

**Steering the Storm: TB and HIV in South Africa**  
**A policy paper of the Treatment Action Campaign**

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## Introduction

This discussion paper sets out the policy positions of the Treatment Action Campaign (TAC) on the relationship between tuberculosis and HIV/AIDS. It is not a final policy paper.

South Africa is experiencing a potent combination of public health epidemics that cause illness, death and economic hardships in families, communities and in the country<sup>1</sup>. These epidemics include HIV/AIDS and tuberculosis.

The high HIV prevalence, a maturing AIDS epidemic and explosive TB incidence deserves more attention because current efforts to control these epidemics are failing for a number of interrelated reasons. There is still a local and global delay in adequately recognizing and responding to the importance of the co-existence and often co-infection of these two diseases in public health settings. The presence of a large number of people with TB infection pre-HIV has led to the steep rise in TB post-HIV. In countries where there was a low prevalence of TB, TB is not one of the commonest opportunistic infections, in fact it is rare.

This paper traces the current crisis of TB/HIV co-infection in South Africa to promote treatment and policy. The science, history, epidemiology, diagnosis and treatment of tuberculosis in the context of the HIV epidemic are examined.

- First, it assesses current research into the biological effects of these two diseases on one another, the mechanisms by which they fuel the TB and HIV epidemics are also examined.
- Second, TB control programs implemented by South Africa in response to global guidelines set by the World Health Organization and other groups demonstrate that these programs are not sufficient in areas with a high incidence of both TB and HIV. Community mobilization and activist pressure are necessary to improve TB prevention, diagnosis, treatment and care.
- Third, analyzing the current diagnostic tools and drugs used in TB programs in South Africa reveals that there is an urgent need for more accurate and sensitive diagnostics as well as drugs with shorter treatment times. Some of the more hopeful diagnostic and drug candidates are also briefly reviewed with special attention paid to the lack of private industry support for developing new diagnostics and drugs.
- Last, a broad overview of recommendations made by academic researchers, doctors, and international organizations in response to the TB/HIV crisis are highlighted for activists and community organizations to ensure better TB/HIV services and healthcare for all.

While this paper focuses on South Africa, the problems mentioned are not unique to this country and in fact are a good example of the situation found in most areas with a high burden of both TB and HIV. As HIV treatment activists, we have a great deal to learn and also to contribute to the development of quality public health care for all people. We have taken control of our illness and learned about its science, politics and economics. We have used songs, posters, video, television, leaflets, articles and books to educate ourselves about HIV/AIDS. Science has always formed the basis of our advocacy and work and this TB Discussion paper will help inform TAC's work in all our communities across the country.

## Summary of Recommendations

An executive summary of the recommendations are included here to help guide people on what to expect and to assist those who will find the paper difficult or may not have time to read the whole document.

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<sup>1</sup> F 400 claimants were paid R10.9 million with an average claim of R27 455.

- The World Health Organization's Directly Observed Therapy Short-course (DOTS) approach to TB control is not adequate in areas with high TB and HIV prevalence. Improved guidelines should be promoted which take into account the high numbers of sputum smear negative and extra-pulmonary tuberculosis cases found in regions with a large number of HIV positive people. WHO and South African Guidelines must be adapted to take culture from all people living with HIV/AIDS when they first present with TB symptoms.
- Directly Observed Therapy (DOT) should be adapted to include a patient-centered approach with increased treatment literacy and support groups. Treatment supporters who understand the science of TB and HIV are an important resource for the health system and the patient. Patients must be empowered to care for themselves.
- Expanded integration of TB and HIV services is necessary at the primary health care level. As results from the ProTEST initiative, work in Khayelitsha and elsewhere indicate, the potential to prevent transmission of both TB and HIV via integration of services is significant. This is a difficult but necessary task.
- More funding and research into TB diagnostics is vital to improve case finding capabilities, especially among HIV positive patients who often go undetected using the current TB diagnostics.
- Training of health workers and diagnostic tools for extra-pulmonary TB also need improvement.
- More funding and research into anti-TB drugs is necessary to reduce the treatment duration and improve completion rates. The pharmaceutical industry must be publicly forced to help in this endeavour.
- A safer and more effective TB vaccine (both priming and boosting) is needed, especially for HIV-positive infants and adults who no longer are protected by a childhood BCG immunization.

### **Recommendations for South Africa**

- TB and HIV in South Africa presents as a crisis of illness and death particularly in poor and working class communities that requires emergency action from communities, government, health professionals, international agencies, the private sector and individuals.
- South Africa's public health system urgently needs vast investment in human resources and physical infrastructure to cope with the crisis.
- The integration of TB and HIV services with treatment supporters can reduce the workload for health workers and improve patient adherence to TB treatment.
- Access to all essential drugs including TB drugs and diagnostics at all primary care facilities remains a top priority for activists, facility managers and health professionals, health departments and communities..
- A primary health care incentive-based education system must be established so that health care workers will improve their education on TB and HIV and other illnesses at community level.
- Via training and collaboration, traditional healers should be more involved in the public health system. Reasons included increased referrals and a potential role as treatment supporters.
- The Operational Plan for Comprehensive Treatment and Care for HIV and AIDS must be fully implemented as soon as possible. The improved health of HIV-positive patients taking ARVs will reduce

TB-related sickness and lower transmission rates.

- A comprehensive social security system that includes a basic income grant for all people will reduce individual and household food security. This will have a direct impact on reducing new TB and assisting adherence in TB and HIV treatment.

## **Background**

Tuberculosis (TB) is a bacterial disease most often caused by *Mycobacterium tuberculosis*. Based on signs of the disease found in Egyptian mummies, TB has affected humans for thousands of years. Once a person becomes infected with the bacteria, it often remains dormant for many years (latent TB) because a properly working immune system is capable of suppressing the infection and preventing the bacteria from multiplying. When the immune system is weakened, by HIV or poor nutrition for example, the bacteria begin to multiply and this often leads to active TB.

The vast majority (90%) of HIV-negative people infected with *M. tuberculosis* never develop TB [1]. However, when a person has active pulmonary TB (infection of the lungs, PTB, is the most common form of TB) they cough up very small infectious particles which can remain in the air for long periods. If these particles, called “droplet nuclei”, are inhaled they can establish an infection in the lungs. Direct sunlight can kill these infectious particles so transmission is most common indoors in over-crowded and poor housing conditions. It is generally accepted that the concentration of droplet nuclei in the air and the length of time a person is exposed to the air are the most important factors in determining a person's risk of exposure. For example, anyone who lives in the same home as a person with active TB is at great risk of contracting TB from them, especially if they share the same room or bed. This is a major source of transmission to young children and infants, whose immune systems are immature and therefore more susceptible to developing TB disease [2]. Although it is changing, this also helps explain why the coloured community in the Western Cape - who often live in crowded housing units - has one of the highest incidence rate for TB by ethnic group [3-6].

Tuberculosis can occur in areas other than the lungs, such as in the lymph nodes, central nervous system, and the gastrointestinal tract. This is referred to as extrapulmonary TB (EPTB) and is most common in HIV-positive people, infants and children.

### **The Epidemiology of TB/HIV**

Worldwide, over 2 billion people are infected with *M. tuberculosis* [7]. TB kills about two million people a year, with 95% of TB cases and 99% of all deaths in developing countries [8]. Of the estimated 44 million people living with HIV/AIDS, 12 million are co-infected with TB and over 66% of them live in sub-Saharan Africa [9]. An example of the rapid rise of HIV co-infection in TB patients can be found in South Africa's gold mines. According to one study in the Free State Province, the HIV prevalence rose from 15% in 1993 to 45% of all TB patients in 1996 [10]. The number of TB cases in Africa is expected to double over the next decade largely due to the HIV epidemic [11].

The risk of developing active TB in an HIV-negative individual is 10% over the course of their lifetime. This risk increases 5-10 times to 7-8% per year in HIV-positive people [1, 12-13]. A retrospective cohort study of South African gold miners found that TB incidence doubled within the first year of HIV infection, thus supporting the need for widespread HIV testing as a preventive measure against TB [14]. Research also shows that HIV infection during infancy increases the risk of developing TB [15].

There is evidence which indicates that the stage of HIV infection is correlated with increased risk of TB infection. One such study, which followed adult patients attending the University of Cape Town's HIV clinics between 1986 and 1996, revealed that a WHO clinical stage 3 or 4 was the most significant risk factor for TB [16]. This agrees with other data stating the incidence of TB in AIDS patients is 500 times that of the general population and TB likely accounts for nearly 40% of AIDS deaths in the African region [17]. TB is one of the most common opportunistic infection among people living with HIV also associated with death. Similarly, HIV is one of the strongest risk factors for developing active TB [18]. Studies show that TB recurrence rates are increasing in relation to relapse rates and this is correlated with HIV co infection. One study found recurrence rates in HIV-positive individuals at 38% compared to 23% for HIV-negative people [19]. Another study looking at South African gold miners found nearly a four-fold increase in TB recurrence rates among HIV-positive miners compared to those without HIV [20].

Not only does South Africa have one of the largest numbers of people living with HIV in the world, it has one of the highest incidence rates for TB worldwide (558 per 100,000) [21]. The TB incidence rate has increased dramatically as the HIV epidemic has worsened, with the number of TB cases more than doubling since 1996 (Tables 1 and 2).

**Table 1: TB Cases in South Africa<sup>2</sup>**

	EC	FS	GP	KZN	LP	MP	NC	NW	WC	ZA
<b>1996</b>	-	-	-	-	-	-	-	-	-	109328
<b>1997</b>	-	-	-	-	-	-	-	-	-	125913
<b>1998</b>	31763	10857	19024	28637	5500	3985	10814	2877	28820	142277
<b>1999</b>	30990	8885	17450	34481	5825	5226	9043	4698	31566	148164
<b>2000</b>	28963	9414	24861	28039	4735	5339	12191	3896	33848	151286
<b>2001</b>	36520	13024	27622	39586	10619	6925	14277	4435	35687	188695
<b>2002</b>	48 130	14 221	30 515	52 016	10 098	6 536	17 612	5 642	39 650	224420

*Source: Department of Health's National TB Control Program 2003 Fact Sheet and Health Systems Trust*

**Table 2: Incidence of TB, all types (per 100 000)**

	EC	FS	GP	KZN	LP	MP	NC	NW	WC	ZA
<b>1999</b>	565	327	224	386	109	174	537	254	757	360
<b>2000</b>	425	341	320	317	86	178	448	345	810	349
<b>2001</b>	523	462	347	436	187	224	504	396	840	426
<b>2002</b>	675	497	376	565	173	207	635	481	919	497

*Source: Health Systems Trust*

As the trends in the above data suggest, it should be no surprise that this increase is directly related to the HIV epidemic. In South Africa, more than 55% of patients with smear or culture positive TB are HIV-positive [22] and one study in hospitals associated with the University of the Witwatersrand's Department of Paediatrics showed that 42% of children with TB are co-infected with HIV [23]. In the 15-49 year old age range, 60% of all TB cases are in HIV positive people [21]. TB associated with HIV is the leading cause of death in this country. [24-25] but this is a contentious issue for politicians as the recent furor over the country's mortality statistics indicates [26-27].

What is not debatable is that co-infection with TB among HIV-positive patients increases the risk of AIDS and death [28]. More than ten years ago the evidence for this was clear. For instance, a study looking at the TB control program in the Hlabisa district of KwaZulu-Natal between 1991-1995 revealed a TB case fatality rate that was twice as high among the HIV positive patients in comparison to those without HIV

<sup>2</sup>Province abbreviations – EC: Eastern Cape; FS: Free State; GP: Gauteng; KZN: KwaZulu-Natal; LP: Limpopo; MP: Mpumalanga; NC: Northern Cape; NW: North West; WC: Western Cape; ZA: South Africa

infection [29]. No matter how politicians try to disguise the issue at hand – there is nearly a three-fold increase in TB deaths in five years aggravated by the worsening HIV epidemic - the science and supporting research cannot be denied (Table 3).

**Table 3: TB Mortality in South Africa (% of all Deaths)**

	EC	FS	GP	KZN	LP	MP	NC	NW	WC	ZA
1997	4103 (9.2)	2008 (8.0)	2834 (4.3)	5880 (8.6)	1193 (5.4)	1198 (6.1)	669 (8.0)	1922 (7.8)	1703 (5.2)	21510 (6.9)
1998	-	-	-	-	-	-	-	-	-	28487 (7.7)
1999	6162 (11.6)	3014 (9.6)	4850 (6.5)	9114 (10.8)	1802 (6.3)	2166 (8.5)	819 (9.0)	3225 (10.1)	2533 (6.7)	33685 (8.9)
2000	-	-	-	-	-	-	-	-	-	42102 (10.2)
2001	8539 (13.1)	4185 (11.4)	7299 (8.5)	15176 (14.6)	2663 (7.7)	3500 (11.2)	1122 (10.8)	4540 (11.5)	3378 (8.3)	50402 (11.2)
2002	-	-	-	-	-	-	-	-	-	59951 (12.0)

Source: Stats SA

### **TB/HIV Interactions**

The science community has responded to the increase in TB/HIV co-infection by conducting research looking at the effects, if any, these two diseases have on the progression of one another. HIV's effect on TB is better understood as it is more straightforward than tuberculosis' effect on HIV disease progression. Because the immune system uses CD4 cells to defend the body against tuberculosis, a decline in CD4 cells (due to HIV) thus lessens the immune systems ability to prevent the growth and spread of *M. tuberculosis* [1]. Additionally, a weakened immune system allows for dissemination of the bacteria to areas other than the lungs, which explains the increased likelihood of extrapulmonary TB among HIV-positive individuals.

TB has a more technical interaction with HIV and is thought to increase HIV replication and viral load, thus worsening the course of HIV-related immunodeficiency. Much research has been done to reveal the mechanisms by which these interactions occur and the general consensus is that both promoter enhancement<sup>3</sup> and cytokine activity<sup>4</sup> play key roles in the heightened HIV activity seen in the presence of *M. tuberculosis* [31-38]. Research also shows that TB may reactivate latent HIV in monocytes recruited to sites of MTB infection via a stimulatory transcription factor [39-40] and that latent HIV reservoirs are established at sites of MTB infection [41]. There is also evidence that TB increases systemic HIV heterogeneity [42-44] which could have future implications for resistance to antiretroviral (ARV) drugs.

### **Globally Coordinated TB Control Programs**

*DOTS has demonstrated serious limitations in its nearly decade-long existence – particularly since the HIV/AIDS pandemic has completely transformed the landscape of TB care.*

-Medecins Sans Frontieres (MSF) [8]

### **DOTS History**

An outbreak of multidrug resistant TB in New York in the 1990s placed the disease back on the agenda of international agencies. This was reinforced by evidence in the US of the link between TB and HIV/AIDS. The World Health Organization (WHO) joined with the International Union Against TB and

<sup>3</sup>Promoters are regions of DNA which can up-regulate the transcription of a gene. In the case of HIV, promoter enhancement can lead to an increase in the number of HIV virions produced and can activate HIV that is latently integrated in the host's DNA [30].

<sup>4</sup>Cytokines are small protein molecules involved in communication primarily between cells of the immune system that cause the cell to react in a variety of ways. For example, cytokines can induce an immune cell to proliferate or produce gene products (proteins) via a signal cascade which then act as promoter enhancers. Tumor Necrosis Factor alpha (TNF- $\alpha$ ) and Interleukin-1 beta (IL-1 $\beta$ ) are examples of cytokines which have known roles in heightening HIV activity [30].

Lung Disease (IUATLD) to develop a global plan to control the burgeoning TB emergency. The resulting program, Directly Observed Treatment, Short-course (DOTS), was launched in 1994 with the goal of controlling TB by prioritizing treatment of the most infectious (smear-positive) patients who self-report to health services. A standardized treatment of 6-8 months for all these sputum smear-positive (sm+) patients with directly observed therapy for at least the initial two months are key tenets of the plan [45]. South Africa first adopted the DOTS strategy in 1996 [21].

The five elements of DOTS<sup>5</sup>

- Sustained political commitment
- Access to quality-assured TB sputum microscopy
- Standardized short-course chemotherapy to all cases of TB under proper case-management conditions
- Uninterrupted supply of quality-assured drugs
- Recording and reporting system enabling outcome assessment

The WHO's decision to advocate DOTS was based in part on data from the Netherlands spanning the 1950s to 1970s that found TB control programs should focus on diagnosis and treatment of active TB cases and that preventive therapy had little effect on TB control [46, 47]. Besides the obvious fact that this data is not representative of TB in poor countries and is from a period in history when HIV was unknown, it is also based on active case-finding, which contradicts the WHO's self-reporting requirement. Furthermore, the WHO goal of detecting 70% of all sm+ cases and curing 85% of them results in at best 26% of all TB cases being treated because only 44% of TB cases are sm+<sup>6</sup> [7]. This also presumes all TB is acquired from smear positive cases. Using 2001 data indicating that only 80% of all PTB cases in South Africa had sputum smear microscopy results available [48], the cure rate following DOTS would be less than 21%! However, this low cure rate is also due in part to diagnostics that are more than 100 years old and inadequate facilities, which we discuss later.

Such a low cure rate is not sufficient to eliminate TB globally or in South Africa – where 182 of 183 sub-districts implement DOTS with a 54% cure rate [13] - as is evidenced by the rising TB incidence seen over the past decade [13, 21, 49]. This is not to say DOTS is an ineffective treatment plan, because in certain settings it has shown promise (i.e. resource-rich and areas with low HIV prevalence). However, in its present form, DOTS is not the best option in poorer countries with high HIV prevalence, such as South Africa, because “...it is difficult to implement DOTS in all but the most stable settings” [8]. In the Eastern Cape, Mpumalanga (and many other areas) facilities regularly run out of TB drugs – it is then impossible to expect a high cure rate.

As a consequence of the WHO focus on sm+ patients, sm- patients are often neglected. Infants, children and late stage HIV-positive patients are most likely to present with sm- results [1, 8, 49]. Between 1998 and 2001, sm- rates increased in South Africa from 10% to 15% and this trend is continuing [50]. The ratio of extra-pulmonary TB to PTB is also increasing in South Africa, with roughly 23% of all 2001 TB cases being classified as EPTB [Table 4]. In particular, the Cape Town metropole region has shown an increase in EPTB from 10% to 16% of all TB cases over the years 1998-2002 [51].

<sup>5</sup> <http://www.who.int/tb/dots/whatisdots/en/>

<sup>6</sup> 70% (.70) x 85% (.85) x 44% (.44) = 26%

**Table 4: TB Cases by Type in South Africa**

	<b>PTB Cases</b>	<b>All TB cases</b>	<b>% PTB</b>	<b>% EPTB</b>
<b>1996</b>	92380	109328	84	16
<b>1997</b>	104141	125913	83	17
<b>1998</b>	115537	142277	81	19
<b>1999</b>	118686	148164	80	20
<b>2000</b>	120075	151286	79	21
<b>2001</b>	144910	188695	77	23

*Source: Health Systems Trust*

The reluctance of some South African health care workers who have specialized in TB management to alter their practices in light of the HIV epidemic is highlighted by the increasing sm- and EPTB case load. For example, an analysis of HCW in Khayelitsha revealed “many of the TB staff do not have the confidence to identify extra-pulmonary or smear negative TB,” [52] so these patients are often untreated. The TB services have been geared to PTB and smear positive. Therefore, a patient with two negative smears will be regarded as not infected with TB. The TB programme rigidity and emphasis on smears means that very often health professionals treat a smear rather than a patient.

Recommendation:

- The paradigm of the TB programme needs to be changed. World Health Organization's Directly Observed Therapy Short-course (DOTS) approach to TB control is not adequate in areas with high TB and HIV prevalence. Improved guidelines should be promoted which take into account the high numbers of sputum smear negative and extra-pulmonary tuberculosis cases found in regions with a large number of HIV positive people. Nurses must be trained to identify smear negative and extra-pulmonary TB. With such training nurses must be allowed to treat smear negative TB patients with TB medicines.

### **DOTS Issues**

Directly Observed Therapy (DOTS) itself is a debatable issue for a number of reasons. The DOTS model has its roots in paternalistic public health approaches that makes the public health official the decision-maker on behalf of the patient and the community. Central to the limitation of DOTS is the fact that people with tuberculosis have to take their treatment under observation by someone else every weekday for six months. Patients are not regarded as independent, autonomous people with the dignity and ability to take control of their own health or illness. People with TB are treated as “public health cases”. The HIV epidemic has shown that in every part of the world, people living with HIV/AIDS learn about the science and clinical progression of HIV/AIDS and most importantly how to play a direct role in their own treatment. People living with HIV/AIDS have demystified the names of drugs and their side-effects. Through treatment literacy programmes and treatment support rather than observation, people with HIV/AIDS understand why adherence is important.

Patients often cannot afford to travel to treatment centers daily just so a health worker can watch them take their drugs [53-54]. With TB loads over 1000 on treatment at any one moment at many clinics it is just physically impossible to observe these sorts of numbers. Because of ambiguous implementation guidelines for DOTS, some health workers purposely de-select patients who are not likely to comply with therapy [47]. In addition, there is conflicting evidence as to whether DOTS is more successful than self-supervision of treatment. Some studies conducted in South Africa show no difference between the two methods [47, 55-57] while others indicate daily supervision by a family member or health worker improves treatment completion rates [13, 58]. The costs associated with DOTS far exceed the drugs themselves and as case loads increase, staff shortages will limit the number of patients receiving DOT [8]. A study in Pakistan suggests that it is the

support that patients get that makes the difference rather than the observation.

Lastly, the contradiction between ARV and TB drug guidelines is unfounded. Both regimens require daily doses of multiple drugs and interruption can be life-threatening in either case yet those taking ARV often collect their drugs only once a month at the clinic and are entrusted to follow the treatment guidelines. For the many HIV-positive patients taking ARVs who must also undergo anti-TB therapy, this DOTS paradox can be a source of aggravation and unnecessary burden. Similarly, a portion of patients perceive DOTS as mistrust in their ability to care for themselves and this may decrease the level of responsibility they take for self-care [59-60].

Recommendation:

- Directly Observed Therapy (DOTS) should be adapted to include a patient-centered approach with increased treatment literacy and support groups. Treatment supporters who understand the science of TB and HIV are an important resource for the health system and the patient. Patients must be empowered to care for themselves.

### **ProTEST Initiative**

In response to the unique public health situation in areas with high incidences of both TB and HIV, WHO established the ProTEST initiative in 1997 to increase collaboration between TB and HIV/AIDS control programs. Key interventions include [61]:

- stakeholder and health service collaboration
- improved access to high-quality voluntary HIV counselling and testing (VCT)
- intensified case-finding and treatment of active TB for HIV-positive clients to reduce transmission of *M. tuberculosis*.
- isoniazid preventive therapy (IPT) to treat latent TB infection in HIV-positive clients
- co-trimoxazole preventive therapy (CPT) to reduce morbidity and mortality due to HIV-related opportunistic infections
- HIV prevention (including condom promotion, treatment of sexually transmitted infections, prevention of mother-to-child HIV transmission)
- improved clinical care for people living with HIV/AIDS (PLWHA)

Of the six initial ProTEST project sites established in 1999, four were spread throughout South Africa (Limpopo, KwaZulu Natal, Eastern Cape, and Western Cape) [61] which had recognized the need to improve collaborations between its TB Control Program and HIV/AIDS & STD Program during national reviews in 1996 and 1997 [25, 61]. Results through 2002 from the four sites in South Africa suggest VCT prevented over 6000 new HIV infections and nearly 2000 new TB cases.<sup>7</sup> Rapid HIV testing resulted in a 10 fold increase in the number of people coming for testing over the trial period and also increased the number of both self-referrals and people receiving their HIV test results. Over 2800 HIV-positive patients were put on IPT to prevent TB and roughly 2400 were put on co-trimoxazole prophylaxis [25, 61].

Recommendation:

- Expanded integration of TB and HIV services is necessary at the primary health care level. As results from the ProTEST initiative indicate, the potential to prevent transmission of both TB and HIV via integration of services is significant.

<sup>7</sup>According to the National Primary Health Care Facilities Survey 2003, 31% of people who get tested for HIV after receiving VCT are HIV-positive [62].

## **South Africa's TB Control Program**

South Africa's TB Monitoring and Evaluation Framework is divided into four components [13]:

1. The International Framework for TB control
  - South Africa signed the Amsterdam Declaration to Stop TB of March 2000 which commits the country to accelerated action against TB
2. The National Strategic Health Plan
  - Health Goals, Objectives and Indicators (HGOI) include a number of indicators related to TB and the co-management of TB and HIV [63]
3. The National TB Control Program (NTCP)
  - Overall objectives outlined in the TB Medium Term Development Plan (MTDP)
  - Short term objectives to be achieved by 2005 include cure rates of 80-85% among sm+ TB cases, detect 70% of new sm+ cases, and achieve DOTS coverage in all districts
4. The TB Recording and Reporting System
  - Based on data collected through TB registers

The ProTEST Initiative results led South Africa to prepare a five-year national plan to implement the lessons learned throughout the country in TB/HIV training districts. The plan is being funded in part by the Belgian Technical Cooperation and \$25.1 million from the Global Fund to Fight AIDS/TB and Malaria [21, 61]. Integrated TB/HIV care will be provided in all districts starting in the 2004/2005 financial year guaranteeing all TB patients will be offered VCT and all HIV-positive clients will be offered screening and treatment with CPT or IPT [13]. Unfortunately, this exists on paper only. There is resistance to integration especially where TB and HIV services are provided by different levels of government.

A specific example of the success of integrating TB and HIV services is the Ubuntu clinic in Site B Khayelitsha. Located just outside Cape Town in the largest township in the Western Province, the integration of services at Ubuntu clinic has been a collaborative process over the past three years incorporating many lessons from the ProTEST initiative. The Health Departments of both the city of Cape Town and the provincial government have assisted Medecins Sans Frontieres and the Infectious Disease Epidemiology Unit of the School of Public Health and Family Medicine at the University of Cape Town in formulating and implementing an integrated response to the TB and HIV epidemics. Highlights of the integration process include [131]:

- Via expanding VCT services, the number of TB patients who know their HIV status increased from 22% to 54% among one cohort
- Development of an algorithm to diagnose TB in patients with smear negative samples, which is common amongst people with advanced stages of HIV infection
- “One-stop” service where patients can be treated simultaneously for both TB and HIV reduces traveling and waiting time
- Increased service efficiency via training TB staff in HIV care and vice-versa leads to better patient care and allows doctors to focus on the more complicated cases
- Using a patient-centered approach to adherence via TB support groups and treatment literacy reduces the DOTS burden on understaffed clinics, patients and improves cure rates
- Experiences from the longer-running TB programs can be used to inform the scale-up of antiretroviral therapy in South Africa

The success of the Ubuntu clinic's integration of services has also revealed pitfalls in the public service system. The clinic has more new patients presenting with TB and/or HIV each month than any other clinic in the province. In addition, chronic staff shortages greatly limit patient care. For example, there are not enough nurses and counsellors to offer VCT to every patient. In addition, integration of TB and HIV services requires the alignment of two distinct service philosophies. This depends upon management

oversight and must be formally advocated by the Department of Health in order to realize the potential of integrating TB and HIV care.<sup>8</sup>

Provincial data indicates that the current attempt to manage the TB epidemic is falling far short of the government's goal (Table 5). Recent national cure rates, 54% in 2001, are well below the WHO goal of 85% and KwaZulu-Natal had a cure rate below 37% in 2001. The interruption rate of new smear positive cases is 12%, which may be a significant future source of multi-drug resistant TB in the population.

**Table 5: TB cure rates and interruption rates of new sm+ cases (%)**

	EC	FS	GP	KZN	LP	MP	NC	NW	WC	ZA
<b>2000 Cure Rate</b>	46.3	54.9	68.1	38.1	48.7	46.7	56.2	47.2	63.4	54
<b>2001 Cure Rate</b>	47	64.1	58.2	36.5	46.7	53.1	58.7	50.4	65.3	53.7
<b>2001 Interruption Rate</b>	12.8	8.9	12.9	12.1	10.2	12.9	15.9	7.9	12.2	12

*Source: Health Systems Trust*

The South African TB control program is hindered by a rigid implementation of the TB guidelines and also by the inadequate TB facilities in the country (Table 6). That less than 90% of facilities surveyed offer TB diagnosis and treatment is inexcusable in a country with the advanced epidemic found in South Africa. With only 89% of all facilities stocking TB drugs nationwide, there are too many opportunities for patients with active TB to go untreated and to transmit infection.

**Table 6: Services available in 2003 at Primary Health Care Facilities (% of all facilities)**

	EC	FS	GP	KZN	LP	MP	NC	NW	WC	ZA
<b>VCT</b>	54	96	76	53	78	88	64	59	81	70
<b>TB Diagnosis and Treatment</b>	92	100	74	91	88	89	88	97	97	89
<b>DOTS available</b>	85	92	71	78	68	88	87	91	86	81
<b>TB Drugs available</b>	91	96	97	90	77	93	100	93	74	89
<b>Off-site access to HIV (ELISA)</b>	78	96	90	56	59	66	43	40	72	70
<b>Off-site access to Sputum Microscopy</b>	92	100	99	89	79	100	100	97	94	93
<b>On-site access to HIV Rapid test</b>	31	22	37	27	64	77	55	59	93	47
<b>On-site access to Sputum Microscopy</b>	33	26	62	60	8	78	97	97	43	50

*Source: Health Systems Trust' National Primary Health Care Facilities Survey 2003*

Roughly half of all facilities offer on-site HIV testing and sputum microscopy, which is far too few considering the transportation and financial difficulties of most patients in rural settings. Such patients are less likely to follow-up on results if the facility they attend has to send their tests off-site, which takes an average of 6.1 and 5.5 days for HIV (ELISA) and sputum microscopy respectively [62]. This situation is the norm in places like Limpopo, where only 8% of facilities have on-site sputum microscopy and helps explain why the number of annual TB cases in this province has nearly doubled since 1998 [64].

What these numbers indicate is that in addition to TB treatment guidelines which do not adequately account for the HIV epidemic in this country, the health care facilities themselves are ill-equipped to properly implement the already ineffective guidelines. The compounding effect is additive at best and exponential at worst as increasing numbers of patients with TB (many HIV positive) are misdiagnosed and continue to infect others. The burden on the public health care system due to inadequate facilities results in a positive-feedback cycle whereby more patients come for help but their needs are not met and thus they continue to get sick (often because of HIV) while also putting healthy individuals at risk who will then also require public health care. Hence the importance of scaling up guidelines and facilities which address the TB/HIV co-epidemics in South Africa in order to integrate chronic and infectious disease management at the primary care level.

<sup>8</sup> In a parliamentary media briefing, Dr Manto Tshabalala-Msimang said it was important to "separate TB from HIV" [132].

As evidenced by the ProTEST initiative, South Africa's response to the TB/HIV crisis mostly mirrors WHO recommendations and guidelines. However, as has been detailed in this section, South Africa is not implementing these less-than-ideal guidelines effectively. While increased TB/HIV collaboration efforts and well-equipped facilities are necessary throughout the country, policy changes will not impede the progression of the TB epidemic in South Africa without significant improvements to the sensitivity, efficacy and price of TB diagnostics and drugs. It is these issues which we turn to next.

Recommendation:

- South Africa's public health system urgently needs vast investment in human resources and physical infrastructure to cope with the crisis.
- This requires the determined and unequivocal support of government and its public acknowledgment of the health crises facing the country.
- Access to all essential drugs including TB drugs and diagnostics at all primary care facilities remains a top priority for activists, facility managers and health professionals, health departments and communities..

## The TB Treatment Tool Case

### Current Diagnostics

This section examines the lack of funding and development that TB diagnostics have received. It includes a brief comparison with HIV diagnostic development. The first AIDS-related deaths were documented in 1981 [65], the HIV virus was discovered in 1983 [66], and the first antibody test for HIV was approved for use in 1985 [67]. These early tests were not widely available as they required well-trained lab technicians and expensive instruments in order to use them. Results took weeks and they were primarily reserved for developed countries which had the infrastructure to implement them.

As the HIV/AIDS epidemic became the leading health crisis the world over through the next decade, vast quantities of money were given to skilled researchers who worked to develop highly sensitive, inexpensive and rapid diagnostics to test for HIV. In less than 20 years since the first antibody test was developed, a person can now wipe a swab stick in their mouth and get their HIV status within 20 minutes. No laboratories or skilled technicians are required, no blood is needed, the test is 99% accurate and it is inexpensive [68]. This rapid improvement in diagnostics was due to prioritizing HIV/AIDS as a global health threat, large increases in funding, and international collaboration to combat the epidemic. Drug companies also invested in such tests because of the market for them in rich countries. As the lack of adequate tuberculosis diagnostics indicates, TB has not received the same level of concern because it is a disease of poor countries and communities..

Despite the research and funding put into TB over the past decades, sputum smear microscopy remains the primary tool to diagnose active tuberculosis. Developed nearly 125 years ago, sputum smear microscopy requires the patient to cough up sputum samples in order to look for the presence of *M. tuberculosis*. Positive results are termed sputum smear-positive (sm+). Children and immunocompromised individuals can rarely cough up enough sputum for adequate results [1]. Gastric lavage and sputum induction help a lot but require expertise. Furthermore, this technique is primarily designed to detect pulmonary TB and is unable to detect extra-pulmonary TB, (smears are generally used to diagnose EPTB – from the fluid from aspirates etc or histology) which is often found in children and HIV-positive patients [1]. It is thought that sputum smear microscopy detects 45-60% of all people with active TB [8] and only 35-38% of HIV+ patients [69-70].

Case-finding results in South Africa indicate that the number of sm+ cases are decreasing in proportion to sm- cases [13] and some believe that by 2005, 45% of TB cases in South Africa will be sm- in HIV+ persons [71]. Currently, 56% of all prevalent TB cases worldwide are sm- (9.1 million people) [7]. Importantly for the growth of the epidemic, sm- individuals can transmit TB infection to others [72] and may be responsible for 1.4 million new cases of TB each year [49].

Diagnosis of these individuals is based on chest x-rays, culture or, most often, the clinicians' judgment. Chest Xrays are often very helpful in diagnosing TB but often there are no changes at all and one can still not stay there is no TB. Also there has often been previous damage to the lung and one does not know what is new and old. Chest x-rays are often inconclusive in children and HIV+ patients because of immature or weakened immune systems [8] Other respiratory infections such as chronic bronchitis or pneumonia may disguise TB or may be mistaken for TB. Clinics in poor communities do not have on-site culturing facilities (Table 6) nobody does culture on site and it takes up to 6 weeks to get results, which increases the time a person with active TB can transmit the disease [1]. The lack of proper diagnostics is exacerbated in HIV+ children [18] and often means that "diagnosis of PTB in children is therefore nearly always presumptive" [1].

An additional diagnostic for determining TB infection is the tuberculin skin test. But in areas like South Africa with a high TB prevalence, the test is of "little value" as it cannot distinguish between infection and active disease [1]. This complicates treatment decisions in HIV+ people where most TB is due to re-activation of latent infection [17] or re-infection with TB. False-positives are common due to previous environmental exposure to the bacteria and false-negatives are common in late stage HIV+ patients [1]. The skin test returns a positive result in only a minority of HIV+ children infected with TB [18]

While the epidemic of multi-drug resistant (MDR) TB in South Africa is not as widespread as it is in Eastern Europe [73], the number of MDR-TB cases in this country is higher than the global median [13] and diagnostic options for screening drug-resistant TB are time-consuming and expensive. Public health facilities rely on culture tests which take up to six weeks for results because they are done off-site. Collection (transport) and communication of results are among the biggest causes of delay

### **New Diagnostics**

The shortfalls of the current TB diagnostic tool case have been publicly noted [74] for over a decade: "...new technologies should be made available without delay to non-industrialised nations...The complexity of health threats posed by TB will not yield to a simple solution" [75]. Yet, the impossibility of controlling the TB epidemic when the tools to diagnose the disease are insufficient did not deter the WHO from continuing to promote its DOTS strategy as a "one size fits all" answer [1, 49]. Showing progress, the WHO has more recently acknowledged the gross disparity between what tools are available for diagnosis and what is needed:

*The statement in the early 1990s that DOTS was the only solution was a great mistake. We now accept that we need both DOTS and new tools, that it is not a competition between these two approaches.*

-Dr. Raviglione, Director, Stop TB. Meeting, July 3<sup>rd</sup>, 2003.

The commercial interest in TB diagnostics and drug resistance tests is higher than that for TB drugs because of significantly lower development costs, a decent developed-country market, and a sufficiently advanced state of TB diagnostic science [8]. Many major drug companies, including GlaxoSmithKline, Astra-Zeneca, and Eli Lilly, no longer invest in TB diagnostic research so the bulk of research is done by academic institutions and smaller biotech firms. Funds for diagnostic research also come from public-groups like the National Institutes for Health, who provides US \$2 million a year for TB diagnostic research [8]. More recently, the Foundation for Innovative New Diagnostics (FIND) launched in 2003 with \$30 million

from the Bill and Melinda Gates Foundation [76]. Several promising diagnostics are being co-developed by FIND as we shall soon discuss.

New TB diagnostics are divided into three main groups: serological tests, phage-based systems, and molecular methods. Serological tests are antibody based and have shown high specificity but low sensitivity which limits their use in PTB diagnosis [77]. A sensitive assay, ELISPOT, was recently developed that is more accurate than tuberculin skin tests for identification of latent TB infection [78] but application in poor settings is still prohibited by technical requirements. A patch test, MPB64, has also shown positive results in detecting active TB and will soon be available on the market [79].

Phage-based diagnostics show more promise in poor settings because they do not require sophisticated materials or lab skills. In May 2004, FIND announced an investment in Biotec Laboratories to speed development of its FASTPlaque™ technology [80]. FASTPlaqueTB is capable of detecting 54% of sm- cases and is more sensitive than standard sputum smear microscopy [81-82]. Results are available in as little as 48 hours and FASTPlaqueTB can also be used to detect MDR from sputum. FIND's backing of this technology indicates the promise it holds for improving diagnosis and also ensures developing countries will have access to the technology, as early as 2005, at the cheapest price [80]. This requires significant community mobilization to ensure access in poor countries and communities globally.

Diagnostics based on molecular methods most often are based on PCR amplification or molecular probes. While some show promise in diagnosing TB in children [83], others have far too much fluctuation in sensitivity and specification [84-89]. Furthermore, the technical requirements for lab staff and equipment may preclude use of these tools in resource-poor settings and have been shown to cause wide variation in results between laboratories [90].

The standard for diagnosis of TB infection has been culture tests because of its high sensitivity. The downside to this method is that it takes between 6-8 weeks to get a result which has serious consequences for increasing transmission of TB. Salubris has developed TK Medium®, an inexpensive media which cuts culture time in half using color dye indicators to allow for early visual detection of the TB bacteria. TK Medium® also can be used to test for drug resistance. FIND began investing in this technology in July 2004 with the aim of introducing TK Medium® in district level laboratories in developing countries that use the slower culture medium or lack culture testing capabilities [91].

Becton, Dickinson and Company (BD) has a technology for rapidly culturing *M. tuberculosis* that has been used by industrialized nations for some time. BD's Mycobacteria Growth Indicator Tube (MGIT) system provides results in 10-14 days and can also determine if the bacteria is resistant to TB drugs but it has not been used in the developing world because of its cost and infrastructure constraints. However, a late 2004 development agreement with FIND aims to introduce this technology into resource-poor settings with high HIV prevalence using a two-phase plan of demonstration and implementation on financial terms that are sustainable for high-burdened countries [92].

These diagnostic tool improvements, when widely used in South Africa and other countries with high rates of both TB and HIV, will be a pronounced step towards reducing the spread of TB. However, current anti-TB drugs also need significant improvements to make a significant long-term reduction in the TB epidemic.

Recommendation:

- More funding and research into TB diagnostics is vital to improve case finding capabilities, especially among HIV positive patients who often go undetected using the current TB diagnostics.

- TAC and its allies locally and internationally must mobilize and advocate for the rapid development through public academic institutions of new point of use TB tests.
- A modification of the TB treatment protocols culture must be taken immediately from every patient so that a smear negative does not mean that active sputum undetectable TB will go untreated.

### **Current Drugs**

The WHO recommends five first line anti-TB drugs: isoniazid(H), rifampicin(R), pyrazinamide(Z), streptomycin (S) and ethambutol (E). Of the, pyrazinamide is the “newest”, having been discovered 35 years ago. While these drugs have been around for many years, they do deliver great results (95% cure rate) in ideal settings [8]. Unfortunately, ideal settings are rare in reality.

TB drug treatment is divided into two phases: the initial phase, lasting two months, contains a combination of four drugs (HRSZ); the continuation phase uses less drugs and lasts either 4 or 6 months depending on the drug regimen used (HR and HE respectively) [1]. Recent evidence indicates that the 6-month continuation phase using HE is “significantly inferior” to the 4-month continuation phase using HR [93]. Although South Africa has altered its treatment guidelines to account for this research, many TB control programs in poorer countries are hesitant to switch over to HR because it is more expensive [11], among other reasons such as program inertia [94]. South Africa has been one of the countries that have pioneered fixed-dose combinations for TB medicines in the last five years. Currently, the WHO recommends the use of fixed-dose combinations for these drugs to simplify treatment [95-96].

The treatment course lasts so long because the drugs have weak sterilizing activity and length of treatment is considered the biggest drawback of the current anti-TB drugs. Side-effects of TB drugs are hardly ever explained to patients. Anecdotal evidence suggests that one of the reasons for treatment interruption is unmanaged side-effects. The extensive treatment period without adequate treatment counseling and support results in many patients not completing the full course of therapy and this serves to increase MDR-TB among the population as well as retreatment rates [13]. In South Africa for example, 12% of new Sm+ patients failed to complete treatment in 2001 (Table 7).

**Table 7: Interruption Rate for New Sm+ Cases**

	<b>EC</b>	<b>FS</b>	<b>GP</b>	<b>KZN</b>	<b>LP</b>	<b>MP</b>	<b>NC</b>	<b>NW</b>	<b>WC</b>	<b>ZA</b>
<b>2001</b>	12.8	8.9	12.9	12.1	10.2	12.9	15.9	7.9	12.2	12

*Source: Health Systems Trust*

While TB treatment is equally effective in early-stage HIV+ and HIV- patients [97], patients in the advanced stages of HIV infection are less responsive to therapy [69]. Furthermore, drug interactions between the two most potent anti-TB drugs and antiretrovirals are now established. Rifampicin interacts with a liver enzyme responsible for metabolizing protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI)<sup>9</sup>. This can cause blood levels of PIs and NNRTIs to fall below the minimum threshold level to prevent HIV replication and can increase resistance to these ARVs. Conversely, PIs and NNRTIs also interact with the same liver enzyme and can alter rifampicin levels [1].

Isoniazid (INH) can cause peripheral neuropathy, with an increased risk in people over 35 years of age. Some of the ARVs, such as stavudine (D4T) and didanosine (ddi), cause peripheral neuropathy. Taking INH and these ARVs simultaneously may increase the likelihood of peripheral neuropathy [1]. In both the rifampicin and isoniazid cases, there is potential for added toxicity which, which is already an area of

<sup>9</sup>Rifampicin interactions with Kaletra (lopinavir/ritonavir combination PI) and Nevirapine (NNRTI) can cause liver toxicity and reduced levels of these ARVs.

concern for people taking ARVs indefinitely. The long term effect of taking ARVs and anti-TB drugs is not well understood because this situation has only recently developed but it is reasonable to assume that a shortened TB treatment regimen would be less damaging to the liver of ARV users.

As mentioned above, the extended treatment time leads many patients to interrupt their course of therapy especially if they have not received counseling or treatment literacy on the need for adherence. Some also fail to complete the course because large health improvements early on lead them to believe they are cured and no longer need to take the drugs. Both of these factors lead to an increased incidence of multi-drug resistant TB [8]. MDR-TB is defined as resistance to both isoniazid and rifampicin and it may be spreading by 250,000 to 400,000 cases per year [98].

Treatment of MDR-TB uses much less effective (60% cure rates) drugs with administration lengths of 18-24 months and increased side effects [99]. Drugs used to treat MDR-TB are primarily of the fluoroquinolone class and are extremely expensive. Prior to the MSF and WHO efforts to reduce the price of these drugs, complete treatment cost US\$8,000-13,000. It is now US\$2,500-3,500, which still makes the cost of treatment prohibitive to provision in most resource-poor settings [8]. A report from the city of Cape Town Cape indicates that the per patient cost for MDR drugs was over R30,158 (\$5,100) in 2002, as compared to R8,428 (\$1,400)<sup>10</sup> for standard TB drugs [51]. Because South Africa's MDR-TB incidence (1.7%) falls below the WHO standard of 3% of new cases [13], the organization does not help procure MDR-TB drugs for the national TB program.

The primary fault of the current anti-TB drugs is the length of treatment necessary when using them. New drugs are thus aimed towards reducing treatment duration.

### **Financial Considerations Relating to New Drugs**

A direct consequence of TB eradication in developed countries because of decreases in poverty and better health care during the 1960s and 1970s was a complete lack of research into new drugs for TB over the course of nearly two decades, despite the fact the epidemic was uncontrolled in developing nations. This was primarily due to drug companies placing higher importance on profits than human lives [11]. The Global Alliance for TB Drug Development(GATB) estimated the worldwide TB drug market to be \$450 million in 2000 expanding up to \$640 million in 2010 [100] with developing countries representing the bulk of the need. Because these countries usually purchase by tender and the private sector for TB drugs is a mere \$113 million, pharmaceutical companies have little financial interest in TB drug research. In fact, only five of the world's 20 largest drug companies self-reported doing TB drug research in 2001 [101].

Further examples of the pharmaceutical industries indifference to the TB epidemic abound. When the GATB was launched in October 2000 its goal was to bring one new TB drug to market by 2010. It had hoped to gain access to “forgotten” pharmaceutical compounds but of the 103 compounds brought in by the GATB's 2000 Call for Proposals, not one was from industry. The second Call for Proposal in 2003 continued the ambivalent pharmaceutical industry trend [8]. This also requires national, regional and global activist mobilization.

Despite the general absence of pharmaceutical corporations from new TB drug development, public groups and academia are aggressively working to help alleviate the epidemic. Funding from GATB (\$150 million over five years) and a multi-billion dollar pledge from the Seven Industrialized Nations for new drugs and vaccines for HIV/AIDS, TB and malaria represent significant global commitment to developing new drugs [11].

<sup>10</sup>Conversion factor is \$1 = R5.84 (March 11, 2005)

## **New Drugs**

New drug research is of two varieties: those that enhance the activity of existing anti-TB drugs and those that develop novel drugs using molecular tools such as genomics, proteomics and combination chemistry [8, 11]. Novel drugs take much longer - upwards of 10 years - to develop. Unfortunately, most of the novel TB drugs are in the earliest stages [8].

The cheaper fluoroquinolone drugs not used extensively in MDR-TB have recently been looked at for use in first-line treatment regimens [102]. Evidence supporting use of these drugs in the first-line regimens is limited and numerous studies are underway to determine optimal dose and duration of administration [11].

Rifabutin and Rifapentine, drugs of the same class (rifamycins) as Rifampicin are also being looked at for anti-*M. tuberculosis* activity. Studies indicate that rifabutin may be more effective than rifampicin and it is as well-tolerated [103-104]. Significant for HIV+ patients, rifabutin has less enzyme-inducing activity than rifampicin, which means it does not interact with ARVs nearly as much [11]. Rifabutin is the US drug of choice for patients coinfecting with TB and HIV taking ARVs [8].

Rifapentine is a long-acting rifamycin with the benefit that it does not need to be given so frequently, which reduces the need for directly observed therapy. Studies have shown that the drug is tolerated at high concentrations [105] and future plans are to market rifapentine as a once weekly dose in combination with a fluoroquinilone [11, 106].

There are few novel drugs in the development pipeline currently but those that are could revolutionize TB treatment. The GATB's most promising drug is the nitroimidazopyran PA-824. It has bactericidal activity against both active and latent *M. tuberculosis* and against drug resistant strains of TB [107]. GATB licensed the drug from Chiron in 2002 and if the drug makes it to market, Chiron has agreed to forgo all royalties on sales in less-developed economies [8]. This would be a tremendous advancement against TB in all areas.

An even more promising anti-TB drug, Compound J, is in the earliest stages of development. The drug works by disrupting a *M. tuberculosis* enzyme critical to providing energy to the bacteria (ATP synthase). Compound J has no interactions with other drugs (including ARVs) and is twice as effective as the best current anti-TB drugs. Additionally, it moves readily to the lungs and is effective against latent and MDR TB. Human studies also show that the drug is well-tolerated [108].

Though the future shows much promise for anti-TB drugs, it will be at least five years before any drugs with great potential make it to market. Steps to speed up this process without jeopardizing the health of future users – via increased funding, public/private collaborations, and clinical trial enhancement in resource-poor settings for example – should be advocated and pursued promptly.

## **The Need for Help from the Pharmaceutical Industry**

Both Compound J and PA-824 serve to highlight the need for pharmaceutical involvement in TB drug development. The researchers behind Compound J are employed by Johnson and Johnson Pharmaceutical Research and Development and PA-824 was originally a by-product of cancer research in the 1990s. The fact that the most promising new anti-TB drugs are both indebted to the pharmaceutical industry is no coincidence and the general negligence on the part of the pharmaceutical industry is a direct reason why so few new anti-TB drugs are on the horizon.

How many possible compounds are currently going unused because of the pharmaceutical industry's profit-based operational model? Research that implicates Toll-like Receptor 2 in induction of HIV

expression by Mycobacteria [109] provides a target that one of these unused compounds may have an effect on. Similarly, a compound may already exist in a drug company vault that inhibits the p38 MAP kinase signaling pathway, which would result in the inhibition of HIV replication [30, 38]. But unless researchers, activists and governments, compel the pharmaceutical industry to make available these and other potentially life-saving compounds, many improved treatments will never be realized.

Recommendation:

- More public funding and research into anti-TB drugs is necessary to reduce the treatment duration and improve completion rates.
- The pharmaceutical industry must be publicly forced to help in this endeavour.

## Vaccines

BCG (Bacille Calmette-Guerin), the only existing TB vaccine, was first used in 1921. It is a live weakened bacteria derived from *M. bovis* (a cousin of the TB bacteria) that is routinely given to newborns in areas with high TB prevalence. While it does confer protection to young children against disseminated and severe TB [110-111], it has little protective benefits for adults [112]. In addition, vaccination of HIV positive infants with BCG can lead to disseminated BCG infection [113]. Despite these limitations, BCG is still the gold standard by which all new vaccines are measured because of its cheapness, safety, and history. Widespread use of BCG means that new vaccines are either designed to be given to newborns as a BCG replacement (priming vaccines) or to individuals already exposed to mycobacteria or vaccinated with BCG (booster vaccines) [114].

The leading candidates for priming vaccines use recombinant BCG or *M. tuberculosis* and show equal or higher rates of efficacy than the current BCG strain used in vaccinations [115-116]. There is also evidence which suggests that a *M. tuberculosis*-derived vaccine could be used safely in areas where HIV and TB co-infection are common. In one study which gave immunodeficient mice a vaccine using a mutant strain of *M. tuberculosis*, the mice were protected against subsequent tuberculosis infection and were not at risk of developing infection from the vaccine itself [117]. Such a vaccine for HIV positive infants is preferable to the current BCG model because the risk of vaccine-induced BCG disease children would be removed. Vaccines using recombinant BCG are close to entering the clinical trial stage but vaccines using weakened strains of *M. tuberculosis* must still undergo extensive tests to verify the bacteria will not revert back to virulence [114].

Booster vaccines are designed to increase waning TB immunity in adults and use DNA and/or protein sub-units of *M. tuberculosis* to accomplish this goal. Animal studies with adjuvanted protein vaccines show BCG-related immunity can be boosted [118-119]. Booster vaccines promoting cell-mediated immunity have shown even greater success and are currently in clinical trials or scheduled to enter human trials this year [120].

The delivery of vaccines is another area of research development and much progress has been made in mucosal delivery mechanisms [114]. This is especially important for TB because *M. tuberculosis* most often establishes infection in the lungs. Such a delivery mechanism is easier to administer than injection and reduces risks associated with blood. This boosting mechanism has proven successful in animal models [121] and the first TB vaccine using this delivery model was expected to enter clinical trials in 2004 [122].

The success of any TB vaccine must be measured by a decrease in the incidence of TB. Since TB is most common in adults, decades must pass before the effectiveness of the vaccine is properly understood [114]. This reduces the likelihood of widespread implementation of any new TB vaccines in South Africa, or

anywhere else for that matter, for a considerable amount of time.

Recommendation:

- A safer and more effective TB vaccine (both priming and boosting) is needed, especially for HIV-positive infants and adults who no longer are protected by a childhood BCG immunization.

## Recommendations

Having briefly outlined the current state of affairs in the world of TB , we look at recommendations to improve the highlighted problems.

A change in the philosophical approach to public health and all people with tuberculosis is necessary. We are not “cases” who should be managed. Public health and the right to dignity requires that every person with tuberculosis receive fullest information about her or his health, how to improve and maintain it. Most importantly, we need to take control of our own health and treatment for illnesses such as tuberculosis. This requires a patient-centred approach rather than direct observation. People with tuberculosis, our families, friends, health care professionals and communities can be mobilized effectively to ensure public education, treatment literacy, sufficient drugs in clinics, support for health professionals, better diagnostics and better living conditions and health care for all.

While the DOTS plan does have its benefits, ample evidence indicates that it is not a sufficient response to control TB in areas with a high prevalence of HIV. This global strategy must be made more flexible to account for the unique epidemiological backgrounds found throughout the world [49]. Though the WHO approach to DOTS has been more expansive in recent years [47], such as promoting FDC of TB drugs and allowing TB patients to select their DOT supervisor, this flexibility is not enough. A change in approach is essential. This is not only necessary to affirm autonomy and dignity of people using health care but it is central to overcome the challenges of limited diagnostic tools noted in the increased smear negative numbers, the problems of preventing and treating TB in children, the specific problems of HIV positive people and coinfecting with tuberculosis.

Research showing treatment of both latent and active TB in HIV+ patients is more effective in controlling the epidemic than current strategies [123-124] is echoed by the WHO/UNAIDS joint recommendation for preventative therapy in HIV+ patients [125] and indicates the WHO is willing to adopt new strategies to combat TB/HIV. Yet the WHO still insists “DOTS is the right approach but that everything must change” [8]. This contradiction creates confusion that muddies the waters for everyone involved, including country program organizers and health practitioners. As the world's leading health institution, the WHO must provide a consistent approach to TB control.

The dearth of both drugs and diagnostics that are inexpensive, efficient, and safe in TB treatment demands increased funding and a fast-track mechanism to bring promising drugs and diagnostics through the development pipeline as quickly as possible. MSF suggests that the WHO team up with governments to develop and fund a clinical research agenda to aid in this endeavour [8]. TAC endorses this demand. MSF also calls on governments to demand that companies make available for development any compounds that have potential anti-TB activity. TAC also endorses this demand. Changes in the current intellectual property regime are necessary for this.

In poor households, communities and countries , those who need treatment the most often are the least able to afford it because the cost of TB and HIV treatment are well over 10% of household income in

most these cases [53]. Governments and global organizations such as WHO, IUATLD, and UNAIDS must collaborate to make treatment more affordable so that health care costs including prices of medicines are no longer a deterrent to receiving health care. If more people can access health care transmission rates will fall.

In addition, the lessons of the ProTEST Initiative and the integration of TB/HIV services in Khayelitha need to be expanded to all areas with high burdens of both TB and HIV as promptly and efficiently as possible. The beneficial effects of this type of TB/HIV collaboration can not be stressed enough and the comprehensive results could far exceed expectations.

A last point to consider is the need to place treatment interventions in the context of those procuring them. The West dictates biomedical guidelines for the rest of the world with relatively little consideration of the cultural milieu in which these guidelines will be implemented. As is evidenced by treatment literacy efforts relating to HIV in African countries, those affected by the disease are eager to educate themselves in a manner specific to their cultural background and their experience with HIV. In bolstering treatment literacy of TB in areas with a high incidence of the disease – a recommendation based in part on the success of such efforts in response to HIV/AIDS - this lesson must be applied to TB such that intervention efforts make sense to people in the context of their everyday life [47].

Most of the above recommendations are applicable to South Africa but others which are specific to this country are reviewed below.

### **South Africa's Specific Issues**

The 2004 South African Health Review suggested that “lack of management capacity, poor management systems and inadequately trained and motivated staff at district levels” were key reasons why the National TB Control Program has failed [13]. These same factors also play an integral role in the HIV epidemic in this country and remedying the situation may require a substantial overhaul of the entire public health system. As Table 8 shows, too few of the primary health care workers in this country are properly trained to handle TB and HIV on their own, let alone during co-infection.

**Table 8: Percent of Staff undergoing PHC Training updates**

	<b>EC</b>	<b>FS</b>	<b>GP</b>	<b>KZN</b>	<b>LP</b>	<b>MP</b>	<b>NC</b>	<b>NW</b>	<b>WC</b>	<b>ZA</b>
<b>HIV/AIDS counselling and testing</b>	29	26	27	24	30	32	37	38	48	30
<b>TB Diagnosis and Management</b>	43	29	33	24	20	23	48	18	32	29
<b>Prevention and Treatment of opportunistic infections and HIV related diseases in adults</b>	39	9	28	20	12	18	48	15	28	24

*Source: Health Systems Trust' National Primary Health Care Facilities Survey 2003*

A comprehensive health human resource plan for the country is overdue. This needs to encompass conditions of employment, under-staffing (including administrative and ancillary staff), salaries, incentives such as bursaries for children if staff remain at district and primary care level. Further education of health professionals need to be scaled up countrywide as soon as possible.

Along these same lines, traditional healers and community health workers need to be utilized as a vital resource in improving the health of all people in South Africa. Considering that significant numbers of our people may use traditional healers as their primary health care source [126], traditional healers should be brought into the fold, so to speak, and receive basic primary health care training including tuberculosis and HIV management.

To ensure a stable and trustworthy partnership, the relationship with traditional healers should not be one-sided. To this end, levels of research by the South African Medical Research Council (MRC) and other institutions into traditional medicines used to treat TB should be increased. Not only would scientific evidence be found confirming or denying a role for these medicines in treating TB, but traditional healers would appreciate the increased respect such research brings from the empirically-based medical community.

As was mentioned in the general recommendation section, TB treatment literacy efforts need to be expanded and improved immediately. Following its pivotal role in treatment literacy related to HIV/AIDS, the Treatment Action Campaign (TAC) should lead this effort at the community level. Furthermore, the Department of Health's plan to implement the ProTEST Initiative lessons country-wide must be put into effect as soon as possible in order to realize the preventative benefits of such TB/HIV collaborations. There is a synergistic potential between the increased integration of TB/HIV services and a more robust treatment literacy program that should not be overlooked by those responsible for these interventions. Subsequently, it is hoped the Department of Health will come to recognize the enormous support the TAC is capable of providing and will embrace the organization as an ally in the improvement of health for all South Africans.

Another plan that must be fully implemented as soon as possible is the Operational Plan for Comprehensive Treatment and Care for HIV and AIDS. While providing life-saving treatment to the 500,000 South Africans that currently need ARVs is reason enough to suggest the South African government follow through on its 2003 promise, a secondary result of implementing the plan would be reduced transmissions of TB and decreased burdens on the public health system due to the improved health of hundreds of thousands of HIV+ individuals on ARV treatment [128-129]. In addition, modeling indicates that such measures would be economically feasible and could save the government over R7 billion in the future [130].

Individually, the South African TB and HIV epidemics are among the world's worst. Yet the combination of the two in a country with the economy, infrastructure and political system of South Africa provides an opportunity to mount a powerful and effective response. For example, South Africa could expand its already impressive clinical trials infrastructure such that any new TB diagnostic or anti-TB drug could efficiently and cheaply undergo Phase I through Phase III testing here. Gearing the clinical trials system towards therapeutics and diagnostics most needed in this country (i.e. those related to TB and HIV) is a strong statement to the international research community that South Africa is prepared to help play its part in research.

## **Conclusion**

TAC requests that everyone forward comments, additions, inaccuracies and views on this paper to [zackie@tac.org.za](mailto:zackie@tac.org.za) before 10 August 2005. And, if you wish to discuss some of the points, please mail [activist@tac.org.za](mailto:activist@tac.org.za) any time. In this way, we can all learn. A special thanks to Dr Hermann Reuter of MSF and Dr Dave Coetzee of UCT.

This paper has attempted to show the complex yet interrelated issues that fuel the TB epidemic in South Africa and other areas with a high HIV burden. While it tries to comprehensively analyze the current situation, some research and insights have definitely been overlooked. For instance, alcohol abuse and its roll in exacerbating TB and undermining adherence. The gender dimensions of tuberculosis is another area not examined. But, the central message is that people living with HIV/AIDS are at greater risk for infection, illness and death with tuberculosis. Our country has among the highest burdens of both illnesses. Prevention, treatment and care of tuberculosis must be on the agenda of every HIV activist. Just as HIV/AIDS should be a priority for everyone involved in health promotion.

By providing evidence to the shortcomings in the global response to TB and HIV , from treatment strategy pitfalls to antiquated diagnostics and sluggish drugs, the need for a new approach is highlighted. Though cutting-edge research in TB diagnostics, drugs and vaccines reveal improvements to the present state are on the horizon, any new approach to TB cannot solely rely on these tools as they are not enough to meet the challenge.

Employment and social security are critical to alleviate poverty in all poor households, communities and countries. Poverty increases vulnerability and risk to tuberculosis and HIV just as all other forms of inequality and subordination undermine prevention, treatment and care. South Africa is no different.

Finally, the recommendations made are only small steps towards an improved approach to TB management and are by no means definitive answers to the problems created by TB and HIV epidemic interactions.

The point is not that there is a specific path that we must take to control TB in HIV settings, but that we must make the best decisions based on lessons from the past, present circumstances and future considerations. This issue will plague many areas of the world, including South Africa, for decades to come. Ignorance cannot be an excuse – South Africa has more useful research on the impact of HIV and TB than most other countries – the problem is activists, government, researchers, trade unions, broader civil society and the private sector do not use research to improve our understanding and real conditions of life.

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