

THE



of **SECURE THE FUTURE**® — Funded Operational Research Programs
Addressing HIV/AIDS in Africa

**The mission of the Bristol-Myers Squibb
Foundation is to help reduce health
disparities by strengthening community-based
health care worker capacity, integrating
medical care and community-based
supportive services, and mobilizing
communities in the fight against disease.**

THE IMPACT of STF Funded Operational Research Programs Addressing HIV/AIDS in Africa

INTRODUCTION

From 1999 to 2007, the Bristol-Myers Squibb *SECURE THE FUTURE* (STF) program funded carefully selected and targeted operational research, including clinical research projects addressing critical issues of the HIV/AIDS epidemic in sub-Saharan Africa, with particular relevance to women and children. The research projects were identified and chosen with the assistance of independent Technical Advisory Committees, consisting of internationally renowned academicians, scientists, and physicians as well as key members of the Ministries of Health of the countries involved: Botswana, Burkina Faso, Cote d'Ivoire, Lesotho, Mali, Namibia, Senegal, South Africa, and Swaziland.

The results were, in many instances, groundbreaking and had far-reaching implications in terms of therapeutic practice and national health policy related to the care and treatment of patients not only in the above mentioned countries but also in resource-limited settings in general. This document highlights the most important projects and their impact.

THE SELECTION PROCESS

The overarching objectives for all STF-funded projects were:

- Prevention of HIV/AIDS mother-to-child transmission
- Reduction of the impact of HIV/AIDS on individuals by empowering infected and affected women and children
- Expansion of access to treatment by informing public health policy

The Technical Advisory Committees were requested to select projects that met the following criteria:

- Compatible with and complementary to health care priorities
- Relevant and sensitive to the local context
- Ethically sound
- Innovative, sustainable and replicable



These overarching objectives and selection criteria helped to ensure that the projects funded were truly relevant to the local context and therefore would stand the best chance of informing medical or care practice and policy in resource-limited settings. For the most part, the research studies could be defined as operational in nature, while other projects served principally to build local capacity.

THE KEY ISSUES

In 1999, when STF was launched, there were many serious obstacles to providing comprehensive prevention, care and treatment services for patients with HIV/AIDS living in sub-Saharan Africa. The key issues initially identified by STF were:

- Lack of political leadership
- Lack of basic and health care infrastructure, particularly in rural environments
- Lack of training and human capacity
- Psychosocial issues
- Treatment and monitoring costs
- Difficulty of ensuring good adherence to highly active antiretroviral therapy (HAART)

The program sought to coordinate with the growing global response and rapidly evolving situation on the ground and adapted accordingly. For example, in 2001, major pharmaceutical companies manufacturing antiretroviral drugs, including Bristol-Myers Squibb, reduced the cost of the drugs basically to the level of cost of goods as part of the UNAIDS Accelerating Access Initiative, thus rendering them affordable in resource-limited settings and removing a key obstacle to treatment. Similarly, recognizing the continuing difficulties of implementing prevention of mother-to-child transmission (PMTCT) services and of dealing effectively with coinfection with tuberculosis, in 2002 STF staff and the Technical Advisory Committees paid particular attention to proposals addressing those two issues.

The STF program was initially launched with \$100 million for both medical and community projects in the five southern African countries of Botswana, Lesotho, Namibia, South Africa and Swaziland. Because those countries were already in the grip of serious epidemics with high prevalences of HIV/AIDS, the projects funded tended to be relevant to mitigation and treatment. In contrast, when it was decided that Bristol-Myers Squibb would commit an additional \$15 million for the four West African countries of Burkina Faso, Cote d'Ivoire, Mali and Senegal, where the prevalence of HIV/AIDS was still relatively low, funding was directed to training



programs and prevention-related projects and research studies. The objective was to build and support efforts to keep the prevalence low.

Subsequently, in 2004, STF committed a further \$35 million, this time for the construction and equipping of five more national Children's Clinical Centers of Excellence and for the recruitment of the Pediatric AIDS Corps of physicians. The rationale was that although significant progress was being made in the treatment of adult patients with HIV/AIDS, there remained a lamentable gap in the treatment of children.

In these ways, STF was able to stay ahead of the curve and adapt its funding priorities to the evolving situation on the ground.

The rest of this document describes the key STF-funded medical projects and research studies and their impact, in logical progression, starting with epidemiology and prevention and then discussing capacity building, then proceeding to diagnosis and disease monitoring and ending with care. STF made high-impact contributions in all of these areas.

EPIDEMIOLOGY

In 1999, when STF was launched, there was, in general, a growing recognition of the huge scale of the HIV/AIDS pandemic in sub-Saharan Africa. However, political leadership and engagement varied from one country to another. Under the courageous and exemplary leadership of President Festus Mogae, Botswana was fully cognizant of the challenge the country faced and was making ambitious plans to address the epidemic. In contrast, other governments appeared indecisive and even espoused denialist views. One form of denial was an unwillingness to acknowledge even the scale of the epidemic and its effect on life expectancy. At the same time, there was an urgent need for rigorously analyzed mortality data, because the first year in which full cause-of-death statistics were available for the entire population of South Africa was only 1996. At an early point in the program, STF funded the South African Medical Research Council's Burden of Disease Research Unit. Under the leadership of Dr. Debbie Bradshaw as principal investigator, analysis of data from 1996 and prediction of future trends were carried out in a study entitled Rapid AIDS Mortality Surveillance in South Africa. The ASSA2000 model⁽¹⁾, calibrated to antenatal survey data as well as mortality data prior to 2000, was used to estimate current levels of mortality and to make projections through 2010.



Table 1. Projected impact of HIV/AIDS on mortality, ASSA2000.

| Indicator | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
|---|------------|------------|------------|------------|------------|------------|-------------|-------------|-------------|-------------|
| Infant mortality rate (per 1000) | 58 | 59 | 59 | 59 | 58 | 58 | 57 | 56 | 56 | 55 |
| Under 5 years mortality rate (per 1000) | 96 | 100 | 104 | 106 | 108 | 108 | 109 | 108 | 108 | 107 |
| Adult mortality 45Q15 (%) | 44.7 | 49.5 | 54.8 | 60.1 | 65.1 | 69.6 | 73.2 | 75.9 | 77.7 | 78.6 |
| Life expectancy at birth (years) | 54 | 52 | 50 | 48 | 46 | 44 | 43 | 42 | 41 | 41 |
| Total deaths | 587 300 | 658 700 | 739 500 | 826 400 | 914 800 | 998 700 | 1071 300 | 1128 900 | 1166 800 | 1185 200 |
| HIV/AIDS deaths | 194 900 | 262 200 | 339 500 | 423 700 | 510 100 | 592 600 | 665 000 | 722 000 | 760 200 | 779 100 |
| Percentage HIV/AIDS deaths (%) | 33.2 | 39.8 | 45.9 | 51.3 | 55.8 | 59.3 | 62.0 | 63.9 | 65.1 | 65.7 |

The analysis demonstrated that in the absence of interventions such as use of antiretroviral therapies (ARVs), there would be an extraordinary change in mortality without parallel in demographic history. Period life expectancy at birth is expected to drop from the current level of 54 years to 41 years in 2010. The total number of deaths per year is expected to increase from 600,000 in 2001 to 1.2 million in 2010 and the proportion of deaths related to HIV will rise from a third in 2001 to two thirds in 2010.⁽²⁾ Although the study also highlighted the fact that poverty contributed significantly to mortality, as the government repeatedly claimed, the data on the increasing and catastrophic effects of HIV/AIDS could no longer be ignored. The results of the study were reported in several publications.^(3,4,5) The publications appeared from 2001 to 2003 and contributed to the Department of Health's decision to implement rollout of ARVs to the general population, beginning in 2004.

BUILDING CAPACITY

STF understood from the beginning that building health care and specialized research capacity would be key to having a significant impact on the epidemic. There was not only inadequate physical infrastructure but also a serious lack of health professionals and the health professionals who were in place required training in the field of HIV/AIDS. The following initiatives were funded to address those issues.



Training Materials

The Baylor HIV Curriculum

Under the guidance of Dr. Mark W. Kline, the Baylor International Pediatric AIDS Initiative (BIPAI) of Baylor College of Medicine and Nursing School, the Southern African Development Community (SADC) AIDS Network of Nurses and Midwives, UNAIDS and the National Nursing Association created an HIV/AIDS training curriculum, initially specifically targeting nurses. The curriculum was intentionally Afro-centric, with case studies involving typical African settings and addressing African concerns. It was designed in a modular format so that elements could be used either collectively or individually – for example, as a single module to supplement a community nursing course or as a group of modules to give a complete review of such factors as clinical manifestations of HIV. However, with appropriate adaptation it could also be used in training health professionals worldwide. The total course comprised 22 modules, with objectives, key points and written lecture material for each, as well as review questions, exam questions, case studies and overhead transparencies illustrating the material.⁽⁶⁾

The first draft of the nursing curriculum was pilot tested in April 2000 and comments from the participants were used to finalize the document. The second edition of the curriculum was rewritten to reflect BIPAI's growing experience in conducting training in southern Africa. It was re-named the HIV Curriculum for Health Professionals because experience had shown that doctors, counselors, and other health professionals in addition to nurses could benefit from the material. Third and fourth editions have been published, with significant updating and enhancement of the material.

Since its creation, over 10,000 hard copies of the curriculum have been distributed free of charge in 51 nations. In addition, the entire curriculum (both text and illustrations) is available to be downloaded from the BIPAI web site (<http://www.bayloraids.org>). The curriculum page of the BIPAI web site is consistently the top-viewed interior page (aside from the home page), indicating that it serves as a well-utilized on line HIV/AIDS resource.

The West African HIV Therapeutic Manual

The West African STF initiative also funded the creation of an independent *Therapeutic Manual of HIV Infection in Sub-Saharan Africa* in French. The motivation for the manual was based on the following needs:



- Linguistic, geographic and economic issues mean that African health care professionals had difficulty in accessing a practical textbook to guide them in the care and treatment of patients with HIV/AIDS. Such a text should also take into consideration the realities on the ground in resource-limited settings.
- The rollout of HAART in many African countries implied that many more physicians would require a comprehensive textbook to acquaint them with ARVs and how to prescribe them.
- Those physicians would also benefit from a text dealing with the many complications of HIV/AIDS such as the complexity of anti-TB therapy and TB prophylaxis, prophylaxis of opportunistic infections, ARV drug interactions and therapeutic issues related to infant feeding by seropositive mothers.
- There was a need for a text that would inform health care professionals about new concepts in the care and treatment of patients such as psychosocial support, adherence to HAART, ARV regimen changes and immune reconstitution.

The manual was published in April 2005 and was met with immediate attention.⁽⁷⁾ The first publishing run of 4,000 copies was rapidly exhausted, necessitating a second printing. A second edition, taking account of the rapidly evolving field of HIV, was published in 2008.

Laboratory Capacity

In 1999, the Botswanan government, in pioneering fashion, was already planning a national rollout of HAART. Botswana had the highest incidence of HIV in the world, at greater than 30%, and it was estimated that more than 80,000 people required HAART. The laboratory capacity to support a rollout on such a scale was absent and one of STF's first grants was awarded to create the HIV Reference Laboratory in the capital city of Gaborone. It was an improvement to an initial laboratory facility and was dedicated in February 2000. It was co-funded by the government of Botswana and was closely aligned with the Botswanan government's national HIV/AIDS agenda and strategy. The three-story, 2,300-square-meter facility was designed to provide laboratory support for the Botswanan National ARV Program.

The HIV Reference Laboratory was a sustainable and appropriate intervention based on the commitment of the Botswanan government. It played a significant role in expanding the laboratory capacity necessary to support implementation of the national AIDS response and treatment.



Infrastructure and Human Resources for Treating Children with HIV/AIDS

Baylor International Pediatric AIDS Initiative Children's Centers of Excellence

From the beginning, STF focused on children. This was particularly important, because in 2001, children constituted less than 2% of patients receiving HAART, even though 15% of all patients with HIV were estimated to be children. This was the impetus behind a major partnership with the Baylor International Pediatric AIDS Initiative, which was established in 1996 by Dr. Mark W. Kline, professor of pediatrics at Baylor College of Medicine, to foster international HIV/AIDS prevention, care and treatment, health professional education, and clinical research. BIPAI had initiated a clinic for treatment of HIV-positive children in Constanta, Romania, in 1996. Now, in addition to the HIV Curriculum mentioned earlier, STF partnered further with BIPAI, initially to fund the building of a state-of-the-art Children's Center of Excellence in Gaborone, Botswana. The center opened in June 2003 and within three years had placed more children on HAART than had any other clinic worldwide. Based on the success of that first center, a further five such centers were funded by Bristol-Myers Squibb's STF in Kenya, Lesotho, Swaziland, Tanzania and Uganda, and the model was replicated with funding from the Abbott Fund in Malawi and Tanzania. Those in Lesotho and Swaziland have been operational since the beginning of 2006. The center in Uganda officially opened in October 2008. Construction of the two sites in Tanzania began in the first quarter of 2009, and the center in Kenya is expected to open in 2010. BIPAI has rapidly grown to become the world's largest university-based program, dedicated to improving the health and lives of HIV-infected children.

BIPAI provides care and treatment in aggregate to more than 28,000 HIV-infected children and their families. More than 14,000 of the children are receiving HAART. The network gives children and families in resource-limited settings access to the same kind of comprehensive HIV/AIDS care and treatment and clinical research that have transformed the health and lives of U.S. children and families. Monitoring and evaluation data derived from the centers using BIPAI-developed electronic medical records have yielded impressive clinical outcomes. The intent-to-treat efficacy responses to ARVs are greater than 70%; more than 80% of children have ARVs adherence rates of greater than 95%; and annual mortality rates are 1.6 to 3.2%.



The Pediatric AIDS Corps

Funding for construction of the Centers of Excellence was later complemented by funding for the Pediatric AIDS Corps (PAC). For a five-year period beginning in 2006, STF is funding the recruitment and stipends of 50 physicians per year, who commit to working in Africa for a minimum of 12 months. The purpose of the PAC is to dramatically increase human capacity at BIPAI sites in Africa and it has the potential to transform the care of HIV-infected children and families. As well as treating children, PAC doctors are training local physicians and other health professionals, thus ensuring that capacity is built to sustain the care and treatment of children in the future. PAC doctors not only work at the Children's Centers of Excellence but also treat and train at BIPAI satellite sites and primary health centers. This type of outreach will ensure that children are treated throughout the rural areas of the countries in question. PAC doctors have contributed greatly to the increased number of children under care over the past three years and will enable BIPAI to reach its target of treating at least 100,000 children by 2012.⁽⁶⁾

PREVENTION

Prevention of Nosocomial Infection

STF in West Africa also had a special focus on prevention of HIV infection. The following three projects took innovative approaches to the issues of nosocomial infection.

Blood-sparing technique

Prof. Abdoul Traore dit Diop of Hôpital du Point G in Bamako, Mali, was funded to investigate the feasibility of blood-sparing techniques for surgical procedures in national hospitals. Although such techniques had been implemented in the developed world, they were not widely available in Mali. The need for these techniques, moreover, was particularly acute in Mali because of a high incidence of transfusion accidents (4.2% in 1995 in Bamako), a relatively high incidence of HIV and HBV infection in the general population and the difficulty of ensuring adequate supplies of blood for transfusion, given the low number of blood donors.

Earlier pilot studies had demonstrated the acceptability among patients of both homologous transfusion (HT) and intentional normovolemic hemodilution (INHD). It was now decided to compare the feasibility of both techniques in Mali's three national hospitals. A total of 148 patients (75 INHD and 73 HT) scheduled for



surgical operations and requiring associated transfusion were enrolled. INHD proved superior in that it did not result in any clinical issues, any hemodynamic disturbance, or any major transfusion complications. During the course of the intervention, the reserve of blood for transfusion was increased by 80 units.

Safety of blood transfusion

Prof. Lassana Sangaré of UFR des Sciences de la Santé, University of Ouédraogo, evaluated a new algorithm for sequential testing of donated blood for infectious microbes, including hepatitis B (HBV), hepatitis C (HCV), HIV and *Treponema pallidum* (the causative agent of syphilis). At the time of initiation of the study, the prevalence of the first three of these infections among blood donors in Burkina Faso was: HBV, 13.3%; HIV, 5.4%; syphilis, 3.0%. Earlier data from 1994 had estimated the incidence of HCV at 5 to 7%, therefore highlighting that it was also a significant problem with regard to the safety of blood transfusion.

The study compared an algorithm of sequential testing with the standard method of simultaneous testing for all four microbes. Five hundred samples of donated blood were tested by both approaches. The sequential approach tested for HBV first. Positive blood was excluded and then the other microbes were tested in sequence: HIV, *T. pallidum* and HCV in that order, discarding positive blood at each step.

The cost of the sequential approach was CFA 2,029,865 compared with CFA 2,626,115 for the standard method — equivalent to a savings of 22%. Both methods resulted in exclusion of the same number of blood donations: 157, or 31.4%. In addition, the study accurately evaluated the prevalence of HCV at 5.2%.⁽⁹⁾

Further to those results, the investigator made the following recommendations to the Ministry of Health of Burkina Faso in July 2003:

- Obligatory testing of donated blood for HCV
- Use of the sequential testing approach to reduce costs
- Replacement of third generation HIV tests by fourth generation tests
- Integration of voluntary-counseling-and-testing (VCT) facilities within blood bank services
- Referral from blood bank services of donors infected by HBV, HIV, HCV and syphilis for care and treatment

The sequential approach to testing of donated blood has been adopted by the Ministry of Health of Burkina Faso.



Training on primary prevention and postexposure prophylaxis of infection through blood-related accidents

The training was provided through a project conducted by Profs. Elisabeth Bouvet and Jean Sylvain Bonny of France's Groupe d'Etude sur le Risque d'Exposition au Sang (GERES) in collaboration with the University Hospitals of Trechville and Yopougon in Cote d'Ivoire. The impetus was given by the fact that 60% of health professionals at University Hospitals in Cote d'Ivoire reported at least once having been exposed to blood through accidents. The overall objectives were to sensitize personnel to the risks of infection and the importance of reporting accidents involving blood and to establish work procedures designed to minimize the risks. The project was implemented in two phases. The first phase consisted of a train-the-trainer exercise. Twenty physicians and 10 nurses were trained. Pre- and post-test results demonstrated significant improvement in knowledge. In the second phase, the new trainers conducted trainings of relevant personnel at six health facilities in Cote d'Ivoire. A total of 535 personnel received the training and again showed significant improvement in knowledge afterward.

Prevention of Mother-to-Child Transmission (PMTCT)

Postexposure prophylaxis

PMTCT is a critically important form of HIV/AIDS prevention. It is the key to reducing and potentially eliminating HIV infection in newborn children. However, it has proved difficult to implement in resource-limited settings mainly because of logistic issues. One such logistical issue is that a significant proportion of pregnant women present to health care facilities having already delivered but without prior antenatal care and, hence, without access to PMTCT medication. The value of administering postexposure prophylaxis to the newborn child alone was investigated by Dr. Glenda Gray and colleagues of the Perinatal HIV Research Unit of Chris Hani Baragwanath Hospital in Johannesburg and two other hospitals in South Africa in a study beginning in 2001.⁽¹⁰⁾ The study randomized 1,040 infants within 24 hours of birth to either single-dose nevirapine or a six-week course of zidovudine.

The overall transmission rate at six weeks of age was 13.1%. The HIV transmission rates in the nevirapine and zidovudine groups were similar: 7.1% and 5.8%, respectively, at birth ($p = 0.4$) and 12.3% and 13.7%, respectively, by six weeks of age ($p = 0.5$).

The results demonstrated for the first time that postpartum voluntary counseling and testing and prophylaxis of infants could be important strategies to reduce



Table 2. Postuterine HIV-1 transmission rates by treatment and feeding method (Kaplan–Meier analysis).

| Total < day 10 (a) | | | Postuterine week 6 (b) | | Postuterine week 12 (c) | | P Value (log rank) |
|--|------------|-----------------|------------------------|------------------|-------------------------|------------------|--------------------|
| No./Total No. | % (95% CI) | No./Total No. | % (95% CI) | No./Total No. | % (95% CI) | | |
| NVP versus ZDV | | | | | | | 0.06 |
| Total | 63/1030 | 6.4 (4.9–7.9) | 48/967 | 6.8 (5.0–8.7) | 65/967 | 10.6 (7.9–13.3) | |
| NVP | 34/510 | 7.0 (4.7–9.3) | 18/476 | 5.3 (2.9–7.8) | 24/476 | 7.9 (4.6–11.2) | |
| ZDV | 29/520 | 5.8 (3.7–7.9) | 30/491 | 8.2 (5.4–11.0) | 41/491 | 13.1 (8.9–17.3) | |
| NVP: EFF versus BME | | | | | | | 0.30 |
| Total | 33/416 | 8.1 (5.5–10.7) | 18/383 | 5.5 (3.0–7.9) | 24/383 | 8.0 (4.7–11.4) | |
| EFF | 24/268 | 9.1 (5.7–12.5) | 12/244 | 5.3 (2.4–8.3) | 14/244 | 7.3 (3.1–11.5) | |
| BME | 9/148 | 6.3 (2.3–10.3) | 6/139 | 5.9 (1.3–10.4) | 10/139 | 9.9 (4.1–15.7) | |
| ZDV: EFF versus BME | | | | | | | 0.004 |
| Total | 29/424 | 7.0 (4.6–9.5) | 30/395 | 8.5 (5.6–11.4) | 41/395 | 13.4 (9.1–17.6) | |
| EFF | 23/302 | 7.7 (4.7–10.7) | 17/279 | 6.4 (3.5–9.4) | 23/279 | 11.1 (6.1–16.1) | |
| BME | 6/122 | 5.1 (1.1–9.1) | 13/116 | 14.5 (7.2–21.8) | 18/116 | 20.6 (12.1–29.1) | |
| EFF: NVP versus ZDV | | | | | | | 0.3 |
| Total | 47/570 | 8.3 (6.0–10.6) | 29/523 | 5.9 (3.8–8.0) | 37/523 | 9.4 (6.0–12.7) | |
| NVP | 24/268 | 9.0 (5.6–12.5) | 12/244 | 5.3 (2.4–8.3) | 14/244 | 7.3 (3.1–11.5) | |
| ZDV | 23/302 | 7.7 (4.7–10.7) | 17/279 | 6.4 (3.5–9.4) | 23/279 | 11.1 (6.1–16.1) | |
| BME: NVP versus ZDV | | | | | | | 0.03 |
| Total | 15/270 | 5.8 (2.9–8.6) | 19/255 | 9.9 (5.7–14.1) | 28/255 | 14.8 (9.7–19.9) | |
| NVP | 9/148 | 6.3 (2.3–10.2) | 6/139 | 5.9 (1.3–10.4) | 10/139 | 9.9 (4.1–15.7) | |
| ZDV 6/122 5.1 (1.1–9.1) CD4 cell count category (X 106 cells/l) | | | | | | | 0.0002 |
| < 500 | 41/592 | 7.3 (5.1–9.4) | 37/551 | 9.2 (6.3–12.0) | 52/551 | 15.2 (10.8–19.6) | |
| 2 500 | 22/438 | 5.2 (3.1–7.4) | 11/416 | 3.7 (1.5–5.8) | 13/416 | 4.4 (2.1–6.8) | |
| Viral load category (copies/ml) | | | | | | | < 0.0001 |
| < 50 000 | 30/691 | 4.5 (3.0–6.1) | 16/661 | 3.2 (1.7–4.8) | 25/661 | 6.0 (3.5–8.5) | |
| 2 50 000 | 33/339 | 10.2 (6.9–13.5) | 32/306 | 14.8 (10.0–19.5) | 40/306 | 20.8 (14.3–27.3) | |

No./total No., number of events/total number of individuals included in analysis (21 individuals with no polymerase chain reaction values were excluded from the analysis); CI, confidence interval; NVP, nevirapine; ZDV, zidovudine; EFF, exclusively formula feeding; BME, breast milk exposure.

(a) Day 0 to day 9. (b) Day 10 to week 6. (c) Day 10 to week 12.

vertical transmission in situations in which many women do not access antenatal care, babies are born at home, or women arrive too late in labor to access HIV testing. Although some countries have subsequently changed their PMTCT guidelines to include combination ARVs, single-dose nevirapine remains the standard of care in many countries – hence another reason for the continuing relevance of the results of Dr. Gray’s study.

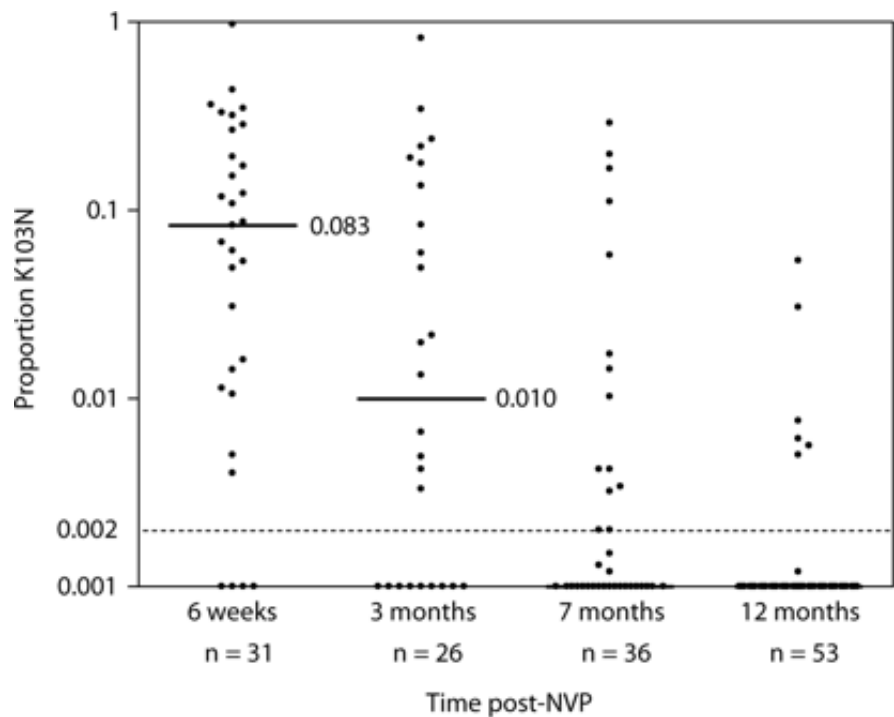
PMTCT medication and development of ARV resistance

STF also funded other research projects in PMTCT. Prof. Lynn Morris and colleagues from the National Institute of Communicable Diseases, Johannesburg, performed a series of laboratory studies to investigate the development of HIV drug resistance in pregnant women and their infants following short-course antiretroviral treatments to prevent perinatal transmission.



The use of AZT/3TC and of d4T/ddI in combinations were not reported to be associated with the development of resistance, whereas single-dose nevirapine did result in resistance development. At the time of these studies, single-dose NVP was the PMTCT medication of choice. There was, however, no doubt about its efficacy in reducing the MTCT rate.^(11,12,13) The research team also developed a real-time, allele-specific, rapid-screening polymerase-chain-reaction (PCR) assay for the NVP-associated resistance mutation, K103N.⁽¹⁴⁾ The assay was used to show that there is no K103N minority population present among drug-naïve pregnant women, thus explaining the high efficacy of NVP as PMTCT medication. By using the highly sensitive assay, they also showed that the majority of women exposed to single-dose NVP developed K103N. These mutations faded with time but were still detectable in a minority of women one year later.^(15,16)

Figure 1: Relative frequency of K103N variants in maternal plasma viral RNA at 6 weeks, 3 months, 7 months and 12 months after single-dose nevirapine.





The development of high-through-put and highly sensitive screening assays for the detection of key resistance mutations, such as K103N, greatly facilitated surveillance efforts. Such assays have been used to monitor the emergence of drug resistance in untreated (transmitted-resistance) and treated (ARV-program-monitoring) cohorts.

It was also important to investigate the clinical significance of NVP resistance in mothers and their infants exposed to NVP at the time of delivery. To this end, STF funded another study, conducted by Dr. Ashraf Coovadia and colleagues, which investigated the incidence of resistance and treatment responses in such mothers and their children up to the age of 18 months. A first publication from that work has been published. It concludes that exposure to single-dose NVP in the prior 18 to 36 months was not associated with a reduced likelihood of achieving and sustaining viral suppression while receiving NNRTI-based therapy.⁽¹⁷⁾ However, women with minority K103N mutations before treatment had a reduced durability of virologic suppression.

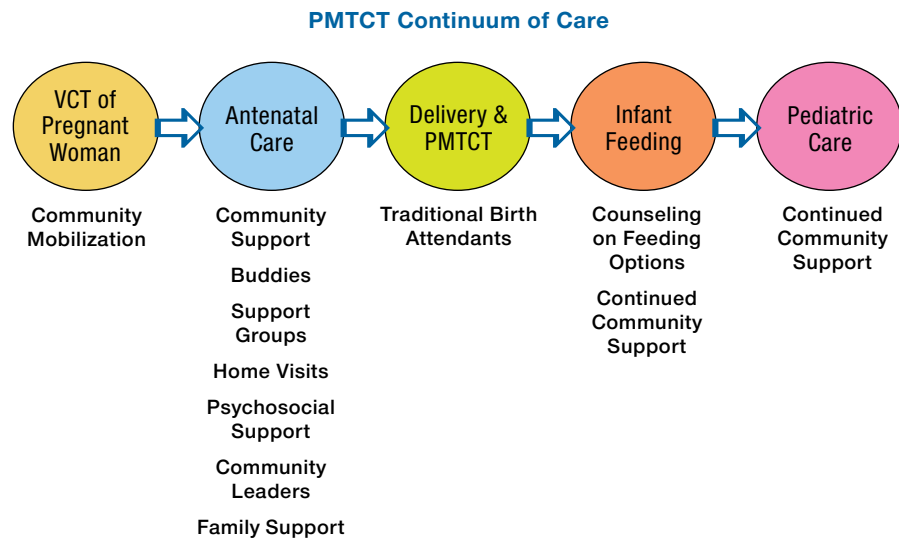
The logistics of PMTCT

The PMTCT-related investigations described earlier were important in that they helped elucidate critical laboratory and clinical issues. However, effective implementation of PMTCT is complicated by a multitude of other logistic issues. In the first instance, a study funded by STF and conducted by Dr. P. Kebaabetswe in Botswana showed that the major deterrent to women accessing PMTCT services was stigma.⁽¹⁸⁾ In other words, as a result of pressure from either the partner or the community, women were not coming forward for VCT at antenatal clinics or were not following through on HIV care and treatment thereafter, if they tested HIV positive.

PMTCT should not be viewed simply in terms of the moments before and after delivery when the mother and newborn child receive prophylactic medication. It is an extended process, starting with community mobilization and education on PMTCT and continuing to the point when a pregnant woman tests positive in VCT, her pregnancy (i.e., antenatal care), delivery, and postnatal and pediatric care up to the point at 12 to 18 months once the child's HIV status has been definitively determined. It also entails good counseling of the mother on infant feeding, either by breast or artificially. Only by following this entire process can the efficacy of the PMTCT intervention be determined. The services that constitute this continuum of care are not usually integrated, so another approach involves coordination of services and establishment of a register that tracks the client throughout the



process. This continuum of care, as illustrated in the diagram below, together with the relevant community services, can support each element of the clinical service.



STF funded a comprehensive PMTCT program in Swaziland that attempted to address the issues by providing community support throughout the continuum of care. The project, PORECO (Pilot Operational Research and Community-Based PMTCT Plus Concept), supplemented the clinical services needed throughout pregnancy and beyond with a variety of community support programs.

The project showed that 70% of the first 200 mothers enrolled and their newborn children could be followed throughout pregnancy and up until the newborn reached 12 months of age. On one hand, this result was not as good as expected, because of issues related to study personnel and data collection. On the other hand, the result was significantly better than those obtained at the time in other parts of southern Africa, where typically a large percentage of the mothers and their offspring are lost to follow-up during pregnancy and throughout the 12 months after birth.^(19,20)

Following the pilot project in Swaziland, STF funded another program in South Africa, that incorporated lessons learned from Swaziland but also expanded the scope to include larger numbers of patients.



DIAGNOSIS AND MONITORING

As mentioned previously, in 1999, when STF was launched, the costs of ARVs and of diagnosis and monitoring of HIV disease did not allow the introduction of large-scale care and treatment programs. ARV costs were gradually reduced beginning in 2001. STF funded two important research programs designed to make the other critical components of treatment, diagnosis and monitoring, more affordable.

Diagnosis

Affordable early infant diagnosis

Dr. Gayle Sherman of the University of the Witwatersrand, Johannesburg, in collaboration with the Department of Molecular Medicine and Hematology, National Health Laboratory Service, studied the impact of early diagnosis of HIV infection in vertically exposed infants from January 2002 to October 2003.^(21,22) At the time, the gold-standard protocol for infant diagnosis of HIV was performed according to the Centers for Disease Control and Prevention requirement of two positive PCR tests, but this was regarded as too costly to implement routinely in resource-limited settings.

The study assessed multiple options for infant diagnostic protocols in low-resource settings, ranging from clinical assessments to early viral detection assays using an ultrasensitive p24 Ag technique, to late HIV-antibody-detection assays in serum and in oral fluid, including cost analysis of the various options.

As part of the extended follow-up of the children, a convenience sample of 30 children enrolled in a costing substudy. Patient and provider costs incurred in establishing the HIV status of an exposed infant were documented by questionnaires to determine the societal and provider cost of performing HIV testing at 6 weeks and 12 months of age.

The diagnostic sensitivity of the p24 Ag assay was determined to be 98.1%, while the specificity was 98.7%. Both the specificity and the sensitivity of the ultrasensitive p24 Ag assay when applied to samples collected as dried-whole-blood spots were determined to be 100%. In contrast, the sensitivity of the then currently available clinical algorithm was shown to be very poor.

The costing substudy showed that the average cost of an earlier diagnosis of HIV was ZAR158 less per patient than the cost of the practice current at the time, as determined from questionnaires. This translated into an average greater



provider cost of R8 per patient. The associated PMTCT clinic attendance rates also predicted that earlier testing would increase by almost threefold the number of infants diagnosed.

Table 3: Results achieved with the p24 Ag assay in comparison with the known positive and negative HIV DNA PCR results at different ages. The number of tests performed in each age group equals the number of patients tested except as noted. The majority (82%) of assays were performed at or before 3 months of age.

| Age | No. of Positive | | No. of Negative | | | | |
|-----------------------|--|--------------------|--|--------------------|------------------|------------|------------|
| | p24 Ag Tests/ No. of Positive PCR Tests | Sensitivity (%) | p24 Ag Tests/ No. of Negative PCR Tests | Specificity (%) | Total Samples | PPV (%) | NPV (%) |
| 6 wk (5.9 wk)* | 22/23 | 95.7 | 62/62 | 100 | 85 (42)‡ | 100 | 98.4 |
| 3 mo (3 mo) | 20/20 | 100 | 62/62 | 100 | 82 (40) | 100 | 100 |
| 4 mo (4.1 mo) | 2/2 | 100 | 3/3 | 100 | 5 (3) | 100 | 100 |
| 7 mo (7.4 mo) | 7/7 | 100 | 22/24§ | 93.6 | 31 (15) | 92.3 | 100 |
| Total samples | 52 | | 151 | | 203 | | |
| Total patients | 24 | | 66 | | 90 | | |

* Numbers in parentheses, median.

‡ Numbers in parentheses, percent.

§ 20 patients. PPV, positive predictive value; NPV, negative predictive value.

Table 4: The average provider and societal costs of the PMTCT program per patient for the two diagnostic options.

| Provider Cost | Range | Societal Cost | Range |
|---------------|---------|---------------|-------------------|
| Option 1 | R375.33 | R474.63 | R330.86 – 789.93 |
| Option 2 | R366.95 | R 632.42 | R271.69 – 1345.59 |
| Difference | R8.38 | R157.79 | |

Current practice represents an average saving of R8 per patient to government but the societal cost of the program is currently R158 per patient more in comparison to introducing an HIV DNA PCR test.

The initial results were published in 2005,^(21,22) adding to the discourse around improving pediatric HIV/AIDS care in developing countries. For example, at that time in South Africa, PMTCT protocols required all children vertically exposed to HIV to be followed up for at least 12 months, until their HIV infection status could be determined by a standard ELISA test. This meant that more than 280,000 HIV-exposed children, up to 90% of whom may not have been infected, had to be followed up. The health system did not have the capacity to do this. As a result,



resources were spent following up infants who may not have been infected, while other children, who may have been infected, fell through the system and were never diagnosed and offered available medical care.

The research showed that the ultrasensitive p24 Ag assay performed as well as HIV DNA PCR for infant diagnosis. The technology required was also less costly and less complex than that required for the PCR. The equipment required was readily available in most laboratories and the assay simpler to perform than the PCR, and so required minimal training. The ability to use dried-whole-blood spots was also an important finding, because it would allow samples to be taken in remote and resource-limited settings and stored for later testing at a central laboratory.⁽²³⁾

Based on the costing substudy, the relative costs of the PMTCT protocol in effect at the time and the costs of the early infant diagnosis approach were extrapolated to annual figures. It was shown that on a national scale in South Africa, based on testing of all exposed infants, the additional provider cost for early PCR testing of 280,000 HIV-exposed infants per annum would be R2.4 million. However, the societal saving would amount to R44 million as a result of the more efficient identification of HIV-infected children.⁽²³⁾ It was further calculated that introduction of earlier HIV testing would give approximately 110,000 infants access to an HIV diagnosis, reaching about 70,000 more infants per annum than was currently being achieved. Although these data were calculated on the basis of the more affordable p24 Ag assay, in reality the societal savings associated with earlier infant diagnosis were so large that even standard HIV DNA PCR testing at six weeks would also prove cost-effective in the long term.

The costing data led to adoption of early infant diagnosis as national policy by the South African Department of Health in 2004. Subsequently, early infant diagnosis has been adopted as policy by many other countries in sub-Saharan Africa.

Evaluation of HIV tests and development of an algorithm for HIV serodiagnosis in Burkina Faso

This study, conducted by Dr. Wamarou Traore of the National AIDS & STIs Council was chosen for funding because Burkina Faso had an HIV prevalence of 2.7% (2003), complicated by the coexistence of HIV1 subtype O and HIV2. Testing was considered necessary not only for HIV diagnosis but also to ensure the safety of blood for transfusion and for purposes of epidemiological surveillance.



The study objectives were to evaluate the validity of ELISA and rapid tests to detect HIV antibodies in the Burkina Faso context and to propose a national algorithm to guide diagnosis of HIV infection.

A total of 450 blood samples were collected from four centers. Fifty percent were from infected patients. Fourteen different tests were used: four mixed ELISA tests, including two that detected HIV, HBV and HCV; six mixed rapid tests; and four rapid tests capable of discriminating between HIV-1 and HIV-2. They were tested and compared with the gold standard: Chiron RIBA SA.

Sensitivity and specificity were determined for all tests. Three of the four ELISA and three of the six rapid tests had good sensitivity ($\geq 99\%$). Two of the four discriminating rapid tests had good sensitivity ($\geq 99\%$) and three were very specific ($> 95\%$).⁽²⁴⁾

On the basis of these results, three algorithms were proposed and were accepted by the Ministry of Health in Burkina Faso:

For blood safety: Use only one test with a high sensitivity.

For epidemic surveillance: Use World Health Organization (WHO) strategy II of mixed ELISA or mixed rapid test with high sensitivity, with subsequent confirmation by a second discriminating rapid test.

For diagnosis, VCT, PMCT, TB-HIV and accidents involving blood: Also use WHO strategy II.

Monitoring

Affordable CD4 measurement

Dr. Debbie Glencross of the University of the Witwatersrand, Johannesburg, was funded by STF to develop a more affordable means of determining CD4 counts, which remains to this day a critically important means of monitoring HIV patients' immunological status.

At the time of the granting of the funds in 2001, North American and European guidelines for dual-platform flow cytometry recommended that absolute CD4 T-cell counts be calculated from two parameters: the absolute lymphocyte counts obtained on a hematology analyzer and the percentages of CD4+ cells among lymphocytes obtained by flow cytometry. This meant that CD4 counts were measured by differentiating between the different types of white blood cells,



counting them and then mathematically calculating the number of CD4 cells in each millionth of a liter of blood. These methods were cumbersome, labor-intensive, and error prone. The main source of the inaccuracy comes from the poor match between the common denominators in the two systems.

The new technique developed by Dr. Glencross was a PanLeucogated CD4 technique that measured all white blood cells (as opposed to just certain types) and used that measurement in the mathematical equation to improve the precision of dual-platform absolute CD4 counting.

The results, published in *Clinical Cytometry* in 2002,⁽²⁵⁾ indicated that dual-platform leukocyte counts could replace lymphocyte counts as the common denominator. The method was shown to be as accurate as the single-platform volumetric techniques, but it lowered the costs of CD4 tests by almost two-thirds. In addition, the technique was validated by the World Health Organization and was quickly adopted by South Africa's National Health Laboratory Service in Cape Town and Johannesburg.

Dynabeads technique for decentralized CD4 monitoring

A frequent issue in sub-Saharan Africa concerns the difficulties of ensuring the affordable monitoring of patients who live in remote areas. STF funded a project under the supervision of Dr. Papa Alassane Diaw in Senegal to determine the feasibility of decentralizing CD4 count monitoring by utilizing Dynabeads. Dynabeads are superparamagnetic, monosized polymer particles with a consistent, defined surface for the absorption or coupling of bioreactive molecules or cells. The measurement of CD4 using Dynabeads is inexpensive (approximately \$7 per test) and relatively easy to perform. Hospital laboratories in five regions of Senegal were involved. After training, decentralized CD4 measurement was implemented with procedures for quality control from a central reference laboratory. The project was successful and led to adoption of the technique by the Senegalese National AIDS Control Program to accompany AIDS treatment throughout the country.

Dried blood spot technique for virological monitoring

Viral load measurement is not available in most sub-Saharan Africa countries. However, STF considered it important to investigate possibilities of making it more accessible and funded in Senegal a study using a dried blood spot technique, conducted by Dr. Coumba Toure-Kane and colleagues. The objective was to determine whether a dried blood spot technique would yield results similar to



those of tests using whole blood or plasma. The advantage of dried blood spot techniques is that samples can be taken easily in remote locations and subsequently easily stored and transported without the need for freezing. The costs are accordingly also reduced.

Blood samples were obtained from 20 HIV-1-positive patients and 3 control subjects. Viral load determinations were made on correctly stored plasma samples of this blood and on dried blood spots from the same patients on days 1, 8, and 15 after taking the blood. Excellent concordance between plasma and dried blood spot measurements was observed, even after incubation of the latter for 15 days at 37°C.⁽²⁶⁾ There could be considerable potential for exploiting this dried blood spot technique in resource-limited settings in the future.

TREATMENT AND CARE

Opportunistic infections

Diagnosis of tuberculosis

STF funded several targeted studies involving opportunistic infections. Perhaps the most important involved tuberculosis (TB), because TB has been estimated to be the most common cause of death in patients with HIV/AIDS in sub-Saharan Africa.⁽²⁷⁾ Diagnosis of TB in HIV/AIDS patients is complicated by the fact that it is often smear negative. In other words, sputum examination often fails to yield mycobacteria. In addition, in resource-limited settings, diagnosis based on sputum microscopy or chest radiography is unreliable. STF funded Dr. Douglas Wilson of GF Jooste Hospital, Cape Town, to develop a clinical algorithm that would facilitate diagnosis of smear-negative TB. Initially, an algorithm was developed and piloted.⁽²⁸⁾ The algorithm is displayed in the figure on page 21.

In a subsequent study, 58 HIV/AIDS patients with suspected smear-negative TB were identified using this algorithm and were initiated on anti-TB therapy. This occurred on average 19.5 days before culture reports were received. For 32 of the 58 patients the culture reports subsequently proved positive. For a further 21 patients, clinical improvement was documented on empirical TB therapy. The algorithm, therefore, allowed earlier initiation of TB therapy in patients presenting with symptoms of pulmonary TB and negative smears or nonproductive cough in a setting of high TB incidence.⁽²⁹⁾



Figure 2: Smear-negative-TB algorithm

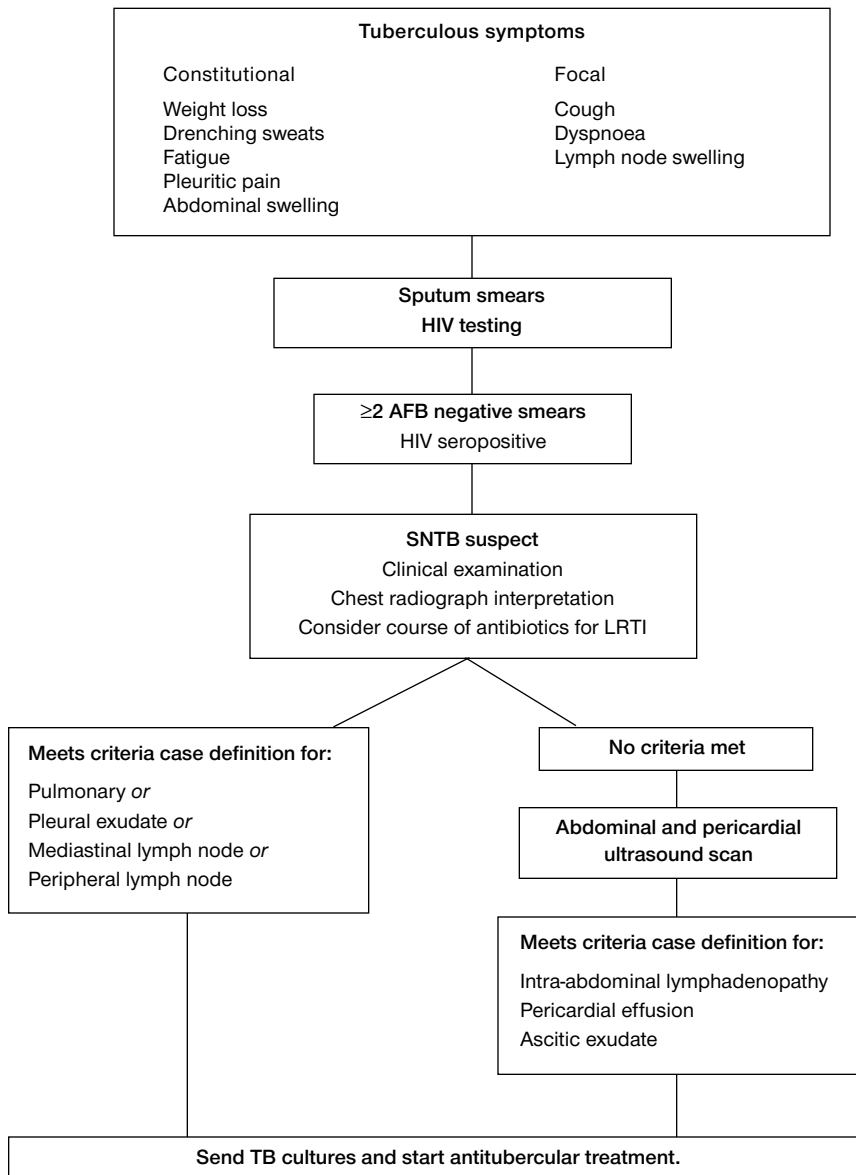


Table 5: Tuberculosis incidence and cases averted, stratified by baseline CD4 count, WHO stage, and socioeconomic status.

| | HAART | | | Non-HAART | | | Adjusted Risk Ratio (95% CI) | p | Adjusted Number of Cases Averted (95% CI) |
|-----------------------------|---------------------------------|---------------|------------|---------------------------------|---------------|------------|------------------------------|---------|---|
| | Number of cases of tuberculosis | Patient-years | Incidence* | Number of cases of tuberculosis | Patient-years | Incidence* | | | |
| Overall | 9 | 375.1 | 2.4 | 82 | 848.2 | 9.7 | 0.19 (0.09–0.38) | <0.0001 | 7.3 (4.7–9.8) |
| CD4 count (cells/μL) | | | | | | | | | |
| <200 | 5 | 148 | 3.4 | 41 | 235 | 17.5 | 0.18 (0.07–0.47) | <0.0001 | 14.2 (9.7–19.7) |
| 200–350 | 2 | 121.2 | 1.7 | 27 | 225 | 12.0 | 0.12 (0.03–0.53) | <0.0001 | 10.6 (6.8–15.9) |
| >350 | 2 | 100.1 | 2.0 | 14 | 388.3 | 3.6 | 0.36 (0.1–1.74) | 0.78 | 2.3 (1.1–4.4) |
| WHO stage | | | | | | | | | |
| 1 or 2 | 1 | 219 | 0.5 | 36 | 657.4 | 5.5 | 0.08 (0.01–0.57) | 0.01 | 5.1 (3.45–7.1) |
| 3 or 4 | 8 | 172.75 | 4.6 | 46 | 190.8 | 24.1 | 0.22 (0.09–0.41) | 0.03 | 18.8 (13.2–26.1) |
| Socioeconomic status | | | | | | | | | |
| Low | 6 | 166.21 | 3.6 | 65 | 514.34 | 10.9 | 0.21 (0.09–0.49) | <0.0001 | 8.6 (6.2–11.5) |
| High | 3 | 208.9 | 1.4 | 17 | 333.86 | 5.09 | 0.17 (0.05–0.57) | <0.0001 | 4.2 (2.3–7.0) |

*Per 100 patient years.

A further study demonstrated the value of using an expanded list of case definitions for smear-negative pulmonary TB and extrapulmonary TB.⁽³⁰⁾ The expanded case definitions were based on WHO guidelines⁽³¹⁾ and South African national guidelines developed by expert consensus. They included pulmonary signs and precise definitions of lymphadenopathy, serositis and constitutional syndrome. In a sample of 147 patients, the positive predictive value for the most common case definitions ranged from 89% to 96%. Criteria for clinically relevant responses to anti-TB therapy were also derived and two or more of them were reached at eight weeks of treatment in 97.5% of subjects with confirmed TB, 91.3% of subjects with possible TB and none of the subjects without TB.

These studies, therefore, demonstrated the value of the algorithm for diagnosis of smear-negative TB and early initiation of anti-TB therapy.

Treatment of tuberculosis

A study by Dr. Motasim Badri et al. conducted at Somerset Hospital, University of Cape Town in South Africa, investigated the risk of developing TB in 264 patients on HAART and in 770 non-HAART patients.⁽³²⁾ Overall HAART was associated with a lower incidence of TB (2.4 versus 9.7 cases per 100 patient-years, $p < 0.0001$), equivalent to a reduction of more than 80%. The number of cases averted was greatest in patients with WHO stage 3 or 4 HIV disease and in those with CD4 counts of less than 200 cells/ μ L.



Respiratory disease:

Prof. K. Klugman and Dr. S. Madhi of Chris Hani Baragwanath Hospital and the University of the Witwatersrand elucidated the burden of diseases caused by respiratory viruses and *Pneumocystis carinii* in children with HIV. At Chris Hani Baragwanath Hospital in 2000, the antenatal seroprevalence rate at the hospital and its associated clinics was 27.8%, which meant that an estimated 1,700 infants of the 24,000 born annually within the system were HIV positive. The outcome of respiratory syncytial virus (RSV) associated lower respiratory tract infections (LRTIs) in HIV-infected children had not previously been well described.

A total of 268 children were enrolled in a prospective study. Nasopharyngeal aspirates were obtained from children within 24 hours of admission. The prevalence of HIV infection was found to be 14.6% (39 of 268) in children with RSV-associated severe LRTI, and HIV-infected children were older than were HIV-uninfected children. Their average age was 7 years, as opposed to 4 months for children who were HIV uninfected ($p = 0.003$). HIV-infected children were found more likely to present with pneumonia than HIV-uninfected children (92.3% versus 68.6%, respectively, $p < 0.002$). In addition, concurrent bacteremia, axillary temperatures of $>38^{\circ}\text{C}$ and leukocyte count $>15\,000/\text{mm}^3$ occurred more commonly in HIV-infected children. The case fatality rate was also greater in HIV-infected than in HIV-uninfected children (7.6% versus 1.7%).⁽³³⁾

It was concluded that HIV-infected children remain predisposed to developing RSV-associated severe LRTI beyond the first six months of life and are more likely to present with pneumonia, to have greater evidence of bacterial coinfection and to experience greater mortality than HIV-uninfected children.

HAART

Cost-effectiveness of HAART

In 1999 when STF was launched, HAART was not available in sub-Saharan Africa through the public health service. In 2001, the major pharmaceutical companies reduced the cost of ARVs in the region to no-profit pricing, which is determined by the cost of goods. In addition, key international players such as the Global Fund committed large sums for the provision of HAART in developing countries worldwide. The scale of the epidemic, nonetheless, implied that proof of the cost-effectiveness of HAART in resource-limited settings could encourage governments

Table 6: Incremental cost-effectiveness ratio (US \$) for current ART rollout prices (US \$730 per annum—scenario 1) and anticipated tender prices (US \$181 per annum—scenario 2), comparing HAART and no-ART groups for non-AIDS and AIDS groups at 25th, 50th (median), and 75th progression-free times percentiles.

| Survival Quartile | Group | Survival Time | ICER (95% CI) | |
|-------------------|----------|----------------|-------------------------|-------------------------|
| | | | Scenario 1 ^a | Scenario 2 ^b |
| 25% | Non-AIDS | HAART (1391) | \$1,578 (1,557 – 1,581) | \$698 (676 – 701) |
| | | no ART (523) | | |
| | AIDS | HAART (739) | \$71 (43 – 111) | Cost-saving |
| | | no ART (309) | | |
| Median 50% | Non-AIDS | HAART (2,641) | \$1,622 (1607 – 1,627) | \$675 (659 – 679) |
| | | no ART (1,111) | | |
| | AIDS | HAART (1,120) | Cost saving | Cost saving |
| | | no ART (510) | | |
| 75% | Non-AIDS | HAART (3,891) | \$1,759 (1,748 – 1,722) | \$608 (597– 621) |
| | | no ART (2,035) | | |
| | AIDS | HAART (1,561) | Cost saving | Cost saving |
| | | no ART (980) | | |

a: Current rollout prices.
b: Anticipated tender prices.
c: CER = incremental cost-effectiveness ratio.

in the region to begin comprehensive roll out. To this end, STF funded a study conducted by Prof. Robin Wood and colleagues of the University of Cape Town in South Africa.⁽³⁴⁾

The study compared the costs and benefits between individuals receiving HAART and individuals not receiving HAART in a cohort of individuals infected with HIV in South Africa. Patients who participated in clinical trials and who received at least three ART drugs were considered the “treated arm” of the study. Patients who did not participate in these trials and who never had access to ART throughout the study period but who received other HIV-related care constituted the sample from which a “comparator” group was identified.

Statistical adjustment was made for important differences between the cohorts, such as age, socioeconomic status, and CD4 count. The authors concluded that individuals on HAART not only live longer, but also may have lower costs, depending on the price structure assumed for HAART. With the pricing of HAART (\$730 per patient-year) at the time of the study, the incremental cost-effectiveness



of HAART versus no HAART was \$1,622 per additional life-year gained for individuals without AIDS. For individuals with AIDS, HAART would be cost-saving at that price.

The analysis suggested that providing HAART in South Africa would be relatively cost-effective for individuals without AIDS and even cost-saving for individuals with AIDS, assuming current drug prices. In addition, if the price of HAART medications were to decrease further through local production, the cost-effectiveness of HAART for individuals without AIDS would become substantially more favorable. Therefore, these results supported providing HAART for individuals with HIV in South Africa.

Community-Based Treatment Support Model of HAART

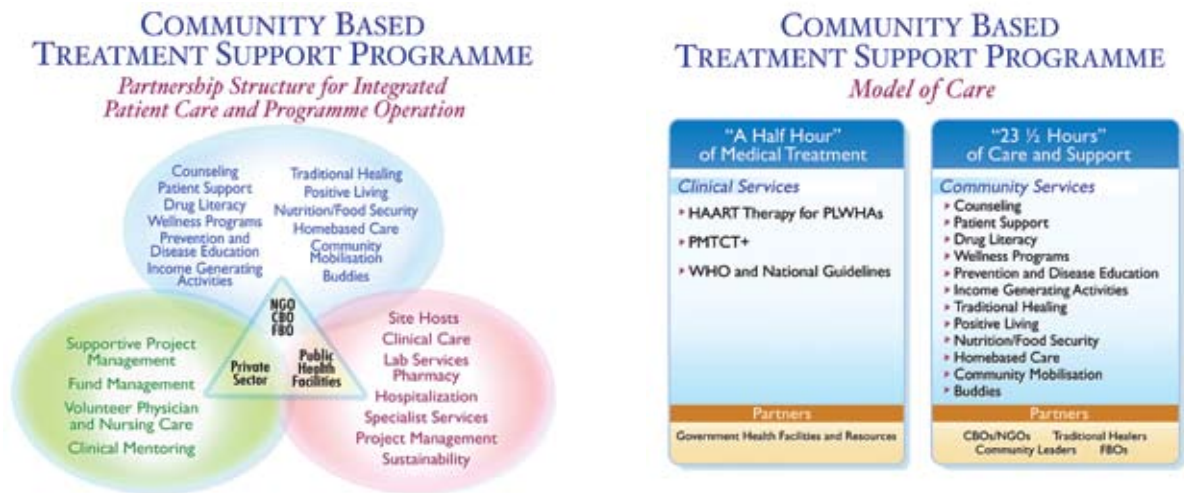
By 2002, it had become evident that the five southern African countries in which STF was active were poised to implement the roll out of HAART through the public health system with the assistance of international funding. STF was at the vanguard of that effort. Based on its extensive experience with community programs supporting patients with HIV/AIDS in those countries, the STF team hypothesized that the effectiveness of HAART in resource-limited settings would be enhanced if patients received appropriate community support in addition to the clinical care provided at hospitals and clinics. The Community-Based Treatment Support (CBTS) model was therefore created and was implemented in Katima-Mulilo in Namibia; in Ladysmith in South Africa; in Maseru in Lesotho; and in Bobonong in Botswana. The programs were complemented by operational research designed to evaluate feasibility, clinical outcomes and the added value of community support to clinical outcomes.

The CBTS model emphasized that people living with HIV/AIDS (PLWHA) in resource-limited settings need both clinical services and community services to effectively enhance their quality of life and outcomes—over the short and long terms. Instead of focusing solely on antiretroviral treatment as a means of reducing mortality rates, the model stressed supportive services like food security and home-based care to help PLWHA manage their chronic HIV disease outside the clinic: in their homes and communities. The program leveraged the strengths of government, private-sector and community-based organizations to offer true continuum of care or, as STF referred to it, “23½ hours” (between clinic appointments) of disease management and psychosocial support that take place in the patient’s home and community following a “half hour” of medical care in the clinic.



As shown in the figure below, all of the providers in this approach, whether serving clients in the clinic or in the community, acted as members of an integrated implementation team.

Figure 3: Community-based treatment support Model of Partnership and Care



The effectiveness of the CBTS model was demonstrated over a three-year period with compelling results. Clinical outcomes and the added value of community support were evaluated by rigorous collection of data according to protocols developed by STF and Family Health International.

An intent-to-treat analysis from the first 941 patients on ARV therapy for 12 months at sites in Botswana, Lesotho, Namibia and South Africa and showed an overall efficacy of 64%, where efficacy was defined as a sustainable, greater-than-50 increase in CD4 count and where all patients failing to reach that increase in CD4 and all deaths, discontinuations and lost-to-follow-up patients were considered as failures. The overall survival rate at 12 months was 84.4%.⁽³⁵⁾ The data also demonstrated adherence rates either similar to or better than those in the United States.



On a subset of 578 patients, the Enhanced Patient Evaluation investigated the added value of community support. The evaluation found that CD4 counts increased to significantly higher levels in patients on ARVs who accessed community support than in those on ARVs who did not: 326 versus 268.

Findings from the program also included:

Increased voluntary counseling and testing and clinical uptake:

- Overall, the uptake of VCT increased approximately 10-fold within two to three months from the start of community mobilization, according to records kept at VCT centers. Uptake of clinic services mirrored that result. By November 2006, more than 16,000 patients had been enrolled.

Excellent adherence:

- At 12 months, participants receiving HBC and/or food support had a higher adherence rate (67%) than those who did not receive those services (58%).

The added value of community support:

- CD4 counts increased to significantly higher levels in patients on ARVs who accessed community support than in those on ARVs who did not: 326 versus 268.⁽³⁵⁾
- Patients satisfied with the level of community support they received also experienced better quality of life and adhered better to their ARV medication than those who were not satisfied.
- Home-based care was the service statistically significant in better adherence.
- The lost-to-follow-up rate in the program was only 5.1% compared with 10% to 20% reported from other comparable ARV sites in South Africa.
- Community services helped prepare patients for antiretroviral therapy and leveled the playing field by dealing with psychosocial problems, inadequate nutrition and logistical issues such as transport to the clinic and disclosure of status to a significant other.

The program found that with community mobilization and support, a patient is more likely to present for testing and treatment, will be better prepared to begin and adhere to ARV therapy, is less likely to default and is more likely to have a better clinical outcome.



FUTURE DEVELOPMENTS

STF-funded research is continuing to produce results. Several long-term studies are either still ongoing or finished and awaiting final analysis. The most important of them are the following:

- The Adult Antiretroviral Treatment and Resistance Study, or the Tshepo Study, conducted by the Harvard AIDS group at Princess Marina Hospital in Gaborone, Botswana. This is the first large-scale research study of antiretroviral therapy to treat AIDS and HIV infection in Botswana. The Tshepo Study is an open-label, randomized study comparing (1) the rate of development and specific types of drug resistance mutations with various antiretroviral combination therapies to HIV-1C, the subtype of HIV found in southern Africa, and (2) the short- and long-term effectiveness of two operational modifications of directly observed therapy (DOT) medication adherence strategies for antiretroviral therapy. Specifically, treatment follow-up via the Standard of Care, the national standard of care as it evolves in Botswana, with intensive clinic-based follow-up including regular adherence education sessions, will be compared with Community-Based Directly Observed Therapy (Com-DOT). Com-DOT involves the Standard of Care with added community or family-based DOT. This Com-DOT component would involve a trained, community- or family-based medication partner (“mopati”) who observes the patient taking medications daily. The study is complete and analysis is under way.
- Efficacy of Primary Isoniazid (INH) Prophylaxis in Increasing Tuberculosis (TB)-Free Survival in HIV-Infected (HIV+) South African Children. This study, conducted by Dr. S. Madhi of the University of the Witwatersrand and colleagues, has been completed and analyzed. Results were published in an abstract at the Interscience Conference on Antimicrobial Agents and Chemotherapy in 2008 but await peer review for journal publication.



- The Botswana-Baylor Antiretroviral Assessment (BANA) trial. This study is being conducted by Prof. Gabriel Anabwani and colleagues at the BIPAI Children's Center of Excellence in Gaborone, Botswana. It is the only ongoing study of the efficacy and safety of structured treatment interruption in children. As such it will provide critically important information. The Strategies for Management of Anti-Retroviral Therapy trial in adults yielded negative data, indicating that structured treatment interruption was less efficacious than continuous HAART and was not associated with a better safety profile.⁽³⁶⁾ The BANA trial has been closely supervised by a Data and Safety Monitoring Board, which to date has found no reason to terminate the trial prematurely. Enrollment is complete and the study will end and be analyzed in 2009.
- In West Africa, the Natural History of Malaria in HIV-1+ Patients on Early Chemoprophylaxis with Cotrimoxazole. The objectives are to describe the natural history of malaria in HIV-infected patients taking daily doses of cotrimoxazole in a regimen of early prevention of opportunistic infections and to evaluate the efficacy of that prophylaxis on the malaria itself.

The GRANTS of STF

(as of December 2003)

Since 1999, 144 operational research grants have been awarded, totaling more than US \$70 million. They run the gamut from theatrical troupes that tour villages to promote HIV education and awareness and sex education and awareness, to programs that offer economic opportunities and training for the grandmothers who have now become the caregivers for many of the millions of AIDS orphans in the region. New, lower-cost tests to monitor HIV blood levels have been developed. New approaches to prevent mother-to-child HIV transmission and treat opportunistic infections as well as operational research involving ARV have been explored. Programs that help orphans deal with the loss of their parents have been established. Public health fellowships have been funded. Lay health workers have been trained. Parish nurses have been given new tools to counsel and care for the sick and dying – and the survivors left behind. Home-based-care solutions have been developed. Counseling programs have been funded. Orphans have been cared for. Capacity has been built. And various forms of community outreach have been encouraged.

Southern Africa – Medical Research Grants

Operational Research Involving ARV

| INSTITUTION | TITLE |
|---|---|
| 1. Botswana-Baylor Children's Clinical Center of Excellence, Princess Marina Hospital, Botswana | The BANA 2 (Children) Trial. A randomized, comparative trial of continuous versus intermittent highly active antiretroviral therapy |
| 2. Botswana-Baylor Partnership, Princess Marina Hospital, Botswana | A pilot trial in Gaborone, Botswana, of long-term therapy with stavudine (d4T) plus didanosine (ddl) versus stavudine plus didanosine plus hydroxyurea (HU) in HIV-infected infants and children (the BANA trial) |
| 3. Botswana-Harvard Partnership, Princess Marina Hospital, Botswana | An adult antiretroviral treatment and resistance study (the Tshepo Study): emergence of HIV-1C nucleoside drug resistance impact on maternal-infant transmission in Botswana |

Operational Research Involving ARV

| INSTITUTION | TITLE |
|--|---|
| 4. Botswana-Harvard Partnership, Princess Marina Hospital, Botswana | Pregnant women's acceptance or rejection of the prevention of HIV transmission from a mother-to-child program (PMTCT) in Gaborone, Botswana |
| 5. Children's Infectious Diseases Clinical Research Unit, Tygerberg Children's Hospital, Stellenbosch University, South Africa | An evaluation of CD4+ and CD8+ T-cell apoptosis as surrogate markers for monitoring progression of disease in HIV-1-infected children: a single-center study |
| 6. Department of Pediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa | Antiretroviral therapy: guidelines for the treatment of a cohort of HIV-infected children and their infected parents at Red Cross Children's Hospital (Study Extension for ARV treatment for patients on both micronutrient study RES094-02 and a TB study) |
| 7. Department of Obstetrics and Gynaecology, University of Cape Town, South Africa | Management of abnormal cytology in HIV-1-infected women (MACH-1) |
| 8. Department of Pediatrics and Child Health, University of Natal, South Africa | Assessment of intermittent and pulse ARV regimens used for HIV-infected newborns and children in Durban, South Africa |
| 9. Department of Pediatrics and Child Health, University of Natal, South Africa | Induction and augmentation of protective immune responses to achieve effective and durable control of HIV in adult and pediatric infection in sub-Saharan Africa |
| 10. National Health Laboratory Services, UCT Clinical Virology Laboratory and School of Child and Adolescent Health, University of Cape Town, South Africa | Field testing of the use of dried blood spot-based viral load assays to monitor ART in children |
| 11. South African Institute of Medical Research and University of the Witwatersrand, South Africa | The impact of an early diagnosis of HIV infection status in vertically exposed infants on the management of pediatric HIV: a multi-center study to explore cost-effective solutions in the South African setting |

Trials in Opportunistic Infections

| INSTITUTION | TITLE |
|--|---|
| 12. Department of Obstetrics and Gynecology, University of Natal, South Africa | Prophylactic intrapartum antibiotics for delivery in HIV-positive women |
| 13. Department of Pediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa | The pharmacokinetics of oral cotrimoxazole in HIV-infected children: phase 1 |
| 14. Department of Pediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa | The pharmacokinetics and efficacy of oral compared with intravenous trimethoprim-sulphamethoxazole (TMP-SMZ) for treatment of <i>Pneumocystis carinii</i> in HIV-infected children (phase 2) |
| 15. Diana Princess of Wales HIV Research Foundation, New Somerset Hospital, South Africa | The cost-effectiveness of HIV/AIDS treatment in the Western Cape, South Africa |
| 16. Diana Princess of Wales HIV Research Foundation, New Somerset Hospital, South Africa | The cost-effectiveness of HIV/AIDS treatment in the Western Cape, South Africa (Extension) |
| 17. Division of Medical Virology, University of Cape Town, South Africa | An investigation into the relationship between HIV-1 injectable progestogen contraceptives, cervical cancer and sexually transmitted infections |
| 18. Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, University of the Witwatersrand, South Africa | Establishing the prevalence of viral hepatitis B and C infection in newly diagnosed HIV-infected patients so as to support the routine screening of these tests in these patients |
| 19. uMngeni AIDS Center, KwaZulu-Natal, South Africa | The impact of incorporating relevant health care options into education and counseling programs |
| 20. University of the Witwatersrand, South Africa | Burden of disease caused by respiratory viruses and South Africa <i>Pneumocystis carinii</i> pneumonia in African HIV-infected children hospitalized for acute lower respiratory tract infections |

Trials of Self-Care, Nutrition and Other ARV Therapies

| INSTITUTION | TITLE |
|---|---|
| 21. City of Tygerberg, Cape Town, and the Child Health Unit, School of Child and Adolescent Health, University of Cape Town, South Africa | The role of tactile stimulation in infants born to HIV-infected mothers in Khayelitsha, Cape Town, South Africa |
| 22. Department of Community Health Systems, School of Nursing, University of California, United States | Self-care symptom management for persons with HIV disease |
| 23. Department of Pediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa | The use of zinc and a trace element mixture plus multivitamin supplement to reduce morbidity in HIV-infected children in Cape Town: an efficacy study (the micronutrient study) |
| 24. National Food Technology Research Center, Botswana | Phase 1: fortification trials of sorghum flour in Botswana Phase 2: the effect of fortified sorghum meal on weight changes and nutrition-related side effects of HIV-positive adults in Botswana |
| 25. Research for the Future, Cape Town, South Africa | How to counsel on infant-feeding practices in southern Africa in a time of HIV/AIDS |

Trials in Mother-to-Child-Transmission

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| 26. Botswana-Harvard Partnership, Princess Marina Hospital, Botswana | Male involvement in mother-to-child HIV transmission prevention in Botswana: maximizing support to the program |
| 27. Department of Pediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa | Acceptability study of a district health service intervention designed to reduce mother-to-child HIV transmission |
| 28. Department of Pediatrics and Child Health, University of Natal, South Africa | HIV seroconversion among women: prevention, diagnosis and mother-to-child transmission of HIV in KwaZulu-Natal, South Africa |

Trials in Mother-to-Child-Transmission

| INSTITUTION | TITLE |
|--|--|
| 29. Department of Pediatrics, Coronation Women and Children's Hospital and University of the Witwatersrand, South Africa | Clinical relevance of nevirapine resistance for the treatment of HIV-infected children exposed to nevirapine through prevention-of-mother-to-child transmission programs |
| 30. National Institute for Communicable Diseases, South Africa | HIV drug resistance in pregnant women and their infants: effects of short-course antiretroviral treatment to prevent perinatal transmission (phase 1) |
| 31. National Institute for Communicable Diseases, South Africa | HIV drug resistance in pregnant women and their infants: effects of short-course ARV; addendum to proposal RES004-02, was previously RES004-12 |
| 32. Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital; University of the Witwatersrand; and University of Cape Town, South Africa | A randomized control study to assess the role of postexposure prophylaxis in reducing mother-to-child transmission of HIV-1 in infants born to mothers without access to antiretroviral therapy; expansion to include a Cape Town site |
| 33. Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, University of the Witwatersrand, South Africa | A randomized control study to assess the role of postexposure prophylaxis in reducing mother-to-child transmission of HIV-1 in infants born without access to antiretroviral therapy |

Trials in TB

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|--|---|
| 34. Department of Pediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa | Natural history of TB-HIV interaction in children |
| 35. E-Agency, Cape Town, South Africa | A pilot study for the development, implementation and evaluation of enhanced informed-consent documentation and processes for smear-negative TB in HIV-positive adults; trial in a developing country |
| 36. Infectious Diseases Research Unit, UCT Lung Institute, University of Cape Town, South Africa | A multicenter study to evaluate an algorithm for the diagnosis of smear-negative tuberculosis in high-HIV-prevalence settings |

Trials in TB

| INSTITUTION | TITLE |
|--|---|
| 37. Infectious Diseases Research UNIT, UCT Lung Institute, University of Cape Town, South Africa | Deriving an accurate and cost-effective approach to the diagnosis of smear-negative tuberculosis in HIV-infected adults in a developing country |
| 38. Pediatric Infectious Disease Research Unit, University of the Witwatersrand, South Africa | Evaluation of the efficacy of isoniazid prophylaxis in preventing tuberculosis and the effectiveness of cotrimoxazole in reducing the burden of <i>Pneumocystis carinii</i> pneumonia in African children |

Training/Education or Capacity Building

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| 39. Baylor College of Medicine Botswana Government, Princess Marina Hospital, Botswana | Botswana-Baylor Children's Clinical Center of Excellence |
| 40. Baylor College of Medicine, Texas Children's Hospital, United States | Baylor International AIDS Initiative <i>SECURE THE FUTURE</i> ® Health Care Professionals Education Program South Africa, Swaziland, Lesotho, Botswana |
| 41. Baylor College of Medicine, Texas Children's Hospital, United States | Expansion and implementation plan for the 14 Southern African Development Community nations |
| 42. Baylor College of Medicine, Texas Children's Hospital, United States | Bidirectional Physician Exchange Program |
| 43. Baylor College of Medicine, Texas Children's Hospital, United States | Art therapy for treating depression in children orphaned by HIV/AIDS |
| 44. Botswana-Harvard Partnership, Princess Marina Hospital, Botswana | Establishment and staffing of the HIV/AIDS Reference Laboratory in Gaborone, Botswana |
| 45. Department of Community Dentistry, University of Stellenbosch, South Africa | Oral HIV/AIDS education, diagnosis and training program for oral-health personnel |
| 46. Division of Bioethics, University of the Witwatersrand, South Africa | HIV/AIDS: ethical and legal issues |

Training/Education or Capacity Building

| INSTITUTION | TITLE |
|---|---|
| 47. International Association of Physicians in AIDS Care (IAPAC), United States | I-Med Exchange Program |
| 48. Medical Research Council of South Africa, South Africa | Establishing an information portal as an integrated system incorporating global health information initiatives related to HIV/AIDS for the benefit of Southern African Development Community countries, with a view toward rolling out into other African countries |
| 49. Swaziland Nursing Association, Swaziland | SNA HIV/AIDS training program application for implementation fund |
| 50. Youth AIDS Project, Claremont, Cape Town, South Africa | Youth AIDS Project |

Laboratory Studies

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|---|--|
| 51. Department of Medical Microbiology, University of Stellenbosch, South Africa | Antibiotic resistance and strain typing of <i>Pneumocystis carinii</i> |
| 52. Department of Pediatrics and Child Health, University of Natal, South Africa | Cell-associated virus in breast milk of HIV-seropositive women |
| 53. Department of Pharmacology, University of the Western Cape, South Africa | The feasibility of performing rapid HIV testing in community pharmacies: a pilot study in the Western Cape |
| 54. National Institute for Communicable Diseases and University of the Witwatersrand, South Africa | Preclinical studies on the effectiveness of a new class of antiretroviral drugs targeting the coreceptor or binding regions of HIV-1 subtype C viruses |
| 55. National Institute for Communicable Diseases, South Africa | Development of rapid screening method for the detection of NVP resistance mutations in the HIV-1 subtype C reverse transcriptase gene |
| 56. Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, University of the Witwatersrand, South Africa | Rapid HIV saliva tests for the surveillance and clinical diagnosis of HIV infection in South African children 12 to 24 months of age |

Laboratory Studies

| INSTITUTION | TITLE |
|--|---|
| 57. School of Child and Adolescent Health, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa | Novel diagnostic tests for the diagnosis and monitoring of childhood and adult TB |
| 58. South African Institute for Medical Research and University of the Witwatersrand, South Africa | Affordable and accessible laboratory monitoring for HIV/AIDS |
| 59. South African Institute for Medical Research and University of the Witwatersrand, South Africa | CD4+ cell enumeration: use of CD45, CD3, CD4, and SS parameter gating without the necessity for a lymphocyte differential |

Psychosocial Studies

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|---|---|
| 60. Bethal Hospital, South Africa | A study to increase partner compliance of STD-diagnosed patients |
| 61. Center for Social Science Research, University of Cape Town, South Africa | Study of stigma and implications for people living with HIV |
| 62. Department of Psychiatry and Mental Health, University of Cape Town, South Africa | Risk, resilience and the psychosocial adjustment of adolescent AIDS orphans |
| 63. School of Oral Health Sciences Department of Community Dentistry, University of the Witwatersrand, South Africa | Traditional healers in the management of HIV/AIDS |
| 64. University of East Anglia, United Kingdom | An investigation into the nature and extent of the impact of AIDS on orphans: a study of conditions for orphans in rural and urban areas of Botswana and the implications for future poverty levels in Botswana |

Epidemiological Studies

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|---|--|
| 65. Department of Community Health, University of Stellenbosch, South Africa | The impact of TB, HIV, STD, hepatitis and substance abuse in correctional service institutions on women and children |
| 66. Medical Research Council—Burden of Disease Research Unit, South Africa. Cofunded by Global Health Forum for Research and UNICEF | Rapid AIDS mortality surveillance in South Africa |

West Africa — Medical Research Grants

Training/Education or Capacity Building

| INSTITUTION | TITLE |
|--|--|
| 1. Association of Assistant Pharmacists of Burkina Faso (APP) | Involvement of assistant pharmacists in dispensing antiretrovirals for care and treatment of people living with HIV/AIDS |
| 2. Association of Nurses in four <i>SECURE THE FUTURE</i> West Africa countries | Training on HIV care (Baylor curriculum) |
| 3. Cheikh Anta Diop University, Dakar | Biological retrovirology course for francophone Africa |
| 4. GERES (Study Group of Risks of Exposure to Infectious Agents) Cheick Anta Diop University Hospital, Dakar | Training in prevention of blood exposure accidents in Senegal |
| 5. GERES (Study Group of Risks of Exposure to Infectious Agents) University of Cocody, Côte d'Ivoire | Project on training in prevention risks associated with blood exposure accidents in Côte d'Ivoire |
| 6. Group for Continuing Medical Training on STI, HIV/AIDS and Infectious Diseases, Côte d'Ivoire | Program on training of health staff in prescribing and dispensing of antiretroviral drugs in Côte d'Ivoire |
| 7. IMEA: French Federative Institute of Tropical Medicine and International Health | International training in mediation in public health for improving access to prevention, care and observance of antiretroviral treatments |
| 8. Infectious and Tropical Diseases Unit, Treichville Teaching Hospital, Abidjan, Côte d'Ivoire and Infectious and Tropical Diseases Unit, Hôpital Saint-Antoine Paris, France | LIPO Africa Project: Incidence of the lipodystrophy syndrome and other clinicobiological anomalies associated with antiretroviral treatments among a cohort of HIV-infected patients from sub-Saharan Africa |
| 9. Point G National Hospital and National AIDS Control Program, Mali | Training course in prescription of antiretroviral drugs, organized in Bamako |
| 10. UFR Medical Sciences, Department of Infectious Diseases, University of Cocody, Côte d'Ivoire | HIV infection in sub-Saharan Africa: Catalogue |

Blood Safety

| INSTITUTION | TITLE |
|---|---|
| 11. Faculty of Medicine, Pharmacy and Dentistry, Bamako, Mali | Use of blood sparing techniques in surgical units of national hospitals in Mali |
| 12. Health Department, High Council for National AIDS Control, Burkina Faso | Evaluation of HIV tests in Burkina Faso |
| 13. UFR- Health Science University of Ouagadougou, Burkina Faso | Evaluation of a new algorithm including the detection of Hepatitis C Virus (HCV) when testing blood transmitted agents in view of ensuring greater blood safety in Burkina Faso |

Good Laboratory Practices

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| 14. Bacteriology and Virology Laboratory, Aristide Le Dantec Teaching Hospital, Dakar | Biological follow-up of patients infected with HIV-2 in Senegal |
| 15. Bacteriology and Virology Laboratory, Aristide Le Dantec Teaching Hospital, Dakar, Senegal | Decentralization of biological follow-up of patients on ARV using Dynabeads, a technique for counting CD4+ T lymphocytes |
| 16. Bacteriology and Virology Laboratory, Aristide Le Dantec Teaching Hospital, Dakar, Senegal | Using filter paper in virological follow-up of HIV-1 patients in Senegal |
| 17. Fann Hospital and Cheikh Anta Diop University, Dakar | Study of the validity of tuberculosis diagnosis on IFN- γ ELISPOT and its significance in setting up anti-tuberculosis chemoprophylaxis among PLWHA in Senegal (ELIPREV) |

Pediatric

| | |
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| 18. CREDOS (Center for Research, Studies and Documentation on Child Survival), Bamako, Mali | Follow-up of children born to HIV-positive mothers in Bamako and Koulikoro |
| 19. Synergy pour l'Enfance, Pikine and Pediatric Unit of HALD, Senegal | Integrated care and support program for HIV-infected children in Dakar |

Co-infections and Drug Resistance

| INSTITUTION | TITLE |
|--|---|
| 20. Infectious Diseases Unit of Treichville Teaching Hospital, Abidjan, Côte d'Ivoire | Clinical and pharmacokinetic study of efavirenz associated with stavudine and lamivudine in the HIV/tuberculosis co-infected African patient taking rifampicine in anti-tuberculosis treatment in Abidjan (Côte d'Ivoire) |
| 21. Infectious Diseases Unit of Treichville Teaching Hospital, Abidjan, Côte d'Ivoire | Natural history of malaria in HIV-1+ Patients on early chemoprophylaxis with co-trimoxazole |
| 22. UFR Health Science and Biochemistry and Microbiology Department, UFR Life and Earth Science, University of Ouagadougou, Burkina Faso. | Study on resistance of pathogenic mycobacteria to antitubercotics in Burkina Faso, a high HIV/AIDS prevalence country |

Other projects : Networking and Publication

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|---|---|
| 23. Infectious Diseases Unit, Fann Hospital, Dakar and Infectious Diseases Unit, Treichville Hospital, Abidjan, Côte d'Ivoire | Establishment of the African network of clinicians providing care and support for patients living with HIV/AIDS |
| 24. Mc Gill University, Canada for the International AIDS Society (IAS) | Participation in the establishment and functionality of an IAS online journal |

Southern Africa — Medical Research Technical Advisory Committee

(1999–2007)

Dr. Matheus Akuaake Chief Medical Officer, National AIDS Coordinating Program, Ministry of Health and Social Services, Namibia (2003)

Prof. Hussein (Jerry) Coovadia Professor of Pediatrics, Medical School, University of Natal, South Africa (1999–2000)

Dr. Mark Cotton Senior Specialist, University of Stellenbosch, South Africa (2002–2007)

Dr. Mulamba Diese Director, International Association of Physicians in AIDS Care, South Africa (2002–2007)

Prof. Vinodh Gathiram Professor of Infectious Diseases, Medical School, University of Natal, South Africa (1999–2000)

Dr. Glenda Gray Director, Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital and University of the Witwatersrand, South Africa (1999–2000)

Southern Africa — Medical Research Technical Advisory Committee

- Dr. Ashraf Grimwood** Principal Medical Officer, City of Cape Town, National Chair of Networking AIDS Community of South Africa (NACOSA), South Africa (1999)
- Prof. Allen Herman** Dean, National School of Public Health, Medical University of Southern Africa, South Africa (1999–2004)
- Prof. Mark W. Kline** Professor of Pediatrics, Baylor School of Medicine and Texas Children's Hospital, United States (1999–2007)
- Dr. John Kunene** Acting Deputy Director, Health Services, Ministry of Health and Social Welfare, Swaziland (1999–2007)
- Prof. Malegapuru Makgoba** President, Medical Research Council, South Africa (1999–2007)
- Dr. Joseph M. Makhema** Private Practitioner, Gaborone Private Hospital, Botswana (2001–2007)
- Dr. Nthabiseng Makoae** Research Specialist, National University of Lesotho, Lesotho (2000–2007)
- Dr. Richard Marlink** Executive Director, Harvard AIDS Institute, United States (1999–2007)
- Dr. Desmon Martin** President-elect, Southern African HIV Clinicians Society, South Africa (1999–2007)
- Dr. Nosisa Matsiliza** Senior Researcher, Liver Research Center, Groote Schuur Hospital, South Africa (2000)
- Dr. Tumelo Mazhani** Dental Specialist, Oral Health Services, Botswana (2000)
- Dr. Steve Miller** Director, Innovir Institute, South Africa (1999–2007)
- Dr. Howard Moffat** Hospital Superintendent, Princess Marina Hospital, Botswana (1999–2007)
- Dr. Maloali Mokotoko** Physician, Botswana (2000–2001)
- Dr. K. Mompoti** Private Physician, Botswana (2002–2007)
- Dr. Thlabi Moorosi** Director of Laboratory Services, Queen Elizabeth II Hospital, Lesotho (2000–2007)
- Dr. Victor Mtetwa** Dean of Science, University of Swaziland, Swaziland (2000–2007)
- Dr. Flavio Mugala-Mukungu** Head of Department of Internal Medicine, Head of STD/HIV Clinic, Chairperson of Treatment Advisory Committee of Antiretroviral Therapy, Ministry of Health and Social Services, Namibia (2001–2002)
- Dr. Joseph Saba** Clinical Research Specialist, UNAIDS. United States (1999–2000)
- Dr. Badara Samb** Formerly Care Advisor, UNAIDS, currently Advisor to the Director of the HIV Department, World Health Organization, Switzerland (2002–2007)
- Dr. Abdul Rauf Sayed** Biostatistician, University of Cape Town, South Africa (2002–2007)
- Dr. Nothemba Simelela** Director, Directorate HIV/AIDS and STIs, Department of Health, South Africa (1999–2007)
- Prof. Raymond A. Smego Jr.** Professor, Infectious Diseases, University of the Witwatersrand, South Africa (1999)
- Dr. Louis Sullivan** President, Morehouse School of Medicine, United States (1999–2004)
- Dr. Mark Wainberg** Director, International AIDS Society, McGill University AIDS Center, Canada (1999–2007)
- Dr. Jose Zuniga** President-elect, International Association of Physicians in AIDS Care, United States (1999–2002)

West Africa — Scientific Research Technical Advisory Committee

(2001–2009)

Prof. François Eba Aoussi Professor, Technical Advisor in charge of HIV/AIDS, Ministry of Health, Abidjan, Côte d'Ivoire (2001–2009)

Prof. Emmanuel Bissagnene Professor, Infectious and Tropical Diseases Unit, Treichville Teaching Hospital, Abidjan, Côte d'Ivoire (2001–2009)

Prof. Flabou Bougoudogo Director of the National Institute for Research on Public Health, Bamako, Mali (2004–2009)

Prof. Elisabeth Bouvet Professor, Bichat Claude Bernard Hospital, Paris, France (2001–2009)

Prof. Jean-Pierre Coulaud Professor, IMEA, Paris, France. (2001–2003)

Prof. Karidiatou Touré Coulibaly Professor (2001–2003)

Prof. Christian Courpotin Professor, Pediatrician, FESTI: International Solidarity against AIDS (2001–2009)

Prof. Pierre Dellamonica Professor, Infectious Diseases Unit, Archet Hospital, Nice, France (2001–2009)

Prof. Serge Paul Eholie Professor, Infectious and Tropical Diseases Unit, Treichville Teaching Hospital, Abidjan, Côte d'Ivoire (2001–2009)

Prof. Mame Awa Faye World Health Organization, Senegal (2001–2009)

Prof. Pierre Marie Girard Professor, Hôpital Saint-Antoine, Paris, France (2001–2009)

Prof. Christine Katlama Professor, Infectious Diseases Unit, Pitié-Salpêtrière Hospital, Paris, France (2001–2009)

Prof. Michel Kazatchkine Director, ANRS, Paris, France (2001–2003)

Prof. Marie Laga Professor, RETRO CI (2001–2002)

Dr. Roland Landman Physician, Bichat Claude Bernard Hospital, Paris, France (2001–2009)

Prof. Soulemayne M'boup President, AARN (African AIDS Research Network), Virology HALD (Aristide Le Dantec Teaching Hospital), Dakar, Senegal (2001–2009)

Dr. Badara Saamb UNAIDS, Geneva, Switzerland (2001–2002)

Dr. Paul Thomas Sanou World Health Organization, Côte d'Ivoire

Dr. Adrien Sawadogo Physician, Head of Médecine Interne, Bobo Dioulasso Hospital, Burkina Faso (2001–2009)

Prof. Papa Salif Sow Professor, Infectious and Tropical Diseases Unit, Fann Teaching Hospital, Dakar, Senegal (2001–2009)

Prof. Hamar Traore Professor, Head of Infectious Diseases Unit of Point G hospital, responsible for IMAARV (Malian Initiative for Access to ARV), Mali (2003–2009)

Dr. Wamarou Traore Head of Health Department, Permanent Secretary/High Council for National AIDS Control, Burkina Faso (2001–2009)

Dr. Mark Wainberg Director, McGill AIDS Center, McGill University, Montreal, Canada (2001–2009)

REFERENCES

1. The model can be downloaded from the Web page of the AIDS Committee of the Actuarial Society of South Africa: www.assa.org.za.
2. Bradshaw D, Schneider M, Dorrington R, Bourne D, Laubscher R. South African cause of death profile in transition – 1996 and future trends: *South African Medical Journal* 2002; 92(8): 618–623.
3. Dorrington R, Bourne D, Bradshaw D, Laubscher R, Timaeus I. The impact of HIV/AIDS on adult mortality in South Africa: South African MRC Burden of Disease Research Unit, 2001.
4. Dorrington R, Bradshaw D, Budlender D. HIV/AIDS profile in the provinces of South Africa. Indicators for 2002: South African MRC Burden of Disease Research Unit, 2002.
5. Bradshaw D, Groenewald P, Laubscher R. et al. Initial burden of disease estimates for South Africa 2002: South African MRC Burden of Disease Research Unit, March 2003.
6. HIV Curriculum for the Health Professional. Baylor International Pediatric AIDS Initiative, 2000; available from the BIPAI Web page: www.bayloraids.org.
7. Eholie S. et al. *Therapeutic Manual of HIV Infection in Sub-Saharan Africa* (in French).
8. Kline M, Ferris M, Jones D et al. The Pediatric AIDS Corps: Responding to the African HIV/AIDS Health Professional Resource Crisis: *Pediatrics* 2009;123(1), 134–136.
9. Sangare L. A new strategy of blood donations screening for HIV, HBV, *Treponema pallidum* and HCV to increase transfusional security in developing countries: Abstract accepted for the XVth International AIDS Conference, Bangkok, July 11–16, 2004.
10. Gray G, Urban M, Chersich M, Bolton C, van Niekerk R, Violari A, Stevens W, McIntyre J. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers: *AIDS* 2005, 19, 1289–1297.
11. Morris L, Bredell H, van Harmelen J, Ping L, et al. No evidence for naturally occurring resistance mutations to HIV-1 reverse-transcriptase inhibitors among South African HIV-1 subtype C isolates. *South African Journal of Science* 2000; 96, 369–370.
12. Morris L, Pillay C, Gray G, McIntyre J. HIV-1 drug resistance and mother-to-child transmission: *Journal of the South African Dental Association* 2001; 56, 614–616.
13. Pillay C, Bredell H, McIntyre J, Gray G, Morris L. HIV-1 subtype C reverse transcriptase sequences from drug-naïve pregnant women in South Africa: *AIDS Res. Hum. Retro.* 2002; 18: 605–610.
14. Loubser S, Balfe P, Sherman G, Hammer S, Kuhn L, Morris L. Loss of the nevirapine resistance mutation K103N in blood leukocyte DNA and plasma RNA after single-dose therapy for prevention of mother-to-child HIV transmission: *AIDS* 2006, 20, 643–651.
15. Shayne L, Balfe P, Sherman G, Hammer S, Kuhn L, Morris L. Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother-to-child HIV transmission: *AIDS* 2006, 20, 995–1002.
16. Pillay V, Ledwaba J, Hunt G, Rakgotho, M et al. Antiretroviral drug resistance surveillance among drug-naïve HIV-1-infected individuals in Gauteng Province, South Africa, in 2002 and 2004. *Antiviral Therapy* 2008, 13, 101–107.
17. Coovadia A, Hunt G, Abrams E, Sherman G, Meyers T, et al. Persistent minority K103N mutations among women exposed to single-dose nevirapine and virologic response to nonnucleoside reverse-transcriptase inhibitor–based therapy. *Clinical Infectious Diseases* 2009, 48, 462–472.
18. Kebaabetswe P. Barriers to participation in the prevention of mother-to-child HIV transmission program in Gaborone, Botswana; a qualitative approach. *AIDS Care* 2007, 19(3), 355–360.
19. Stringer E, Chi B, Chintu N, et al. Monitoring effectiveness of programs to prevent mother-to-child HIV transmission in lower-income countries. *Bulletin of the World Health Organization* 2008, 86(1).
20. Jones S, Sherman G, Varga C. Exploring socio-economic conditions and poor follow-up rates of HIV-exposed infants in Johannesburg, South Africa. *AIDS Care* 2005, 17(4), 466–470.

REFERENCES

21. Sherman G, Matsebula T, Jones S. Is early HIV testing of infants in poorly resourced prevention of mother to child transmission programs unaffordable? *Tropical Medicine & Internal Health* 2005, 10 (11), 1108–1113.
22. Sherman G, Cooper P, Coovadia A, et al. Polymerase chain reaction for diagnosis of human immunodeficiency virus infection in infancy in low resource settings. *Pediatric Infectious Disease Journal* 2005, 24(11), 993–997.
23. Patton J, Sherman G, Coovadia A, Stevens W, Meyers T. Ultrasensitive human immunodeficiency virus type 1 p24 antigen assay modified for use on dried whole-blood spots as a reliable, affordable test for infant diagnosis: *Clinical and Vaccine Immunology* 2006, 13(1), 152–155.
24. Traore W. Evaluation of HIV testing devices and production of algorithm for HIV sero-diagnosis in Burkina Faso. Abstract accepted for the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, July 24–27, 2005.
25. Glencross D, Scott L, Jani I, Barnett D, Janossy G. CD45-assisted panLeucogating for accurate, cost-effective dual-platform CD4+ T-cell enumeration. *Cytometry* 2002, 50(2), 69–77.
26. Toure Kane C, Diop Ndiaye H, Sada D, et al. Quantification of HIV-1 RNA in dried blood spots by the real-time NucliSENS Easy Q HIV-1 assay in Senegal. *Journal of Virologic Methods* 2008, 148, 291–295.
27. Harris A, Hargreaves N, Kemp J, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. *Lancet* 2001, 357, 1519–1523.
28. Wilson D, Nachega J, Chaisson R, Maartens G. Diagnostic yield of peripheral lymph node needle-core biopsies in HIV-infected adults with suspected smear-negative tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2005, 9(2), 220–222.
29. Saranchuk P, Boule A, Hilderbrand K, et al. Evaluation of a diagnostic algorithm for smear-negative pulmonary tuberculosis in HIV-infected adults: *South African Medical Journal* 2007, 97(7), 517–523.
30. Wilson D, Nachega J, Morroni C, Chaisson R, Maartens G. Diagnosing smear-negative tuberculosis using case definitions and treatment response in HIV-infected adults: *International Journal of Tuberculosis and Lung Disease* 2006, 10(1), 31–38.
31. Stop TB, World Health Organization. An expanded DOTS framework for effective tuberculosis control. *International Journal of Tuberculosis and Lung Disease* 2002, 6, 378–388.
32. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: A cohort study. *Lancet* 2002, 359, 2059–2064.
33. Madhi S, Venter M, Madhi A, Peterson K, Klugman K. Differing manifestations of respiratory syncytial virus-associated severe lower respiratory tract infections in human immunodeficiency virus type 1–infected and –uninfected children. *Pediatric Infectious Disease Journal* 2001, 20(2), 164–170.
34. Badri M, Maartens G, Mandalia S, et al. Cost-effectiveness of highly active antiretroviral therapy in South Africa: *PLoS Medicine* 2006, 3 e4, doi:10.1371/journal.pmed.0030004.
35. Wanless R, Sattie H, Chirwa Z, Khan S, Kabengele J, Mahaliyana P, Sayed R. *SECURE THE FUTURE* community-based treatment support programs deliver quality care for HIV patients in resource-limited settings in southern Africa. International AIDS Conference, 2006, August 13–18; 16 abstract no. thpe0210.
36. El-Sadr WM, et al. CD4+ Count-Guided Interruption of Antiretroviral Treatment. <<http://content.nejm.org/cgi/content/abstract/355/22/2283>> *New England Journal of Medicine* 2006, 355, 2283–2296.



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