



## FINAL REPORT

### Costs and Cost Effectiveness of Treatment Delivery in South Africa (Associate Award)

(Cooperative Agreement 674-A-00-09-00018-00)

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## I. Background

Boston University's (BU) cooperative agreement with USAID/South Africa, entitled "Costs and Cost Effectiveness of Treatment Delivery in South Africa" (Associate Cooperative Agreement No. 674-A-00-09-00018-00) and known as the Associate Award, was active during the five-year period from December 19, 2008 to December 30, 2013. It continued USAID/South Africa support for BU's work in South Africa under Country Research Activity Leader Award Number GHS-A-00-03-00020 and was succeeded by the INROADS Cooperative Agreement to the Wits Health Consortium.

All activities under the Associate Award were conducted by Boston University's Center for Global Health & Development (CGHD) in collaboration with the Health Economics and Epidemiology Research Office (HE<sup>2</sup>RO), a division of the Wits Health Consortium. The Principal Investigator of the Award for BU was Professor Sydney Rosen. The Principal Investigators for HE<sup>2</sup>RO were Dr. Ian Sanne and Mr. Lawrence Long.

## II. Project Objectives and Structure

The primary aim of the Associate Award was to support the USAID/South Africa strategic objective "Increased use of HIV/AIDS and other primary health care services." Specific goals included:

- Conduct applied epidemiologic and economic studies on the HIV/AIDS prevention and treatment roll-out of services;
- Address high-priority policy and program-relevant questions and disseminate the results widely;
- Broaden and deepen the abilities of South African personnel and institutions to address national issues of critical importance to the success of the national response to the HIV/AIDS pandemic;
- Improve the quality, efficiency, and sustainability of existing PEPFAR-supported treatment programs.

Although activities under the Associate Award evolved over its five-year duration, during much of that period it was divided into five technical focus areas. Each area and the major activities completed under it are listed below.

- ***Cost and cost-effectiveness of treatment.*** This area comprised the core treatment costing research that BU and HE<sup>2</sup>RO pioneered under the previous USAID agreement. Major studies completed under the Associate Award included:
  - Analysis of the costs and outcomes of models for delivering adult and pediatric antiretroviral therapy for HIV/AIDS in South Africa

- A retrospective cost-effectiveness analysis of nurse- initiated and managed antiretroviral treatment (NIMART) for HIV/AIDS in South Africa
  - Analyses of the costs of HIV-related inpatient care
  - Estimates of the costs and outcomes of second-line antiretroviral therapy
  - A model of the cost of incorporating resistance testing into HIV/AIDS treatment
  - Development of and support for the National ART Cost Model for the National Department of Health and National Treasury
- **Linkage to and retention in care.** Work on “loss to ART initiation” (linkage to care) and on retention on ART comprised an important part of the operations research completed under the Associate Award. Major activities in this area included:
    - Estimates of linkage from HIV testing to HIV care using retrospective data
    - Evaluations of the effectiveness and cost of using point-of-care CD4 count technologies in fixed and mobile clinic settings to improve uptake of HIV care and ART
    - Assessment of the feasibility of using screening criteria to reduce clinic visits for stable patients on antiretroviral therapy
    - Loss to follow up of pregnant women before and after delivery
    - A systematic review of loss to follow up before ART initiation
- **Tuberculosis economics.** As attention turned to the growing epidemic of tuberculosis and multi-drug resistant TB amongst South Africa’s HIV-infected population, BU and HE<sup>2</sup>RO developed a TB economics research program under the Associate Award. Major studies in this area included:
    - Estimates of the costs and outcomes of inpatient treatment for MDR-TB
    - Development of and support for the National TB Cost Model for the National Health Laboratory Service and the National Department of Health
    - A model of the cost of scaling up Xpert MTB/RIF technology and of alternative scenarios for its placement and use
- **Improving treatment outcomes.** A large body of work under the Associate Award was developed to take advantage of the high-quality HIV treatment database maintained by PEPFAR partner and BU/HE<sup>2</sup>RO collaborator Right to Care. Analyses completed during this period include work on:
    - Long-term outcomes of ART
    - Outcomes of second line ART
    - Comparisons between tenofovir- and stavudine-based first line regimens
    - Relationships between baseline conditions (co-morbidities, CD4 count, etc.) and treatment outcomes

- **Economic outcomes of treatment.** Under the Associate Award, a six-year prospective cohort study investigating the effect of ART on patients' economic well-being, with data collected in interviews during routine clinic visits, was completed. Results of this study have included:
  - Estimates of the effect of ART in reducing patients' symptoms of illness (pain, fatigue, nausea, etc.)
  - Impact of ART on patients' ability to perform normal activities and secure and retain employment
  - Estimates of the costs to patients of seeking treatment

### III. Major Accomplishments of the Associate Award

Over its five-year duration, the Associate Award made a number of valuable contributions to HIV-related policies, guidelines, and practices in South Africa. While it is difficult to link specific research outputs to specific changes, many of the project's results almost certainly contributed to the success of South Africa's HIV response over the past five years. In the following pages of this report, we summarize the most important accomplishments of the Associate Award in each of its five main technical areas.

A full listing of presentations and publications under the Associate Award is included as an Appendix to this report. Many can be downloaded in full text format (pdf files) from the websites of CGHD ([www.bu.edu/cghd](http://www.bu.edu/cghd)) or HE<sup>2</sup>RO ([www.heroza.org](http://www.heroza.org)). All publications are also available from HE<sup>2</sup>RO ([information@heroza.org](mailto:information@heroza.org)) or from the Principal Investigator ([sbrosen@bu.edu](mailto:sbrosen@bu.edu)).

#### A. Cost and Cost-Effectiveness of Treatment

As noted above, the Associate Award's initial focus was on estimating the costs of antiretroviral therapy in South Africa and the cost-effectiveness of different approaches to treatment delivery. In this section we highlight three of the team's most important products in this area.

##### 1. Costs and outcomes of adult and pediatric ART

When the rollout of ART in South Africa began in 2004, there were no reliable estimates of treatment costs for adults or children, nor any information about how different models of treatment delivery affected costs. BU and HE<sup>2</sup>RO launched the Associate Award with a study of the costs and outcomes of adult ART at four treatment sites that reflected four different contexts for delivering care: a public, urban hospital-based HIV clinic; a nongovernmental primary health clinic serving urban informal settlements; a rural, nongovernmental HIV clinic; and a private GP reimbursement program. The costing methodology developed incorporated the costs of patients who discontinued care (died, lost to follow up) or failed treatment as well as those who remained in care and responding. Table 1 summarizes the findings of this study, which are reported in detail in (Rosen, Long, & Sanne, 2008).

**Table 1. Average cost per patient for adult ART (2006 USD, R6.8/\$1)**

Site	Cost per patient treated	Cost per patient in care and responding	Average cost to produce a patient in care and responding
Site 1 (large public hospital)	\$756	\$903	\$1128
Site 2 (private GPs)	\$896	\$1168	\$1723
Site 3 (NGO HIV clinic)	\$932	\$1157	\$1480
Site 4 (NGO primary clinic)	\$1126	\$1210	\$1482
All sites	\$928	\$1109	\$1438

This analysis provided the National Department of Health and the National Treasury with some of the first estimates available of the cost of providing ART per patient served and was the first analysis of ART costs that incorporated patient outcomes, which serves as a proxy for quality of care.

The adult study was followed by a parallel study of pediatric ART, comparing two pediatric ART clinics based at urban hospitals in Gauteng. In Table 2, the key results of the pediatric cost-outcomes study are reported; full study findings can be found in (Meyer-Rath et al., 2013). This study suggested that, contrary to common views, providing pediatric ART was not more expensive than adult ART on a per-patient basis.

**Table 2. Distribution of average cost per pediatric ART patient in care and responding (2009 USD, R8.3/\$1)**

Cost category	Site 1		Site 2		Both sites and years
	Year 1	Year 2	Year 1	Year 2	
ARV drugs	\$343	\$375	\$226	\$274	\$302
Non-ARV drugs	\$23	\$28	\$19	\$21	\$23
Diagnostic tests	\$103	\$88	\$105	\$106	\$101
Clinic visits	\$255	\$168	\$207	\$242	\$219
Fixed costs	\$106	\$58	\$120	\$139	\$107
Total	\$830	\$717	\$678	\$782	\$752

## 2. Cost-effectiveness of down-referring stable ART patients

In 2010, Ian Sanne and his team published a landmark study of the effectiveness of nurse-managed ART (Sanne et al., 2010), providing the first evidence that nurses can successfully manage adult ART patients in a clinical trial setting. To determine whether the findings of that controlled trial applied to routine primary health care settings, HE<sup>2</sup>RO and BU undertook a study of the cost-effectiveness of down referral of stable ART patients to primary health clinics and nurse-managed care. For this study, the research team worked closely with USAID treatment partner Right to Care, which implemented down referral at pilot locations. Using retrospective data, estimates were made of the costs and outcomes for clinic-based, nurse-

managed ART and compared to costs and outcomes for hospital-based, doctor-managed ART. Results of this study are summarized in Table 3 and provided in detail in (Long et al., 2011)

**Table 3. Outcomes and costs of hospital-based, doctor managed care and clinic-based, nurse-managed care for stable ART patients**

<b>Result</b>	<b>Hospital/doctor managed (n=2,136)</b>	<b>Clinic/nurse managed (n=712)</b>
<b>Outcomes (%)</b>		
In care and responding	89.5%	95.5%
In care but not responding	4.3%	2.8%
No longer in care	6.2%	1.7%
<b>Cost per patient (2009 USD, R8.4/\$1)</b>		
All patients	\$539	\$486
In care and responding	\$551	\$492
Cost to produce a patient in care and responding*	\$602	\$509

\*Total cost for sample divided by number of patients in care and responding

### 3. Modeling the national ART budget

South Africa is home to both the largest number of HIV-positive people in the world and the largest and most ambitious HIV/AIDS treatment program. By the end of 2009, close to a million South Africans were receiving antiretroviral therapy from hundreds of public sector health care facilities. The success of the South African program, in terms of patient demand for treatment and the sheer numbers of patients in care, led to a budgetary crisis and a suspension of initiation of new patients in some provinces.

To prevent such occurrences in the future, in March 2009, the South African Department of Health and National Treasury asked a BU/HE<sup>2</sup>RO team to model the future size and costs of the national treatment effort. The team built a Markov (state-transition) model to estimate the annual expected costs of the program between 2010 and 2017 and evaluate proposed changes to treatment guidelines. The model, which was the first to incorporate CD4 count strata into its transition probabilities, used projections of the number of patients in need of treatment and the proportion actually receiving treatment from ASSA, along with primary cost and outcome data from HE<sup>2</sup>RO own studies.

The model projected that under the new treatment guidelines, patient numbers would more than double between 2010 and 2017, and program costs would rise from just over \$1 billion in 2010 to nearly \$3 billion in 2017. Savings from task shifting from doctors to nurses and more flexible ARV procurement rules allowing more competitive drug prices were expected to more than offset the cost impact of the new guidelines, however. This information allowed the South African government to adopt the new guidelines in 2010, led to a doubling of the domestic budget for HIV treatment, and helped produce a consensus among government, civil society, and donor agencies over future budgetary needs.

## B. Linkage to and Retention in Care

As increasing numbers of South Africans were tested for HIV and the national ART program expanded, attrition from treatment programs, whether due to death or the catchall explanation of “loss to follow up,” gradually gained in importance as one of the major challenges of the national HIV program. This was followed soon thereafter by concern about patients who tested positive for HIV and were eligible for ART but were never “linked” to care and were “lost to initiation” before starting ART. BU and HE<sup>2</sup>RO contributed data and recommendations to help address both of these concerns.

### 1. Retention in care

BU’s work in the area of retention of patients on ART began with two highly-cited systematic reviews on retention in care in sub-Saharan Africa (Fox & Rosen, 2010; Rosen, Fox, & Gill, 2007) which estimated average retention on ART at 60-80% two years after treatment initiation. Since then the BU/HE<sup>2</sup>RO team has analyzed primary data from South Africa to obtain a better understanding of retention in care issues. Much of this work has been done under other funding mechanisms, but the Associate Award contributed to a number of studies. One of these examined the impact of missed visits on treatment outcomes in the Themba Lethu HIV cohort, which is described in detail in (Fox, Maskew, & MacPhail, 2013).

Numerous studies have documented the impact of loss to follow up on mortality in South Africa. When we matched data on patients lost to follow up to the national vital registration system we demonstrated that roughly 40% of patients lost from the clinic had died (Fox, Brennan, Maskew, MacPhail, & Sanne, 2010). Few studies have focused on a related issue, however: remaining in care but being non-adherent to visit schedules (i.e. temporary interruptions to treatment). Patients who miss visits are likely to run out of ARVs and spend weeks or months without taking any drugs, which would put them at increased risk for poor treatment outcomes and drug resistance.

In this analysis, described in detail in (Brennan, Maskew, Sanne, & Fox, 2010), we found that among 4,476 patients starting HIV treatment, missed visits in the first six months on ART were common, with 26% missing one visit and 9% missing two or more visits. As hypothesized, these early missed visits had implications for treatment outcomes. Patients who missed three or more medical or medication pickup visits had twice the risk of a poor CD4 response by six months, while patients who missed medical visits had a 2-4 fold increased risk of death depending on the number of visits missed compared to patients who missed no visits.

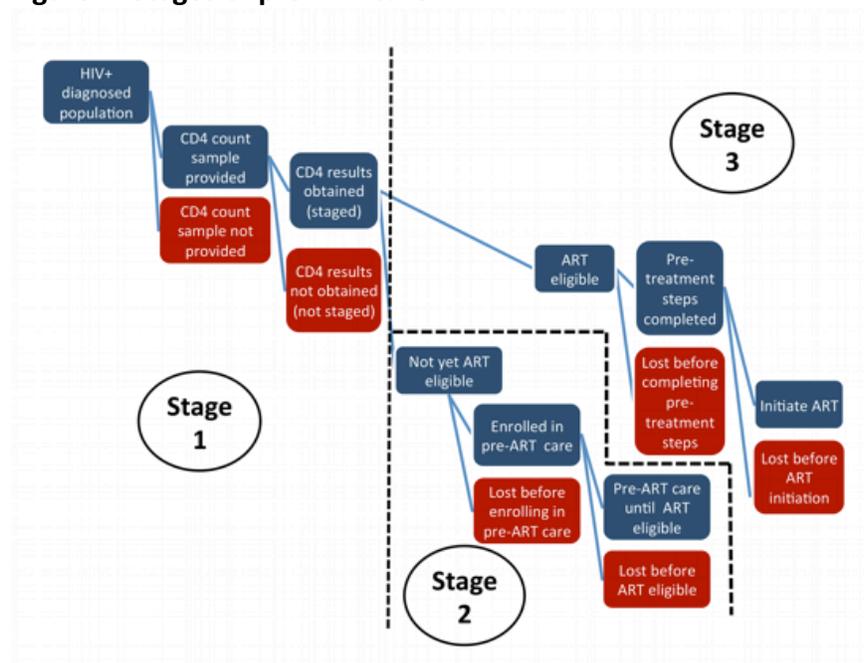
This study demonstrated the importance of attending regular clinic visits in the first six months of care and suggested that maintaining patients on a regular schedule during this early period of care is critical to the success of treatment programs.

Most of the costing studies completed under the Associate Award, such as those of adult and pediatric treatment costs described above, also used retention in care as a primary outcome and measure of effectiveness.

## 2. Linkage to care—systematic review

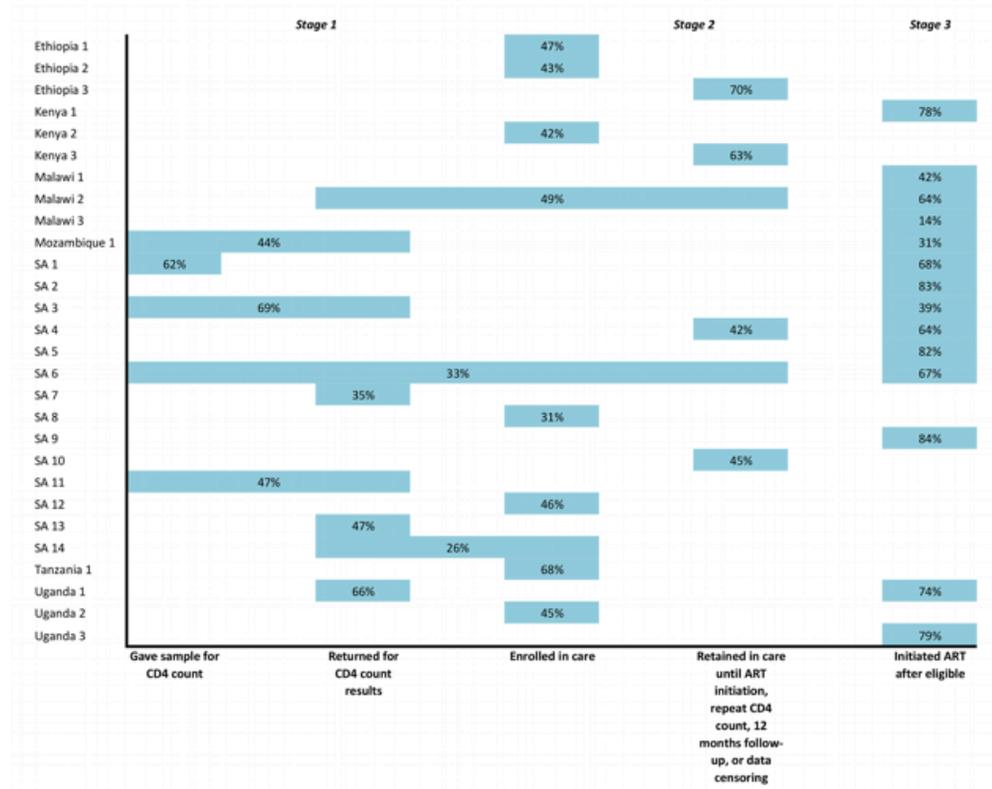
The successful expansion of access to HIV testing in sub-Saharan Africa led to hundreds of thousands of people learning that they are HIV-positive. Only a small fraction of these individuals, however, enrolled in HIV/AIDS care and treatment programs at the time of diagnosis or at any time before they become seriously ill. As a result, most patients sought HIV/AIDS treatment long after they were eligible and with severe illness. In a systematic review partially conducted under the Associate Award, BU identified the various points at which pre-ART patients are lost to care, as shown in Figure 1. This paper was widely referenced, with nearly 200 citations in other publications as of early 2014, and helped to launch a new area of operational research focused on retention in pre-ART care.

**Figure 1. Stages of pre-ART care**



The results of this systematic review are summarized in Figure 2 and discussed in detail in (Rosen & Fox, 2011).

**Figure 2. Proportions of patients completing steps within each stage of pre-ART care**



### 3. Linkage to care—primary research

BU and HE<sup>2</sup>RO also conducted several studies that aimed to quantify the problem of poor linkage between testing and care and low retention of patients prior to starting ART. The first two studies analyzed testing and care records at one large public-sector treatment program in Johannesburg to estimate rates of loss at two points in the testing-to-treatment continuum: 1) between testing positive for HIV and returning for CD4 count (staging) results and 2) between enrolling in the pre-ART care program and returning for the first medical appointment. Results are summarized in Table 4; further details can be found in (Larson et al., 2010a, 2010b).

**Table 4. Loss to follow up before initiating ART at Themba Lethu Clinic, Johannesburg**

Action	% of study sample that completed the action
<b><i>From testing positive for HIV to receiving results of a CD4 count</i></b>	
Newly diagnosed HIV patients who gave a blood sample for a CD4 count	85%
Of those eligible for ART, returned for CD4 count results ≤ 3 months	51%
Of those not eligible for ART, returned for CD4 counts results ≤ 3 months	15%
<b><i>From enrolling in pre-ART care to returning for first routine monitoring visit</i></b>	
Of those with CD4 count 250-350, returned within 1 year	41%
Of those with CD4 count >350, returned within 1 year	26%

As Table 4 indicates, loss to follow up during the initial steps of HIV care—completing a CD4 count and returning for pre-ART care—was found to be extremely high, with no more than half of patients completing the next step in the process.

One strategy to reduce attrition before patients receive their CD4 count results and thus learn whether they were eligible for ART is to use a rapid, point-of-care CD4 testing instrument that allows patients to be told their results shortly after providing a blood sample, rather than days or weeks later. Working with PEPFAR partner Right to Care, the BU/HE<sup>2</sup>RO team evaluated the use of such technology in a mobile HIV counseling and testing (HCT) service. For the evaluation, a rapid point of care (POC) CD4 count was offered to some HIV-positive HCT clients, while others were referred to a clinic for CD4 testing, with telephone follow up 8 weeks later to determine what proportion of HCT clients had completed a referral clinic visit. Overall, 59% of those offered the POC test reported having completed a referral visit for enrollment in HIV care, compared to 47% of those who were not offered the POC test. Further details of this pilot project are reported in (Larson, Bistline, et al., 2012); related analyses are described in (Larson et al., 2013; Larson, Schnippel, et al., 2012).

## **C. Tuberculosis Economics**

South Africa bears a disproportionately large burden of HIV/tuberculosis (TB) co-infection and of multi-drug resistant tuberculosis (MDR-TB). Although the successful scale-up of antiretroviral therapy for HIV/AIDS has reduced HIV-related mortality, TB continues to be the largest single cause of adult deaths in the country, and MDR-TB accounts for a very large share of the national TB control budget. To help the Government of South Africa, PEPFAR, the WHO, and other organizations improve TB prevention, case-finding, diagnosis, and treatment, BU and HE<sup>2</sup>RO launched a program of research on the economics of TB in 2010.

### **1. Cost of treating MDR-TB**

The initial study used patient-level records to estimate the cost of inpatient treatment for MDR-TB. Although national guidelines for treating MDR-TB called for at least 6 months of inpatient care in specialized TB wards, there were no estimates available of the cost of this service. The study found that although most patients were discharged in less than 6 months, with a mean hospital stay of 105 days, the average cost per patient during this stay was \$17,164, with inpatient “hotel” costs, rather than drugs or lab tests, accounting for 95% of this amount. This cost was estimated to be nearly 40 times the average cost of treating drug-susceptible TB and 25 times the cost of a year of first-line ART. A breakdown of costs by resource utilized and by patient outcome is provided in (Schnippel et al., 2013).

### **2. Modeling the cost of scaling up Xpert MTB/RIF**

In May 2011, the National Health Laboratory Service asked the BU/HE<sup>2</sup>RO team to help estimate the costs of introducing GeneXpert MTB/RIF (Cepheid) technology into public sector laboratories across the country, a policy announced by the Minister of Health earlier that year.

Two cost models were developed for this purpose, the Xpert Implementation Cost Model and the National TB Cost Model (NTCM). Results of the models were used to guide decisions about the pace of scaleup of Xpert capacity, the numbers and sizes of machines required, and the algorithms to be used to diagnose TB.

The same models were used to explore different approaches to scaling up and utilizing Xpert. One analysis, for example, estimated the difference in cost per test and total cost per year between placing Xpert instruments in centralized laboratories serving multiple treatment facilities and placing Xpert instruments at every treatment facility (point of care). Table 5 presents the cost differences between the two scenarios.

**Table 5. Cost per test and total cost of placing Xpert instruments at point of care and at centralized laboratories**

Item	Point of care	Laboratory	Difference
<b><i>Scale-up requirements</i></b>			
Number of testing sites	3,799	223	n.a.
Number of Xpert instruments required	4,020	274	n.a.
Number of Xpert modules required	5,056	2,739	n.a.
<b><i>Cost per test performed</i></b>			
Xpert cartridge	\$14.00	\$14.00	\$0.00
Cartridge procurement	\$2.68	\$2.68	\$0.00
Labor	\$5.35	\$2.90	\$2.45
Overhead	\$4.25	\$2.68	\$1.57
Transport of supplies and samples	\$0.68	\$1.36	-\$0.68
Module calibration	\$1.47	\$0.60	\$0.87
Consumables	\$1.20	\$0.36	\$0.84
Quality assessment and training	\$3.87	\$0.15	\$3.72
Instrument procurement	\$4.16	\$1.66	\$2.50
Equipment and renovations	\$1.25	\$0.15	\$1.10
Total cost per test	\$38.91	\$26.54	\$12.37
<b><i>Annual cost for South Africa</i></b>	\$107 million	\$71 million	\$36 million

This analysis, detailed in (Schnippel et al., 2012), estimated that placing Xpert at points of treatment would increase the total cost of the program by more than 50%. It concluded that the incremental benefits of point-of-treatment placement, in terms of better patient outcomes, would have to be equally substantial to justify the additional cost to the national health budget.

#### **D. Improving Treatment Outcomes**

In order to generate the nearly exponential increase in the number of patients on antiretroviral therapy in South Africa since April of 2004, the emphasis of HIV care and treatment programs had to be on initiating as many patients on therapy as possible. This required a standardized

public health approach with limited treatment options and clearly defined eligibility criteria. As the number of patients continued to grow, however, evaluating the effectiveness of current treatment guidelines became an important strategy for identifying ways to improve outcomes while continuing to scale up care.

The BU/HE<sup>2</sup>RO team was in a unique position to evaluate aspects of the treatment rollout because of its partnership with Right to Care, which maintained a very large database of patients on HIV treatment at the Themba Lethu HIV Clinic. Our efforts in evaluating treatment outcomes of the ART rollout were made possible by the up-front investment in robust patient-level data capture systems. Having access to a high-quality longitudinal database with over 25,000 patients on treatment allowed us to ask questions that couldn't be answered in smaller programs: what are the longterm outcomes on treatment, how effective is second-line treatment for patients who have failed first line treatment and what was the impact of phasing out a less expensive drug like stavudine in favor of a better but more expensive drug like tenofovir?

Below we highlight three of BU's most important studies of HIV treatment outcomes:

#### 1. Survival and virologic suppression on second-line HIV treatment

Despite the clear reduction on morbidity and mortality as the number of patients on ART in South Africa continued to grow, a certain percentage of patients were experiencing detectable viral loads on first-line therapy that required switching them to more expensive second line regimens. As part of the public health approach to treatment, the 2004 South African national treatment guidelines called for a second line regimen of zidovudine, didanosine, and lopinavir/ritonavir. While the original treatment guidelines clearly anticipated the need for switching to second line drugs, there was little evidence that these regimens would produce positive outcomes, particularly given that patients would be switched without resistance testing.

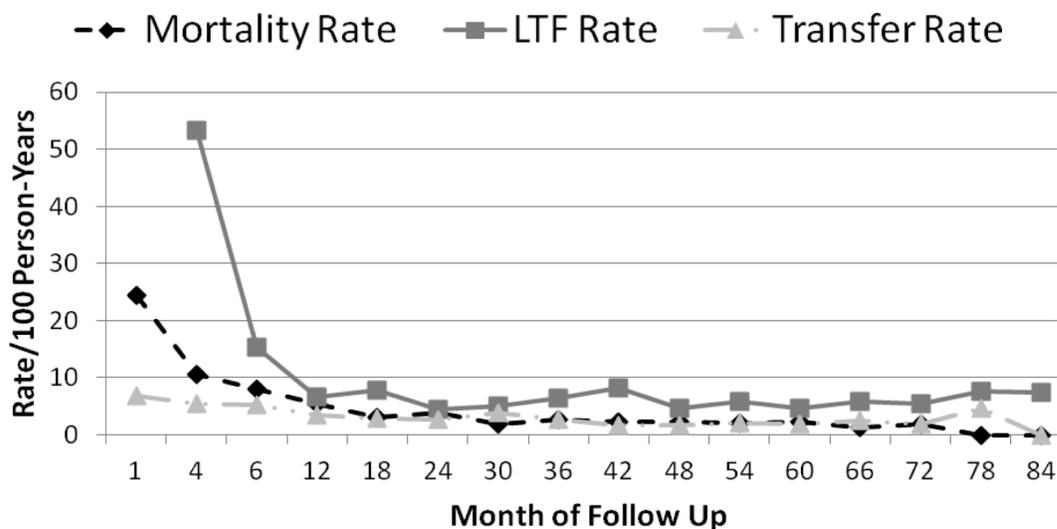
Using data from the Themba Lethu HIV Clinic, BU conducted a cohort study among 328 patients initiated on second line treatment. The study found that one year after initiating second line therapy 78% (243/313) of patients were alive and in care and 77% (203/262) had a suppressed viral load on the new drugs. In order to evaluate the effectiveness of second line ART, patients on second-line therapy were matched to a group of patients still on first line but for a similar total time on treatment, and outcomes were compared. Those switched to second line ART had a slightly (16%) decreased likelihood of being alive and in care by one year as patients on first-line therapy for a similar amount of time. This finding suggested that while those on second line were not doing as well as those still on first line, the differences were not large. As rates of treatment failure over the first year on second line therapy were low, the analysis described in (Fox, Ive, Long, Maskew, & Sanne, 2010) concluded that provision of second line treatment to patients who fail their first line treatment should be a high priority.

## 2. Outcomes after seven years of HIV treatment

While more and more evidence accumulates on the impressive short-term benefits of HIV treatment, focus has shifted to evaluating the long-term impacts of treatment scaleup. While the early benefits are clear in terms of a reduction in mortality and morbidity, it is possible that as patients spend longer on treatment and no longer experience the symptoms of the disease, adherence may decline and loss to follow up and mortality increase over time. Because Themba Lethu had such a large cohort of patients enrolled in 2004 and continued to initiate large numbers of patients each year, we were able to assess long-term responses to treatment. The seven-year follow up data analyzed in this study represented one of the longest durations that any cohort in Africa had been under observation at that time.

As figure 3 shows, most of the mortality and loss to follow up on treatment occurred in the first six months after initiation. After the first six months, attrition (defined as death and loss to follow up) declined dramatically and remained stable throughout the rest of the seven years of follow up. Because attrition is cumulative over time, however, long term retention in care continued to decline. The analysis, detailed in (Fox et al., 2012), found that among the 1,794 patients initiated on ART between April 2004 and March of 2005, the first year of the public sector rollout, 25% of patients were lost and 16% had died by six years after initiation, leaving only about 60% of patients alive and still on ART at the site.

**Figure 3. Monthly mortality, loss to follow-up and transfer over seven years at Themba Lethu**



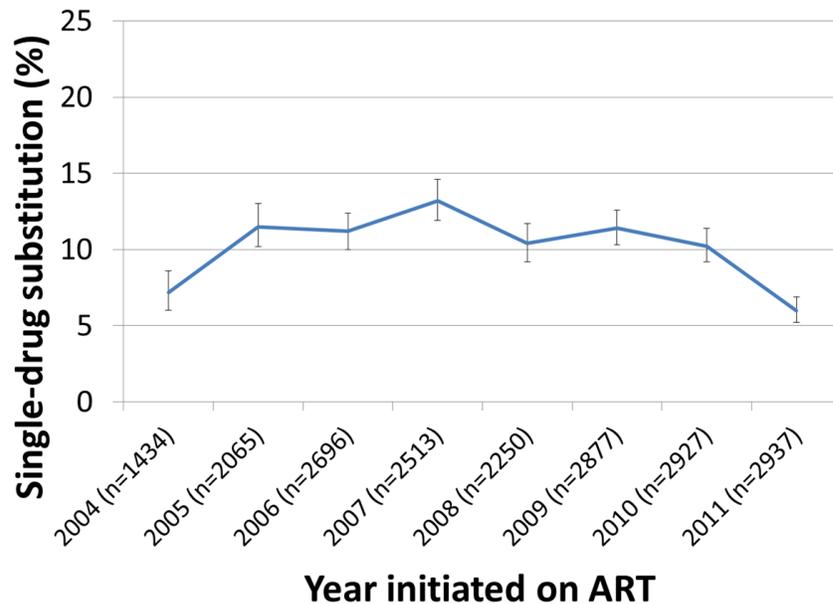
## 3. Increases in regimen durability associated with the introduction of tenofovir

In April 2010 the South African government amended its treatment guidelines to replace the drug stavudine with tenofovir in public-sector first line antiretroviral therapy. While tenofovir was far more expensive than stavudine, it had fewer side effects and drug toxicities. For this reason, the switch to tenofovir was expected to translate into an increase in the durability of first line regimens. Such an increase in durability would preserve future treatment regimens

and possibly reduce switching to far more expensive second line treatment. To assess if such a benefit was actually achieved, BU evaluated the change in ART regimen durability over time at Themba Lethu, using a cohort analysis of patients initiated on ART between April 2004 and December 2012.

Figure 4 shows the change in the proportion of patients requiring a single drug substitution (i.e. change of a single drug within a three drug regimen, typically for toxicity rather than treatment failure) over their first year on treatment. Excluding 2004 when the national ART program had just begun, before 2010 the percentage of patients experiencing single drug substitutions during their first year on therapy ranged from 15.7% in 2005 to 17.8% in 2009. With tenofovir’s introduction, single-drug substitutions decreased substantially to 9.7% in 2010 and 5.9% in 2011.

**Figure 4. Proportion of single drug changes over the first 12-months on ART**



After tenofovir was introduced in 2010, the proportion of patients experiencing neuropathy decreased from 14.5 % to 2.1%, hyperlactatemia and lactic acidosis decreased from 13.8% to 1.5%, and lipodystrophy decreased from 7.6% to 1.2%.

The detailed analysis described in (Brennan et al., 2013) concluded that the decline in single drug substitutions in the first 12 months on ART appeared to be related to the introduction of tenofovir, resulting in fewer drug toxicities, and that increased use of tenofovir could have important benefits within South Africa and could improve treatment outcomes in other resource-limited settings.

## **E. Economic Outcomes of Treatment**

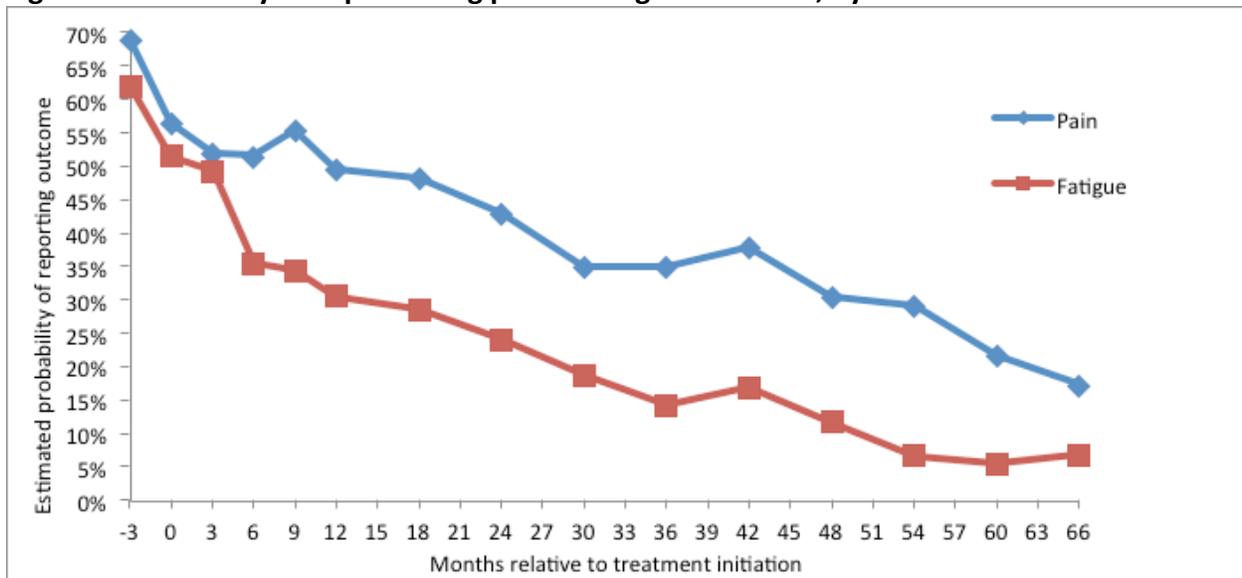
As treatment rollout began in South Africa, the BU/HE<sup>2</sup>RO team realized that almost nothing was known about how ART would affect patients’ lives outside the clinic. Clinical outcomes

were well-established: ART saved lives and reduced morbidity. But would it allow patients to engage in their normal activities and gain or keep employment? Would they feel well on ART, or would HIV and the toxicities associated with ART itself create a population that survived but was not “well”? In 2005, the team launched the “patient economic outcomes study” to try to answer some of these questions.

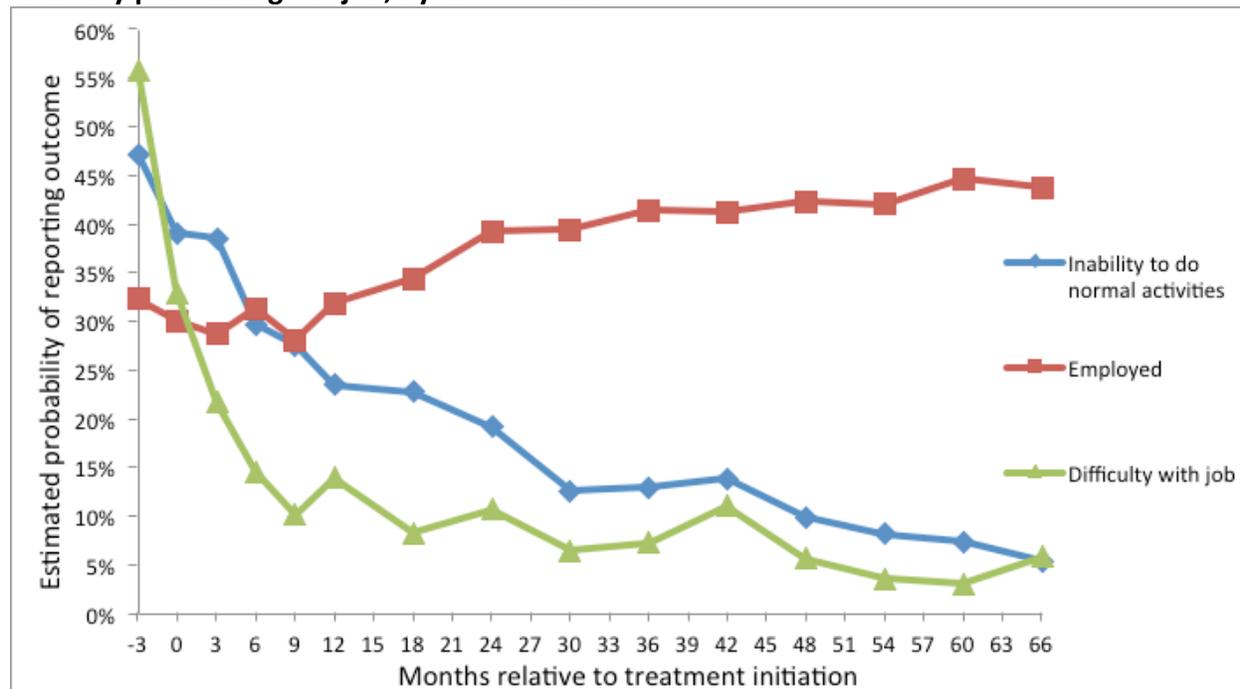
The patient economic outcomes study enrolled approximately 1100 adult pre-ART and early ART patients from three clinics in South Africa. Each study subject was interviewed at enrollment and then as often as possible over the next 5-6 years. The questionnaire elicited information about symptoms, ability to engage in normal activities, employment, household income, and the costs to patients of seeking treatment. The study also had access to subjects’ medical records, maintained electronically by PEPFAR partner Right to Care.

By the time data collection ended in 2011, this cohort was the longest-followed cohort being studied for “non-clinical” outcomes of treatment in sub-Saharan Africa. Results were published for baseline data, after 3 years of follow up, and after 5 years of follow up. Figures 5 and 6 highlight the key findings of this study. In general, the study found that for patients who remained on ART, outcomes improved significantly and steadily over the first five years after treatment initiation. Further details can be found in (Rosen, Ketlhapile, Sanne, & Desilva, 2007; Rosen, Ketlhapile, Sanne, & DeSilva, 2008; Rosen et al., 2010, 2013).

**Figure 5. Probability of experiencing pain or fatigue last week, by time on ART**



**Figure 6. Probability of being unable to perform normal activities, having a job, and having difficulty performing the job, by time on ART**



## IV. Lessons Learned

Through the past five years of activities under the Associate Award and the previous five years under other USAID cooperative agreements, the BU/HE2RO team identified a number of key principles required to make applied research and evaluation successful in improving policies and programs.

1. *Always have a relevant client for your work.* Unlike traditional academic research, applied research is conducted with the express purpose of improving policies and programs. This is best achieved by ensuring that one or more potential users of the work, such as the Department or Ministry of Health, are interested in receiving the results. Ideally, research questions should be posed by the end users of the work, though the researchers may need to guide the choice and specification of questions. BU made a concerted effort always to have a client who asked the questions and was actively involved in discussions of how to answer it (study design, data sources, analytic approach). In South Africa this was most often the National Department of Health, though some studies were done for other clients (e.g. PEPFAR implementing partners). By ensuring that there was a client waiting for our findings, we were able to maximize the likelihood that our work would bridge the “knowing/doing” divide.
2. *Ask policy-relevant questions.* Another difference between traditional academic research and the applied research conducted under the Associate Award is that the research

questions addressed by BU were almost always of immediate relevance to impending policy or programmatic decisions. In some cases these questions came directly from the client, such as the National Department of Health; in others, the researchers anticipated what information would be needed based on an in-depth understanding of the context. For example, the study of the cost-effectiveness of down-referring ART patients to nurse-managed clinics, described above, was conducted after a clinical trial demonstrated potential efficacy but before South African guidelines allowed nurse-initiated and managed antiretroviral treatment (NIMART). The question it asked—can nurses manage down-referred ART patients successfully in a routine care setting, and will this approach save money—thus generated information that the National Department of Health had not directly requested but did find valuable in revising its treatment guidelines.

3. *Work with and alongside an implementer.* Most policy makers and program managers want to know whether an intervention will work, and how much it will cost, in a routine practice setting, such as existing primary health clinics. Evidence from randomized controlled trials rarely addresses these questions, because the nature of a trial creates a large gap between even the control arm and routine practice. Operational research that is conducted in partnership with an implementer, such as a PEPFAR implementing partner or the department of health itself, typically produces results that are less “clean” than in a controlled trial but more relevant to the local setting and circumstances. Such results can then be used to parameterize models and plan programs with greater confidence that they represent what will actually happen.
4. *It’s better to be 90% right at the time the answer is needed than 100% right after the fact.* In the face of rapidly changing disease burdens, new research findings and international guidelines, and evolving costs, decision-makers can rarely wait for perfect information. Providing better information than they already have, and doing it within the time frame and context required, is more useful than designing and conducting the perfect analysis and producing results long after the relevant decisions have been made. The goal of applied research is to provide information that is better than the status quo, and then to improve it as experience is gained over time.
5. *Retaining flexibility is important.* New policy questions can emerge rapidly, and questions that are relevant when a study starts may be obsolete by the time it ends. For example, the BU/HE<sup>2</sup>RO project to build a cost model for scaling up Xpert MTB/RIF arose as an urgent request from the National Health Laboratory Service and had a very tight timeline for completion. The team was able to respond because the Associate Award allowed us the flexibility to postpone other activities and direct our resources toward this request. Maintaining enough flexibility under a funding agreement to be able to respond to new requests and make changes mid-course is important if the work produced is to contribute to improving healthcare.
6. *Investments in collecting and managing primary data pay off.* Much of the value of the research findings produced by BU under this cooperative agreement resulted from the

team's commitment to using primary data whenever possible. Patient and facility-level data extracted from medical records or generated through surveys and interviews ensured that the results of the research were locally relevant and internally consistent, and thus were more readily accepted by policy makers than would modeled or estimated results have been. Access to a comprehensive and well managed patient cohort database allowed questions to be answered quickly and well. Dedicated funding and staff should be allocated to collecting, cleaning, and managing primary data.

7. *Present results in their contexts.* While policy makers and program managers often would prefer to be given “the answer” in the form of a single number, such as a cost per patient treated or the prevalence of TB in HIV-infected adults, most values are only meaningful in the context in which they were generated. Taking research findings out of context can be misleading and abet poor decision-making. The more we can do to embed results in their contexts, the more useful our information will be.
8. *Capacity takes time to build.* The value of BU's and HE<sup>2</sup>RO's work increased steadily over time, as staff gained experience, new methods were developed and applied, and longitudinal data sets were created. By the time the BU/HE<sup>2</sup>RO team were called on to help the Government of South Africa improve its budgeting for HIV treatment, a body of research and expertise had been developed that allowed us to provide the technical assistance needed. Uncertain annual funding decisions make it difficult to invest in long-term results, and commitments of long-term funding are an important contributor to capacity development.

## V. Future Plans

In 2012, one year before the end of the Associate Award, BU helped its local partner, HE<sup>2</sup>RO, to serve as the primary applicant for a major new grant from USAID/South Africa. That grant, known as INROADS (Innovations Research on HIV/AIDS), supports the further development of local capacity at HE<sup>2</sup>RO, with ongoing technical assistance and mentoring by Boston University. Much of the work conducted under the Associate Award will continue under INROADS. INROADS also adds new areas of research and evaluation, however, such as the intersection between HIV and sexual and reproductive health, the challenges faced by HIV-infected adolescents, and the integration of HIV, TB, and other health services. INROADS also provides resources for formal and informal training in health economics and epidemiology, helping to build the local skills base in these fields. Activities under INROADS will continue through 2017, allowing a number of long-term studies to be completed.

Due in large part to the expertise and experience developed under the Associate Award, BU and HE<sup>2</sup>RO have also been able to diversify their sources of support. Funding has been received from the U.S. National Institutes of Health, the Gates Foundation, and the World Health Organization. In addition, the South African National Health Laboratory Service and the World Bank have both invited BU and HE<sup>2</sup>RO to collaborate on funded projects. The Associate Award

has thus helped to create a sustainable resource for applying the tools of epidemiology and health economics to improving public health in South Africa.

## Appendices: Research Outputs of the Associate Award, 2009-2013

### Appendix 1. Peer-Reviewed Publications

Approximately 40 peer-reviewed articles were published under the Associate Award. These are listed below, by primary technical area.

Authors	Title	Publication
<b><i>Cost and Cost-Effectiveness of Treatment</i></b>		
Long L, Fox MP, Sanne I, Rosen S	The high cost of second line antiretroviral therapy for HIV/AIDS in South Africa	<i>AIDS</i> 2010; 24(6): 915-919 PMID: 20042849
Long L, Brennan A, Fox M, Ndibongo B, Jaffray I, Sanne I, Rosen S	Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort	<i>PLoS Med</i> 2011; 8: e1001055 PMID: 21811402
Rosen S, Long L, Sanne I, Stevens W, Fox M	The net cost of incorporating resistance testing into HIV/AIDS treatment in South Africa: a Markov model with primary data	<i>J Int AIDS Soc</i> 2011; 14: 24
Larson B, Schnippel K, Ndibongo B, Long L, Fox M, Rosen S	How to estimate the cost of point-of-care CD4 testing in program settings: An example using the Alere Pima™ Analyzer in South Africa	<i>PLoS ONE</i> 2012; 7(4): e35444 PMID: 22532854
Meyer-Rath G, Brennan A, Long L, Ndibongo B, Technau K, Moultrie H, Fairlie L, Coovadia A, Rosen S	Cost and outcomes of paediatric antiretroviral treatment in South Africa	<i>AIDS</i> 2012; 27:243-250
Meyer-Rath G, Brennan AT, Fox MP, Modisenyane T, Tshabangu N, Mohapi L, Rosen S, Martinson N	Rates and cost of hospitalisation before and after initiation of antiretroviral therapy in urban and rural settings in South Africa	<i>J Acquir Immune Defic Syndr</i> 2013;62:322–328
<b><i>Linkage to and Retention in Care</i></b>		
Brennan AT, Maskew M, Sanne I, Fox MP	The importance of clinic attendance in the first six months on antiretroviral treatment: a retrospective analysis at a large public sector HIV clinic in South Africa	<i>J Int AIDS Soc</i> 2010; 13:49
Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I, Fox MP	Lost opportunities to complete CD4+ lymphocyte testing among patients who tested positive for HIV in South Africa	<i>Bull World Health Organ</i> 2010; 88: 675-80 PMID: 20865072
Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I, Fox MP	Early loss to follow up after enrollment in pre-ART care at a large public clinic in Johannesburg, South Africa	<i>Trop Med Int Health</i> 2010; 15 Suppl 1: 43-47 PMID: 20586959

<b>Authors</b>	<b>Title</b>	<b>Publication</b>
Rosen S, Fox M	Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review	<i>PLoS Med</i> 2011; 8: e1001056 PMID: 21811403
Larson B, Schnippel K, Ndibongo B, Xulu T, Brennan A, Long L, Fox M, Rosen S	Rapid point-of-care CD4 testing at mobile HIV testing sites to increase linkage to care: An evaluation of a pilot program in South Africa	<i>J Acquir Immune Defic Syndr</i> 2012; 61:e13–e17
Fox MP, Larson B, Rosen S	Defining retention and attrition in pre-antiretroviral HIV care: proposals based on experience in Africa	<i>Trop Med Int Health</i> 2012; ; 17: 1235-44 PMID: 22863075
Clouse K, Pettifor A, Shearer K, Maskew M, Bassett J, Larson B, Van Rie A, Sanne I, Fox MP	Loss to follow-up before and after delivery among women testing HIV-positive during pregnancy in Johannesburg, South Africa	<i>Trop Med Int Health</i> 2013;18:451-60
Macleod W, Maskew M, Jaffray I, MacPhail P, Ive P, Fox M	The feasibility of using screening criteria to reduce clinic visits for stable patients on antiretroviral therapy in South Africa	<i>J Acquir Immune Defic Syndr</i> 2013; 62(3):e82-6
Larson B, Schnippel K, Brennan A, Long L, Xulu T, Maotoe T, Rosen S, Sanne I, Fox M	Same-day CD4 testing to improve uptake of HIV care and treatment in South Africa: point-of-care is not enough	<i>AIDS Research and Treatment</i> 2013: 941493
<b><i>Tuberculosis Economics</i></b>		
Meyer-Rath G, Schnippel K, Long L, MacLeod W, Sanne I, Stevens W, Pillay S, Pillay Y, Rosen S	The impact and cost of scaling up GeneXpert MTB/RIF in South Africa	<i>PLoS ONE</i> 2012; 7: e36966 PMID: 22693561
Schnippel K, Meyer-Rath G, Long L, Macleod W, Sanne I, Stevens W, Rosen S	Scaling up Xpert MTB/RIF technology: the costs of laboratory- vs clinic-based roll-out in South Africa	<i>Trop Med Int Health</i> 2012; 17: 1142-51 PMID: 22686606
Schnippel K, Rosen S, Shearer K, Martinson N, Long L, Sanne I, Variava E	Costs of inpatient treatment for multi-drug resistant tuberculosis in South Africa	<i>Trop Med Int Health</i> 2012;18: 109-16 PMID: 23170876
Schnippel K, Meyer-Rath G, Long L, Stevens W, Sanne I, Rosen S	Diagnosing Xpert MTB/RIF-negative TB suspects: impact and cost of alternative algorithms in South Africa	<i>So Afr Med J</i> 2013: 103;101-106 PMID: 23374320
Schnippel K, Long L, Meyer-Rath G, Sanne I, Rosen S, Stevens W	Impact and costs of algorithms for the diagnosis of adults with pulmonary tuberculosis in South Africa	<i>S Afr Med J</i> 2013;103:436
<b><i>Improving Treatment Outcomes</i></b>		
Fox MP, Ive P, Long L, Maskew M, Sanne I	High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa	<i>J Acquir Immune Defic Syndr</i> 2010;53:500–506
Fox MP, Brennan AT, Maskew M, MacPhail P, Sanne I	Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa	<i>Trop Med Int Health</i> 2010; 15: 405-13

<b>Authors</b>	<b>Title</b>	<b>Publication</b>
Brennan A, Evans D, Maskew M, Ive P, Naicker S, Sanne I, Fox MP	Relationship between renal dysfunction, nephrotoxicity and death among HIV adults on tenofovir	<i>AIDS</i> 2011; 25:1603–09
Brennan A, Long L, Maskew M, Sanne I, Jaffray I, MacPhail P, Fox MP	One-year outcomes of stable HIV-positive patients down-referred from ART clinics to primary health clinics for monitoring and treatment	<i>AIDS</i> 2011; 25:2027–36
Fox M, Shearer K, Maskew M, Macleod W, Majuba P, MacPhail P, Sanne I	HIV treatment outcomes after seven years in a large public-sector HIV treatment program in Johannesburg, South Africa	<i>AIDS</i> 2012; 26:1823–1828
Maskew M, Brennan A, MacPhail P, Sanne I, Fox MP	Poorer ART outcomes with increasing age in a large South Africa cohort	<i>JAPAC</i> 2012; 11: 57-65
Wandeler G, Keiser O, Mulenga L, Hoffmann CJ, Wood R, Chaweza T, Brennan A, Prozesky H, Garone D, Giddy J, Chimbetete C, Boulle A, Egger M; IeDEA Southern Africa Collaboration	Tenofovir in second-line ART in Zambia and South Africa: collaborative analysis of cohort studies	<i>J Acquir Immune Defic Syndr</i> 2012; 61:41-8
Fox MP, Maskew M, MacPhail P, Long L, Brennan AT, Westreich D, MacLeod WB, Majuba P, Sanne IM	Cohort profile: the Themba Lethu Clinical Cohort, Johannesburg, South Africa	<i>Int J Epidemiol</i> 2013; 42(2):430-9
Maskew M, Shearer, K, MacPhail P, Fox MP	Kaposi sarcoma herpes virus and mortality following initiation with antiretroviral therapy: a prospective study among HIV infected adults in South Africa	<i>JAIDS</i> 2013; 63: 442-448
Brennan AT, Maskew M, Sanne I, Fox MP	The interplay between CD4 cell count, viral load suppression and duration of antiretroviral therapy on mortality in a resource-limited setting	<i>Trop Med Int Health</i> 2013;18(5):619-31
Maskew M, Brennan AT, Westreich D, McNamara L, MacPhail AP, Fox MP	Gender differences in mortality and CD4 count response among HIV-positive patients virally suppressed within 6 months of antiretroviral therapy initiation	<i>J Women's Health</i> 2013; 22: 113-20
Evans D, Menezes C, Mohamed K, Macdonald P, Untiedt S, Levin L, Jaffray I, Bhana N, Maskew N	Treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics across Gauteng and Mpumalanga, South Africa	<i>AIDS Res Hum Retroviruses</i> 2013; 29:892-900
Shearer K, Fox MP, Maskew M, Berhanu R, Long L, Sanne I	The impact of choice of NNRTI on short-term treatment outcomes among HIV-infected patients prescribed tenofovir and lamivudine in Johannesburg, South Africa	<i>PLoS ONE</i> 2013; 8: e71719
Takuva S, Maskew M, Brennan AT, Fox M, MacPhail P, Sanne I	Anemia among HIV- infected patients initiating antiretroviral therapy in South Africa: improvement in hemoglobin regardless of degree of immunosuppression and the initiating ART regimen	<i>J Trop Med</i> 2013; 162950

<b>Authors</b>	<b>Title</b>	<b>Publication</b>
Brennan AT, Maskew M, Ive P, Shearer K, Long L, Sanne I, Fox MP	Increases in regimen durability associated with the introduction of tenofovir at a large public sector clinic in Johannesburg, South Africa	<i>J Int AIDS Soc</i> 2013; 16:18794
Brennan AT, Shearer K, Maskew M, Long L, Sanne I, Fox MP	Impact of choice of NRTI in first-line antiretroviral therapy: a cohort analysis of stavudine vs. tenofovir	<i>Trop Med Int Health</i> 2014; in press
<b><i>Economic Outcomes of Treatment</i></b>		
Beard J, Feeley F, Rosen S	Economic and quality-of-life outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review	<i>AIDS Care</i> 2009; 21: 1343-56 PMID: 20024710
Rosen S, Larson B, Brennan A, Long L, Fox M, Mongwenyana C, Ketlhapile M, Sanne I	Economic outcomes of patients receiving antiretroviral therapy for HIV/AIDS in South Africa are sustained through three years on treatment	<i>PLoS ONE</i> 2010; 5(9): e12731 PMID: 20856821
Thirumirthy H, Galarraga O, Larson B, Rosen S	Valuing the economic benefits of PEPFAR: the effects of antiretroviral therapy on individuals, households and firms	<i>Health Affairs</i> 2012; 31: 1470-77
Rosen S, Larson B, Rohr J, Sanne I, Mongwenyana C, Brennan AT, Galarraga O	Effect of antiretroviral therapy on patients' economic well-being: five-year follow up in South Africa	<i>AIDS</i> 2014; 28: 417-24

## **Appendix 2. Conference Presentations**

<b>Title</b>	<b>Authors</b>	<b>Conference</b>
<b><i>Costs and Cost-Effectiveness of Treatment</i></b>		
Cost and outcomes of patients on second line antiretroviral treatment	Long L, Fox M, Sanne I, Rosen S	Abstract MOPE016, 5th IAS, Cape Town, South Africa, July 19-22, 2009.
The outcomes and costs of second line ART at a public treatment site in South Africa	Long L, Rosen S	4th Annual Workshop the Economic Consequences on HIV/AIDS, Amsterdam, The Netherlands, Dec 18-19, 2009
Cost of hospitalization for those presenting at an HIV treatment center in South Africa	Long L, Fox M, Rosen S	Abstract THPE0859, AIDS 2010, Vienna, Austria, July 18-23, 2010
In and out: what changes and outpatient to an inpatient and why does it cost so much?	Long L, Fox M, Rosen S	Abstract XXX, AIDS 2010, Vienna, Austria, July 16-17, 2010
Total cost and potential cost savings of the national antiretroviral treatment (ART) programme in South Africa 2010 to 2017	Meyer-Rath G, Pillay Y, Blecher M, Brennan A, Long L, Johnson LF, Moultrie H, Sanne I, Fox MP, Rosen S	Abstract WEAE0201, AIDS 2010, Vienna, Austria, July 18-23, 2010

<b>Title</b>	<b>Authors</b>	<b>Conference</b>
The cost of early versus deferred paediatric antiretroviral treatment in South Africa: A comparative cost analysis of the first year of the Children with HIV Early Antiretroviral Therapy (CHER) trial	Meyer-Rath G, Violari A, Cotton M, Ndibongo B, Brennan A, Long L, Panchia R, Coovadia A, Gibb DM, Rosen S	Abstract THLBB103, AIDS 2010, Vienna, Austria, July 18-23, 2010
The net cost of incorporating resistance testing into HIV treatment in South Africa	Rosen S, Long L, Sanne I, Stevens W, Fox MP	Abstract Z-120, CROI 2010, San Francisco, CA, Feb 16-19, 2010
Shifting management of stable ART patients from doctors to nurses in South Africa: excellent outcomes and lower costs	Long L, Brennan A, Fox M, Ndibongo B, Jaffrey I, Maskew M, MacPhail P, Sanne I, Rosen S	Abstract 43, CROI 2011, Boston, MA, Feb 27-March 2, 2011
Does time really matter? A prospective study assessing clinic flow at a large public sector HIV clinic in Johannesburg, South Africa	Magagula T, Brennan A, Ive P, Jaffray I, Matoe T, Maskew M	6th Sahara Conference, Port Elizabeth, South Africa, Nov 2011
The outcomes and outpatient costs of pediatric antiretroviral treatment in Zambia and South Africa	Meyer-Rath G, McCoy K, Ndibongo B, Nalubamba-Phiri M, Brennan A, Long L, Bolton-Moore C, Technau K, Coovadia A, Rosen S	Abstract 685, CROI 2011, Boston, MA, Feb 27-March 2, 2011
The impact of a new reference price list mechanism for drugs on the total cost of the national antiretroviral treatment programme in South Africa 2011 to 2017	Meyer-Rath G, Pillay Y, Blecher M, Brennan A, Long L, Johnson LF, Moultrie H, Sanne I, Fox MP, Rosen S	Abstract 621, SA AIDS, Durban, South Africa, June 7-10, 2011
HIV-related burden on South African hospitals in the era of large-scale access to antiretroviral therapy	Long L, Sauls C, Sanne I, Rosen S	Abstract 659, CROI 2012, Seattle, WA, March 5-8, 2012
Financial sustainability of the response to HIV and AIDS in South Africa: comparing the estimated costs of the new South African National Strategic Plan with projected estimates of available funds – exploring alternative funding options	Simelela N, Senabe S, Cleary S, Meyer-Rath G, Cohen S, Eagan D, Sozi C, Damisoni H, Guthrie T	Abstract THPE700, AIDS 2012, Washington, DC, July 22-27, 2012
<b><i>Linkage to and Retention in Care</i></b>		
What Happens to Patients Lost to Follow-up from ART Programs?: Evidence from the Themba Lethu Clinic, South Africa	Fox MP, Brennan A, Maskew M, MacPhail P, Sanne I	Abstract Z-119, CROI 2010, San Francisco, CA, 40210
Early loss to follow up after enrollment in pre-ART care at a large public clinic in Johannesburg, South Africa	Larson B, Brennan A, McNamara L, Long L, Rosen S, Sanne I, Fox M	Abstract TUPE0860, AIDS 2010, Vienna, Austria, July 18-23, 2010

<b>Title</b>	<b>Authors</b>	<b>Conference</b>
A lost opportunity: most VCT patients who test positive for HIV in a large South African clinic do not initiate HIV care	Larson B, Brennan A, McNamara L, Long L, Rosen S, Sanne I, Fox MP	Abstract Z-167, CROI 2010, San Francisco, CA, Feb 16-19, 2010
Rapid point-of-care CD4 testing at mobile HIV testing sites to increase linkage to care: an evaluation of a pilot program in South Africa	Larson B, Bistline K, Ndibongo B, Xulu T, Brennan A, Long L, Fox M, Rosen S	Abstract MOAD0103, 6th IAS, Rome, Italy, July 17-20, 2011
Point-of-care CD4 testing after HIV diagnosis to reduce losses to initiation of antiretroviral therapy: an evaluation of a pilot program of Themba Lethu Clinic, Johannesburg, South Africa	Larson B, Ndibongo B, Brennan A, Bistline K, Xulu T, Maotoe T, Long L, Rosen S, Sanne I, Fox M	Abstract MOPE450, 6th IAS, Rome, Italy, July 17-20, 2011
Rapid point-of-care CD4 testing at mobile HIV testing sites to increase linkage to care: an evaluation of a pilot program in South Africa	Larson BA, Bistline K, Ndibongo B et al	Abstract 160, SA AIDS, Durban, South Africa, June 7-10, 2011
Point-of-care CD4 testing after HIV diagnosis to reduce losses to initiation of antiretroviral therapy: an evaluation of a pilot program at the Themba Lethu Clinic, Johannesburg, South Africa	Larson BA, Ndibongo B, Brennan A et al	SA AIDS, Durban, South Africa, June 7-10, 2011
Patient retention from HIV testing to treatment initiation in Africa	Rosen S, Fox M	6th International Conference on HIV Treatment and Prevention Adherence, Miami, FL, May 22-24, 2011
From HIV testing to treatment initiation: the missing link	Rosen S, Fox M, Larson B	Abstract 110, CROI 2011, Boston, MA, Feb 27-March 2, 2011
Delayed diagnosis of HIV and high rates of loss to follow-up among pregnant women attending antenatal services at a primary health clinic in Johannesburg, South Africa	Clouse K, Maskew M, Bassett J, Larson BA	Abstract 1004, CROI 2012, Seattle, WA, March 5-8, 2012
Reduced loss to ART initiation among patients initiating cotrimoxazole prophylaxis therapy in Johannesburg, South Africa	Clouse K, Shearer K, Bassett J, Maskew M, Fox MP	Abstract TUPE737, AIDS 2012, Washington, DC, July 22-27, 2012
Attrition through multiple stages of HIV care in South Africa: a challenge for test-and-treat	Fox MP, Shearer K	Abstract Y-110, CROI 2013, Atlanta, GA, March 3-6, 2013
Current CD4 count, more than baseline, predictive of loss to follow up from HIV care	Fox MP, Shearer K, Maskew M, Sanne I	Abstract 2287906, SA AIDS, Durban, South Africa, June 18-21, 2013
Missing visits, missing opportunities: losses from care during PMTCT at primary health care clinics in Johannesburg, South Africa	Schnippel K, Mongwenyana C, Long L, Larson B	ICASA 2013, Cape Town, South Africa, Dec 8-11, 2013

<b>Title</b>	<b>Authors</b>	<b>Conference</b>
Current CD4 count, more than baseline, predictive of loss to follow-up from HIV care	Shearer K	Abstract 2287906, SA AIDS, Durban, South Africa, 41426
<b><i>Tuberculosis Economics</i></b>		
The incremental cost and diagnostic impact of rolling out the GeneXpert MTB/ RIF platform in the public sector of South Africa	Meyer-Rath G, Schnippel K, Long L, MacLeod W, Sanne I, Stevens W, Pillay S, Pillay Y, Mametja D, Mvusi L, Mabope R, Rosen S	42th Union World Conference on Lung Health, Lille, France, Oct 26-30, 2011
What to do with Xpert negatives? The cost of alternative diagnostic algorithms for TB suspects who are Xpert MTB negative in a high HIV/MDR-TB burden setting	Meyer-Rath G, Schnippel K, Long L, Macleod W, Sanne I, Rosen S	Abstract 140, CROI 2012, Seattle, WA, March 5-8, 2012
Costs of inpatient treatment for multi-drug resistant tuberculosis in South Africa	Schnippel K, Rosen S, Shearer K, Martinson N, Long L, Sanne I, Variava E	IAEN Symposium, Washington, DC, July 20-21, 2012
<b><i>Improving Treatment Outcomes</i></b>		
Examining The Interaction Between Current CD4 Cell Count, Viral Load Suppression and Time on ART and Mortality	Brennan A, Fox MP, Maskew M, MacPhail P, Sanne I.	Abstract 14-97, 14th COHORTS, Sitges, Spain, 25-27th March 2010
Importance of Clinic Attendance in the First 6 Months on ART: Missing Medical Visits Increases Mortality	Brennan A, Maskew M, MacPhail P, Sanne I, Fox M.	Abstract 821, CROI 2010, San Francisco, CA, 16-19th Feb 2010
Survival in care and CD4 cell count gain on first-line ART depend on prior CD4 cell count and time on treatment: Evidence from a large South African cohort	Meyer-Rath G, Brennan A, Long L, Rosen S, Fox MP	Abstract Z-184, CROI 2010, San Francisco, CA, Feb 16-19, 2010
The Relationship between Renal Insufficiency and Nephrotoxicity and Mortality among HIV-infected Adults on Tenofovir in a South African Cohort: A Marginal Structural Models Analysis.	Brennan A, Evans D, Fox M, Maskew M, Ive P, Naicker S, Sanne I.	Abstract O-211, CROI 2011, Boston, MA, Feb 27-March 2 2011
Rates and Cost of Hospitalization before and after Initiation of Antiretroviral Therapy in South Africa	Brennan AT, Meyer-Rath G, Modisenyane T, Fox MP, Martinson N	Abstract 15-29, 15th COHORTS, Prague, Czech Republic, 24-26th March 2011
Patient characteristics, treatment outcomes and monitoring of HIV-positive adults on ART in a large urban cohort in Johannesburg, South Africa	Evans D, Brennan A, McNamara L, Mathews C, Fox M, MacPhail P, Sanne I and Maskew M	Women in Science and Education, Kuala Lumpur Malaysia, Sept 28-30, 2011
Are sicker patients fast-tracked?	Sauls C, Brennan A, Long L, Macleod W	Public Health Association of South Africa, 2011

<b>Title</b>	<b>Authors</b>	<b>Conference</b>
Short-term impacts of a change in ART initiation threshold for patients co-infected with TB in Johannesburg, South Africa	Fox M, Shearer K, Maskew M, Brennan A, Long L, Majuba P, Sanne I	Abstract Z-104, CROI 2012, Seattle, WA, March 5-8, 2012
HIV treatment outcomes after seven years in a large public-sector HIV treatment program in Johannesburg, South Africa	Fox M, Shearer K, Maskew M, Macleod W, Majuba P, MacPhail P, Sanne I	Abstract Z-105, CROI 2012, Seattle, WA, March 5-8, 2012
Differences in virologic suppression and treatment failure over the first year on ART among patients on tenofovir comparing those given efavirenz to those given nevirapine	Fox MP, Shearer K	Abstract 16_31, 16th COHORTS, Athens, Greece, March 29-31, 2012
Incident pulmonary tuberculosis on antiretroviral therapy: 7 years of experience at the Themba Lethu Clinic in Johannesburg, South Africa	Fox MP, Shearer K, Maskew M, Brennan AT, Sanne I	Abstract TUPE120, AIDS 2012, Washington, DC, July 22-27, 2012
The Feasibility of Using Criteria to Identify Stable Patients on HAART at Themba Lethu Clinic, Johannesburg, South Africa	MacLeod W, Maskew M, Jaffray I, MacPhail P, Ive P, Fox MP	Abstract Z-172 , CROI 2012, Seattle, WA, 40969
A comparison of traditional and competing risks approaches to assess programmatic outcomes in an observational HIV treatment cohort in Johannesburg, South Africa	Shearer K, Maskew M, Fox MP	Abstract 360, Society for Epidemiologic Research 2012, Minneapolis, MN, June 27-30, 2012
Effect of 30 vs 40mg of Stavudine vs Tenofovir on Treatment Outcomes amongst HIV-positive Patients in Johannesburg, South Africa	Brennan AT, Mhairi Maskew, Ian Sanne, Matthew P Fox	Abstract Y-106, CROI 2013, Atlanta, GA, 3-6th March 2013
Incidence and risk factors associated with tuberculosis in HIV-positive children receiving antiretroviral therapy in a large South African multicenter cohort	Brennan AT, Maskew M, Schnippel K, Sanne I, Fox MP	Abstract 17_197, 17th COHORTS, Cavtat, Croatia, 11-13th April 2013
Viremia copy-years as a measure of viral load burden and associated mortality risk among antiretroviral therapy Patients in Johannesburg, South Africa	Brennan AT, Ive P, Maskew M, Sanne I, Fox MP	Abstract M-106, CROI 2013, Atlanta, GA, 3-6 March 2013
Antiretroviral treatment outcomes after the introduction of tenofovir in the public-sector in South Africa	Brennan AT, Shearer K, Maskew M, Ive P, Sanne I, Fox MP.	Abstract 17-58 and 17-59, 17th COHORTS, Cavtat, Croatia, 11-13 April 2013
The need for quantitative bias analysis in HIV/AIDS research: The case of nevirapine vs efavirenz on virologic failure in Johannesburg, South Africa	Fox MP, Shearer K, Maskew M	Abstract 17_9, 17th COHORTS, Cavtat, Croatia, 11-13 April 2013

<b>Title</b>	<b>Authors</b>	<b>Conference</b>
Human papillomavirus (HPV) testing on self-collected specimens: Perceptions among HIV-positive women attending rural and urban clinics in South Africa	Mahomed K, Evans D, Sauls C, Richter K, Smith J, Firnhaber C	Abstract 2288175, SA AIDS, Durban, South Africa, 2013
Impact of varying CD4 count levels on the prognostic value of baseline and last haemoglobin measurement on death among patients on antiretroviral therapy	Takuva S, Maskew M, Evans D, Sanne I, MacPhail P, Fox M	Abstract TUPE254, 7th IAS, Kuala Lumpur, Malaysia, June 30-July 3, 2013
The relation between NNRTI and virologic failure among HIV-infected patients in Johannesburg, South Africa	Shearer K, Brennan A, Maskew M, Sanne I, Fox MP	Abstract 2287877, SA AIDS, Durban, South Africa, June 18-21, 2013
Incidence of herpes zoster among HIV-infected patients on antiretroviral therapy in Johannesburg, South Africa - who should we vaccinate?	Shearer K, Maskew M, Majuba P, Sanne I, Fox MP	Abstract S-102, CROI 2013, Atlanta, GA, March 3-6, 2013
Predictors for discordant CD4 T-lymphocyte response in a large African cohort: an analysis comparing modelling approaches and outcome definitions	Takuva S, Maskew M, Evans D, Sanne I	Abstract MOPE207, 6th IAS Conference on HIV Pathogenesis and Treatment, Rome, July 17-20, 2011
<b><i>Economic Outcomes of Treatment</i></b>		
Non-clinical outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review	Beard J, Feeley F, Rosen S	Abstract WEPED210, 5th IAS, Cape Town, South Africa, July 19-22, 2009
The economic outcomes of ART for individual patients: three-year follow up in South Africa	Rosen S, Larson B, Darby D, Ketlhapile M, Sanne I	Abstract WEPED194, 5th IAS, Cape Town, South Africa, July 19-22, 2009.
The impact of antiretroviral therapy on quality of life and economic outcomes for South African patients: five year follow-up	Rosen S, Larson B, Rohr JK, Sanne I, Mongwenyana C, Brennan A, Galarraga O	IAEN Symposium, Washington, DC, July 20-21, 2012
The impact of antiretroviral therapy on quality of life and economic outcomes for South African patients: five year follow-up	Rosen S, Larson B, Rohr JK, Sanne I, Mongwenyana C, Brennan AT, Galarraga O	Abstract MOPE760, AIDS 2012, Washington, DC, July 22-27, 2012

### **Appendix 3. Policy Briefs and Reports**

Meyer-Rath G, Bistline K, Long L, et al. The incremental cost of introducing Xpert® MTB/RIF into the South African national tuberculosis programme: Results of the National TB Cost Model 2011/12 - 2016/17. Johannesburg: HE2RO Policy Brief Number 1, Health Economics and Epidemiology Research Office, 2011.

Long L, Brennan A, Fox M, et al. Shifting management of stable ART patients to nurses. Johannesburg: HE2RO Policy Brief Number 2, Health Economics and Epidemiology Research Office, 2011.

Larson B, Schnippel K, Ndibongo B, et al. Rapid, point-of-care CD4 testing at mobile and fixed HIV testing sites: Does it increase linkage to HIV care? Johannesburg: HE2RO Policy Brief Number 3, Health Economics and Epidemiology Research Office, 2011.

Brennan A, Shearer K, Fox M. The impact of the change from stavudine to tenofovir in first-line antiretroviral therapy in South Africa. Johannesburg: HE2RO Policy Brief Number 4, Health Economics and Epidemiology Research Office, 2012.

Meyer-Rath G, Brennan A, Long L, et al. Cost and outcomes of paediatric antiretroviral treatment in South Africa. Johannesburg: HE2RO Policy Brief Number 5, Health Economics and Epidemiology Research Office, 2013.

Rosen S, Larson B, Rohr J, Sanne I, Mongwenyana C, Brennan AT, Galarraga O. The benefits of antiretroviral therapy for patients' economic well-being. Johannesburg: HE2RO Policy Brief Number 6, Health Economics and Epidemiology Research Office, 2013.

Meyer-Rath G, Bistline K, Long L, Macleod W, Sanne I, Rosen S. The cost of the Xpert diagnostic algorithm for TB: results of the National TB Cost Model (NTCM) 2011/12 to 2016/17. Johannesburg, 2011.

Meyer-Rath G, Brennan A, Fox M, Long L, Rosen S. National ART Cost Model for South Africa. Johannesburg, 2009.

Fox M, Larson B, Rosen S. Defining retention and attrition in pre-antiretroviral HIV care: proposals based on experience in Africa. Health and Development Discussion Paper No. 15, Center for Global Health & Development, Boston University, Boston, MA, March 2012.