

# ANNUAL REPORT 2003/2004



## SOUTH AFRICAN AIDS VACCINE INITIATIVE (SAAVI)

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## Report from the SAAVI Directorate

In a year of progress, the highlight was the commencement of two phase I clinical trials at two trial sites. This catapulted South Africa to the forefront of vaccine development as the first country to test a clade C vaccine and the first African country to be running multiple, concurrent clinical trials.

The two trials commenced within a week in November at the Soweto and Durban trial sites. The two products — the VEE clade C candidate and the MVA clade A candidate — represent international collaborative efforts involving many partners. The Venezuelan Equine Encephalitis (VEE) candidate was developed by researchers from the Universities of North Carolina and Cape Town, manufactured by AlphaVax, and the trial is being run by the HIV Vaccine Trials Network of the US National Institutes of Health. The Modified Vaccinia Ankara (MVA) candidate was developed by researchers of the Universities of Oxford and Kenya, and sponsored by the International AIDS Vaccine Initiative. It has already been tested in Kenya and the UK.

A third trial is with a Merck vaccine, which uses replication deficient adenovirus as the vector technology. This trial should start during 2004.

These trials will feed into local knowledge and development, and also into international efforts to find a successful vaccine. Because of the many unanswered questions in vaccine development and the urgent need for an effective vaccine, running simultaneous multiple phase I trials of different approaches is essential.



Other highlights have included the progression to initial manufacture of three wholly SAAVI-developed candidate vaccines that have now entered the regulatory processes in preparation for trials. These are two 'DNA vaccines' and one 'MVA vaccine'. The SAAVI-NIH development team completed the pre-IND (Investigational New Drug) application with the US Food and Drug Administration (FDA) in October 2003. This is a milestone, and will allow preclinical toxicity testing to start. SAAVI has raised further capital to perform these preclinical toxicity tests at Gene Logic in the USA. These skills/facilities are not available in the country. This is a 'first' for SAAVI/MRC, as no developing country-made HIV vaccine has ever been lodged with the FDA. Human clinical trials with the DNA vaccines could begin in 2004/2005. This is very rapid progress.

Other progress has included the leveraging of additional funding from international organisations such as the HIV Vaccine Trials Network and the European Union, and the cementing and forging of important local partnerships with the South African government, Eskom and with organisations such as the Nelson Mandela Foundation.

The initiative has also expanded — additional groups have joined including further trial sites; an expanded research agenda to include socio-behavioural aspects; the inclusion of groups investigating the actuarial, bioinformatics and data management aspects of vaccine development, as well as the expansion of the Directorate's skills base to include legal, business and communication's expertise.

In terms of the primary funders — the Department of Health doubled its funding from R5 to R10 million per annum while the Department of Science & Technology continues to commit R10 million per annum. Eskom increased its funding from R7,5 to R15 million per annum and agreed to fund SAAVI for an additional five years – making this the largest-ever corporate contribution to HIV vaccine R&D in the world.

Importantly also, the Department of Science & Technology has expanded its commitment by initiating fundraising activities targeting big business in South Africa on behalf of SAAVI. It is hoped that this will lead to increased private sector funding over the long term.

SAAVI is a highly integrated part of the worldwide drive by global organisations to develop an HIV/AIDS vaccine, and enjoys close collaboration with many global players including the US National Institutes of Health (NIH), the NIH-funded HIV Vaccine Trials Network (HVTN), the International AIDS Vaccine Initiative (IAVI), the European Union (EU), the African AIDS Vaccine Programme (AAVP), the European Developing Country Trial Programme (EDCTP) which recently selected the MRC to host its African office, the Ethiopian AIDS Vaccine Initiative (EAVI), the Nigerian AIDS Vaccine Programme (NAVP) and the Botswana Harvard AIDS Institute, as well as international companies such as Cobra, Therion, Merck, Chiron, Large Scale Biology Corporation and Microscience.

International collaboration is essential to fast track the development of an HIV/AIDS vaccine and SAAVI values these collaborative ventures. Although closely collaborating with these and other organisations, SAAVI operates independently allowing it to pursue its own goals and maintain its focus on the needs of the southern African region.

### Summary of highlights

#### **SAAVI continues to make substantial progress. Highlights include:**

- The commencement of two phase I trials of two candidate vaccines in collaboration with local and international partners.
- Increased support from the primary funders.
- Continuation of a grant from the US NIH HIV Vaccines Trial Network (HVTN) to prepare clinical trial sites.
- Expanded funding from the EU for vaccine preparedness and community education initiatives.
- The accreditation of the SAAVI group at the National Institute for Communicable Diseases as the only laboratory outside the US mandated to perform HVTN-related clinical trial immunological end-point analyses.
- Active collaborative projects with foreign institutions and companies have allowed SAAVI to increase the number of candidate vaccines in development. There are now five candidate vaccines under evaluation by researchers at the Universities of Cape Town and Stellenbosch. There are also many collaborative projects using SAAVI genes.
- SAAVI continues to manufacture HIV/AIDS vaccines and perform toxicity testing using support awarded by the NIH. Trials with SAAVI products could begin in 2004/2005.
- The HIV/AIDS Vaccines Ethics Group (HAVEG) was chosen by the chair of the South African MRC Ethics Committee to co-ordinate the development of national ethical guidelines for HIV/AIDS vaccine trials in South Africa. These guidelines have been accepted by the National Health Research Ethics Committee. HAVEG also co-ordinates the Ethics, Law, Human & Legal Rights Working Group of the AAVP.

## SAAVI phase III preparation

The SAAVI consortium is preparing for a national programme to prepare for phase III trials. This is a collaborative project involving the clinical trial sites (Soweto, Durban, Hlabisa, Cape Town and Orkney), and the combined efforts of the SAAVI-funded personnel at the South African National Bioinformatics Institute, the Universities of Cape Town, Stellenbosch, the Western Cape and KwaZulu-Natal, the National Institute for Communicable Diseases and the MRC.

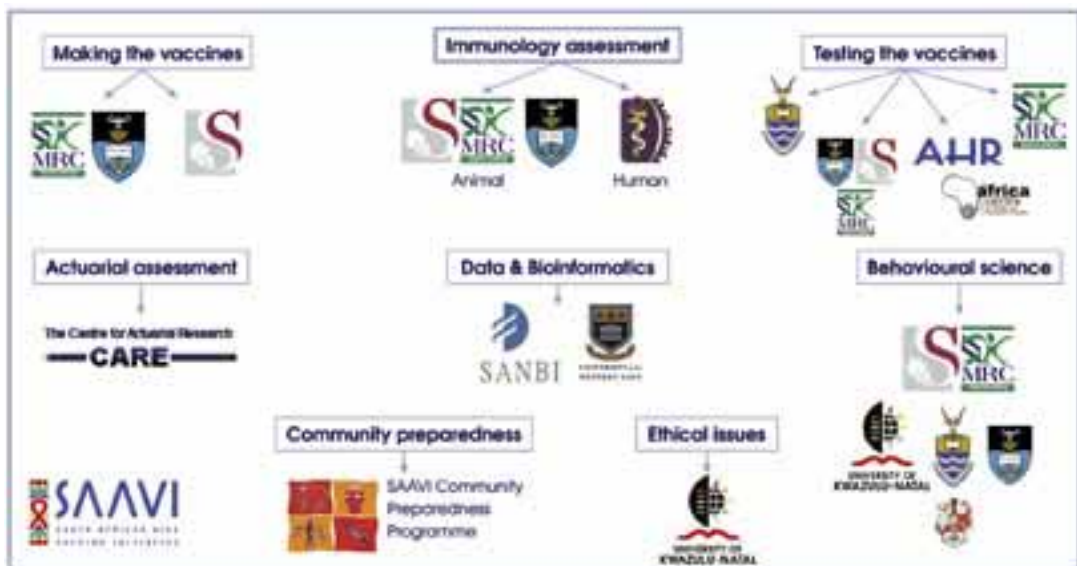
The goal is to measure the HIV incidence (the rate of new infections/ seroconversions) in high-risk volunteer communities that would potentially be involved in phase III trials.

The programme will follow about 500 volunteers per trial site over a two-year period. The preparation programme will involve a complex and integrated analysis of the human and viral factors influencing infection and immunity. It is projected that this will provide a comprehensive guide for future phase III trial strategies. Despite intensive and ongoing risk-reduction counselling, it is estimated that many people on phase III trials will seroconvert each year.

The information gathered will include data on the genetic variability of the community (through human leukocyte antigen [HLA] typing); determining the genetic variability of the virus (through viral genetic analysis); and, measuring and analysing immune system responses in those who become infected. Assessments will include analysing antibody and cellular immune responses (measured CD4 and CD8 epitope responses); and, the measurement and monitoring of CD4 count and viral load to establish viral set points – vital information to establish the natural set point and its effects on disease progression.

## SAAVI groups

The core activities of SAAVI fall within the following categories:



## Scientific summaries

### Laboratory development of vaccines

#### 1) University of Cape Town (UCT)

##### Developing novel candidate vaccines

The UCT group is investigating different strategies to make vaccines, based on the HIV-1 subtype C virus, the dominant strain circulating in southern Africa. The mission is to develop HIV-1C vaccines that are effective and affordable, and, through a comparative strategy, to advance the most promising vaccines or combination vaccines to clinical trial. 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. They are backed up by a competent team of over 30 people.

The first vaccines selected to move forward to clinical trials are DNA vaccines and a modified vaccinia Ankara vaccine (MVA). This DNA prime-MVA boost combination is regarded as one of the most promising vaccine strategies. The subunit vaccine group is making candidate vaccines using baculovirus and tobacco expression systems while the bacterial vaccine group is developing vaccines based on live-recombinant BCG and Salmonella bacteria.

The highlight of 2003 UCT programme is the commercial manufacture of the two DNA vaccines constructed in our laboratory: one expresses a polyprotein comprising modified gag, reverse transcriptase, tat and nef, and the other expresses a truncated gp160. Cobra Therapeutics, UK, is manufacturing these vaccines for clinical trial. The UCT SAAVI development team includes Carolyn Williamson, Anna-Lise Williamson, Enid Shephard, Joanne van Harmelen and Wendy Burgers. They are working in partnership with the National Institute for Allergy and Infectious Diseases of the US National Institutes of Health, the HIV Vaccine Trials Network also of the NIH, the National Institute for Communicable Diseases, the Perinatal HIV Research Unit and SAAVI. Clinical trials are planned for 2004/2005. In addition, Therion Biologics Corporation in Boston is manufacturing a MVA-based vaccine, designed to boost the DNA vaccine prime. The NIH funds the MVA manufacturing contract.

The next most promising vaccine, developed by Ed Rybicki and Ann Jaffray, is the virus-like particle (VLP) vaccine based on an HIV-1 subtype C Pr55 gag protein, 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, by Enid Shephard's group and Gerald Chege, show good immune responses in baboons primed with DNA gag C vaccine and boosted with gag C VLPs. 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 subunit vaccines.

A longer-term project by Anna-Lise Williamson's group, with William Bourn, is aiming to optimise bacterial vectors as vaccine delivery vehicles. BCG — better known as the TB vaccine — would have many advantages as a vector, as production capacity is available at a local vaccine factory, the Biovac Institute. Production costs are also low in comparison to other vaccine production strategies. Although rBCG expressing our HIV-1 proteins induces an immune response in animal models, it is not yet optimal for use as a vaccine. Several approaches are being taken to improve this response.

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 vaccine trials

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 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. It also aims to investigate the relevance of viral diversity in vaccine design by integration of sequence data with immunological and host data generated by the NICD. This work forms part of the SAAVI incidence study.

The project was initiated in January 2003. Characterisation of viruses from the Cape Town clinical trial site have shown a predominantly subtype C epidemic with 54/55 viruses classified as subtype C in both gag and env. One subtype B virus was identified. Two phylogenetically supported clusters, comprising four and three sequences each, suggests transmission is occurring within this community.

The group has also been involved in: (i) infrastructure development including renovation and equipping laboratories; (ii) establishing management and laboratory structures; (iii) establishment of the clinical trial sites as part of the Cape Town Clinical Trials Consortium; (iv) protocol development as part of the 'SAAVI incidence study'; and, (v) assay development including multi-probe hybridisation assay (MHA) and full-length genome sequencing.

## 2) University of Stellenbosch (US)

### **Assessment of immunogenicity of candidate HIV-1 subtype C vaccine constructs in animal models**

The immunology laboratory in the Department of Medical Virology at Stellenbosch University was established to monitor the immunogenicity of HIV-1 subtype C vaccine constructs. The current focus is on monitoring the immune responses of baboons following vaccination with DNA plasmid constructs and also in assessing the immunogenicity of mutated tat, rev and nef constructs in mice.

The baboon study is the first primate vaccination study carried out in the laboratory. The strategy is a DNA prime combined with a recombinant protein boost. Twelve baboons are being used in three groups, defined as follows: (i) animals receiving naked DNA plasmid followed by protein boost; (ii) animals receiving PLG-DNA followed by protein boost; and, (iii) control animals receiving recombinant protein alone. To date, animals have received three DNA prime vaccinations and immune responses have been assessed at various time points. Intracellular cytokine (ICC) analysis of interferon gamma (IFN- $\gamma$ ) production by flow cytometry and detection of secreted IFN- $\gamma$  by ELISPOT both indicate optimal T cell responsiveness to HIV-1C peptides at week 12 (i.e. four weeks post third DNA prime vaccination). Responses were still detected at week 16 in certain animals against certain peptides, however, by week 20 most responses had diminished considerably. ICC and ELISPOT data indicate that the DNA and DNA-PLG groups were comparable with regard to IFN- $\gamma$  production. Up to 0,6% of CD8+ T cells responded to pooled peptides in the two groups receiving DNA prime vaccinations as assessed by ICC. Lymphoproliferative responses were also monitored at the same time points – and optimal responses were observed at week 12. Interestingly the PLG-DNA group appeared to display a broader and greater CD4+ T-cell memory response. Antibody responses following DNA vaccination are being assessed by determining total anti-HIV IgG and also determining neutralising capacity of sera against homologous and heterologous clade isolates. This work is performed in collaboration with the Chiron Corporation and Duke University.

A study of baboon dendritic cell transfection by plasmid DNA delivered in different forms (naked DNA diffusion, naked DNA electroporation, liposome) is also under way to determine whether alternate delivery systems will enhance DC transfection and how that may impact on DC function and the immune responses generated.

In addition to the primate study, there is a mouse study in progress using mutated tat, rev and nef DNA plasmids. The magnitude of the responses in immunised animals has been assessed by ICC. There is an indication of generation of antigen-specific CD8+ T cell responses to all of these mutated constructs as well as the combined tatrevnef construct. A more detailed investigation of the responsiveness of splenocytes following *in vitro* stimulation is being planned and the functional capabilities of the antigen responsive cells will also be assessed (CTL assays and lymphoproliferation assays). Ultimately the aim is to use the mutated tatrevnef construct in a primate vaccination study including the current gagpol and gp140dv2 vaccinated animals and also in a vaccine-naïve group.



## Development of a subtype C HIV-1 vaccine using the prime-boost strategy to induce a CTL response and neutralising antibodies

The molecular epidemiology study has delivered remarkable results over the past year. The first full-length genomes in the country for subtypes A, B and G have been sequenced. The description of subtype G and the circulation of recombinant viruses in the country is not surprising, but is of interest because of the well-entrenched concept of a fairly homogenous subtype C epidemic. If HIV diversification expands, the development of a monotypic vaccine for South Africa will need to be revisited. This study has established fruitful collaborations with ABBOTT laboratories, Chicago (generating multi sub-genomic PCR fragments across the genome) and the Bioinformatics Unit, Africa Centre, University of Natal, Durban (sequence phylogeny and evolutionary analysis). Background monitoring of circulating viruses goes hand-in-hand with vaccine development.

The production of a pathogenic SHIV is notoriously difficult, hence the limited number of subtype B constructs available with no pathogenic subtype-C SHIV to date. The difficulties experienced this year resulted in adopting a change in methodology after consultation with Dr Ndung'u from Harvard, who has successfully constructed a subtype-C SHIV (non pathogenic). He supplied a partial construct, which will be used in efforts to construct the SHIV. This is a high-risk project, but it is hoped that success will be achieved with the amended programme. Once a complete infectious chimeric virus has been achieved, the strain will be adapted to primate cells before *in vivo* passaging is attempted. If this project is unsuccessful, alternate options will be considered to ensure that a challenge study is possible. One option would be to use a heterologous pathogenic subtype-B SHIV. This is not optimal since it will be difficult to compare the results of such a study with others where a same clade virus was used.

The Aspergillus study is in its fourth year. Marked progress has been made since a post doc was employed. The establishment of a protein-producing laboratory has been another major challenge and, even in experienced hands, consistency and repeatability of producing protein products is not easily obtained. Protein is currently being purified in the laboratory and will be tested for immunogenicity. The protein expressed at this stage is not optimal and experiments are under way to optimise the Aspergillus system. It is too premature to decide whether this system will produce proteins comparable to those produced in mammalian cells, but an indication on the viability of the system should be available soon.

## Immunology

### 1) National Institute for Communicable Diseases (NICD)

#### Cellular Immunology Core

This Core will conduct all cellular-based immunological assays in the SAAVI incident cohort study. These will include: CTL assays, MHC/tetramer staining and tracking of responses over time, T-helper cell assays and HLA typing at high resolution. The aim will be to identify the evolution of CD4+ and CD8+ epitope-specific class I and II restricted T cell responses from acute infection and track these responses over two years. This will run as an ancillary study to the main goal of measuring HIV-1 incidence at four potential phase III vaccine trial sites.

The first funding period has seen the preparation of assays to be used in the incidence study. For the ELISPOT assay, study-specific validation was performed where a dynamic range of responses were assessed using overlapping peptides to the complete subtype C HIV-1 genome in 25 sero-negative and 50 HIV-1 sero-positive individuals. Cut-off values were established by which to measure positive responses and it was calculated that a response <104 spot-forming units (sfu)/10<sup>6</sup> PBMC was considered negative.

Assessing quality control and assurance in the assay was established by using PBMC sets that respond to pools of optimal CMV, EBV and Flu (CEF) peptides. A control PBMC programme has been established within the Core where one vial of control cells are thawed per day, added to each plate and stimulated with PHA and CEF peptides. This approach has been used to monitor assay variation over time as well as inter-operator variability complemented with ongoing training of the Standard Operating Procedure for technicians who set up assays that fall out of specification.

The MHC/tetramer facility has started cloning relatively common HLA alleles in South Africa with the aim of making tetramers to dissect out epitope-specific CD8+ T cells. Complementary to this has been fine epitope mapping in gag and nef, to identify optimal epitopes restricted by common HLA alleles. These epitopes will be used for synthesis of MHC/tetramers. The use of autologous-derived dendritic cells has commenced to augment very weak CD8+ T cell responses and the possible identity of sub-dominant responses. This is still in early development.

T-helper CD4+ responses are being examined using intracellular cytokine staining utilising a cocktail of anticytokine monoclonal antibodies: IFN $\gamma$ , TNF $\alpha$  and IL-2. To date, whole blood assays have been established from a donor who responds strongly to a secretory TB antigen: ESAT-6. Assays to optimise responses from cryopreserved PBMC are under way.

The HLA Laboratory has continued to participate in proficiency panels as part of the external quality assurance programme. Results for the first two cycles: 100% achieved for low-resolution Class I and II typing and 100% for Class II high-resolution typing. For high-resolution Class I HLA typing the results were: 83,3 and 100% for the first and second cycles. A total of 200 Black South Africans have also been typed at high resolution and the following two locus haplotypes (A/B) were observed at frequencies above 2%: 3001/4201, 6802/1510, 6801/5802, 0301/5802, 3402/0801, 2902/4201, 6802/5801, and 3020/1510. There is a statistically significant difference between the Black and Caucasian populations at the three Class I loci A, B and C (Fischer's RxC test,  $P < 0,0001$ ). These data indicate that wide divergences exist in HLA haplotypes between Black and Caucasian populations in South Africa.

### **Humoral Immunity Core**

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. The core comprises three salaried and two non-salaried research assistants as well as two students and administrative support. The Core actively interfaces with Dr Clive Gray who heads the HIV Vaccine Trials Network South African Immunology Laboratory (HVTN SAIL) and will be responsible for performing HIV antibody assessments on HVTN-sponsored trials.

The first trial is the HVTN 040 VEE trial and preparations are under way to ensure the quality and reliability of data emanating from the Humoral Immunity Core for this trial. The Core will also be participating in a WHO-UNAIDS sponsored initiative to assess progress in the development and standardisation of methods to measure anti-HIV-1 neutralising antibodies in HIV vaccine research and clinical trials. For this, the Core will be contributing a subtype-C neutralisation-sensitive isolate, Du174, as well as large volumes of HIV-subtype C-infected plasma that has strong neutralising activity. We have been communicating with Dr Georgia Tomaras who is responsible for these assays in the USA. Preliminary experiments have been conducted and a Standard Operating Procedure has been documented. Compatibility of all equipment and reagents has been ensured and in some cases this has meant motivating for purchasing new equipment. A strategy to cross-validate data obtained in both laboratories has been devised. A proficiency panel with samples from HIV-1 infected and HIV-1 negative individuals as well as vaccines will be tested in both laboratories.

The Core houses the SAAVI Repository for HIV isolates which includes many of the strains used in vaccine development. The Core has also made significant progress in establishing and evaluating new methods for measuring neutralising antibody responses. This includes the single-cycle flow based assay that measures intracellular p24 antigen levels devised by John Mascola. In collaboration with Dr Mascola we have replicated this assay using the subtype C Du151 vaccine strain and shown an excellent correlation with the standard PBMC-based neutralisation assay that measures extracellular p24 antigen levels. We have also continued work on the subtype-C T-cell line adapted (TCLA) neutralisation assay which we showed earlier correlates better with subtype C neutralisation in PBMC than a subtype B TCLA assay. Further studies have shown that neutralisation of SW7-TCLA is largely V3-loop dependent.

In collaboration with Dr David Montefiori of Duke University we have done an extensive analysis of the magnitude and breadth of subtype C sera against subtype C and B viruses, and shown that subtype C sera are highly effective at neutralising South African subtype B viruses. This has implica-

tions when considering the cross-clade neutralisation of vaccinee sera. We have confirmed an earlier observation that subtype C isolates are generally insensitive to the 2G12 and 2F5 monoclonal antibodies that are considered to be broadly neutralising. We have expanded this panel to include an additional four subtype B isolates. Data indicate that subtype C sera neutralise both subtype C and subtype B isolates, however, neutralisation of subtype C viruses was significantly more potent against subtype C viruses than subtype B isolates. This finding supports earlier data suggesting that some subtype-specific neutralisation determinations exist.

We have therefore embarked on a project to identify new anti-HIV monoclonal antibodies using B cells from subtype C-infected patients and, to date, have produced five such antibodies that await further characterisation. Should they be of interest, they will be included in the antibody repository which has been established as part of this Core.

Large quantities of four monoclonal antibodies have been produced from cell lines provided by Dr James Robinson from Tulane University that are used as capture antibodies in ELISAs as well as for purifying envelope glycoproteins. This project is being conducted by Dr Maria Papathanasopoulos who also provides the Core with recombinant envelope antigens. Further work is progressing to identify the epitopes defined by these Mabs. The env plasmid (codon optimised Du151 Env-pTH) was obtained from UCT and used to transfect 293T cells. The data show the ability of the purified proteins to bind to selected monoclonal antibodies (A32, C11, IgG1b12 and 17b coated onto ELISA plates at 5 ug/ml). These data confirm that the gp150 purified protein is functional and conformationally intact. To date, 1-2 mg/m of this protein has been produced and will be sent to UCT for animal studies.

Prof. Lynn Morris participated in a workshop held at Duke University to discuss suitable virus panels for neutralising antibody assays. This meeting was organised by Dr David Montefiori and Dr John Mascola, and was funded by the NIH Division of AIDS. Prof. Morris gave a short oral presentation on the neutralisation profiles of HIV-1 subtype C isolates. A number of these isolates will be included in standard virus panels that will be widely used by those in the neutralising antibody field.

Prof. Morris was also invited to participate in the Enterprise Laboratory Working Group which aims to assist in selecting suitable assays for monitoring neutralising antibody assays in vaccine trials. Two meetings have been held and the committee has drafted recommendations that will be forwarded to the Enterprise group.

Collectively the Humoral Immunity Core is poised to play a significant role in providing laboratory support for assessing humoral immunity in HIV-infected individuals and recipients of candidate HIV vaccines

## 2) Animals – Medical Research Council, University of Stellenbosch and University of Cape Town

### SAAVI breeding and holding facility at the MRC's Delft Centre

The SAAVI rhesus macaque colony was developed as a strategic venture to provide Asian macaques to support local initiatives to produce candidate HIV vaccines by the Universities of Stellenbosch and Cape Town.

The current inventory of the colony is:

Breeding males	4
Breeding females	45
Juveniles 4 — 7 months of age	32
Breeding success in first year	71% (0,7 offspring per bred female)

The bred animals are conservatively valued at R2,1 million and the capital costs of the venture to date to SAAVI is R3,0 million. The total market value of the monkeys (breeders and offspring) is currently estimated at R5,3 million.

## Clinical sites

### 1) Perinatal HIV Research Unit, HIV Vaccine Division

The Perinatal HIV Research Unit, which is affiliated to the University of the Witwatersrand, based in Soweto, South Africa, established an HIV Vaccine Clinical Trials Unit in 2001. This unit receives funding from the NIH-HVTN network, the International AIDS Vaccine Initiative (IAVI), the European Union as part of the AIDS Vaccine Integrated Programme (AVIP), and the South African AIDS Vaccine Initiative (SAAVI). Presently, SAAVI contributes approximately 10% of the funding for the HIV Vaccine Programme. This funding has strengthened the clinical, community and laboratory capacity of the unit to conduct HIV vaccine-related research, and has been used for the following activities:

- Continued development of phase I/II HIV vaccine clinical trial capacity.
- Continued support for community outreach and education in HIV vaccine research, as well as Community Advisory Board (CAB) development and empowerment.
- Cohort recruitment, preparation and maintenance through the pre-screening protocol.
- Continued training and support of staff involved in HIV vaccine-related clinical trials.



One of the first volunteers, Fikile Mkhathswa, receives her injection at the Soweto site.

#### **Highlights of these activities include:**

##### ***Developing a cohort of potential trial participants:***

During 2003, the unit offered 3024 clients HIV testing and counselling as part of the HIV vaccine voluntary counseling and testing (VCT) programme. Most were women (62,6%) and in the 20 – 29-year age group (46%). HIV prevalence was 47,2%. Of the group, 1581 (52,3%) participants were HIV negative and eligible for entry into the pre-screening protocol. Of the negative clients, 21,3% (336) entered the first vaccine discussion groups (VDGs) and 57,7% (194) continued with the pre-screening protocol. Of these, 32 (17,5%) were found to be eligible for vaccine study entry. Reasons for discontinuation include loss to follow-up (14,8%), laboratory abnormalities (12,3%), chronic illnesses (9%) and participant decision (7%).

##### ***Empowering communities for HIV vaccine trials:***

The unit has also spearheaded the community outreach programme in Gauteng and has run workshops for over 400 community stakeholders and members in the past year. In addition, it has expanded its VCT activity within the region, making HIV vaccine trials accessible to other communities within Gauteng.

##### ***Advancing the careers of previously disadvantaged researchers/doctors:***

As part of its mission, PHRU has continued the advancement of previously disadvantaged researchers with ongoing mentoring, training and development.

### 2) HIV Vaccine Research Unit, MRC, Durban

The Durban HIV Vaccine Research Unit is now recognised as an established phase I/II clinical trial unit. It has the necessary equipment, facilities, Community Advisory Board (CAB), community linkages and trained research team. The first two phase I trials commenced at the site in November 2003.

The unit is currently expanding its capacity to perform phase III efficacy work. This is being done with the Africa Centre in the uMkhanyakude Health District. In addition to this rural community-based phase III potential, similar phase III capacity could be developed within the Durban metropolitan area if the need arises.

An approved HIV vaccine screening study is steadily, on a weekly basis, enrolling participants into an HIV vaccine research-ready cohort.

An Elispot standardisation study has been completed with the NICD. The

unit has 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 through regular forums and newsletters. The KZN AIDS Forum has expanded to Pietermaritzburg and Mtunzini, and now has membership in each health district in the province. Relationships are maintained and developed with key role players and institutions at local, regional, national and international levels.

### 3) Cape Town HIV Vaccine Clinical Trials Consortium

The reported antenatal HIV prevalence in the Western Cape rose to 11,8% in 2003 and in certain communities such as Nyanga the reported prevalence is as high as 28%. There is also preliminary evidence that incidence is rising in so-called 'coloured' communities, the ethnic group that makes up 50% of the Western Cape population. This signals a growing HIV epidemic in the region and it is therefore appropriate that communities are prepared to be receptive to vaccine clinical trials from phase I to III.

The Cape Town HIV Vaccine Clinical Trials Consortium was established in October 2002 and comprises a multifaceted group of HIV researchers in Cape Town who conduct multidisciplinary research in HIV and are part of SAAVI. 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 preventative candidate vaccines under good clinical and ethical practice for all age and ethnic groups in South Africa, with a focus on adolescents. It is currently actively engaged in socio-behavioural, educational and infrastructural development of phase III sites in the communities of Masiphumelele and Nyanga/Mitchell's Plain, Cape Town.

To date, the consortium has focused on site, protocol and research tool development; the commencement of two retention studies; the national incidence study; enhancing communication between community structures and researchers; and, developing culturally attuned education programmes.

### 4) Aurum Health Research

#### **HIV incidence and community preparedness in preparation for phase III HIV vaccine trials among South African gold miners**

##### **1. Community programme**

The aim is to develop and sustain a Community Advisory Group (CAG) and to implement a site-specific Community Education Plan to ensure broad community support for and participation in HIV vaccine research and development.

The community preparedness and education programme identifies four objectives: raising community awareness, fostering trust, community facilitation and mobilisation.

Since September 2003 key informants in the area have been consulted in an attempt to build knowledge about the programme. By the end of 2003, 17 CAG members had been recruited. The first CAG meeting was held in December 2003 and a two-day workshop was held in January 2004 to further increase awareness. T-shirts for the CAG members and a CAG logo were also designed. A further eight CAG members were recruited during January 2004. The elected CAG met on 18 February 2004, where the needs assessment and strategic planning were completed.

The next phase of the community programme will be building willingness and skills for the CAG members and the commencement of the first round of community education.

##### **2. Estimating HIV incidence among an HIV-uninfected cohort of gold miners in preparation for phase III vaccine trials**

To accurately estimate sample size requirements for phase III HIV vaccine trials, it is desirable to know HIV incidence among HIV-uninfected individuals who would be eligible to participate.

A cohort of mineworkers, representative of the general workforce, was recruited in Orkney between October 2000 and April 2001. The HIV prevalence

was 26,7%. At recruitment, participants were asked for permission to repeat the survey after a two-year interval.

SAAVI has funded the completion of the second round HIV incidence survey in the Orkney cohort, which started in 2003. Of the original cohort, 87% (1753) are still in service. This study will provide the community-based estimate of HIV incidence among mineworkers, in the presence of a routine VCT programme.

Participants in the HIV vaccine preparedness study will be exposed to regular voluntary HIV testing and harm-reduction counselling. For the planning of phase III HIV vaccine studies it will be valuable to know the impact of regular HIV testing and harm-reduction counselling on HIV incidence. By comparing the HIV incidence in the general population and the HIV vaccine preparedness cohort it will be possible to estimate the likely impact of regular HIV testing and harm-reduction counselling on HIV incidence.

An interim analysis was done at the end of December 2003. Among 831 workers from one mineshaft, HIV prevalence at baseline was 29,4% (95% confidence interval, 26,3% — 32,6%). Risk factors for HIV infection at baseline included age group (HIV prevalence in age groups <40, 40 — 49, 50+ years: 34,8%, 28,0%, 14% respectively,  $P < 0,001$ ), living in a hostel and having signs or symptoms of an active sexually transmitted infection (STI). Of these workers, 692 (83%) were still employed as of July 2003 and to date 428 (62%) have been retested. Among these, 42 were HIV infected among 324 who were uninfected at baseline, contributing 874,8 person years of follow-up. This gives an estimated annual HIV incidence of 4,8% (95% CI, 3,5% — 6,5%). Individuals with an active STI at baseline had a higher risk of becoming HIV infected (incidence 14,8% vs. 4,5%, incidence rate ratio 3,31); there was a non-significant trend for higher incidence among younger age groups.

HIV incidence was high suggesting a generalised high risk among this community. Interventions are urgently required to reduce this risk. In addition, this setting has potential for trials of candidate HIV vaccines.

In preparation for joining the national incidence study, the following has been done:

- Contribution to protocol development.
- Development of the study budget and site-specific preparation phase budget.
- Assisted with the recruitment of the study director.
- Identified a new site, Tshepong, from where particularly female participants could be recruited. Recruitment will be from the surrounding mining communities of Klerksdorp, Stilfontein, Hartebeesfontein and Orkney, with an estimated population of 350 000.
- Reviewed the infrastructural requirements for both recruitment sites. These include necessary renovations, the staff, furniture and equipment and identification of training needs.


## Ethics

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

HIV preventative 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 research, capacity building and consensus-building activities. These are addressed below:

#### **How can the current ethical-legal framework be strengthened?**

At present, there are no national ethical guidelines for HIV preventative vaccine research. HAVEG 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 preventative 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. A future focus will be advocating for a stronger ethical-legal framework through conceptual research, interview research with stakeholder groups (see activity below), and a workshop in July 2004, to critically review the current regulatory environment. We aim to review the strengths and limitations of *MRC Guidelines on medical ethics: HIV preventative vaccine research*, and to commission an independent review of these guidelines.



**What are the challenges, resources and needs identified by key stakeholders in relation to HIV vaccine trials?**

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 have developed an empirical research protocol to explore 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 focus in the next two years 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*).

**How can adequate, culturally sensitive informed consent for participation be ensured?**

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. We have developed diverse tools (including qualitative 'narratives' with scoring templates) in collaboration with site staff and community advisory boards (CABs). We have begun a pilot of these tools with CAB members. During the year prospective trial participants will be recruited for participation in a full study after which recommendations will be made to sites for rigorous methods to assess understanding. This research activity also aims to support recommendations for comprehension made in the *MRC Guidelines on ethics for medical research: HIV preventive vaccine research*.

**What quality of care should be provided to participants who become infected with HIV during the course of HIV vaccine trials?**

A most 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 submitted for publication and a series of presentations in international and national contexts, including a national stakeholder meeting, convened by INHREC, to move towards consensus. Outcomes of this meeting were used to draft the guidance point on treatment in *MRC Guidelines on medical ethics: HIV preventive vaccine research*. Our current focus is to consider the implications of recent government commitment to public sector antiretroviral treatment; to create a forum in July 2004 for stakeholders to review previous consensus on this issue and mechanisms for access; and, to explore stakeholder perceptions of sponsor obligations through collaborative research with Johns Hopkins University – including the controversial issue of 'undue inducement'.

**Under what conditions should children be involved in HIV preventive vaccine trials?**

South African trials are currently focusing on adults who are able to give independent consent for participation. However, it is necessary to consider in advance the complex ethical and legal issues raised by the participation of children. In the wake of a national stakeholder Child Forum we convened in August 2003, we have developed conceptual papers on the enabling and constraining elements of our current ethical-legal framework, including the National Health Bill, and the *MRC's Guidelines on ethics for medical research: General Principles (Book 1)*. We have consulted with the MRC on the need to revise the current edition of their General Principles to remove prohibitive sections on research with children. A future focus will be to impact on the ethical-legal framework for research with children (e.g. Children's Bill and MRC General Principles), to create a forum in July 2004 to explore the implications of the new legislation and guidelines for stakeholders and to further debate this complex issue.

### ***How can awareness of the ethical-legal complexities of HIV vaccine development be advanced?***

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 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, our focus in the past few months has been to re-write our *HAVEG Resource Manual* (3<sup>rd</sup> Edition) to meet identified needs for materials that can assist site staff to help prospective participants to make decisions about participation. We are working with the International AIDS Vaccine Initiative to consider ways of collaborating in this capacity-building activity. A future focus will be to pilot the materials with users at sites, and to evaluate their adequacy with site staff and CABs. In July 2004, we will host 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 and standard of care.

### ***Developing the capacity of young South African researchers***

We have recruited and appointed two young South African researchers from previously disadvantaged backgrounds. A future focus will be to build their capacity in research ethics and research, to provide opportunities to manage HAVEG's activities, and contribute to SAAVI.

## **Community education and mobilisation**

### **SAAVI Community preparedness Programme (SAAVI CPP)**

This period has seen an expansion of community preparedness activities with SA HIVAC developing into the SAAVI Community Preparedness Programme (CPP).

Lobbying and networking activities have been undertaken at local, regional and international levels, providing several opportunities to share experiences and materials, and to strategise and arrange further knowledge-sharing opportunities with 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 in May 2003 and March 2004. The current draft will be submitted to all relevant parties for endorsement. Input has also been made into strengthening arrangements with the Life Offices' 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 (key opinion leaders who can disseminate information on vaccines to their communities and organisations) in 20 targeted sectors (e.g. trade unions, education, health, etc.) with about 70 workshops held in and around trial site regions reaching almost 2200 people in this period.

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

Partnerships continue to grow. A draft MOU has been formulated with the City of Cape Town's SmartCape Initiative which could 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 first phase of an education strategy for HIV vaccines has been developed. Using this strategy, it is hoped to incorporate information on HIV vaccines and possibly other preventative HIV research information into relevant textbooks for adults and learners. Discussions have begun with the relevant publishers and information has already been included in one textbook.



## New Areas

### Socio-behavioural research group

#### Building national socio-behavioural research capacity for HIV vaccines in South Africa

In 2003 the Stress and Anxiety Research Unit at the University of Stellenbosch was asked by SAAVI to develop a socio-behavioural research arm for the Cape Town HIV Vaccine Trials Consortium. This included providing input to the national incidence study protocol. During these discussions key issues emerged with respect to the broader national initiative. These included a need to integrate socio-behavioural research into the main incidence study (NIS); the fact that there was no dedicated socio-behavioural research agenda and a shortage of personnel to provide conceptual and methodological input to the NIS; the need for social science research capacity at all four sites; the need for a dedicated team to co-ordinate socio-behavioural research studies; as well as central leadership to initiate, implement and co-ordinate socio-behavioural research. The research activities at the different sites were fragmented and although there was much that was useful to inform HIV vaccine research, there was no direct focus on HIV vaccines. Despite these deficits there was enormous enthusiasm for developing social science research capacity within the four sites.

The national incidence study is the first and perhaps only opportunity to ask important socio-behavioural questions related to future HIV vaccine trials in South Africa. There is thus a clear need to strengthen current socio-behavioural activities within SAAVI by forming a national body to co-ordinate and implement research activities nationally.

The group therefore 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.

A literature review has highlighted issues to examine in preparation for future HIV vaccine trials. Immediately important are 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 have been produced on the following issues 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 CPP.
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 CPP 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 national incidence 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 CPP

**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

### Assessment of HIV vaccine requirements and effects of HIV vaccination in southern Africa

The key objective of this research is to develop a mathematical model capable of:

- Assessing the most appropriate strategy for distributing HIV/AIDS vaccines in South Africa when vaccine supply is limited.
- Identifying the total demand for vaccination in South Africa, for both short-term scenarios (vaccination targeted at particular groups) and long-term scenarios (supply-side constraints are removed).
- Identifying the total demand for vaccination in other Southern African Development Community (SADC) countries, for long-term scenarios.
- Evaluating the potential long-term demographic and epidemiological effects of vaccination in SADC countries.

This will be achieved by adapting the ASSA2000 Interventions model (a model for the South African population) and the ASSA2000 Urban-rural model (a model for other African countries). Uncertainty and sensitivity analyses will be conducted to assess the dependence of the model results on the assumptions regarding vaccine characteristics, vaccine efficacy, vaccine distribution and behaviour change in response to vaccination. In addition, sensitivity and uncertainty analyses will be conducted for standard epidemiological and behavioural



parameters, not specifically related to vaccine modelling.

As the project was only approved recently, there is little progress to report. The key accomplishments are described below.

#### **Review of other models of HIV vaccine effects**

The review of other HIV vaccine models has been completed. Sixteen papers on modelling HIV vaccine effects were identified as well as three World Bank papers that assessed vaccine requirements and cost-effectiveness of different vaccination strategies, although they were not based on epidemiological or demographic modelling.

The review shows that much work has been done to model the potential effects of HIV vaccines. Areas that have been studied extensively are the effects of different forms of vaccine imperfection, and the likely dangers associated with 'behavioural disinhibition'. However, most studies have assumed that the vaccines will only reduce susceptibility to HIV infection. While this was a reasonable assumption in the early days of HIV vaccine research, the shift towards cytotoxic T-lymphocyte responses suggests that it is no longer reasonable to ignore the effects vaccines are likely to have on infectiousness and disease progression. A further key shortcoming in models of 'behavioural disinhibition' is that they fail to link behavioural responses to AIDS and to vaccines – with the result that the dangers associated with behaviour change are frequently exaggerated.

Very little work has been done to explore the effects of vaccines when there is heterogeneity between strains or subtypes in terms of their susceptibility to vaccine-induced immune responses.

Assessments of the impact of targeting vaccination at particular sub-populations have been limited to the consideration of different theoretical 'risk groups', and age and gender groups.

#### **Review of factors affecting vaccine efficacy in southern Africa**

Factors specific to southern Africa likely to affect HIV vaccine efficacy have been reviewed. The high degree of viral diversity in southern Africa, the unique features of HIV-1 subtype C, and the existence of bias towards Th2 immunity have all been identified as factors that may reduce vaccine efficacy in the local context. These will be considered when making assumptions about vaccine efficacy.

#### **Updating the ASSA2000 Urban-rural model**

The Urban-rural version of the ASSA2000 AIDS and Demographic model has been updated to ensure consistency with the ASSA2002 model that will be used to model the demographic impact of the disease in South Africa. This has required the modelling of prevention and treatment programmes, the division of the HIV-positive population according to WHO clinical stage, the allowance for varying HIV transmission rates according to disease stage, and several other key parameter changes. The models for Botswana, Lesotho, Malawi, Mozambique, Namibia, Swaziland, Tanzania, Zambia and Zimbabwe are currently being calibrated. Models for Angola and the DRC still need to be constructed.

#### **Sensitivity and uncertainty analysis for behavioural and epidemiological parameters**

Initial exploratory work has been conducted. Alan Mathews, a physicist from the University of KwaZulu-Natal, and Rob Dorrington have programmed the ASSA2000 AIDS and Demographic model in C++. This will be used to assess the range of uncertainty around the model projections.

Discussions have also been held with statisticians from Stellenbosch University and the MRC to assess the potential for Bayesian simulation techniques to be used in the uncertainty analysis. A provisional plan has been drafted for applying the Metropolis algorithm to the C++ version, once this version has been updated.

In the original proposal, it was indicated that the ASSA2000 Interventions model would be used. It is likely that the ASSA2002 AIDS and Demographic model will be used instead. This model is close to completion, and will provide a more accurate estimate of current and future HIV prevalence levels. It will also incorporate the modelling of interventions. This model allows for 'behavioural inhibition' in response to AIDS. This is achieved by assuming substantial increases in condom usage over time, particularly at young ages, and delayed onset of sexual activity. The modelling of 'behavioural disinhibition' will be linked to the modelling of 'behavioural inhibition', to achieve a more realistic assessment of the impact of behaviour change following the

introduction of vaccines.

The Urban-rural version of the ASSA2000 model has also been updated to allow for the modelling of interventions. However, results will still be prepared for other African countries on the assumption that no interventions (other than HIV vaccines) will be implemented, as there is a lack of data on the extent of HIV prevention and treatment programmes in other African countries. It will, however, be simple to extend the analysis of interactions between vaccination and other HIV/AIDS interventions (performed for South Africa) to other SADC countries, if data become available.

Individuals seeking voluntary counselling and testing may be added to the list of subpopulations targeted for early vaccination as this is likely to be a successful strategy.

A potential problem relates to the sensitivity and uncertainty analyses of the behavioural and epidemiological parameters. The Bayesian approach may prove unsuccessful, or may be capable of handling only a limited range of model parameters. If it is impossible or impractical to conduct uncertainty and sensitivity analyses for these parameters, these analyses will be performed only for those parameters that relate to vaccine efficacy, vaccine distribution and behaviour change.

## **Bioinformatics and Data Management**

The MRC's Research Information Systems Division is responsible for co-ordinating the development and operation of SAAVI's data management infrastructure under the auspices of the Bioinformatics and Data Working Group. The system is designed to be compliant with the requirements of various regulatory authorities and relevant information is published to the division's secure web server at [www.healthware.org](http://www.healthware.org) for collaborative development with other partners at participating study sites and laboratories.

To date, the data management group has developed a data collection and management plan and budget for the SAAVI incidence study. The DataFax facility at PHRU 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. Once the budget has been approved, it is intended to install and configure the system's infrastructure in the period leading up to September 2004. An additional goal is to establish systems that comply with the guidelines published by the US FDA. 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.

## Finances

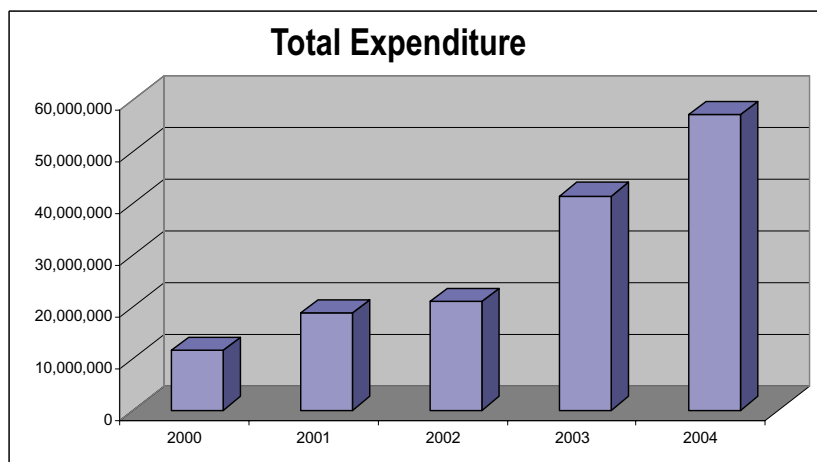
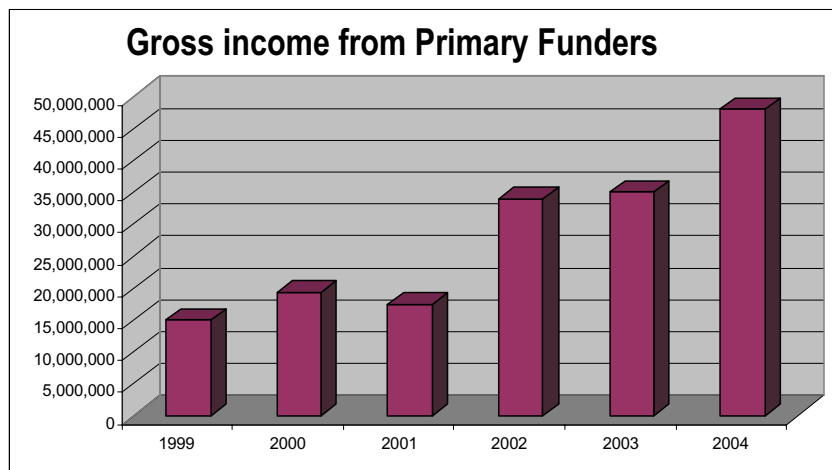
The finances of SAAVI are in a good state, and the predicted cash flow is positive for 2004, due to increased income from various sources and the strengthening of the Rand. SAAVI was able to meet its commitments for 2003, and will increase expenditure in 2004, including the funding of the consortium partners, vaccine manufacturing, the running of the directorate and support functions, as well as some expansion of basic research activities. Predicted expenditure for 2004 through the SAAVI directorate (including HVTN and EU monies) will be in excess of R70 million.

Of note:

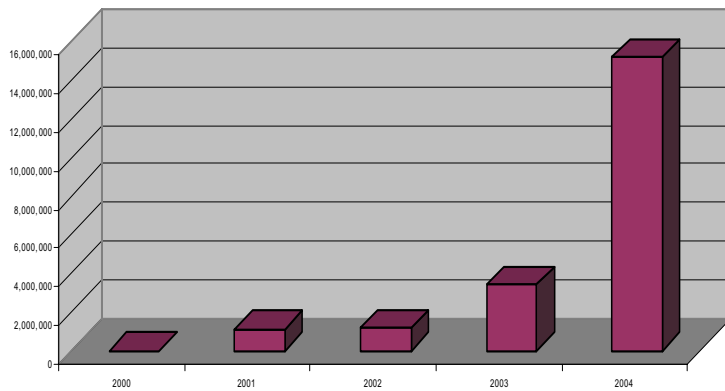
- The Department of Science and Technology has committed to increase their SAAVI funding to R15 million in 2004.
- The EU has awarded a second grant to SAAVI Community Preparedness Programme over three years.
- Another EU grant of approximately R10 million has been awarded to SAAVI for the year 2004 for the SAAVI Incidence study. This must be spent by September 2004.
- A joint major fundraising venture is being run with the Department of Science & Technology and the SAAVI Directorate which is aimed at raising millions from the private sector.

SAAVI allocations to the various groups have steadily increased over the period 2000 to 2003.

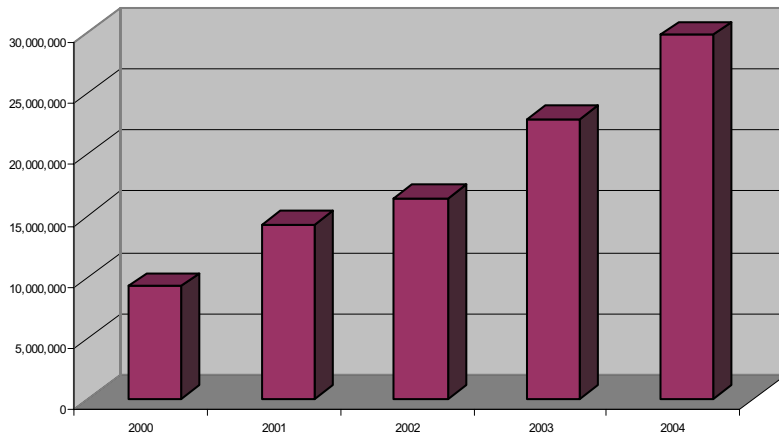
SAAVI is committed to funding its collaborating groups at an appropriate level, in keeping with international agencies, so as to maximise speed and progress. The following graphs illustrate SAAVI's financial position.



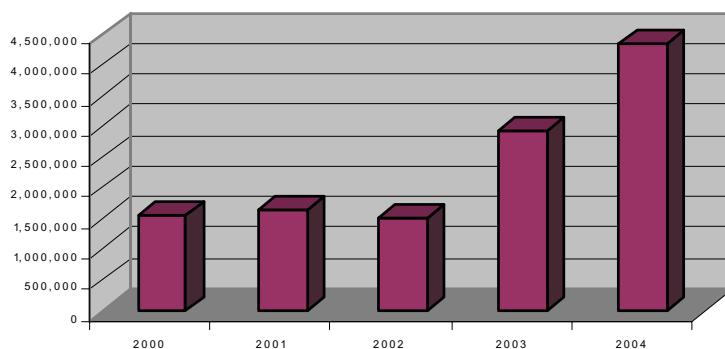
### SAAVI Expenditure on Clinical Groups



### SAAVI Expenditure on Biotechnology-related Areas



### SAAVI Expenditure on Community-based Areas



## Publications and conference presentations 2003

### SAAVI Directorate

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2. Tim Tucker – Director of the South African AIDS Vaccine Initiative – interviewed by Pam Das. *Lancet Infect Dis* 2003; March **3** (3): 173 – 175.
3. Galloway M. Two HIV/AIDS candidate vaccines enter human trials in South Africa. *Southern African Journal of HIV Medicine* 2003; **13**: 43.
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6. Millions of dollars versus millions of lives – investing in the people of South Africa. *Opportunity* 4<sup>th</sup> issue, 2003: 50.
7. First HIV vaccine trials underway. *Informer* 2003; **1** (7): 2.
8. Galloway MR. Progress in HIV vaccine research in South Africa. *Informer* 2003; **1** (6): 3.
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1. Gordon M, De Oliveira T, Bishop K, Coovadia HM, Madurai L, Engelbrecht S, Janse van Rensburg E, Mosam A, Smith A, Cassol S. Molecular Characteristics of HIV-1 Subtype C Viruses from KwaZulu-Natal, South Africa: Implications for Vaccine and Antiretroviral Control Strategies. *J Virol* 2003; **77**: 2587 – 2599.
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2. Barnett SW, Srivastava I, Stamatatos L, zur Megede J, Lian Y, Otten G, Montefiori D, Lewis M, Engelbrecht S, Janse van Rensburg E, Widera G, O'Hagan D, Polo J, Ulmer J, Donnelly J. Next generation HIV DNA prime-protein boost vaccines induce potent and protective immune responses. HIV Vaccine Development: Immunological and Biological Challenges, *Keystone Symposia 2003*, Alberta, Canada.
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4. Engelbrecht S, Holzmayer V, Bodelle P, Brennan CA, Hackett J, Janse van Rensburg E. The changing face of the HIV-1 epidemic in South Africa: detection of subtypes A, B, C, G and recombinants. *HIV Dynamics & Evolution 10<sup>th</sup> International Workshop, 2003*, CA, USA.
5. Lian Y, Srivastava I, zur Megede J, Sun Y, Kan E, Hilt S, Leung L, Himathongkham S, Luciw P, Ulmer J, Donnelly J, Engelbrecht S, van Rensburg J, Barnett S. Envelope DNA Vaccines Derived from the South African Subtype C HIV-1 TV1 Isolate Induce Neutralizing Antibody Responses against R5 HIV-1 Strains. *AIDS Vaccine 2003 Annual Conference*, New York, 18 – 21 September 2003.
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## University of Cape Town

### Publications

1. 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.
2. Van Harmelen JH, Sheppard E, Thomas R, Hanke T, Williamson AL, Williamson C. Construction and characterisation of a candidate HIV-1 subtype C DNA vaccine for South Africa. *Vaccine* 2003 Oct; **21** (27 — 28): 4380 — 4389
3. Williamson C, Morris L, Maughan MF, Ping LH, Dryga SA, Thomas R, Reap EA, Cilliers T, Van Harmelen J, Pascual A, Ramjee G, Gray G, Johnston R, Karim SA, Swanstrom R. Characterization and Selection of HIV-1 Subtype C Isolates for Use in Vaccine Development. *AIDS Res Hum Retroviruses* 2003; **19** (2): 133 — 44.

### Conference presentations

1. Bredell H, Gilfillan J, Seoighe C, Gray C, Williamson C and HIVNET028 Team. Defining HIV-1 gag genetic diversity in southern African and possible impact on proposed cytotoxic T-lymphocyte epitope recognition. *South African AIDS Conference*, ICC Durban, 3 — 6 August 2003.
2. Burgers W, van Harmelen J, Shephard E, Bourn W, Williamson A-L, Williamson C. Assessment of Candidate HIV-1 Subtype C DNA Vaccines Targeted for Clinical Trials in Southern Africa. Abstract number 309. *AIDS Vaccines 2003*. New York Hilton, NY, USA. 18 – 21 September 2003.
3. Chege GK, Williamson A-L, van Harmelen JH, Williamson C, Shephard EG. Pre-Clinical evaluation of a DNA HIV Vaccine using the Baboon Model. *ICASA Conference, 2003*. Nairobi, Kenya, 21 — 26 September 2003.
4. Chin'ombe N, Williamson A-L, Shephard E, Bourn W. Development of recombinant Salmonella vectors for HIV-1 subtype C vaccine for Southern Africa. Oral presentation by Chin'ombe. *Fifth Congress of the Federation of African Immunological Societies (FAIS)*. Victoria Falls, Zimbabwe 27 April — 1 May 2003.
5. Grobler J, Rademeyer C, Gray CM, Ramjee G, Abdool-Karim SS, Morris L, Williamson C. Frequency of Dual Infection with Two Distinct Subtype C Viral Populations in a Female Sex Worker Cohort. Abstract number 221. *Keystone Symposia, 2003*. HIV Vaccine Development: Immunological and Biological Challenges, Banff, Canada, 2003.
6. Grobler J, Rademeyer C, Gray CM, Ramjee G, Abdool-Karim SS, Morris L, Williamson C. Incidence of dual infection in a South African sex worker cohort infected with two distinct HIV-1 subtype C viruses. Abstract number T1-S1-A5. *South African AIDS Conference*, ICC Durban, 3 — 6 August 2003.
7. Heath LE, Tanzer F, Shephard E, Bandawe G, Williamson A-L, Rybicki EP. Immunogenicity Of Hiv-1 Gp120 V3 Loop and various CTL Epitopes expressed on the surface of recombinant tobacco mosaic virus. HIV Vaccine Development and Twenty Years of HIV Research *Keystone meeting*, Banff Canada, 29 March — 4 April 2003.
8. Jaffray A, Shephard E, Williamson C, van Harmelen J, Williamson A-L, Rybicki EP. Investigation Of HIV-1 Subtype C Pr55gag Virus-Like Particles As A Potential Vaccine. HIV Vaccine Development and Twenty Years of HIV Research. *Keystone meeting*, Banff Canada, 29 March — 4 April 2003.
9. Machaba M, Bredell H, Morris L, Tucker T, Williamson C. Genotyping nevirapine and zidovudine resistance in HIV-1 subtype C infections. *South African AIDS Conference*, ICC Durban, 3 — 6 August 2003.
10. Masemola A, Mashishi T, Khoury G, Puren A, Paximadis M, Williamson C, van Harmelen J, Sheppard H, Gray C. Hierarchical targeting of subtype C HIV-1 gene regions by CD8+ T cells in recently infected individuals from southern Africa: correlation with viral control. Poster session: 2003 Fellows and New Investigators Workshop on HIV (Concurrent with *2003 Keystone Symposia*, Twenty Years of HIV Research and HIV Vaccine Development), Keystone, USA, April 2003.
11. Van Harmelen JH, Londt B, Mashishi T, Gray C, Williamson C. Evolution of nef sequences in HIV-1 subtype C infection over time. *South African AIDS Conference*, ICC Durban, 3 — 6 August 2003.
12. Rademeyer C, van Harmelen J, Ramjee G, Abdool-Karim S, Williamson C. An investigation of HIV-1 diversity following heterosexual transmission in recently infected women from a South African sex worker cohort. *South African AIDS Conference*, ICC Durban, 3 — 6 August 2003.
13. Shephard EG. Immunogenicity of candidate DNA HIV subtype C vaccines targeted for Southern Africa. *5<sup>th</sup> Federation of African Immunological Societies*, Victoria Falls, Zimbabwe, 27 April — 1 May 2003.
14. Shephard EG. Immunogenicity of SAAVI candidate HIV-I Subtype C Vaccines.



MRC In-House Symposium HIV/AIDS Symposium, MRC, 28 July 2003.

15. Shephard EG. SAAVI Pipeline of candidate HIV Vaccines Targeted for Africa. *The African AIDS Vaccine programme (AAVP) Workshop on Strategies for the development of HIV Vaccine trial Sites in Africa: Challenges and Opportunities*. Addis Abbaba, Ethiopia, 16 — 18 June 2003.
16. Thomas R, Shephard E, Bourn W, Jaffray A, Tanzer F, Rybicki E, Williamson A-L. Stability of Recombinant BCG: HIV-1 Gag Vectors and Induction of Interferon-gamma Production in Mice. *AIDS Vaccine 2003 Conference*. New York, USA, 2003.
17. Van Harmelen JH, Londt B, Mashishi T, Gray C, Williamson C. Evolution of nef sequences in HIV-1 subtype C infection over time. *South African AIDS Conference, ICC Durban, RSA*, 3 — 6 August 2003.
18. Williamson AL. The development of HIV-1 subtype C vaccines for Southern Africa. Invited lecture. *Fifth Congress of the Federation of African Immunological Societies (FAIS)*. Victoria Falls, Zimbabwe 27 April — 1 May 2003. Invited Lecture.
19. Williamson AL. Overview of critical issues in the scientific design of HIV vaccines SARETI/HAVEG workshop, Pretoria 7 — 9 November 2003. Invited Lecture.
20. Williamson C. HIV Vaccine Development. *South African AIDS Conference, 2003*. Durban, SA, 3 — 6 August 2003.
21. Williamson C. Implications of HIV diversity in vaccine development and pathogenesis. *WHO/AAVP workshop on research grant application and scientific manuscript writing for African scientist involved in AIDS vaccine research and development /AIDS-related research*. Nelson R. Mandela School of Medicine: University of Natal, 2003. Durban, SA, 22 July 2003.
22. Williamson C. Towards a subtype C vaccine. *International Congress of Chemotherapy, 2003*. Durban, 8 June 2003.
23. Williamson C. Development of HIV subtype C DNA and MVA vaccines. *HIV Pathogenesis Programme Annual Meeting on Immune Control, Translation Research and Treatment Initiative*. Doris Duke Workshop, Nelson R. Mandela School of Medicine, University of Natal, 2 May 2003.
24. Williamson C. Implications of HIV diversity in the development of vaccines for Africa. *Federation of African Immunological Society, 2003*. Victoria Falls, Zimbabwe, 27 April — 1 May 2003.
25. Williamson C. HIV Vaccine development. *The Human Genome and Africa Conference, 2003*. Spier, Stellenbosch, Cape Town, 19 — 22 March, 2003.
26. Williamson C. Development of subtype C DNA and MVA vaccines. *HIV Vaccine Trials Network (HVTN), 2003*. Washington DC, USA, 18 — 21 May 2003.
27. Williamson C. Towards a subtype C vaccine. *International Congress of Chemotherapy (ICC)*, Durban, 8 June 2003. Invited Lecture.
28. Williamson C, van Harmelen J, Burgers W, Shephard E, Burgers W, Jaffray A, Rybicki E, Williamson A-L. The development of HIV-1 subtype C vaccines for southern Africa. Oral presentation by A-L Williamson. *Medical Virology Congress of South Africa*, Berg-en-Dal, South Africa, 2003.

## HAVEG

### Publications

1. Tucker T, Slack C. Not if, but how? Caring for HIV-1 vaccine trial participants in South Africa. *The Lancet* 2003; **362**, 955.

### Conference presentations

1. Slack C, Stobie M, Lindegger G, Milford C, Wassenaar D, Strode A, IJsselmuiden C. Access to treatment for participants who become infected during the course of an HIV vaccine trial. *Paper presented at the NIH Third Bioethics Conference in Africa*. Kampala, Uganda, 21 March 2003.
2. Slack C, Stobie M, Lindegger G, Milford C, Wassenaar D, Strode A., IJsselmuiden C. Ethical considerations in HIV vaccine trials in South Africa: A focus on standard of care. *Paper presented at the 23<sup>rd</sup> International Congress of Chemotherapy*, Durban, South Africa, 7 — 9 June 2003.
3. Strode A, Slack C, Milford C, Stobie M. A critical evaluation of South Africa's ethical-legal framework. *Paper presented at the First South African AIDS Conference*, Durban, South Africa, 3 — 6 August 2003.
4. Milford C, Wassenaar DR, Slack C, Strode, A, Khan, N. Identifying resources and needs of research ethics committees in Africa in preparation for HIV vaccine trials. *Paper presented at First South African AIDS Conference*, Durban, South Africa, 3 — 6 August 2003.

### International consultations

1. 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.
2. Slack C, Stobie M, Lindegger G, Milford C, Wassenaar D, Strode A, IJsselmuiden C. Access to treatment in HIV vaccine trials. *Paper presented at the WHO-UNAIDS consultation on modalities for treatment for trial participants who become infected during HIV prevention trials*, Geneva, Switzerland, 17 — 18 July 2003.
3. Slack C, Stobie M, Lindegger G, Milford C, Wassenaar D, Strode A, IJsselmuiden



- C. Standard of care in HIV preventive vaccine trials. *Paper presented at the Second Annual Meeting of the African AIDS Vaccine Programme*, Addis Ababa, Ethiopia, 16 — 19 June 2003.
4. Lindegger G, Slack C, Wassenaar D. Culture and informed consent: Implications for HIV vaccine trials. *Paper presented at the Second Annual Meeting of the African AIDS Vaccine Programme*, Addis Ababa, Ethiopia, 16 - 19 June 2003.
  5. Slack C, Stobie M, Lindegger G, Milford C, Wassenaar D, Strode A, IJsselmuiden C. Access to treatment for participants who become infected during the course of an HIV vaccine trial: A report on the South African experience. *Paper presented at Ethics, Law and Human Rights Working group of the African AIDS Vaccine Programme (AAVP)*, Kampala, Uganda, 17 March 2003.
  6. Lindegger G, Slack C. Culture and informed consent: Implications for HIV vaccine trials. *Paper presented at the Full Group Meeting of the HIV Vaccine Trials Network (HVTN)*, Bethesda, Maryland, USA, 19 — 21 May 2003.

#### National meetings and consultations

1. Lindegger G, Slack C. Quality of care for trial participants who become infected during the course of an HIV vaccine trial. *Paper presented at National Health Research Ethics Committee (NHREC) meeting*; Pretoria, South Africa, 24 February 2003.

### Perinatal HIV/AIDS Research Unit

#### Publications

1. Hunt GM, Papathanasopoulos MA, Gray GE, Tiemessen CT. Characterisation of near-full length genome sequences of three South African Human Immunodeficiency virus type 1 subtype C isolates. *Virus Genes* 2003; **26**: 49.
2. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntyre JA, Harlow SD. Gender-based violence, relationship power and risk of prevalent HIV infection among women attending antenatal clinics in Soweto, South Africa. *The Lancet*, In Press.
3. Dunkle KL, Jewkes RK, Brown HC, Yoshihama M, Gray GE, McIntyre JA, Harlow SD. Prevalence and patterns of gender-based violence and revictimization among women attending antenatal clinics in Soweto, South Africa. *Am J Epidemiol*, In Press.
4. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntyre JA, Harlow SD. Transactional sex among women in Soweto, South Africa: prevalence, risk factors and association with HIV infection. *Soc Sci Med*. In Press.
5. Gray GE. Conducting HIV Vaccine Trials—Challenges for South Africa. *Southern African J HIV Med*; May 2003: 36 — 38.
6. Williamson C, Morris L, Maughan M, Ping Li-Hua, Dryga SA, Thomas R, Reap E, Cilliers T, Van Harmelen J, Pascual A, Ramjee G, Gray G, Johnston R, Karim SA, Swanstrom R. Characterization and selection of HIV-1 Subtype C Isolates For Use in Vaccine Development. *AIDS Res Human Retroviruses* 2003; **19**: 133 — 144.
7. Fanales-Belasio E, Cafaro A, Cara A, Negri DRM, Fiorelli V, Butto S, Moretti S, Maggiorella MT, Sericola L, Scoglio A, Borsetti A, Ridolfi B, Bona R, Ten Haarft P, Macchia I, Leone P, Pavone-Cossut MR, Nappi F, Vardas E, Magnani M, Laguardia E, Caputo A, Titti F, Ensoli B. HIV-1 Tat based Vaccines: From basic science to clinical trials. *DNA and Cell Biology*, 2002, **21** (9): 599 — 610.
8. Buttò S, Fiorelli V, Tripiciano A, Ruiz-Alvarez MJ, Scoglio A, Ensoli F, Ciccozzi M, Collacchi B, Sabbatucci M, Cafaro A, Guzmán CA, Borsetti A, Caputo A, Vardas E, Colvin M, Lukwiya M, Rezza G, Ensoli B. Sequence Conservation and Antibody Cross-Recognition of the Clade B HIV-1 Tat Protein Vaccine Candidate in HIV-1-Infected Italian, Ugandan and South African Individuals. *J Infectious Dis*, 2003, **188** (8): 1171 - 1180.
9. Nwanegbo E, Vardas E, Gao W, Whittle H, Sun H, Robbins PD, Gambotto A. Prevalence of Neutralizing Antibodies to Adenoviral Serotypes 5 and 35 in the Populations of Gambia, South Africa, and the United States. *Clin Diag Lab Immunol J* (Accepted).
10. Masemola A, Mashishi T, Khoury G, Mokube P, Mogofo P, Vardas E, Colvin M, Zienjenah L, Katzenstein D, Masondo R, Allen S, Kumwenda N, Taha T, Gray G, McIntyre J, Karim S, Sheppard HW, Gray CM. Hierarchical Targeting of HIV-1 Subtype C proteins by CD8+ T cells: Correlation with Viral Load. *J Virol* (Accepted).
11. Coplan PM, Gupta SB, Dubey SA, Pitisuttithum P, Nikas A, Mbewe B, Vardas E, Schecter M, Kallas EG, Freed DC, Fu TM, Mast CT, Puthavathana P, Kublin J, Brown Collins K, Chisi J, Pendame R, Thales SJ, Gray G, McIntyre J, Staus WL, Condra JH, Mehrota DV, Guess HA, Emini EA, Shiver JW. Substantial Cross Reactivity of Anti-HIV-1-Cell Immune Responses Among the Major HIV-1 clades in Infected Individuals from Four Continents. (Submitted).

#### Conference presentations

1. Gray GE. Conducting clinical trials in South Africa: steps necessary for HIV vaccine related research. *Trezieme Colloque Des Cent Gardes—2003*. Retroviruses of Human AIDS and Related Animal Diseases.



## HIV Vaccine Research Unit – Durban

### Publications

1. Robinson A, The infrastructure supporting HIV vaccine clinical trials. *Southern African Journal of HIV Medicine* 2003; **11**, May: 39 – 41.

### NICD

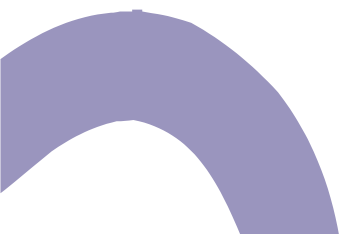
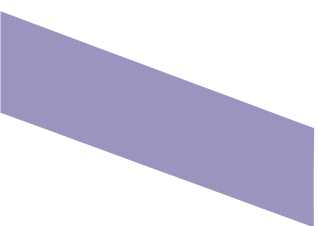
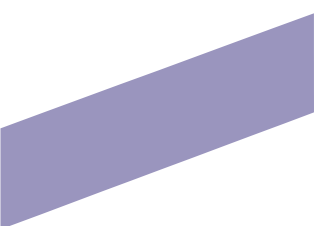
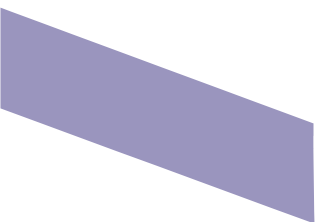
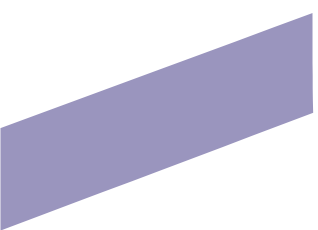
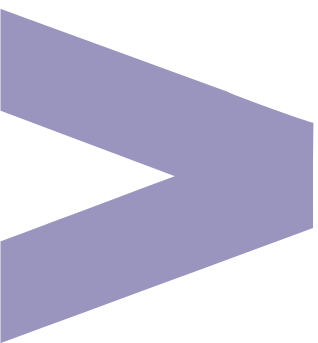
### Publications

1. Williamson C, Morris L, Maughan MF, Ping L-H, Dryga SA, Thomas R, Reap EA, Cilliers T, van Harmelen J, Pascual A, Ramjee G, Gray G, Johnston R, Abdool-Karim S, Swanstrom R. Characterization and selection of HIV-1 subtype C isolates for use in vaccine development. *AIDS Res Hum Retro* 2003, **19**: 133 – 144.
2. Cilliers T, Nhlapo J, Coetzer M, Orlovic D, Ketas T, Olson WC, Moore JP, Trkola A, Morris L. The CCR5 and CXCR4 coreceptors are both used by human immunodeficiency virus type 1 primary isolates from subtype C. *J Virol* 2003, **77**: 4449 – 4456.
3. Papathanasopoulos MA, Patience T, Meyers TM, McCutchan FE, Morris L. Full-length genome characterization of HIV-1 subtype C isolates from two slow progressing perinatally infected siblings in South Africa. *AIDS Res Hum Retro* 2003; **19**: 1033 – 1037.
4. Grobler J, Gray CM, Rademeyer C, Seoighe C, Ramjee G, Karim SA, 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*. In Press.

### Conference presentations

1. Gray E, Taylor N, Patience T, Papathanasopoulos M, Morris L. Establishing a subtype C TCLA strain-based neutralization assay. *Keystone Symposia*, Banff, Canada, March – April 2003 (poster).
2. Morris L. Neutralizing antibody responses in HIV-1 infected South Africans. *Fifth Congress of the Federation of African Immunological Societies (FAIS)*, Victoria Falls, Zimbabwe, April – May 2003 (invited speaker).
3. Gray E, Taylor N, Morris L. Evaluation of an HIV-1 subtype C neutralization by flow cytometric quantitation of intracellular p24 antigen in single round infection of primary cells. *2<sup>nd</sup> IAS Conference on HIV Pathogenesis and Treatment*, Paris, France, July 2003 (poster).
4. Nhlapo J, Gray E, Meyers T, Karim SA, Robinson J, Morris L. Generation of anti-HIV-1 env monoclonal antibodies using B cells from HIV-1 subtype C infected individuals with high levels of neutralizing antibodies. *South African AIDS Conference*. Durban August 2003 (poster).
5. Taylor N, Phoswa M, Montefiori D, Hanson C, Vardas E, Colvin M, Karim SA, Musonda R, Allen S, Zijenah L, Mbizo M, Katzenstein D, Kumwenda N, Taha Taha, Gray G, McIntyre J, Sheppard HW, Gray C, Morris L. Neutralization-sensitivity of HIV-1 subtype C and B viruses to subtype C serum antibodies. *South African AIDS Conference*, Durban 2003.
6. Choge I, Taylor N, Gray E, Meyers T, Papathanasopoulos MA, Morris L. The use of a gp120 V1/V2 heteroduplex tracking assay for identifying antibody neutralization sensitive viral quasi-species. *South African AIDS Conference*. Durban August 2003 (poster).
7. Choge I, Meyers T, Papathanasopoulos MA, Morris L. Use of a gp120 V1/V2 heteroduplex mobility assay for genetic analysis of HIV-1 subtype C isolates from children with slow and rapid disease progression. *International Conference of AIDS in Africa*, Nairobi, Kenya, September 2003.







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