- 18 Khuri SK. Quality, advocacy, healthcare policy and the surgeon. *Ann Thorac Surg* 2002;74:641-94.
- 19 Albert A, Walter J, Arnrich B, Hassanein W, Rosendahl U, Bauer S, et al. On-line variable live-adjusted displays with internal and external risk-adjusted mortalities. A valuable method for benchmarking and early detection of unfavourable trends in cardiac surgery. *Eur J Cardiothorac Surg* 2004;25:312-9.
- 20 Chassin MR. Improving the quality of care. Part 3: improving the quality of care. *N Engl J Med* 1996;335:1060-3.
- 21 Marshall M, Shekelle P, Leatherman S, Brook R. The public release of performance data. What do we expect to gain? A review of the evidence. *JAMA* 2000;283:1866-74.
- 22 Hannan E, Radzyner M, Rubin D, Dougherty J, Brennan M. The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy and lung lobectomy in patients with cancer *Surgery* 2002;131:6-15.
- 23 Bridgewater B, Grayson A, Jackson M, Brooks N, Grotte G, Keenan D, et al. Surgeon specific mortality in adult cardiac surgery: comparison between crude and risk stratified data. *BMJ* 2003;327:13-7.
- 24 Department of Health. *Coronary heart disease: national service framework for coronary heart disease: modern standards and service models*. London: DoH, 2000. (Search at www.dh.gov.uk/).
- 25 Department of Health. *Coronary heart disease information strategy*. London: DoH, 2001. www.dh.gov.uk/PolicyAndGuidance/InformationPolicy/InformationSupportingNSFAndNCASP/InformationPolicyCoronaryHeartDisease/fs/
- en?CONTENT_ID=4015656&chk=HUnWUQ (accessed 9 August 2004).
- 26 National clinical audit support programme: support for national service frameworks and clinical governance. www.dh.gov.uk/assetRoot/04/05/95/61/04059561.pdf (accessed 9 August 2004).
- 27 Fine L, Keogh B, Orlando M, Cretin S, Gould M. *Improving the credibility of information on healthcare outcomes*. London: Nuffield Trust, 2003.
- 28 Fine L, Keogh B, Cretin S, Orlando M, Gould M. How to evaluate and improve the quality and credibility of an outcomes database: validation and feedback study on the UK Cardiac Surgery Experience. *BMJ* 2003;326:25-8.
- 29 Sergeant P, Blackstone E, Meyns B. Validation and interdependence with patient-variables of the influence of procedural variables on early and late survival after CABG. KU Leuven coronary surgery program. *Eur J Cardiothorac Surg* 1997;12:1-19.
- 30 Healthcare Commission. Clinical indicator. Deaths following a heart bypass operation. 2004. http://ratings.healthcarecommission.org.uk/indicators_2004/trust/indicator/indicatordescriptionshort.asp?indicatorid=1400 (accessed 9 August 2004).
- 31 Shahian D, Normand S, Torchiana D, Lewis SM, Pastore JO, Kuntz RE, et al. Cardiac surgery report cards; comprehensive review and statistical critique. *Ann Thorac Surg* 2001;72:2155-68.
- 32 Iezzoni L. The risks of risk adjustment. *JAMA* 1997;278:1600-11.

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Development of an AIDS vaccine: perspective from the South African AIDS Vaccine Initiative

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Most work on HIV vaccines is being done in the public sector rather than the pharmaceutical industry. Although international cooperation is producing candidate vaccines, greater investment is needed to speed up progress

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The HIV epidemic continues to expand at an alarming rate¹ and is predicted to be the worst infectious disease ever to affect humanity. Other infectious diseases such as smallpox and polio have been controlled or eradicated by vaccination, and vaccines continue to be the most cost efficient and effective intervention available for preventing infectious diseases.²

Although investment in HIV vaccines was initially small, support has increased greatly over the past decade. This article describes the experience of vaccine development in South Africa.

Early development

The processes of developing a vaccine against HIV have been distinct from that of any previous pharmaceutical product. Although most existing vaccine capacity resides within the private sector, most research into an HIV vaccine has taken place (or been funded from) within the public sector. This is because manufacture and distribution of an HIV vaccine is unlikely to generate much profit.³

HIV is a genetically diverse microbe that is categorised into many genetic subtypes. Although HIV subtype B is responsible for a minority of HIV infections, it is the predominant subtype in developed countries.⁴ Early vaccine development focused on subtype B genes and proteins, and clinical trials were predominantly in the United States and Europe. However, in the mid to late 1990s groups such as the International AIDS Vaccine Initiative and the South African AIDS Vaccine Initiative (SAAVI), placed the development of vaccines against different subtypes on

the global agenda. In addition, greater investment went into clinical trials of products in developing countries.

South African AIDS Vaccine Initiative

SAAVI was established in 1999 by the South African government, Eskom (a private sector electricity supplier), and the Medical Research Council to coordinate development and testing of HIV vaccines

The South African AIDS Vaccine Initiative is developing vaccines against different subtypes of HIV

Core activities supported by the South African AIDS Vaccine Initiative

- Laboratory development of novel vaccine constructs based on HIV subtype C
- Sophisticated preclinical and clinical immunology
- Clinical trials
- Community preparedness activities and sociobehavioural investigation
- Investigation into ethics of HIV vaccine studies
- Human rights research
- Actuarial predictions of vaccine requirements and best use of vaccine
- Bioinformatics and data management

in the country. The initiative has supported a comprehensive list of core activities within South Africa (box). Scientific programmes have developed novel candidate HIV vaccines that are currently undergoing toxicity testing before phase I clinical trials start in 2005. The trials will be conducted in South Africa and the United States, in collaboration with the HIV Vaccine Trials Network, which is funded by the National Institutes of Health. The SAAVI immunology laboratory infrastructure operates according to the highest international standards and is an endpoint laboratory for both SAAVI and other international agencies. In addition, the community preparedness programme and ethics components have developed a large body of local expertise and materials and have facilitated community education and involvement at various levels.

South Africa reached a major milestone in 2003 with the start of its first two HIV vaccine trials, after many years of planning. The first trial, of a vaccine developed by AlphaVax and SAAVI scientists, is coordinated in collaboration with the HIV Vaccine Trials Network. The second trial is of a vaccine developed by Oxford University scientists, Kenyan scientists, and the International AIDS Vaccine Initiative.

SAAVI's current priorities include pushing its own HIV vaccines into clinical trials as rapidly as possible and developing increased capacity for multiple, large scale clinical trials in South Africa, particularly for phase III trials. These phase III trials, which are predicted to start in 2006-7, require considerable preparatory efforts to ensure that communities, scientists, clinicians, and laboratories are appropriately equipped and have adequate staff and physical infrastructure. Phase III trials are best performed in areas of high HIV incidence; South Africa is well placed to be an important contributor to these as it has both a high number of new infections annually and an excellent infrastructure.

Global integration and collaboration

SAAVI is an autonomous consortium with extensive links to other global HIV vaccine efforts. It has worked extensively with bodies such as the US National Institutes of Health, the HIV Vaccine Trials Network, the Joint United Nations Programme on HIV/AIDS, and the African AIDS Vaccine Programme both to build internal capacity as well as to share expertise, experience, and products. These international bodies

have contributed importantly to the funding of SAAVI and the development of South Africa's human and infrastructural capacity.

An example of this positive engagement is the product development and clinical trial programme, which has been funded jointly by SAAVI and the National Institutes of Health. The resultant candidate vaccine will be tested in South Africa and the United States in 2005, the first time this has occurred for a vaccine produced in a developing country. It is also a marker of the increasing collaborative efforts between developed and developing world groups.

South Africa has also been part of other international collaborative efforts. Early strategic investment by the International AIDS Vaccine Initiative to facilitate increased genetic characterisation of the circulating subtype C viruses at the University of Cape Town led to patent protection of South African HIV isolate genes and encouraged the use of these genes in many international HIV vaccine constructs. This foresight and local ownership of HIV gene intellectual property has allowed SAAVI to use the same HIV genes that many other groups are also working on in various candidate HIV vaccine technology platforms. This bodes well for later "prime-boost" clinical trial strategies (where more than one vaccine is used sequentially to induce a stronger immune response). A similar collaboration exists between SAAVI, Stellenbosch University, and Chiron Corporation, through which South African (and Botswanan) HIV genes have been used in Chiron-owned constructs.

International collaboration extends beyond biological product development and clinical trials. Many ethical and sociobehavioural complexities require clarification, and forging links between communities involved in these studies and scientists or clinicians is important. SAAVI has worked closely with international bodies to increase these links and collaborative activities in Africa, India, the United States, and elsewhere.

Maximising international partnerships

People are increasingly realising that no one body or consortium currently has the required capacity, budget, infrastructure, or product pipeline to develop an effective HIV vaccine, particularly with limited private sector involvement. Clinical trials take many years, and the urgency of the situation demands that many development programmes be run in parallel; this will ensure that additional options are available if early results of one product are disappointing.

Product development requires large financial reserves and human and infrastructural components. Investments of this size require scientific rationale, clinical judgment, political commitment, and insight. Naturally, people have different international priorities, and the recent bitter criticism of resource allocation and scientific rationale for the Thai phase III trial (using Aventis Pasteur's ALVAC-HIV (vCP1521) as prime vaccine and VaxGen's rgp120 (AIDSVAX B/E) as boost) is indicative of this tension.^{4,5} Adequate scientific rationale for the initiation of a phase III trial should never be negotiable. However, quantifying "scientific rationale" is not exact, and no single factor can be taken in

isolation from the myriad of other factors influencing such decisions. The public spat between such senior international HIV vaccine practitioners is not good for the field but will have been valuable if it results in a greater consensus on which products should be allocated such huge resources.

Resource mobilisation

International funds for HIV vaccines and clinical trials are increasing steadily, although at an inadequate pace. It has been argued that the magnitude of government and private sector investment in a product is an indicator of the social value that a society attaches to that product. The massive recent investment in vaccine development related to biological warfare, SARS, and avian influenza outbreaks, is an indicator of how great a social value can be attached to vaccines. The speed with which international funds have been mobilised for products protecting society against biological warfare and newly described infectious agents is impressive and laudable. However, we need to replicate that sense of urgency for HIV vaccines, in response to the 60 million people infected or already dead from HIV infection.⁶

That said, there are promising signs of change. The recent announcement of a possible massive investment in HIV vaccines by the Bill and Melinda Gates Foundation is encouraging because this investment seems to be directed at strategic gaps in the existing global infrastructure and support for HIV vaccine development.⁷ The probable additional \$1bn (£540m, €811m) investment discussed will inevitably alter the power dynamics in the field and lead to new modes of operating. The European and Developing Country Trial Partnership, a vehicle of the European Union, has also been awarded about €600m (£400m, \$740m) for developing capacity for trials and novel approaches to drugs, vaccines, microbicides, etc for neglected diseases. This is the only major recent announcement of new investment from the developed world in which a fixed minimum proportion (80%) needs to be spent in developing countries. Within the context of increasingly conservative global health (and general) policies, this amount of new funding specifically for developing countries is welcome.

What is certain is that we have not yet managed to raise sufficient resources globally for rapid development of an HIV vaccine. The size and manner of global investment needs a major rethink if we are to respond with the vigour and speed required by this epidemic.

Useful websites

South African AIDS Vaccine Initiative (www.saaavi.org.za)
 International AIDS Vaccine Initiative (www.iavi.org)
 National Institute of Allergy and Infectious Diseases (www.niaid.nih.gov/daids/vaccine/default.htm)
 HIV Vaccines Trial Network (www.hvtn.org)
 European and Developing Country Trial Partnership (www.edctp.org)
 AIDS Vaccine Advocacy Coalition (www.avac.org)

Summary points

Development of vaccines against HIV has been slow

International collaboration and investment is needed for success

The South African initiative shows how resources can be used in developing countries

Future developments

The successes of the international HIV vaccine efforts are considerable. Yet immense efforts are still required to find an effective HIV vaccine. The fact that only one HIV candidate vaccine has completed the full testing process (phases I, II, and III) in more than 20 years of the epidemic is testament to the fact that a far more coordinated and sizeable effort is required.

We hope that the SAAVI model will have relevance in other developing countries, and that many other similar initiatives will emerge shortly. Central to their sustainability and success will be their ability to gain consensus within the country for the establishment of such an initiative, as well as broad support from government and the private sector. Developing countries will always have a relative lack of human and infrastructural capacity. Harnessing all experienced people will be important, and investing in younger scientists, clinicians, ethicists, etc should be an integral part of such an initiative, and the mentoring of younger members should be encouraged. Developing countries will not have the capacity or finances to operate successfully alone. Such groups should develop a robust autonomy while ensuring that they are seamlessly integrated into the global efforts. An HIV vaccine is our best hope to eradicate HIV, and this end point should always be central in biomedical decisions.

Contributors and sources: TT and GM lead the SAAVI team of over 200 people. TT has had extensive experience in running clinical trials, molecular virology research, and public policy development in HIV in South Africa. GM has a background in molecular virology and the management of intellectual property within the biotechnology industry and formal training in business. This paper was developed after multiple presentations about SAAVI in forums describing global public-private partnerships.

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- 1 United Nations. *AIDS report*. New York: UN, 2003.
- 2 Dayan GH, Cairns L, Sangrue N, Mtonga A, Nguyen V, Strebel P. Cost-effectiveness of three different vaccination strategies against measles in Zambian children. *Vaccine* 2004;22:475-84.
- 3 Bronnenkant L. Panel discussion on vaccine development to meet US and international needs. Strategies for reducing the disincentives to HIV vaccine development: description of a successful public-private sector international collaboration. *AIDS Res Hum Retroviruses* 1994;10(suppl 2):S311-3.
- 4 Burton DR, Desrosiers RC, Doms RW, Feinberg MB, Gallo RC, Hahn B, et al. A sound rationale needed for phase III HIV-1 vaccine trials. *Science* 2004;303:316.
- 5 McNeil JG, Johnston MI, Birk DL, Tramont EC. Policy rebuttal. HIV vaccine trial justified. *Science* 2004;303:961.
- 6 Stebbing J, Moyle G. The clades of HIV: their origins and clinical significance. *AIDS Rev* 2003;5:205-13.
- 7 Klausner RD, Fauci AS, Corey L, Nabel GJ, Gayle H, Berkley S, et al. The need for a global HIV vaccine enterprise. *Science* 2003;300:2036-9.