and inter-clade cross-reactivity of HIV-1 subtype C sera.

## Laboratory accreditation

The Humoral Immunity Core is working towards accreditation for the T cell line adapted neutralising antibody assay (TCLA). The laboratory passed an internal audit in July 2004 and will be audited by the South African National Accreditation Society (SANAS) in November 2004. We are also looking into an EQA PP for TCLA neutralisation with Dr David Montefiori's laboratory.

# Clinical sites

## Perinatal HIV Research Unit, HIV Vaccine Division

**PRINCIPAL INVESTIGATORS:** Dr Glenda Gray, Dr Eftyhia Vardas, Dr James McIntyre, E-mails: gray@pixie.co.za; vardase@mweb.co.za, mcintyre@pixie.co.za, Tel: +27 (0) 11 989 9700, <http://www.hivsa.com/phru/default2.asp>.

The funding for this period has been used for the following activities:

- Continued development of phase I/II capacity.
- Continued community outreach programme and education in HIV vaccine research, and CAB development and empowerment.
- Vaccine VCT expansion.
- Baseline studies for phase III trials.
- Continued training and support of staff in clinical trials.

## Continued development of phase I/II capacity

### a) Voluntary Counselling and Testing (VCT)

Table 1: VCT Summary March – August 2004:

VCT	Females N (%)	Negative N (%)	VDG N (%)	Enrolment N (%)
1380	783 (57)	606 (44)	165 (27)	102 (62)

There is a big drop off from identifying HIV-negative clients and them being offered enrolment into our Vaccine Discussion Groups (VDGs). Just over a quarter of HIV-negative clients in this period entered the VDG programme. However, retention was good with 62% of enrolled clients being able to participate in our pre-screening protocol. Our VCT continues to attract women, which is a strength for our site.

Table 2: VDG summary March – August 2004

VARIABLE	TOTAL NUMBER
VDGs conducted/Being conducted	22 groups (165 participants)
Completed VDGs	75 participants
Participants attended VDGs	165
Number enrolled into Pre-screening Protocol	102
Participants attending extra sessions	53
Number who did not complete VDG (loss to follow-up; availability; lost interest; excluded; abnormal laboratory results; difficult phlebotomy)	90

### b) Vaccine Discussion Groups (VDGs) and pre-screening for HIV vaccine trials:

- One hundred and ninety eight (198) volunteers aged between 18 and 53 entered and completed the programme, 99 (50%) were women.
- Only 66 (33,3%) met all the eligibility criteria for enrolment into a phase I/II vaccine trial.
- Three volunteers (1,5%) seroconverted whilst on the programme.

Other reasons for ineligibility include:

- High-risk behaviour including STDs, discordant couples, drug use and multiple partners, 24,8% (49).
- Participant withdrawals including work related, planning pregnancy and voluntary withdrawal, 17,7% (35).
- Medical conditions including chronic conditions and abnormal laboratory results, 10,6% (21).
- Lost to follow up, 9,1% (18).
- Difficult phlebotomy, 4,5% (9).

These data were presented as a poster at the Lausanne Vaccine Conference.

### c) Life Style Risk Questionnaire

A survey to measure sexual risk using a partnership model to collect data on individual sex partners was developed. Focus groups were conducted and surveys were test piloted to assure appropriate content. HIV-negative potential volunteers were recruited from VCT.

Data are available on the first 87 volunteers screened. All were black residents of Soweto and all had at least a primary school education. The HVTN algorithm for higher/intermediate/lower risk classified males as 20%/36%/44% and females as 8%/43%/49% respectively.



	Females (37)	Males (50)
Median age [range]	25 (18–43)	25 (18–53)
Median members in household	6	4
Median household income	R1500 – R1999	R1500 – R1999
Proportion living in households below poverty level (R500/month/capita)	69%	62%
Proportion reporting a new STD in prior six months	8%	16%
Proportion reporting > 3 partners in prior six months	0%	6%
Proportion reporting any unsafe sexual activity in prior six months	51%	48%
Proportion reporting any sexual activity with a known/suspected HIV-positive individual	3%	20%
Proportion classified as low or intermediate risk	92%	80%

This was presented as a poster in Bangkok.

### Phase I trials

We have completed our enrolment for the HVTN 040 trial.

### Phase III development

We have developed a protocol for phase III expansion in Soweto. This was presented to the HVTN.

### Continued community outreach and education in HIV vaccine research and CAB development and empowerment

We have continued with our community education plan approved by the HVTN.

### Baseline studies for future phase III sites

We are collaborators on the SHIELD study which will be conducted at multiple sites in South Africa. We will be enrolling around 500 high-risk participants into a cohort study that will be conducted over an 18-month period.

### Planning for testing of paediatric HIV vaccines and initiating research into adolescent populations

We continue to work in the SAAVI paediatric and adolescent working group as well as in the HVTN adolescent working group.

### Continued training and capacity development of staff

Dr Mayaphi presented a poster at the Lausanne Vaccine Meeting. Dr Bogoshi attended the XV International AIDS Conference, Bangkok, 2004.

## HIV Vaccine Research Unit, MRC, Durban

**PRINCIPAL INVESTIGATOR:** Dr Andrew Robinson, HIV Vaccine Research Unit, Medical Research Council, E-mail: andrew.robinson@mrc.ac.za, Tel: +27 (0) 31 203 4739.

The Durban HIV Vaccine Research Unit is an established phase I/II clinical trial unit. It has the necessary trained research team, Community Advisory Board (CAB) and community linkages. The SAAVI-funded facilities and equipment continue to be maintained

and updated to meet the requirements of international multicentre HIV vaccine research. The working relationship between the site and the CAB has been strengthened following a recent joint strategic planning workshop.

The HIV vaccine screening study has been revised based on the experience over the last two years of implementation and enrolment. This revised version is currently under review by the ethics committee as a pre-screening protocol. Nearly eighty participants have been screened by this protocol, with 18 enrolled into HIV vaccine trials and a further 30 eligible for enrolment into HIV vaccine trials.

Two phase I HIV vaccine trials have completed enrolment and vaccinations. A further three phase I/II trials are being reviewed.

The unit embarked on phase III HIV vaccine efficacy preparatory work at the Africa Centre in the uMkhanyakude Health District by its involvement in the SAAVI incidence study and with site expansion meetings with international HIV vaccine research networks.

The KwaZulu-Natal AIDS Forum continues to reach each district in the province through regular forums and newsletters. The KZN AIDS Forum expansion to Pietermaritzburg and Mntunzini has been very successful and, in line with its aim of holding forums in each district, is expanding to the uMkhanyekude district. The KZN AIDS forum provides a valuable community liaison function between the unit and community. Through its novel community-initiated dynamic, it is sharing HIV vaccinology and all the related science in a meaningful way with stakeholders in the region, providing an invaluable platform for HIV vaccine clinical research.

## Cape Town HIV Vaccine Clinical Trials Consortium

**PRINCIPAL INVESTIGATOR:** Linda-Gail Bekker, Desmond Tutu HIV Centre, Infectious Diseases Clinical Research Unit, University of Cape Town. E-mail: linda-gail.bekker@hiv-research.org.za, Tel: 27 (0) 21 650 6959.

The Western Cape continues to have evidence of a growing epidemic: reported antenatal HIV prevalence in 2002 rose to 12% and in certain communities such as Gugulethu the reported prevalence is as high as 28,3%. The Cape Town HIV Vaccine Clinical Trials Consortium was established in October 2002 and comprises a multifaceted group of HIV researchers who conduct multidisciplinary research in HIV vaccinology. The Consortium offers a fully functional and sustainable HIV Vaccine Clinical Trials Unit in Cape Town able to conduct phase I and II human trials of HIV/AIDS candidate preventive vaccines under good clinical and ethical practice for all age and ethnic groups in South Africa, with a special interest in adolescents. It is currently actively engaged in socio-behavioural, educational and infrastructural development of phase III sites in the two communities of Masiphumelele and Nyanga/Mitchell's Plain, chosen as phase II and III vaccine sites in Cape Town.

The Masiphumelele site is well established. Valuable lessons learnt in Masiphumelele with regards to community education and recruitment are now being utilised in the Nyanga site, where the consortium is currently focusing on site development.

## Aurum Health Research

**PRINCIPAL INVESTIGATOR:** Prof. Gavin J Churchyard, Aurum Health Research, E-mail: gchurch@mjvn.co.za, Tel: +27 57 900 4392.

The communities of the gold mining district of Klerksdorp, Orkney, Stilfontein and Hartebeesfontein (KOSH) in the southern part of the North West Province of South Africa have a high prevalence of HIV infection. Part of SAAVI's mission is to prepare communities for HIV



vaccine efficacy trials. In this regard SAAVI has funded Aurum to:

- develop and sustain a Community Advisory Group (CAG);
- implement a site-specific education programme in the KOSH community;
- determine the HIV incidence rate among HIV-uninfected gold miners in preparation for HIV vaccine efficacy trials; and,
- manage the scientific, administrative and fiduciary aspects of the **SAAVI HIV Incidence and EarLy Disease (SHIELD) Study**.

#### Progress:

- Broad stakeholder support for HIV vaccine research has been established.
- A 35-member community advisory group representing 25 organisations has been established.
- An HIV vaccine education programme has been developed.
- 48 HIV vaccine educators have been trained.
- The HIV incidence among gold miners is estimated as 4,11 per 100 person years (95% confidence interval 3,34 – 5,07).
- Ethics approval has been obtained for the SHIELD study from three ethics committees. Approval is awaited from a further two ethics committees.

#### Plans:

- To establish two HIV Vaccine Trials Units (HVTUs), one at the West Vaal Hospital in Orkney, and one at the Tshepong Hospital in Klerksdorp.
- To provide HIV vaccine education through community outreach to 100 000 people in the KOSH community by the end of the year.
- To train health service staff working at recruitment sites as vaccine recruiters from November 2004.
- To develop a video that will provide education on HIV and HIV vaccines and promote participation in HIV vaccine studies.
- To re-scope the SHIELD study to reduce the cost without compromising the study objectives.

## Ethics

### HIV/AIDS Vaccines Ethics Group (HAVEG)

**PRINCIPAL INVESTIGATOR:** Prof. Graham Lindegger, HIV/AIDS Vaccine Ethics Group, School of Psychology, University of KwaZulu-Natal. E-mail: lindegger@ukzn.ac.za. Tel: + 27 (0) 33 260 5335.

**H**IV preventive vaccine trials present a number of ethical complexities. The HIV/AIDS Vaccines Ethics Group (HAVEG) aims to facilitate the ethical conduct of trials and address several important issues through conceptual and empirical research, consensus building and capacity building activities. These are addressed below:

#### Strengthening the current ethical-legal framework

At present there are no national ethical guidelines dedicated to HIV preventive vaccine research. We collaborated with the Interim National Health Research Ethics Committee (INHREC), charged with setting standards for research, and the Medical Research Council (MRC), to draft and finalise the MRC Guidelines on medical ethics: HIV preventive vaccine research. INHREC is located within the Department of Health's Health Monitoring and Evaluation Sub-directorate. Their input to, and endorsement of, Book 5 reflects a close collaboration with

this government-based committee.

HAVEG hosted a large national stakeholder workshop in July 2004, to critically review the current regulatory environment, including the National Health Bill. A paper on the South African ethical legal environment for health research has been submitted to the *South African Medical Journal*.

The future focus will be to further explore gaps and challenges in the ethical-legal framework through research with stakeholders, and to impact on the ethical-legal framework through submissions on pending legislation and guidelines (see below).

#### Promoting child research participation and the protection of child rights

Our aim is to facilitate a sound ethical-legal framework that promotes the participation of South African children in relevant research and promotes their welfare. To this end, we have undertaken background research into the legislative framework for child research participation in other countries and South Africa, in preparation for a submission on the South African Children's Bill in 2005, and focused on child research participation in our national stakeholder forum in July 2004. We undertook a critique of the South African National Health Bill and the Medical Research Council's *Guidelines on ethics for medical research: General Principles (Book 1)* – both of which were developed into publications that have been submitted to the *South African Medical Journal*. We lobbied the MRC on the need to revise their general guidelines to remove restrictive provisions on research with children. We presented conceptual research into the ethical legal challenges of enrolling and maintaining adolescents in HIV vaccine trials at the XV International AIDS Conference in Bangkok, Thailand.

We are currently focusing on impacting on the regulations that will be drafted in the wake of the National Health Bill, drafting and advocating for a section on research protection in the Children's Bill, and making submissions on those guidelines in revision – *DOH Good Clinical Practice Guidelines* and the *MRC General Principles*.

#### Optimising informed consent practices

While consent is accepted as an ethical imperative for trials, there are some complex and contested aspects. We are addressing various aspects of consent. Ensuring that trial participants understand the implications of participation is critical, and forced choice checklists tend to be the preferred and normative method of 'testing' understanding. We are implementing empirical research to investigate a range of methods to test understanding. Members of vaccine discussion groups at the Durban site have participated in the research, and we hope to secure vaccine trial participants and participants from other sites in the near future. This research was presented in a poster at the XV International AIDS Conference in Bangkok, Thailand, and has been accepted for an oral presentation at the International Association for Bioethics in Sydney, Australia. This research activity also aims to support recommendations for comprehension made in the *MRC Guidelines on ethics for medical research: HIV preventive vaccine research*.

Based on the findings of current research, a future focus will be to make recommendations to sites for rigorous methods to assess understanding and consider the implications for adolescent participation.

#### Identifying the challenges, resources and needs identified by key stakeholders

HIV vaccine trials pose complex ethical dilemmas for a variety of stakeholder groups. It is necessary to acquire a more advanced understanding of the critical issues and challenges role-players experience in relation to these trials. We are in the advanced stages of ethical approval for our empirical research protocol exploring the challenges key stakeholders are facing (e.g. Medicines



Control Council, Research Ethics committees, Community Advisory Boards, Media) in order to recommend interventions to strengthen responses (such as training, changes to the ethical-legal framework, or networking).

Our future focus will be to progressively implement this research. We also aim via this research to explore the adequacy of several HAVEG activities and contributions over the past years (e.g. *MRC Guidelines on medical ethics: HIV preventive vaccine research*).

### **Determining quality of care for infected participants**

A controversial issue in HIV vaccine trials is the obligation of sponsor-investigators to participants who become infected. We have critically examined this issue in a paper accepted for publication in *Social Science and Medicine*. Outcomes of a national meeting convened by INHREC determined that sponsors must ensure that participants have access to antiretroviral therapy, and this has been captured in the guidance point on treatment in *MRC Guidelines on medical ethics: HIV preventive vaccine research*.

A future focus will be to assess the adequacy of this guidance, and investigate community perceptions of sponsor obligations to infected participants.

### **Raising awareness of the ethical-legal complexities**

There is a need to raise awareness of the ethical-legal issues relating to HIV vaccine development. HAVEG has participated in a range of activities to promote understanding and debate on key ethical issues, at national and international conferences and community-based meetings. The majority of our capacity-building activities have been collaborations with other national partners. After canvassing sites to find out what material support they require, we are supporting capacity building for site counsellors, community advisory boards and recruiters by revising our *HAVEG Resource Manual (3rd Edition)* to assist them help prospective participants to make decisions about participation. We hosted a workshop to critically review the current regulation of research in SA and its implications for HIV vaccine trials, and new legislation and guidelines impacting on the participation of children.

A future focus is to support HIV vaccine specific ethics training for select Research Ethics Committee members and get feedback from site staff regarding capacity building materials.

### **Capacity building and training**

Two young black South African researchers have over the past year been exposed to protocol development, research implementation, capacity building in research ethics, and the development of papers for publication. A continued future focus will be to build their capacity in research ethics and research, in order to provide opportunities to manage HAVEG's activities.

HAVEG staff have been actively involved in the design of a module on ethical issues in HIV vaccine trials that is offered as part of the NIH Fogarty funded Southern African Research Ethics Training Initiative SARETI program.

## **Community involvement SAAVI Community Involvement Programme (SAAVI CIP) – Masikhulisane**

**PRINCIPAL INVESTIGATOR:** Elise Levendal, Medical Research Council.  
E-mail: elise.levendal@mrc.ac.za, Tel: +27 (0) 938 0826.

SAAVI CIP's purpose is to develop and implement a relevant intervention model to provide the prerequisite enabling environment for HIV/AIDS vaccine research and development in South Africa. CIP disseminates information, raises awareness and promotes human rights in relation to the development of HIV vaccines within South African communities.

Lobbying and networking activities have been undertaken at local, regional and international levels, providing opportunities to share experiences and materials, and to strategise and arrange further knowledge-sharing opportunities with other countries undertaking similar initiatives.

The Programme's research has led to meaningful input into debates on the level of care for breakthrough infections and participation of minors (particularly adolescents) in HIV vaccine trials. The work on minors, and especially research regarding level of risk was fed into Parliamentary submissions to the Portfolio Committee on Health and the relevant committee of the National Council of the Provinces for consideration for the National Health Bill.

After broad-ranging consultations, further drafts of the 'HIV Vaccine Trial Participant Charter of Rights' were completed and submitted to relevant parties for further consultation. Input has also been made into strengthening arrangements with the Life Office's Association and a process to lobby the health insurance industry, efforts which aim to minimise trial-related discrimination or social harm with respect to life insurance and health insurance, has begun.

The activities of the vaccine educators have been streamlined with a focus on educating change agents in about 20 target sectors.

Additional materials, with new branding, have been developed to assist with information dissemination via workshops and other gatherings.

Partnerships continue to grow with the drawing up of an MOU with the City of Cape Town's SmartCape Initiative to make HIV vaccine information accessible via information kiosks at libraries in the Western Cape. It is hoped that this will be duplicated at libraries around the country.

The expected results and activities of the project are set out in the contract between the MRC and the European Commission.

### **Achievement of results and activities**

**Activity 1:** *Research into identifying the enablers and or inhibitors to participation in HIV vaccine research.*

SAAVI's Socio-Behavioural Group will undertake this research.

**Activity 2.1:** *The appropriate contextualisation of HIV vaccine research as part of the general HIV/AIDS preventative research strategy, not neglecting treatment, care and support, to be described in a National HIV/AIDS vaccine strategy.*

*Development of a National HIV/AIDS Vaccine Strategy*

A draft proposal on the process and content issues was developed by CIP and presented to the wider SAAVI group. The CIP Project Manager and the Human Rights Advisor also undertook a study visit to Kenya, Uganda and Nigeria to investigate the processes followed by these countries in the development of their National HIV Vaccine Strategies.

**Activity 2.2:** *A lobbying process that includes local, provincial and national structures, unions and the private sector to ensure an enabling environment for HIV vaccine preparedness.*

Groups have been identified to assist in development of a lobbying strategy.



**Activity 3:** *Implementation of a National HIV vaccine preparedness educational strategy, being developed with several role players and partners, aimed at learners (schools).*

Contacts within school educational publishing and the Department of Education have been identified to assist with the development of an educational strategy.

Mass HIV communication campaigns such as Soul City, and other media development organisations have been consulted and a review of their materials development process undertaken. This will inform CIP's materials development process and will feed into the overall education strategy.

**Activity 4:** *Development of best-practice models and implementation of research outcomes as regards relevant ethical, human rights and legal issues, pertaining to the HIV vaccine community mobilisation programme.*

#### *Participants' Charter of Rights*

Consultations have continued with community educators, other trial site staff and relevant stakeholders in Kenya, Uganda and Nigeria. A fourth draft of the Charter was developed in May 2004 and is available for comment. A poster of the Charter was developed for the International AIDS Conference in Bangkok and displayed for comment.

#### *Developing continuity mechanisms to protect the rights of trial participants*

Agreement has been reached between SAAVI and the Life Office Association about continuity mechanisms to address the issue of 'false positive' trial participants.

#### *Level of care for breakthrough infections from a constitutional and legal perspective*

A draft paper was produced. We are near resolution of this issue due to the government roll-out of ARVs (except for continued treatment advocacy and access at or near trial sites required). There is a clause in the National Ethics Council 'agreement' that specific legal mechanism would not be required if roll-out commences.

#### *Introduction to general safety aspects of experimental vaccines, e.g. third-generation recombinant DNA vaccines, including vectors, constituents, etc. without reference to using any specific protocols*

From a human rights, legal and ethical point of view, the issues of vaccine liability, liability regimes and insurance are more important to research, as the main risk assessment is done by the MCC and ethics committees. Safety/ data monitoring is also done, although there is a need to continue to monitor and gather information on general safety aspects.

#### *Update of legal and policy (baseline) audit of HIV vaccine trials/development*

There is continued research on the changing legal framework for research with children, and in general. Now that the National Health Act has been published, the legal and policy audit can be further addressed.

#### *Constitutional human rights perspective on question/policy relating to subtype C vaccine testing in South Africa, and the possibilities and parameters of other research using other subtypes or recombinant viruses*

A draft document was produced but this issue has resolved itself in South Africa in line with the notions of the draft document. It may not be necessary to publish as a separate document.

#### *A human rights analysis of the position of children including neonates and adolescents in HIV vaccine trials*

A brief assessment was done via an interview with a Portfolio Committee

member on the 2003 submission to Parliament on the National Health Bill. A presentation was made to the SAAVI Adolescent Working Group. There was also participation in meetings of the Children's Advocacy Group with HAVEG, including preparation for the parliamentary submission on the Children's Bill.

#### *The role and function of the South African Community Advisory Boards in respecting, protecting, promoting and fulfilling human rights of HIV/AIDS vaccine trial participants and affected communities.*

Meetings were held with the trial site PIs to discuss CPP support to CABs and with the Durban CAB to set out crucial issues regarding CAB development.

**Activity 5:** *Linking with international and regional vaccine preparedness activities, facilitated by IAVI.*

#### *International*

A presentation on CIP work was made in March 2004 at an EU meeting in Ethiopia. This provided an opportunity to link with the Kenyan AIDS Vaccine Initiative and to share experiences.

Meetings have been held with HVTN and IAVI community preparedness representatives to discuss joint collaboration.

#### *Regional*

The Project Manager and Legal and Human Rights Advisor undertook a study visit to Kenya, Uganda and Nigeria to explore the community preparedness programmes, the process of developing a vaccine strategy, and the Trial Participant Charter.

#### *Satellite meeting XVI Bangkok AIDS conference*

A satellite meeting was held at XVI Bangkok AIDS conference with regional representatives involved in HIV vaccine community preparedness, as well as representatives from IAVI and AVAC.

#### *WHO-UNAIDS consultative workshop*

Three presentations were made at WHO-UNAIDS consultative workshops in Switzerland on various issues related to HIV vaccines. Presentations were on the following: 'Gender, race and age in HIV vaccine trials', 'Community preparedness – towards a common understanding', and 'Legal issues in regional frameworks and national plans'.

**Activity 6:** *Knowledge translation*

A memorandum of agreement for the SmartCape partnership was finalised.

A SAAVI exhibit was developed for the International AIDS Conference in Bangkok. This generated interest in HIV vaccine development.

**Activity 7:** *Capacity development*

There have been various staff development activities including participation in an adult education workshop at the UCT Winter School, and attendance at a one-week workshop on Human Rights by the Human Rights and Legal Advisor. Various information sessions on HIV vaccine development and the local education system were held at staff meetings.

**Activity 8:** *Continuation of existing SA HIVAC activities*

#### *Community workshops and other events*

During 2004, 15 community education workshops on HIV vaccines were held. There were also 24 presentations on HIV vaccines and 38 related meetings attended. International HIV Vaccine Awareness Day events were organised in Cape Town and Durban on 18 May 2004. CIP also developed



and provided exhibition and outreach materials for the Durban, Orkney and Soweto trial sites for use on the day.

#### *HIV Vaccine Trainer's Manual*

Based on feedback on the final draft of the HIV Vaccine Trainer's Manual at two workshops the Trainer's Manual has been extensively revised and is currently in production.

## Masikhulisane – let us grow together

The programme underwent an extensive strategic planning process at the end of 2004. Based on this it has refocused and revamped its activities, changed its name, and adopted a new vision and mission.

The programme is now called the Masikhulisane Community Involvement Programme reflecting the need to involve communities and individuals in many different ways and to develop in a two-way process along with communities in terms of educational initiatives for HIV/AIDS vaccines.

#### *Vision*

A South African society working in a mutually beneficial and meaningful partnership with AIDS vaccine researchers within a vibrant human and legal rights environment.

#### *Mission*

A sustainable, accountable, learning organisation, founded on a human rights ethos to ensure an informed and educated South African society with active and sustained community involvement in the AIDS vaccine development process.

# Socio-behavioural research

## Human Sciences Research Council and University of Stellenbosch

**PRINCIPAL INVESTIGATORS:** Leslie Schwartz and Ashraf Kagee, Human Sciences Research Council and University of Stellenbosch. E-mails: lswartz@hsrc.ac.za, skagee@sun.ac.za

The socio-behavioural group was formed with the following objectives:

1. National co-ordination of all SAAVI-funded socio-behavioural activities.
2. To provide a methodologically sound framework for socio-behavioural research as part of HIV vaccine trials in South Africa.
3. To become a national resource for all SAAVI-funded sites: strengthening capacity-building; providing input into staff needs and recruitment; providing assistance with protocol development, funding requirements and training of staff; facilitating co-ordination between existing research; and, managing data among sites.
4. To facilitate communication among national and regional socio-behavioural researchers, trial-site PIs and CAB members on socio-behavioural issues.

5. To liaise, inform and educate researchers, CAB members and fieldworkers on socio-behavioural research.

Some of the issues that will be examined in preparation for future HIV vaccine trials include obtaining baseline data on issues such as retention of participants, sexual risk reporting and reduction, willingness to participate, and social harms. These issues become more complex given the diverse cultural and social matrix of South African society. It is imperative for SAAVI to build capacity and infrastructure to examine them in a structured, empirical and methodologically sound way.

The key socio-behavioural activities outlined below fall within the broader aim of providing national support for all socio-behavioural research related to HIV vaccines in South Africa. The activities completed as well as those in progress are outlined.

### **Activity 1: Developing a national socio-behavioural structure**

### **Activity 2: Developing a national socio-behavioural agenda**

The aim is to provide a national framework with a mandate, staff and funding to conceptualise the main socio-behavioural issues and to develop methodologically sound research initiatives to examine them. The broader aim is to provide input and co-ordination for all SAAVI-related behavioural/social science research.

### **Activity 3: Developing national socio-behavioural capacity**

The aim is to strengthen existing research capacity within SAAVI trial sites and to bring key expertise on board. The following has been achieved:

1. Developing resource documents
  - Draft discussion documents on the following issues have been produced and distributed for input:
    - Socio-behavioural issues related to HIV vaccine trials.
    - Developing a knowledge, attitudes and practices questionnaire in preparation for a phase III HIV vaccine trial site in Cape Town.
    - Risk assessment (and draft questionnaire).
    - Social harms during phase III HIV vaccine trials (and draft questionnaire).
    - Willingness to participate in future HIV vaccine trials (and draft questionnaire).
    - Cultural sensitivity in informed consent (HAVEG).
2. Providing central access to source documents and related SAAVI-owned research material via an electronic library for all SAAVI-generated research material in co-operation with CIP.
3. Fostering collaborative relationships
  - a) The initial group consists of social science researchers at the four SAAVI-funded trial-sites
  - b) New relationships are being developed with other SAAVI partners:
    - Collaborative projects between the regional socio-behavioural researchers, HAVEG and CIP have been identified and are in development.
  - c) Experts in related fields are being identified and brought on board:
    - The group currently has expertise in HIV risk behaviour, clinical and cross-cultural epidemiology, all aspects of social science research, including model building, data management, counselling and training, ethics and mental health issues.



## Activity 4: Provide socio-behavioural input to the SHIELD study

Key studies have been initiated in this regard:

1. Developing a comprehensive, quantitative risk-assessment measure.
2. Identifying national socio-behavioural sub-studies. These include sub-studies on sexual risk assessment; willingness to participate; attrition and retention; and, social harms
3. A number of standardised tools such as standard operating manuals, checklists and other materials will be needed during the NIS. The SB group will co-ordinate the development and implementation of these tools at each site, including:
  - Tool 1: Knowledge checklist to be used for recruitment procedures
  - Tool 2: Voluntary counselling & Testing (VCT) manual for harm reduction
  - Tool 3: HIV vaccine education manuals for the national willingness to participate study – to be developed by CIP
  - Tool 4: Standard Operating Procedures for piloting of the sexual risk questionnaire
  - Tool 5: A manual outlining SOP for implementation of socio-behavioural sub-studies and staff training

## Actuarial assessments

### University of Cape Town

**PRINCIPAL INVESTIGATOR:** Rob Dorrington, E-mail: [rdorrington@commerce.uct.ac.za](mailto:rdorrington@commerce.uct.ac.za), Tel: +27 (0) 21 650 2467.

The most significant progress made is the completion and public release of the ASSA2002 AIDS and Demographic model. Improvements in our understanding of the dynamics of the epidemic and the allowance for interventions have resulted in a model that produces substantially lower estimates of HIV prevalence and AIDS mortality in South Africa than the earlier ASSA2000 model. This has significant implications for both the estimation of numbers of individuals requiring vaccination and the estimation of the effectiveness of vaccination. The ASSA2002 model also allows more accurately for the HIV transmission dynamics in young adults, which is likely to be important in modelling the effects of vaccination strategies targeting youth and children in schools. Publications are being prepared on the results of the ASSA2002 model, the mathematics and assumptions defining the model, and the data underlying the model.

Progress has also been made in developing sensitivity and uncertainty analysis tools for use in conjunction with the ASSA2002 model. Experimentation with the Metropolis algorithm has not proven successful. However, a variation of the Latin Hypercube Sampling method, incorporating a likelihood maximisation routine, has produced some promising initial results. The only limitation of this method is its computational slowness, which we intend to address by acquiring more computing power and possibly moving to a compiled language such as C++.

Other work has been conducted to explore the evidence of 'behavioural disinhibition' in the context of widespread availability of highly active antiretroviral treatment (HAART). Although there is evidence of increasing sexual risk behaviour in the HAART era, it is not clear that this is the result of behavioural disinhibition. The likely extent of behavioural disinhibition in the context of an HIV vaccine is therefore highly uncertain.

## SAAVI Bioinformatics and Data Management Medical Research Council and University of the Western Cape

**PRINCIPAL INVESTIGATORS:** Chris Seebregts and Win Hyde, E-mails: [chris.seebregts@mrc.ac.za](mailto:chris.seebregts@mrc.ac.za), [win.hide@sanbi.ac.za](mailto:win.hide@sanbi.ac.za)

The data management group has developed a data collection and management plan and budget for the SAAVI incidence study. The DataFAX facility at the Perinatal HIV Research Unit at Chris Hani Baragwanath is already up and running, and initial work has been done in configuring a similar laboratory information management system (LIMS) at the CAPRISA laboratory in Durban. The systems infrastructure is being installed and configured. An additional goal is to establish systems that comply with the guidelines published by the US Food and Drug Administration. Case and laboratory Report forms will be developed and used to guide the configuration of the DataFAX and LabWare servers. Data management staff will also be appointed.

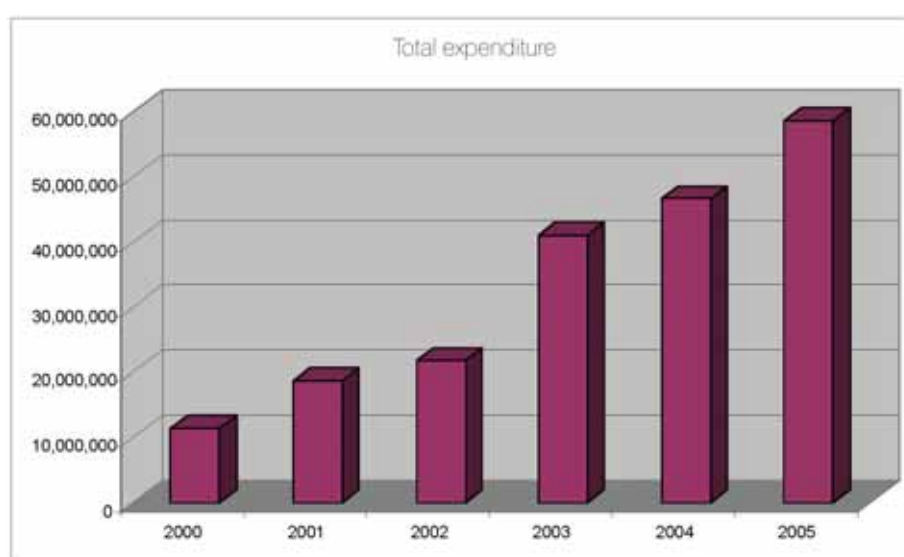
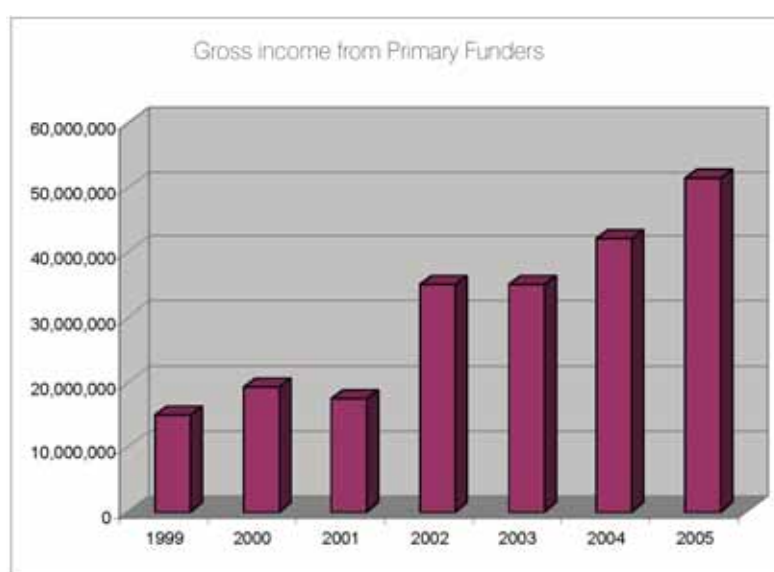


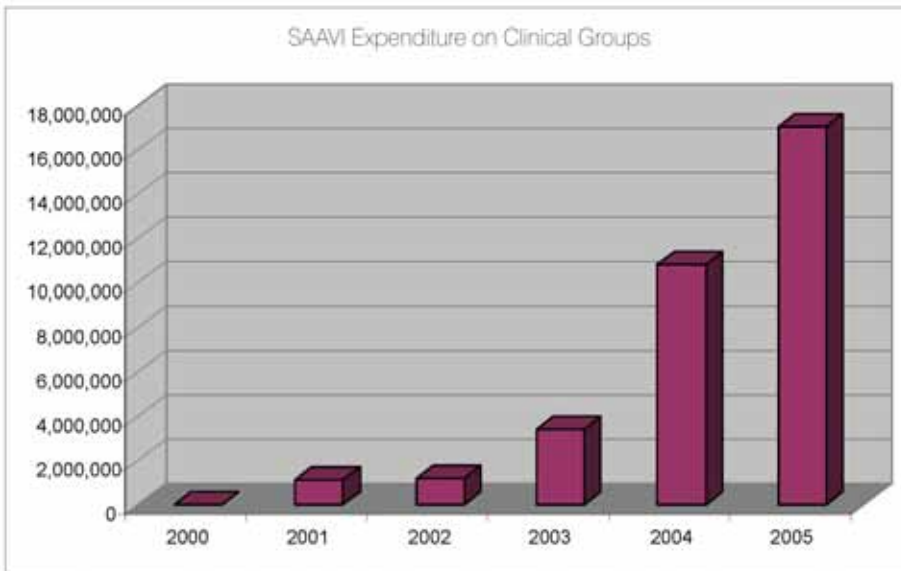
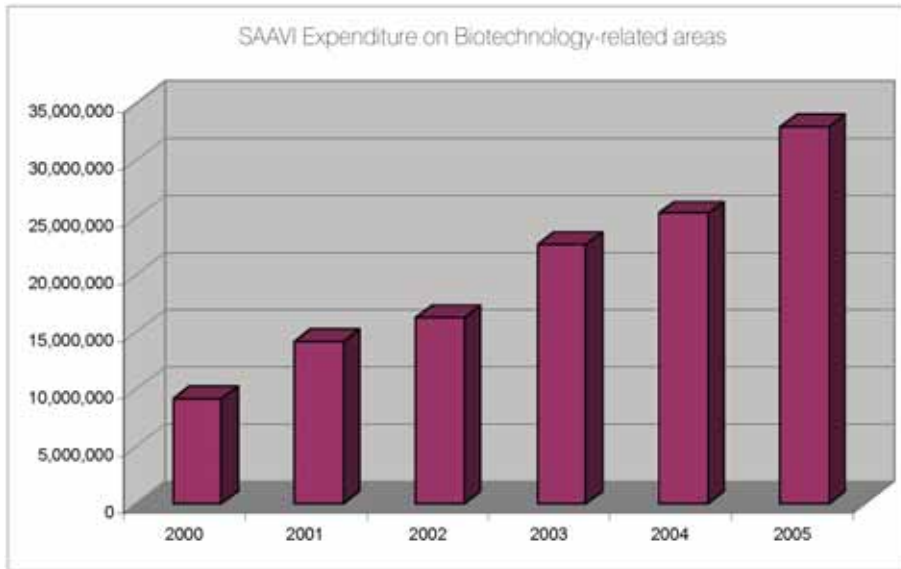
SOUTH AFRICAN AIDS VACCINE INITIATIVE ANNUAL REPORT 2004/2005



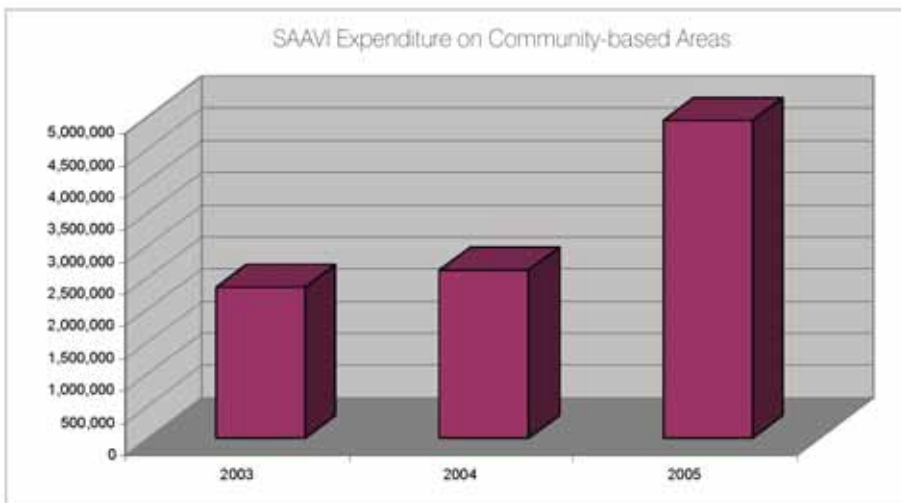
# Finances

**SAAVI'S financial progress is outlined in the following graphs:**





\*\*\* Clinical spend predictions are based on the SAAVI 'SHIELD' study going forward in 2005.



# Publications and presentations 2004

## SAAVI Directorate

### Publications

1. Tucker TJ, Mazithulela G. Development of an AIDS vaccine: perspective from the South African AIDS Vaccine Initiative. *BMJ* 2004; **329** (7463): 454 – 456.
2. Reporting back on World AIDS Vaccine Awareness Day. *Southern African Journal of HIV Medicine* 2004; **15**: 42 – 43.

### Presentations

### Conferences

1. Levendal E, Smit T. Considering Gender, Race and Age in preparing communities for the HIV and AIDS Vaccine Development Process. *AIDS Vaccine 2004*, Lausanne, 1 – 2 September.
2. Levendal E. Community Preparedness: Towards a common understanding. *AIDS Vaccine 2004*, Lausanne, 1 – 2 September 2004.

Invited presentations have included:

- Presentation to the Norwegian Standing Committee on Health and Social Services – 21 January 2004
- Cape Technikon AIDS Committee – 15 April 2004
- Higher Education Sector AIDS Programme – 11 June 2004
- Technikon and Universities AIDS Representatives – 19 August 2004
- Employees Professional Assistance Conference – 2 September 2004
- Presentations on SAAVI CPP in Kenya, Uganda & Nigeria
- Correctional Services, Pollsmoor Prison – 7 October 2004
- Keynote address Astra Zeneca Open Day, University of Stellenbosch, October 2004
- The SAAVI model. Workshop on PPPs: are they the answer, University of Edinburgh, Edinburgh, December 2004

### Press releases

- Implats to fund vaccine development – 18 May 2004
- Transnet comes on board to fund HIV/AIDS vaccine development – 18 May 2004
- Nelson Mandela Foundation and SAAVI announce partnership – 12 August 2004
- Ukukhanya photographic exhibition – 1 December 2004

## University of Cape Town

### Publications

1. Gottlieb GS, Nickle DC, Jensen MA, Wong KG, Grobler J, Li F, Liu SL, Rademeyer C, Learn GH, Abdool Karim SA, Williamson C, Corey L, Mragolick

JB, Mullins JI. Dual HIV-1 infection associated with rapid disease progression. *Lancet* 2004; **363**, 21 February 2004.

2. Jaffray A, Shephard E, van Harmelen J, Williamson C, Williamson AL, Rybicki EP. HIV-1 subtype C Gag VLP boost substantially improves the immune response to a subtype C Gag DNA vaccine in mice. *J Gen Virol* 2004; **85** (Pt 2): 409-413.
3. Grobler J, Gray CM, Rademeyer C, Seoighe C, Ramjee G, Abdool Karim S, Morris L, Williamson C. The incidence of HIV-1 dual infection and its association with increased viral load set point in a cohort of subtype C infected female sex-workers. *J Inf Dis* 2004. In press.
4. Rademeyer C, van Harmelen JH, Ramjee G, Abdool Karim SS, Williamson C. Heterosexual transmission of multiple highly conserved viral variants in HIV-1 subtype C infected seronegative women. *AIDS* 2004. In press.
5. Martin D, Williamson C. Human Immunodeficiency Virus – One of nature's greatest evolutionary machines. *S Afr J Science*. In press.
6. Martin D, Williamson C. Origin, diversity and spread of HIV-1. In: Abdool Karim SS, ed. *HIV/AIDS in South Africa*, Cambridge University Press, 2004.
7. Martin DP, Posada D, Williamson C. RDP2: Recombination detection and analysis from sequence alignments. *Bioinformatics*. In Press.
8. Martin DP, Posada D, Williamson C. An improved bootscanning method for automated detection and description of recombination events in HIV-1 genomes. *AIDS and Human Retroviruses*. In Press.

### Conference presentations

1. Van Harmelen JH, Bodley M, Adams C, Burgers W, Blanckensee T, Williamson C, Quality Management System (QMS) for preclinical potency evaluation of DNA vaccines for phase I clinical trials. *AIDS Vaccines 2004*, Lausanne, Switzerland, 30 August to 1 September 2004.
2. Washington, *Acute Infection Meeting* two posters: HIV-1 viral loads in early HIV-1 subtype C infection and long-term follow-up. (Koleka P, Mlisana, Van Loggarenberg F, Gray CM, Williamson C, Morris L, Ramjee G, Abdool Karim S). High risk cohorts - Challenges and Lessons in Recruitment and Retention of a cohort of Female Sex workers (FSWs) in and around Durban, South Africa (Van Loggarenberg F, Mlisana K, Williamson C & Abdool Karim S)
3. *International Microbicide Conference*, London, March 2004 and UCT research day: Characterisation of recently transmitted HIV-1 variants in subtype C infected women (Rademeyer C, Grobler j, van Harmelen J, Ramjee G, Abdool-Karim S, Williamson C).

## HAVEG

### Publications

1. Barsdorf N, Wassenaar D. Racial differences in public perceptions of voluntariness of medical research participants. *Soc Sci Med*. In Press.
2. Slack C, Stobie M, Milford C, Lindegger G, Wassenaar D, Strode A,



- Ijsselmuiden C.. Provision of HIV treatment in HIV preventive vaccine trials: A developing country perspective. *Soc Sci Med*. In press.
3. Lindegger G. Informed consent in clinical trials. Submitted to AIDS Vaccine Advocacy Coalition (AVAC) Handbook, 2004.
  4. Wassenaar D, Ijsselmuiden C. Obligations to provide care and information to participants harmed in the course of a multi-center vaginal microbicide trial in Asia and Africa. Chapter submitted to *Ethical issues in international biomedical research: A casebook*. Lavery J, Wahl E, Grady C, Emanuel E, eds. Oxford University Press. In press.
  5. Slack C, Stobie M, Barsdorf N. Phase 1 trials of preventive HIV vaccines in South Africa: Access to treatment for trial participants who become infected during the course of a trial. Chapter accepted for publication in *Ethical issues in international biomedical research: A casebook*. Lavery J, Wahl E, Grady C, Emanuel E, eds. Oxford University Press. In press.
  6. Ijsselmuiden C, Wassenaar D. Comments on Wellcome Trust documents to guide application for research in developing countries. Submitted to the Wellcome Trust, 9 June 2004.
  7. Lindegger G, Quayle M, Ndlovu M. Local knowledge and experiences of vaccination: Implications for HIV preventive vaccine trials in South Africa. *J Health Educ and Behaviour*. Submitted.
  8. Strode A, Slack C, Mushariwa M. An evaluation of South Africa's ethical-legal framework and its ability to promote the welfare of trial participants involved in HIV vaccine research. *SAMJ*. Submitted.
  9. Slack C, Kruger M. The South African Medical Research Council's: Guidelines on ethics for medical research: General Principles: Implications for HIV preventive vaccine trials in children. *SAMJ*. Submitted.
  10. Strode A, Grant C, Slack C, Mushariwa M. How well does South Africa's National Health Bill regulate research with children? *SAMJ*. Submitted.
  11. Milford C, Wassenaar D, Slack C. Resources and needs of research ethics committees in Africa: Preparation for HIV vaccine trials. *J Medical Ethics*. Submitted.
  12. Strode A, Slack C, Grant K, Mushariwa M. Ethical-legal challenges in adolescent participation in HIV vaccine trials. *SAMJ*. Submitted.

## Conference presentations

1. Milford C, Lindegger G, Slack C. Developing tools to "test " understanding in HIV vaccine trials in South Africa. Poster at the *XV International AIDS Conference*, Bangkok Thailand, 11-16 July 2004.
2. Strode A, Slack C. Ethical-legal complexities in adolescent participation in HIV vaccine trials. A South Africa case study. Paper presented at the *XV International AIDS Conference*, Bangkok, Thailand, 11 -16 July 2004.
3. Slack C, Strode A, Kruger M. Developing guidelines for the South African Medical Research Council on HIV vaccine research. Paper presented at the Nuffield Council on *Bioethics workshop on the ethics of research related to health-care in developing countries*, 12 - 14 February 2004.
4. Slack C, Stobie M, Lindegger G, Milford C, Wassenaar D, Strode A, Ijsselmuiden C. Standard of care in international trials of HIV vaccines and Microbicides. Paper presented at the *International Consultation on ethical issues in the clinical testing of Microbicides*, 23 - 24 October 2003.
5. Ijsselmuiden C. International research ethics and key debates. Paper presented at the *International Consultation on ethical issues in the clinical testing of Microbicides*, 23 - 24 October 2003.
6. Lindegger G, Van Loon K, Maxwell J, Slack C, Milford C. Experiences of informed consent in a culturally diverse context. Oral presentation at the *7<sup>th</sup> World Congress of Bioethics*, University of New South Wales, Sydney, Australia, 9 - 12 November 2004.
7. Lindegger G, Milford C, Slack C. The development and comparison of methods to assess understanding for informed consent for phase I HIV vaccine trials. Oral presentation at the *7<sup>th</sup> World Congress of Bioethics*, University of New South Wales, Sydney, Australia, 9 - 12 November 2004.
8. Stobie M, Lindegger G. Children's capacity for altruistic choices:

- Implications for the enrollment of children in HIV vaccine trials. Oral presentation at the *7<sup>th</sup> World Congress of Bioethics*, University of New South Wales, Sydney, Australia, 9 - 12 November 2004.
9. Lindegger G. Ethical concerns in HIV vaccine trials. Invited address at University of Western Australia, July 2004.
  10. Stobie M. Enrolling children in HIV vaccine trials: Balancing justice and beneficence. Paper presented at the *Philosophical Society of South Africa Conference*, Fernhill, KwaZulu-Natal, 19 January 2004.
  11. Slack C. Ethical considerations in HIV vaccine trials. Presentation at the Association for HIV collaborations at UKZN Higher Education Institutions, Durban, 30 March 2004.
  12. Slack C. Ethical issues in HIV vaccine trials: Some controversies. Presentation at the Bioethics Reference Group, UKZN, Durban, 31 March 2004.
  13. Slack C. Ethical considerations in HIV vaccine trials. Presentation at the International AIDS Vaccine Initiative (IAVI), New York, New York, 27 October 2003.
  14. Slack C. Ethical considerations in HIV vaccine trials: A focus on standard of care. Presentation at the HIV AIDS Public Health Journal Club, Durban, 5 September 2003.

## Reviews

- Milford C. Invited reviewer for *Journal of Medical Ethics*.

# Perinatal HIV/AIDS Research Unit

## Publications

1. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntyre JA, Harlow. Gender-based violence, relationship power and risk of prevalent HIV infection among women attending antenatal clinics in Soweto, South Africa. *The Lancet*, 2004 May 1; **363** (9419): 1415-21.
2. McClure CA, Gray G, Rybczyk GK, Wright PF. Challenges to Conducting HIV Preventative Vaccine Trials with Adolescents. *J Acquir Immune Defic Syndr* 2004 June 1; **36** (2): 726-733.
3. Masemola A, Mashishi T, Khoury G, Mohube P, Mokotho P, Vardas E, Colvin M, Zijenah L, Katzenstein D, Musonda R, Allen S, Kumwenda N, Taha T, Gray G, McIntyre J, Abdool Karim S, Sheppard HW, Gray C and the HIVNET 028 Study Team: Hierarchical Targeting of Sub-type C Human Immunodeficiency Virus Type 1 CD8+ T cells: Correlation with Viral Load. *J Virol* 2004 Apr; **78** (7): 3233-43.

## Conference presentations

1. Lane T, Struthers HE, Hamilton R, Gray G, McIntyre J. HIV risk behaviours among black MSM in Johannesburg, South Africa. *XV International AIDS Conference*, Bangkok, 2004 (WePeD6267).
2. Mokaotle M, Martinson N, McIntyre J, Gray G, Chaisson RE. Comparing two methods of ascertaining sexually transmitted infections in HIV-infected adults. *XV International AIDS Conference*, Bangkok, 2004 (ThPeC7363).
3. Vardas E, Mayaphi S, Mashego T, Mogale M, Molapo-Matsoso M, McIntyre J, Khabule V, Gray GE. Voluntary HIV counseling and testing as a source of participants for phase I/II HIV vaccine trials in Soweto, South Africa. *XV International AIDS Conference*, Bangkok, 2004 (ThPeC7436).
4. Mesesan K, Bogoshi M, Niccolai L, Gray G, McIntyre J, Vardas E. Measuring the sexual risk behavior of a cohort undergoing screening and enrollment into multiple Phase I/II HIV vaccine trials in Soweto, South Africa. *XV International AIDS Conference*, Bangkok, 2004 (ThPeC7438).



5. Meddows-Taylor S, Schramm D, Gray GE, Kuhn L, Tiemessen CT. Reduced ability of newborns to produce MIP-1 and MIP-1 is associated with an increased susceptibility to perinatal HIV-1 transmission. *XV International AIDS Conference*, Bangkok, 2004 (MoPeA3051).
6. Mayaphi SH, Gray G, McIntyre J, Vardas E. Challenges in recruiting participants for phase I/II HIV vaccine trials in an urban African setting. *AIDS Vaccine 2004*, Lausanne (P248).
7. De Bruyn G, Molao-Matsoso M, Nuwe N, Vardas N, Corey L, Gray G. Low prevalence of helminth infections in Soweto, South Africa indicates helminths are unlikely to influence HIV vaccine evaluation. *AIDS Vaccine 2004*, Lausanne (P252).
2. Grobler J, Gray CM, Rademeyer C, Seoighe C, Ramjee G, Abdool-Karim SS, Morris L and Williamson C. The frequency of HIV-1 dual infection and its association with increased viral set-point in a subtype C incident cohort. *J Inf Dis* 2004, **190**: 1355-1359.
3. Day JH, Grant AD, Fielding KL, Morris L, Moloi V, Charalambous S, Puren AJ, Chaisson RE, De Cock KM, Hayes RJ and Churchyard GJ. Does tuberculosis increase HIV viral load? *J Inf Dis*. In press.
4. Stein L, Carrara, Norman R, Alagiozoglou L, Morris L and Sitas F. Antibodies against human Herpesvirus 8 in a selected group of South African renal transplant recipients and blood donors. *Transplant Infectious Diseases*. In press.
5. Moore P, Cilliers T and Morris L. Predicted Genotypic Resistance to the Novel Entry Inhibitor, BMS-378806, among HIV-1 isolates of subtypes A to G. *AIDS*. In press.
6. Bessong P, Obi L, Cilliers T, Choge I, Phoswa M, Pillay C, Papathanasopoulos M and Morris L. Characterization of Human Immunodeficiency Virus type 1 from a previously unexplored region of South Africa with a high HIV-1 prevalence. *AIDS Res Hum Retroviruses*. In Press.

# HIV Vaccine Research Unit – Durban

KZN E News - KwaZulu-Natal AIDS Forum Newsletter

## NICD Cellular Immunology Core

### Conferences

Sharon Shalekoff attended the *XXII ISAC* (International Society for Analytical Cytology) International Congress, 22 – 27 May, 2004.

Morafo V. Immunological reactivities of "optimal" subtype B-derived Epitopes in subtype C HIV-1 infected individuals reveals a high degree of epitope degeneracy. Poster presented at *AIDS Vaccine 2004*, Lausanne, 30 Aug - 1 Sept 2004.

Clive Gray was an invited speaker at *AIDS Vaccine 2004*, Lausanne, 30 Aug - 1 Sept 2004.

### Publications

1. Masemola A, Mashishi TN, Khoury G, Bredell H, Paximadis M, Mathebula T, Barkhan D, Puren A, Vardas E, Colvin M, Zijenah L, Katzenstein D, Musondo R, Allen S, Kumwenda N, Taha T, Gray G, McIntyre J, Abdool Karim S, Sheppard HW, Gray CM. Novel and Promiscuous Cytotoxic T Lymphocyte Epitopes in Conserved Regions of Gag Targeted by Individuals with Early Subtype C Human Immunodeficiency Virus Type-1 Infection from Southern Africa. *J Immunology*, In Press.

### Neutralising antibody core

### Participation in meetings/conferences

- Jabulani Nhlapo and Tonie Cilliers attended the Keystone Symposia in Whistler, Canada, March-April 2004.
- Members of the Humoral Immunity Core met with the Cape Town-based SAAVI Vaccine Group in June 2004 to discuss the need to develop HIV subtype C envelope immunogens in SAAVI and to develop stronger links with international groups working on envelope immunogens.
- Lynn Morris, Natasha Taylor and Elin Gray attended the HVTN Full Group Meeting in Seattle, Washington, October 2004.

### Publications

1. Cilliers T, Patience T, Pillay C, Papathanasopoulos M and Morris L. Sensitivity of HIV-1 subtype C isolates to the entry inhibitor T-20. *AIDS Res Hum Retro*. 2004, **20**: 477-482.

### Training

- Mia Coetzer spent one month in Dr Jim Mullin's laboratory funded by the Fogarty International Center (FIC) designing and testing algorithms for predicting coreceptor usage among HIV-1 subtype C isolates.
- Jabulani Nhlapo spent four months in Dr Jim Robinson's laboratory visit at Tulane Medical Center funded by FIC characterizing anti-HIV-1 monoclonal antibodies.
- Dr Penny Moore is spending seven weeks in Dr James Binley's laboratory at the Torrey Pines Institute for Molecular Studies, San Diego, followed by a one-week visit to Dr David Montefiori laboratory at Duke University. During this time she will be acquiring skills to enable the establishment of a molecular assay for measuring neutralising antibody responses and examining aspects of HIV entry.
- Natasha Taylor and Isaac Choge were both awarded their Masters degrees in Virology from the University of the Witwatersrand in June 2004.

## Cape Town Clinical Trials Consortium Publications

1. Smit J. Socio-behavioural challenges to phase III HIV vaccine trials in developing countries. In preparation.
2. Smit J. The association between sexual risk behaviour and psychopathology. Submitted.

### Presentations

1. Mendelson F. Knowledge, attitudes and practices in a life skills programme in Masiphumelele High School. Oral presentation, *XIV International AIDS Conference*, Bangkok, July 2004.
2. Jaspan H. Risk of HIV-1 acquisition in South African youth. Oral presentation, *XIV International AIDS Conference*, Bangkok, July 2004.
3. Middelkoop K. An innovative community HIV education program to improve VCT uptake. Oral presentation, *XIV International AIDS Conference*, Bangkok, July 2004.
4. Smit J. Who will volunteer for HIV-related research? Oral presentation, *XIV International AIDS Conference*, Bangkok, July 2004.
5. Jaspan H. Children and SA Vaccine Trials. Oral presentation at the *HAVEG Adolescent Ethics Workshop*, Durban.
6. Bekker LG. HIV vaccine and the South African HIV Vaccine Initiative. *Antiretroviral Workshop*, Johannesburg, April.
7. Bekker LG. HIV vaccines and adolescent involvement. Youth Week at a pre-conference workshop in Bangkok.





## 2004/2005 Annual Report

Tel: +27 (0) 21 938 0262, e-mail: [saavi@mrc.ac.za](mailto:saavi@mrc.ac.za)  
SAAVI Vaccine Info-line 080 VACCINE  
[www.saavi.org.za](http://www.saavi.org.za)