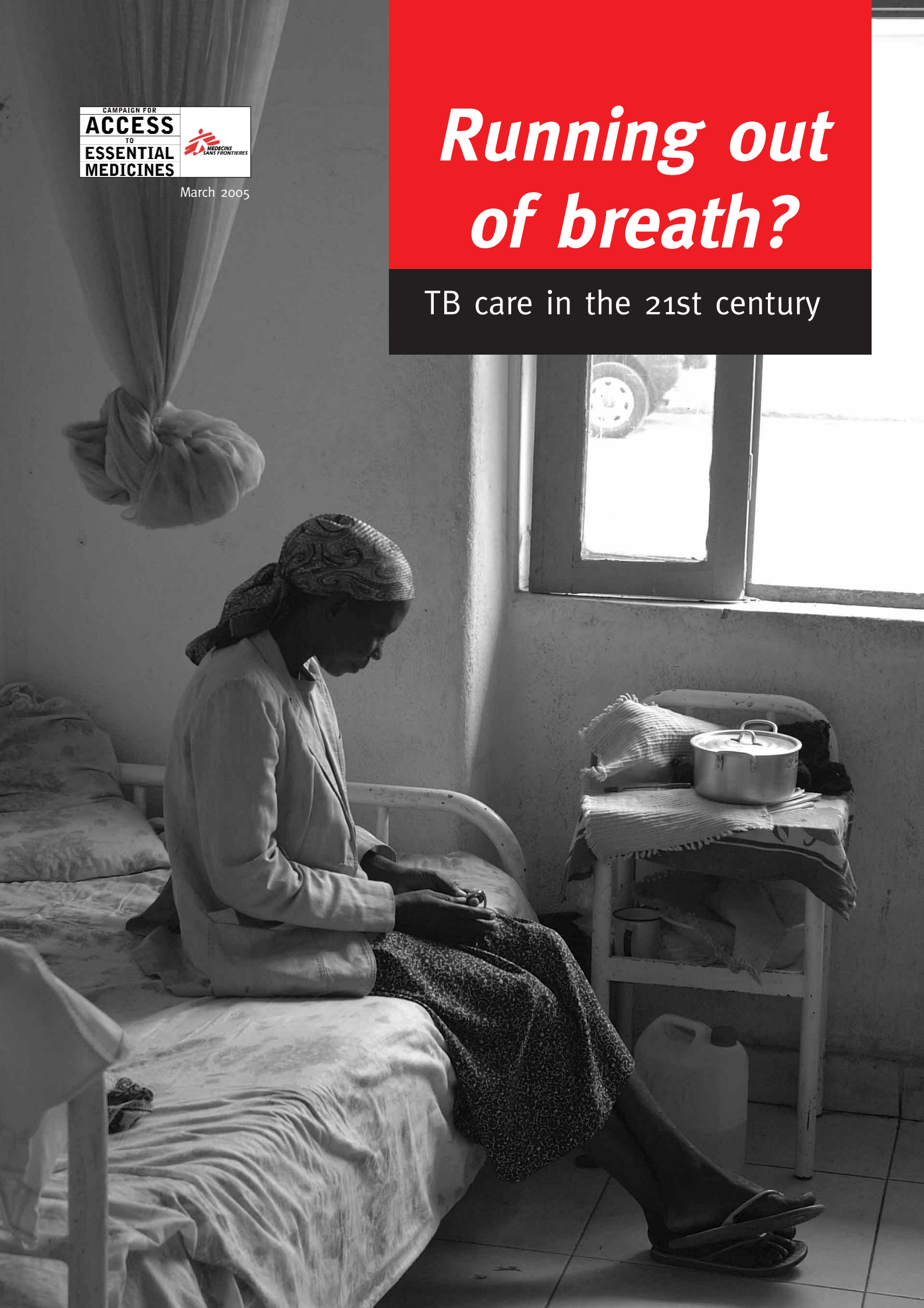

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

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Running out of breath?

TB care in the 21st century

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1. INTRODUCTION

1.1. Purpose of the document

Like other organizations and health care providers involved in treating people with tuberculosis (TB), MSF has first-hand experience of the current WHO-recommended strategy to control TB, DOTS (Directly Observed Treatment Short-Course). While most MSF and other experts agree that DOTS is the "best approach we have", 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. In the past three years, MSF has been delivering antiretroviral (ARV) treatment to individuals in need in even the most resource-poor settings by adapting treatment protocols and counselling and monitoring methods accordingly. The HIV/TB co-infection has magnified the limitations of DOTS and is changing MSF's thinking on how care provided to people living with TB might be improved.

This paper takes a critical look at current TB control efforts: programme strategy (DOTS), diagnostic tools and treatments, as well as research and development (R&D) needs. It hopes to spark debate about how people suffering from TB can best be helped, and especially what role MSF can play on the medical, operational and political levels. Recommendations are made in Section 6.

This current version of the report is intended for MSF staff and will be shared with members of the international TB community in order to stimulate debate and contribute to the overall effort to dramatically improve TB diagnosis and treatment.

1.2. Background on tuberculosis

TB has afflicted humans for thousands of years; signs of the disease were found in Egyptian mummies. In the 19th century TB killed an estimated one-quarter of the adult population of Europe. Due to improved standards of living and the discovery of antibiotics in the 20th century, the disease had all but disappeared in industrialized countries by the 1950s.

But today TB is making a comeback. One in three people in the world is infected with the tuberculosis bacillus – they have latent TB. Normally only a small proportion – roughly eight million people per year - of these progress to the clinical disease known as active TB, in the vast majority of cases characterized by a lung infection. Those with active pulmonary TB are the most likely to spread the TB bacilli to others.

TB kills roughly two million people every year. Around 95% of all patients with active TB live in the developing world, where 99% of all TB deaths occur.

1.3. 19th and 20th century tools still used

TB is one of the world's best-studied killers. Yet TB tools have remained unchanged for decades, despite their acknowledged poor performance.

The fundamental diagnostic test for active tuberculosis – sputum smear microscopy for acid-fast bacilli – was developed by Robert Koch, the discoverer of *Mycobacterium tuberculosis*, in 1882. If a person's sputum sample tests positive by microscopy, they are called smear-positive: they have active TB and are infectious. Designed to detect pulmonary forms of TB, the test doesn't spot the 20% of patients who have extra-pulmonary TB. Its detection rates in children with pulmonary TB are even lower, at only 5%, because children aren't able to cough up sputum samples with detectable levels of bacteria. Overall, smear microscopy can at best detect around 45-60% of people who have active TB.

Tuberculin, the basis of the screening test for latent TB, was also developed by Dr Koch in 1890. It delivers unreliable results in patients who have previously received a TB vaccination or been infected with other species of mycobacteria. Severely immunodeficient patients test negative with tuberculin, which limits the test's usefulness in screening people with AIDS.

The existing TB vaccine, BCG, was first used in 1921. Although it has been widely used to vaccinate children around the world, it offers limited protection to adults and its overall efficacy is considered modest[1].

The first TB drug, streptomycin, was developed in 1944 followed by the discovery of p-aminosalicylic acid (PAS) in 1949, isoniazid in 1952, cycloserine in 1955, rifampicin in 1965, ethambutol in 1968 and

[1] Colditz GA et al. Efficacy of BCG vaccine in the prevention of tuberculosis; JAMA 1994 Mar 2; 271 (9):698-702.

Photo © Robert Malleta / MSF H

pyrazinamide in 1970[2]. PAS and cycloserine were rapidly abandoned due to their toxicity, but the rest of these old drugs still form the backbone of standard TB treatment to date. In ideal settings (i.e. in countries with functioning infrastructure and low HIV-prevalence), they deliver excellent results with cure rates of up to 95% in drug sensitive TB. This success depends on accurate diagnosis and the patient complying with six to eight months' treatment.

1.4. Emergence of resistant strains

Because TB treatment is so arduous, people often interrupt it. Exact data is hard to come by, but at least 4% of all TB patients worldwide are resistant to at least one of the current first-line drugs. In parts of Eastern Europe, nearly half of all TB cases resist at least one first-line drug. Multidrug-resistant TB (MDR-TB), defined as resistance to at least rifampicin and isoniazid, the two most powerful TB drugs, might be spreading as fast as by 250,000 - 400,000 new cases each year[3]. Their treatment relies on "second-line" TB drugs that have far lower efficacy and require even longer administration periods (18-24 months) – with much higher cost and much higher rates of adverse effects.

While MDR-TB affects countries with poor health infrastructure, it is just as likely to break out in industrialized economies. During the late 1980s and early 1990s outbreaks of MDR-TB in North America and Europe killed over 80% of those who contracted it[4]; e.g. in 1993, a total of 488 MDR-TB cases were reported in the US[5].

[2] Duncan K. Progress in TB Drug development and what is still needed; Tuberculosis (2003) 83, 201-207
[3] Dye C, Williams B et al. Erasing the World's Slow Stain: Strategies to Beat Multidrug-Resistant Tuberculosis; Science, 15 Mar 2002, Vol 295: 2042-46; www.tballiance.org/2_1_2_MDR_TB.asp
[4] www.tballiance.org/2_1_2_MDR_TB.asp
[5] Bulletin of the World Health Organization, 2000, 78 (2), p. 239.

1.5. MSF and TB

MSF has been confronted with tuberculosis since its first day of operation more than 30 years ago. In 2004, 16,500 patients were treated for TB in 50 MSF projects in 24 countries[6].

Although treating a large number of patients in its clinics, MSF used to be reluctant to cover TB more extensively. This was because MSF was concerned that due to the temporary nature of its medical relief work, patients under treatment would be lost to follow-up, which in turn would create community drug-resistance. This is why, as a rule, very few patients in conflict areas and refugee camps were treated against TB[7].

However, in the past few years, MSF has expanded TB treatment to include a growing number of projects, and the focus has shifted from disease control to patient care. Alternative models have been found to treat migrants or nomadic people who are extremely difficult to follow[8]; for instance, efforts to facilitate patients' lives by reducing their need to come to a clinic have been made, including home-based care in Cambodia and factory-based treatment in Thailand. Fifteen MSF projects now treat TB patients in chronic conflicts, including work in Abkhazia, South Sudan and in refugee camps in Chad and Thailand. An increasing number of patients receive TB care through MSF in general health centres, e.g. in South Sudan, Congo, DRC and Angola. MSF has worked to identify reliable sources of easier-to-use fixed-dose combinations (FDCs) of TB drugs and expand their use in its own projects.

But many patients still have no access to TB treatment in countries where MSF has missions. For instance, not all MSF HIV/AIDS programmes directly provide TB treatment in sub-Saharan countries although TB is the most important opportunistic disease affecting HIV/AIDS patients.[9] Often patients are referred to national TB programmes which are not able to effectively treat co-infected patients. In addition, too few patients have access to second-line treatment for MDR-TB: although MSF has documented high rates of drug-resistance in six programmes in the Former Soviet Union (FSU), currently only 200 patients receive MDR-TB treatment[10]. Three projects treat TB patients exclusively in therapeutic feeding centres (TFC) and two offer treatment in prison settings (Abkhazia/ Georgia, Abijan/Côte d'Ivoire) – a third project (Kemerovo/Russia) was closed in September 2003 because national authorities disagreed with MSF's proposed treatment strategy although it was in accordance with WHO guidelines. Finally, paediatric formulations of FDCs are not widely available in the countries MSF works in.

MSF staff generally confirm that DOTS doesn't work in many of the environments MSF projects are, and that it is difficult to implement DOTS in all but the most stable settings. The following sections take a closer look at the major shortcomings of the DOTS strategy and tools and some potential avenues for change.

[6] Angola, Afghanistan(*), Abkhazia/Georgia, Burundi, Cambodia, Caucasus/Chechnya, Chad, China, Congo, Côte d'Ivoire, DRC, Ethiopia, Guinea, Kenya, Liberia, Malawi, Myanmar, Nepal, Nigeria, Sudan, Somalia, Thailand, Uganda and Uzbekistan.

[7] "In active conflict areas, with open warfare and/or great instability TB programmes are precluded, given that their continuity cannot be guaranteed for a sufficiently long period, and that activities may be disrupted at any moment. In some areas of relatively low intensity conflict, there may be an acceptable level of tranquillity and stability. MSF often works in such areas for extensive periods; assuming that basic health needs are adequately addressed, the initiation of a TB programme may be worthwhile, but only under exceptional circumstances." MSF Medical News: MSF and Tuberculosis. Policy Paper. Vol 4, 1, April 1995.

[8] TB villages (Manyatta) in South Sudan, Ethiopia; treatment delivery for illegal Burmese migrants in factories in Thailand.

[9] Tyholo in Malawi where all the TB patients have access to VCT, cotrimoxazole prophylaxis and ARVs. HIV patients can be treated for TB in Mathare, Kenya, but in most of the HIV/AIDS programmes once a patient is confirmed or suspect of having TB, (s)he is usually referred to the NTP.

[10] The following rates of MDR have been recorded: 31% in Kemerovo prison in Siberia, 27% in Karakalpakstan (Uzbekistan), 11% in Dashoguz Veylat (Turkmenistan), 24% in Almaty Oblast (Kazakhstan), 12% in Abkhazia (Georgia) and 6% in Karabagh (Azerbaijan). Patients are treated in Karabagh, Abkhazia and since September 2003, TB treatment has been provided in Uzbekistan.

2. LIMITATIONS OF THE CURRENT GLOBAL STRATEGY FOR CONTROLLING TB

2.1. The introduction of DOTS

Up until the 1990s, TB management had been disorganised and ineffective. Treatment regimens varied widely; ambulatory non-observed treatment was common; and reporting mechanisms were largely absent. There was little interest in TB, including from WHO, which had a TB budget of only $10 million in 1992-93.

Due to various factors, including an outbreak of multidrug-resistant TB in New York in 1991-93 and growing evidence of the link between TB and HIV/AIDS, this began to change. The WHO and IUATLD (International Union Against TB and Lung Disease[11]) started to raise the profile of TB as a global emergency and developing a new global approach to it. DOTS, i.e. Directly Observed Treatment Short-Course, was launched in 1994. It is a public health-based management strategy aimed at controlling TB by focussing on the most infectious (smear-positive) patients.

DOTS is based on five key principles[12]:

- Government commitment to sustained TB control activities.
- Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services.
- Standardised treatment regimen of six to eight months for at least all sputum smear-positive cases, with Directly Observed Therapy (DOT) for at least the initial two months.
- A regular, uninterrupted supply of all essential anti-TB drugs.
- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control programme overall.

The DOTS approach was partly based on evidence that detecting 70% of smear-positive, i.e. the most infectious patients and curing 85% of these could reduce TB incidence by 6% per year – effectively halving TB in 10 years. In order to ensure resources were primarily directed towards infectious patients, DOTS divides patients into four categories ranging from high priority smear-positive patients (Cat. I) to low priority (MDR-TB) and chronic cases (Cat. IV)[13], recommending that "at least all" Category I patients be treated, with other categories being treated as resources allowed.[14]

DOTS drugs: First-line TB treatment relies on six drugs: isoniazid, thiacetazone, rifampicin, pyrazinamide, streptomycin and ethambutol. The drugs complement each other and are used in various combinations. They are available in cheap, generic forms and are effective if taken as prescribed. Unfortunately their weak sterilising activity means they must be administered for 6-8 months to achieve cure; and the patient must take them under the surveillance of a health worker or equivalent for the first two months, due to the rapid development of resistance if treatment is not completed.

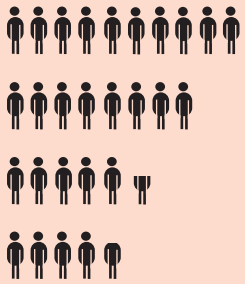
WHO sources say DOTS was not only conceived as a medical approach but also as a brand, designed to provide a simple clear message to Western donors and developing country policy-makers.[15] The message was that the five DOTS principles – and only the five DOTS principles - could deliver global TB control.

DOTS supporters believed that DOTS was the most realistic approach: even by using existing tools, finding and treating the most infectious TB patients could deliver global TB control – this was an improvement compared to the low cure rates and the generation of abundant drug resistance linked to non-DOTS approaches.

Figure 1 illustrates that DOTS minimum goals exclude a large number of TB patients – even if there was a 100% reliable diagnostic tool with which to detect the desired 70% of all people with active pulmonary TB. In real-life circumstances, case finding rates are much lower: the most commonly used existing test, smear microscopy, only detects 45-60% of all pulmonary TB cases (36-48% of all people with TB).

[11] The IUATLD is a scientific umbrella organisation of 140 member countries and 100 voluntary scientific societies working on TB and other lung diseases in middle- and low-income countries.
[12] www/who.int/gtb/dots/whatisdots.htm
[13] Treatment of TB: Guidelines for National Programmes. WHO/CDC/TB 2003.313: p. 33
[14] Category I is new smear-positive pulmonary patients plus severe cases from category III. Category II is previously treated smear-positive patients who have relapsed, failed treatment or defaulted; Category III is new smear-negative pulmonary patients and extra-pulmonary TB; Category IV is chronic patients and MDR-TB cases (still sputum-positive after supervised re-treatment).
[15] Ogden J et al. The politics of "branding" in policy transfer: the case of DOTS for TB control; Social Science & Medicine 57 2003, pp.179-188

Figure 1. DOTS detection and cure rate goals:



100% All people with active TB (about 8 million new cases per year)

80% People with active pulmonary TB

56% DOTS case finding goal: 70% of all active pulmonary patients

48% DOTS treatment goal: 85% cure rate for detected smear-positive patients

In the pre-AIDS era, the decision to focus on smear-positive patients was less controversial than today, since non-infectious smear-negative patients had less progression to life-threatening TB disease and lower mortality rates (around 40-50% overall within two years)[16]. It was argued that the risks of excluding many smear-negative patients from treatment were outweighed by the overall public health benefit of treating more infectious TB patients – and that, in any case, there were no tools to diagnose, monitor or track smear-negative patients[17].

2.2. Concerns largely ignored

The decision by WHO to back DOTS as the answer to TB was questioned by the medical, academic and scientific communities. There were widespread objections in industrialized countries to WHO's conservative decision to build their TB strategy around existing TB tools rather than developing more effective diagnostics, vaccines and drugs[18]. WHO and its supporters, on the other hand, argued for "restraint in the adaptation of new technologies by non-industrialised nations"[19], noting that "new technologies are expensive and there is a danger that their introduction would divert attention and money away from the real issues ... the global challenge of TB lies in the implementation of old, tried and tested technologies."[20]

Others were troubled by DOTS' simplified "one size fits all" strategy, noting that it was based on pilot studies in nine developing countries[21], and that the results, particularly the failures (Senegal, Mali and Yemen), were not properly analysed.

Objections were also raised over the lack of evidence in favour of direct observation in different social and economic contexts as well as ethical concerns about patients' rights to privacy in the DOTS treatment and reporting process (see also p. 11-13). Among MSF and others, there were also concerns about a framework that prioritised public health over individual patient rights, evaluating the patient's right to treatment in terms of their potential to spread the disease[22]. This argument has become even more resonant in the era of AIDS.

2.3. DOTS: what has been achieved

The debate over DOTS has calmed down over the past five years. Critics have learnt to appreciate DOTS' good points and WHO has toned down what some saw as an inflexible approach to DOTS implementation, in particular as regards direct observation.[23] The supporters of DOTS and those pushing for new and better tools are finding some mutual ground.[24] DOTS' strong focus on smear-positive patients has also softened, with Stop TB now stating that DOTS programmes should aim for around 60% smear-positive patients. In the latter half of the 1990s, WHO developed the DOTS-Plus strategy to include MDR treatment as a public health activity.

After nearly 10 years, DOTS is now in place in 155 out of 210 countries. More than ten million patients were diagnosed by DOTS programmes between 1995 and 2001[25]. It has proven to have significant advantages over the previous chaotic management of TB in three particular areas that stand out if successes are examined in isolation:

[16] Bedell R. Tuberculose, sida, ethique; Utopies Sanitaires 2000, p.153
[17] For an excellent critique on the ethics of these policies, see Bedell R, op.cit; pp.147-164
[18] The Editor of Lancet wrote in 1994 that "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"; a prescient comment, given current difficulties in managing HIV/TB co-infected patients. (Editorial: Tuberculosis in HIV infection; Lancet, 1994, 344, 277-278.)
[19] Kochi A, Global challenge of tuberculosis control (Letter); Lancet: 1994, 344, p.608-9
[20] Maher D. (Letter); Lancet: 1994, 344, p.610
[21] Malawi, Mozambique, Tanzania, Kenya, Benin, Senegal, Mali, Nicaragua and Yemen, and later Vietnam and China. Personal correspondence with Donald Enarson, IUATLD, August 18th 2003.
[22] Brauman R. (conference proceeding) in "Human Rights Dialogue", review of the Carnegie Council on Ethics and International Affairs, Spring/Summer 2001, series 2 number 6.
[23] Ogden J et al. Op. cit., pp.179-188
[24] Dr Raviglione, Director, Stop TB. Meeting, July 3rd 2003.
[25] WHO Global TB Control report 2003, pp.1, 37 www.who.int/gtb/publications/globrep/pdf/tb_reprint_final.pdf

1. DOTS consistently delivers better results than non-DOTS TB programmes. The percentage of notified new smear-positive pulmonary cases is 60 under DOTS compared to 36 under non-DOTS programmes (because sputum microscopy is one of the cornerstones of DOTS); overall cure rates for new smear-positive patients are 77% compared to 52%; and treatment success (cure or completion of treatment) is 82% under DOTS compared to 67% under non-DOTS.[26] Non-DOTS programmes also have high rates of default (14%) and non-evaluation of outcome (8%).

2. DOTS allows improved management and monitoring of TB. TB programme managers can use smear-positive incidence to develop a TB treatment delivery structure and track quality of care, while WHO/Stop TB can use more reliable DOTS statistics to track the course of TB globally and in each country. In non-DOTS programmes, where smear microscopy is inconsistently used, it is impossible to follow the outcome of individual patients since both diagnosis and cure are frequently based on clinical judgement alone.

3. The DOTS branding process has garnered increased attention and resources for TB, in particular in developing countries who now fund 69% of DOTS treatment. Although many poor countries fail to spend adequately on TB, others devote a substantial percentage of the national health budget to it, for example Cambodia (9%), Zimbabwe (8%) and Kenya, Uganda and Nigeria (all over 6%). Multilateral funding has also increased, with new Global Fund and World Bank money (a grant to China) reducing the estimated TB funding gap for 2001-2005 from $1.4 billion (WHO 2002 estimate) to the current figure of $1.2 billion.[27] Nevertheless, many countries continue to fall short of the funds needed for further DOTS implementation, with WHO reporting the documented country-level gap in high-burden countries at $219 million and the probable gap at $838 million for 2001-2005. Funding of operational research and research into new TB tools is also sub-optimal.

Successful examples of DOTS implementation cited include Peru, Nicaragua, Sudan, Middle Eastern countries (Iran, Syria, Morocco) and Beijing's 1978 DOTS-style programme.

Specialists agree that DOTS can and does work in "normal settings", e.g. in the absence of HIV or MDR-TB, where targeting the most infected patients can still deliver 6-10% annual declines in TB incidence.

2.4. What DOTS hasn't done

DOTS is still far from reaching its targets. Only two high-burden countries, Vietnam and Peru, have been able to reach the DOTS targets of 70% detection and 85% cure rates. Treatment success – measured as cure and completion rates – under DOTS globally is now 82% (around four in five patients) with cure rates of 74%. Results in Africa are worse, with treatment success rates at only 72% (less than three in four patients).[28]

The importance of three of the DOTS pillars – political commitment, regular drug supply and systematic reporting – is uncontested: they provide a useful framework for tackling TB from a managerial, although not from a technical or medical, point of view.

But both the original DOTS trials and the final design of DOTS were based on an acceptance of certain central limitations. It was thought that funding for TB would remain insufficient at national or global level and that countries should therefore prioritise infectious patients. It was also accepted that diagnosis and reporting be based on the existing sputum smear microscopy test which can only pick up smear-positive patients, representing only 45-60% of patients overall. Finally, the design relied on old drugs which require long treatment to eradicate the mycobacterium and prevent development of resistance.

The following sections look more closely at some of the limitations of DOTS and attempt to identify ways in which DOTS could be improved – in other words, how the DOTS framework could be supported with better tools achieving better results for individuals as well as public health.

Uncomfortable questions and need for research brushed aside

"We still don't know what works best, although we have a good idea of what doesn't work".

Clinician supporting an MSF TB project

[26] WHO Global TB Control report 2003, pp. 19, 22 and 23.
[27] All statistics from WHO Global TB Control report 2003; p. 33
[28] All statistics from WHO Global TB Report 2003; pp. 22-23, 37

Some of DOTS tenets, protocols and recommendations have not been substantiated in large-scale clinical trials and have little empirical basis. Patients undergo intensive observation, months of extended treatment, or specific drug combinations based on little or no empirical evidence, although DOTS tools have been used for 30-60 years and DOTS itself has been in operation for nearly 10 years.

Examples:

- The eight month ethambutol-based regimen has recently been shown to have a 12% failure and relapse rate compared to 3% failure and relapse rate with the 6-month rifampicin regimen[29], but has nevertheless been widely recommended and used until recently;
- The dosage of ethambutol-isoniazid in children is, according to WHO, "based on research in adults (...) and has never been studied in children"[30];
- The IUATLD notes that the optimum length of treatment for CNS TB is "unknown but, based on limited information, a seven month continuation phase has been advocated"[31].

Although DOTS was based on a few controlled trials in Africa and Asia[32], the normal scientific process of scrutinising and testing DOTS premises and principles was cut short by the launch of DOTS as a brand or advocacy tool and WHO promoting DOTS as the solution to TB. For instance, in 1997 WHO announced that: "For the first time in the 6000-year history of TB we have the tools, strategies and medicines to defeat the epidemic in all parts of the world"[33]. It was difficult for clinicians to question DOTS brand fundamentals (in particular direct observation), and NTP's were rarely willing to risk their TB funding by asking uncomfortable questions.

Operational research about DOTS has been neglected[34]. This may improve with the advent of substantial new funding for clinical trials via the European and Developing Countries Clinical Trials Partnership. Both TDR (WHO's Special Programme for Research and Training in Tropical Diseases) and the IUATLD are pushing for a much greater focus on the "largely unaddressed" area of operational research into existing tools.[35]

The pie is too small: Exclusion of "low-priority" patients

The conviction that TB control was the main goal led to an acceptance that the individual needs of the "few" – actually almost 50% of all TB patients – were outweighed by the public health good of the "many". Existing tools, although poor, were sufficient to detect and treat enough infectious patients to deliver TB control, and there was little interest in developing better tools or strategies for "low-priority" patients, i.e. anyone not testing smear-positive and therefore not considered as infectious.

Although WHO's latest (2003) guideline for NTPs gives more importance to the management of children, extra-pulmonary and chronic cases, the WHO advice to National TB Programmes still states that "the highest priority for an NTP is the identification and cure of infectious cases, i.e. patients with smear-positive pulmonary TB"; that one of the roles of case definition is to "prioritise treatment of sputum smear-positive cases"; and that "from a public health perspective, extra-pulmonary TB is not of great importance because patients with this form of disease are not infectious". Treatment for chronic and MDR-TB patients is discouraged with Stop TB advising that such patients should only be treated "when the DOTS strategy is fully implemented" to prevent generating more MDR-TB and that treatment of MDR "may be an unacceptable drain on resources" in poor countries.[36]

This is compounded by WHO's strongly target-driven approach. The measure of a "good" TB programme is its ability to deliver continual progress towards WHO goals of detecting 70% of smear-positive patients and curing 85% of these, as well as achieving a 60:40 positive/negative ratio[37].

The result is that a significant number of countries continue to neglect "non-target" patients in an effort to secure ongoing international or bilateral funding for their TB programmes. Table 2 lists countries that notify implausibly high percentages of smear-positive patients particularly since resource-poor countries rarely have access to other forms of diagnosis to confirm the smear microscopy test that is poorly sensitive with HIV-positive patients. This implies that

[29] Treatment of Tuberculosis. Guidelines for national programmes. WHO, 2003. p. 34: Results of a clinical trial comparing 6- and 8-month rifampicin regimens.
[30] WHO guidelines, op.cit. p.64
[31] Interventions for Tuberculosis Control and Elimination. IUATLD, 2002. p.74 http://www.iuatld.org/pdf/en/guides_publications/interventions.pdf
[32] Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999: 3:S231-S279.
[33] Ogden J et al, op cit, p.185
[34] All statistics from WHO Global Plan to Stop TB, 2001; p.98 www.stoptb.org/GPSTB/default.asp
[35] Conversation w. Mark Perkins, Head of Diagnostics, TDR, WHO Geneva; March 10th 2003
[36] Treatment of TB: Guidelines for National Programmes 2003. WHO/CDS/TB 2003.313; p.39 & 43
[37] Meeting w. Dr Raviglione, WHO Geneva, July 3rd 2003; Global TB Report 2001, p. 16

Table 2[39]

Country	HIV prevalence (Source: UNAIDS 2003)	New smear+/all cases (%) in DOTS programmes[40]
Expected smear-positive % in poor country-setting (even lower if high HIV prevalence)		45-60%
Cambodia	2.7%	75
Cote d'Ivoire	9.7%	71
Madagascar	0.3%	67
Ghana	3.0%	65
Burkina Faso	6.5%	65
Nigeria	5.8%	64
DRC	(no figure available)	63
Mozambique	13%	63
Bangladesh	<0.1%	62
Vietnam	0.3%	59
Indonesia	0.1%	58
Uganda	5%	47
Burundi	8.3%	47

large numbers of smear-negative and extra-pulmonary patients probably go untreated[38].

MSF staff has observed that in some countries smear-negative patients are deliberately not treated, particularly when there are resource constraints. For instance in Honduras, MSF treated smear-negative cases who were refused by the NTP. Finally, MSF negotiated access to treatment for smear-negative cases on a national level. In some cases, countries exclude patients previously treated under non-DOTS regimens even though this may represent 10-50% of patients in some settings[41]; or disadvantaged patients are excluded from best available treatment[42].

The overall result is that smear-negative, extra-pulmonary and paediatric TB patients continue to be second-class citizens in the management of TB. Resources must be increased so that infectious and non-infectious patients can be targeted.

Tools of low quality

WHO and CDC staff wrote in a 2001 article that "as DOTS coverage has expanded, it has become apparent that the performance of existing tools for TB diagnosis and treatment limits more efficient implementation of the strategy". They cited in particular the lack of diagnostics; long duration of treatment with old drugs; and burden on health care systems of administering the "cumbersome, labour intensive and expensive" DOTS system.[43] The problems and potential solutions of TB diagnosis and the need for new TB drugs are discussed in more detail in separate chapters.

Heavy burden on patients and health infrastructures

DOTS' poor results have been attributed by WHO to external factors, in particular to the lack of human resources; poor health system infrastructure, organisation and management; private sector treatment; the impact of health system restructuring, in particular decentralisation; and lack of political commitment.

[38] A view confirmed by Dr R Colebunders, Institute of Tropical Medicine, Antwerp. Teleconference July 2nd 2003.
[39] WHO Global TB Control report 2003 Country Profiles, pp. 54-125
[40] The percentage of smear-positive patients in most of these countries has trended slightly downwards over the last 5 years, although it is unclear if this is due to increased HIV incidence, declining microscopy standards or more liberal treatment policies.
[41] Cox H & Hargreaves S. To treat or not to treat? Implementation of DOTS in Central Asia; Lancet, 2003, Vol 361, p. 715. Reported cases in Kazakhstan, China and India.
[42] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12167096&dopt=Abstract): Singh V. et al. TB control, poverty, and vulnerability in Delhi, India, in Trop Med Int Health. 2002 Aug;7(8):693-700. Operational research studies in two pilot sites in New Delhi from 1996 to 1998 showed that health workers screened patients to determine their ability to conform to the direct observation. If the health worker was confident that the patient would comply and/or be easy to trace in the community in the event of 'default', they were provided with short-course treatment under the RNTCP. Other patients, largely those who were in absolute poverty and socially marginalized, were put on standard TB treatment as for the previous National TB Programme. The programme was evidently excluding the most vulnerable from the best available care.
[43] O'Brien R & Nunn P. The need for new drugs against tuberculosis. Am J Resp Crit Care Med, 2001;163:1056. See also Perkins M, New diagnostic tools for tuberculosis. Int J Tuberc Lung Dis 2000; 4: S182-188.

In addition, DOTS places an enormous social and financial burden on patients, who are sometimes required to undergo lengthy hospitalisation or stays in or near treatment centres in order to meet the direct observation (DO) requirement.

DO continues to be one of the most contentious aspects of DOTS. Designed and first introduced in India more than 40 years ago, the DO method aimed to ensure that the patient completed the lengthy TB treatment and that response to treatment as well as potential side-effects were adequately monitored. In the early 1990s, DO became one of the cornerstones of the DOTS strategy. But DO is time-consuming and labour-intensive and requires continuous motivation and training of health care workers to be effective. Individuals suffering from TB sometimes perceive the DO requirement as implying that they are incapable or irresponsible with regards to their own health – some patients even view DO as demeaning or punitive[44].

DO does not systematically improve adherence to treatment: compliance depends on a whole range of cultural, social and economical factors, and other strategies for improving adherence might be as effective as DO[45,46]. In a randomised controlled trial comparing self-administered and directly observed treatment of TB, self-supervision outcomes equivalent to DO were reported[47].

The challenges of DO have been both highlighted and made more acute by the HIV/AIDS pandemic. MSF, delivering antiretroviral (ARV) treatment to over 11,000 patients in over 20 developing countries and working to expand treatment to larger numbers, is fast recognising the paradox in the approaches to treating these two often coinciding diseases. In most MSF ARV programmes, people living with HIV/AIDS only come to the clinic once a month for follow up and to pick up their next monthly treatment dose. In standard TB programmes, patients are required to report to a health

[44] CDC. Patient adherence to tuberculosis treatment. Self-study modules of tuberculosis 1999, p. 49.
[45] Pope DS, Chaisson RE. TB treatment: as simple as DOT? Int J Tuberc Lung Dis 2003 7(7): 611-5
[46] Volmink J, Garner P. Intervention for promoting adherence to tuberculosis management. Cochrane library, Issue 3, 2000.
[47] Zwarenstein M et al. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. Lancet 1998; 352:1340-43.

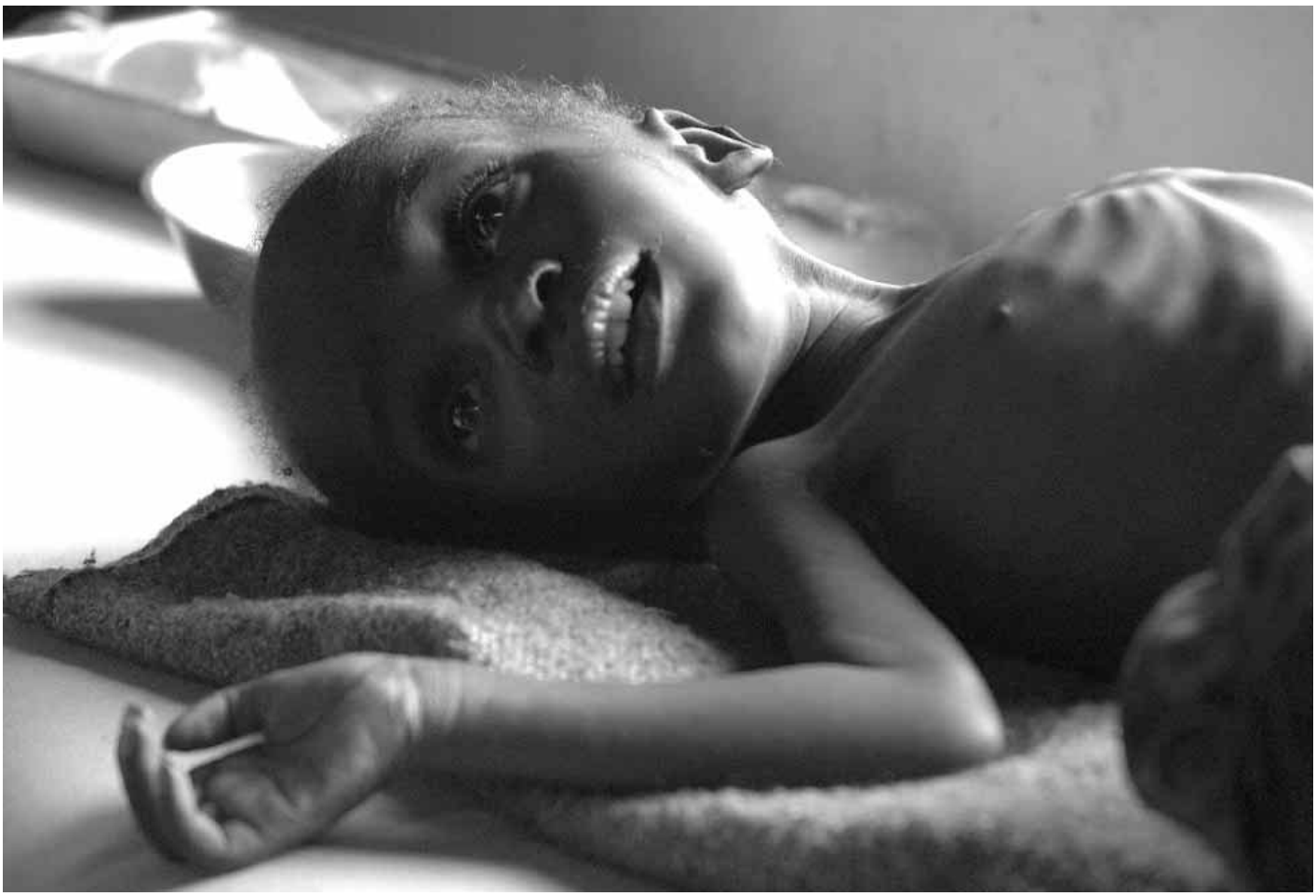


Photo © Sebastian Rich

Table 3: Estimated public sector health system costs per treated case of infectious TB ($)*

Country	Drugs	Total
India	$7	$57-$201
China	$18	$61-$75
Uganda	$32	$430-$541
Thailand	$43	$219-$280
Russia	$83	$1,115-$1,395

** Abstract from full table, Executive Summary for the Economics of TB Drug Development, Global Alliance for TB Drug Development, Oct 2001, p.8*

care worker several times a week, even every day. Yet both treatments require taking several drugs and doses a day, and interrupting either has equally life-threatening consequences.

This problem is now urgent since national TB programmes in many high HIV-prevalence areas cannot continue DO at the recommended levels because of growing caseloads. They will either have to reduce observation (with the risk of rifampicin-resistance), exclude patients due to lack of resources for intensive DO or develop alternative strategies to ensure and improve adherence.

Implementing a system that requires trained laboratory staff and resource-intensive reporting will always be problematic in resource-poor settings. While first-line TB drugs are affordable, they require an expensive and cumbersome system of administration. Table 3 shows that the cost of administering the drugs in the recommended manner is far higher than the cost of the drugs themselves. These costs are one of the chief obstacles to expanding DOTS, in particular in high-burden TB/HIV settings.

A further obstacle to DOTS expansion is the difficulty countries have in reaching the WHO smear-positive case detection goal: even with 100% DOTS coverage, case detection targets of 70% cannot be met and will plateau at 40-50% of smear-positive patients in most countries unless radical programmatic changes take place[48].

DOTS and HIV/AIDS

> *"TB control just doesn't work in high HIV-prevalence areas."*
> IUATLD staff member

The greatest challenge to TB control, however, is HIV/AIDS: DOTS was not designed to address the specific context of HIV/AIDS and TB.

HIV/AIDS and TB

An estimated 12 million people are now co-infected with HIV and TB, over two-thirds of these living in sub-Saharan Africa and 22% in South East Asia. In 1995, HIV-related TB only represented 4% of the global TB burden but by 2000 this had tripled to 12%.[49]

Why is TB control so difficult in high prevalence HIV/AIDS settings?

Epidemiological and physiopathological reasons: identifying and treating infectious smear-positive patients will not control TB due to the high proportion of reactivation of latent TB in immunodeficient patients. In addition, recurrence after treatment is more frequent in HIV-positive patients. In Malawi, the NTP reported 9% recurrence rates in 2000 and 2001[50].

TB diagnostic tools are also less reliable in HIV-positive patients:

The smear microscopy test has even lower pick-up rates in AIDS settings, since HIV-positive patients increasingly tend to be smear-negative as AIDS progresses. Multiple studies suggest the test works in only 35-38% of HIV-positive patients[51,52]. National TB statistics show an increasing proportion of smear-negative cases in most AIDS-affected countries in Africa[53]. For example, between 1998 and 2001, smear-negative rates increased in Kenya (42 to 53%), South Africa (10 to 15%), Uganda (39 to 48%), Zimbabwe (47 to 53%). In Tanzania, smear-negative cases increased at 2.5 times the rate of smear-positive cases between 1985 and 1995[54].

Clinical diagnosis of TB, historically the backbone of smear-negative detection, is also more difficult in co-infected patients as weight loss, swelling of lymph

[48] Dye C et al; What is the limit to case detection under the DOTS strategy for TB control? Tuberculosis, 2003 Vol 83, Issues 1-3, pp.35-43
[49] WHO Global Plan to Stop TB 2001, p.53
[50] AD Harries et al. Preventing recurrent tuberculosis in high HIV-prevalent areas in sub-Saharan Africa: what are the options for tuberculosis control programmes? Int J Tuberc Lung Dis 2003;7: 616-22
[51] Elliott AM, Halwiindi B, Hayes RJ, Luo N, Tembo G, Machiels L et al. The impact of human immunodeficiency virus on presentation and diagnosis of tuberculosis in a cohort study in Zambia. J Tro Med Hyg 1993; 96(1): 1-11.
[52] Harries AD, Nayngulu DS, Banda H, Kang'ombe C, Van Der Paal L, Glynn JR et al. Efficacy of an unsupervised ambulatory treatment regimen for smear negative pulmonary tuberculosis and tuberculosis pleural effusion in Malawi. Int J Tuberc Lung Dis 1999; 3(5): 402-8.
[53] Bruchfeld J et al, Trans R Soc Trop Med Hyg; Nov-Dec 2000. Hawken et al, Int J TB Lung Dis, Apr 2000. Samb B et al, Int J TB Lung Dis Apr '99. Samb notes that "this phenomenon has now been observed in 7 out of 8 Sub-Saharan countries with varying HIV prevalence from which reports are available". These findings must be interpreted with caution, since patients in these studies have already sought medical care, so may already be in more advanced stages of AIDS.
[54] All stats from WHO Global TB Control Report 2003, Country Profiles, pp. 54-125. This increase may be influenced by deterioration of microscopy services or over-diagnosis of smear-negative status in the absence of a diagnostic test.

nodes, and pulmonary infections can be caused by various infections in HIV co-infected patients.

On the other hand, Chest X-ray lesions are less typical of tuberculosis in immunodeficient patients. The only way to significantly improve diagnosis is introducing new diagnostic tools.

Treatment-related reasons:
Prophylactic treatment is recommended to prevent the activation of latent TB despite the lack of reliable means to determine whether an HIV/AIDS positive person has active TB. Through the ProTEST initiative, WHO proposes giving a six month course of INH prophylaxis to "asymptomatic HIV-positive patients whose smear test is negative"[55]. MSF programmes generally do not implement this recommendation because there is no way of knowing whether an asymptomatic smear-negative HIV-positive patient has active TB, latent TB or no TB at all, and administering prophylaxis could create drug resistance, although some experts say the associated risk of promoting drug resistance this way is small[56].

As noted, treatment success rates are substantially lower in high HIV-prevalent settings (72% in Africa compared to 82% globally), partly due to high mortality (7%)[57]. Some African NTPs are using the eight month drug regimen with a six month ethambutol-isoniazid continuation phase instead of the six month rifampicin-based regimen, although some studies have shown lower efficacy and higher relapses when rifampicin is stopped after two months[58].

ARV treatment presents its own set of challenges. Problems of simultaneous treatment are multiple: increased pill burden, reduced tolerability, cumulative toxicity (liver, skin, haematology), compliance difficulties and drug interaction, especially with rifampicin.

[55] The WHO ProTEST initiative has been piloted in half a dozen African countries since 1998. It aims to increase TB case detection through AIDS testing (VCT), with subsequent prophylaxis (as described above) or referral to TB programmes for smear-positive or TB-symptomatic HIV+ patients.
[56] Meeting with Peter Godfrey-Faussett, London School of Hygiene and Tropical Medicine, London (WHO adviser on TB), July 8th 2003.
[57] All stats from WHO Global TB Control Report 2003, p.23
[58] AD Harries et al. Op. cit, pp. 616-22

Photo © Alexander Glydadelov

3. TB DIAGNOSTICS

"Currently, less than 20% of the roughly eight million predicted annual cases of tuberculosis are identified as smear-positive."[59]

3.1. Current diagnostic test for TB: sputum smear microscopy

Diagnosis of active pulmonary tuberculosis is based on the isolation of *M. tuberculosis* in sputum using direct microscopy, culture or new technologies such as PCR (Polymerase Chain Reaction, a molecular method based on identifying the DNA of *M. tuberculosis* in sputum). The diagnosis of extra-pulmonary tuberculosis is often based on new technologies (PCR) or clinical, radiological and histo-pathological findings due to the poor diagnostic yield of bacteriology in body fluids.

MSF and others working in resource-poor settings still rely heavily on smear microscopy test, occasionally supplemented with manual culture and chest X-rays for pulmonary TB, and on clinical algorithm for extra-pulmonary TB.

Smear microscopy is inexpensive and requires only basic laboratory equipment, although some of this may be difficult to maintain in field settings. In well-trained hands, the test has a sensitivity of 75% in pulmonary TB – but this falls to 45-60% in "real life" circumstances.

Since the detection of TB requires 5,000 to 10,000 bacilli per ml of sputum, the test's sensitivity is reduced in early-stage pulmonary patients, HIV co-infected patients and paediatric patients, whose sputum contains fewer bacilli. In other samples than sputum, the sensitivity is very low: less than 10% in cerebrospinal fluid and almost insignificant in other fluids, such as urine, blood or aspiration of lymph node[60]. HIV co-infected patients and children are more likely than other patients to have extra-pulmonary TB.

The low sensitivity of the sputum microscopy test often leads to the need to repeat smears, which causes delays in receiving results and initiating treatment; it also causes loss of patients to follow up.

The limitation of smear microscopy has led to 50% of patients (smear-negative pulmonary, extra-pulmonary and paediatric) being started on treatment based on clinical judgment. The inability to accurately diagnose latent or even active TB in many HIV-positive patients complicates both prophylaxis and treatment.

In addition, since the effectiveness of this test depends on the lab technician's performance, regular training and quality control are essential, adding significantly to overall costs.

3.2. Newer TB diagnostics

There is a fairly high level of commercial interest in both TB diagnostic and drug resistance tests, reflecting their lower development costs (compared to drugs), the relatively advanced state of TB diagnostics science and the presence of a modest developed-country market.

The major new groups of TB diagnostics include:

- serological tests (Ab-based)
- phage-based systems, (e.g. FastPlaqueTB)
- molecular methods (nucleic acid amplification including PCR & non-PCR probes).

Over 50 groups in 18 countries are developing or already marketing newer TB tests[61]. These are predominantly biotech firms and a few academic researcher institutions. On the other hand, very few companies have retained diagnostics capability: Becton Dickinson, Roche and Abbott have DNA-based tests. Other manufacturers, including GlaxoSmithKline, Astra-Zeneca, Aventis[62] and Eli Lilly, have disinvested themselves of diagnostics.

These newer tests are used in developed countries, where they have significantly improved TB diagnosis. For instance, the UK Government announced its TB Action Plan including new DNA-based tests for community TB screening in 2003.[63]

Most of these tests are designed for use in developed countries, not TB-endemic countries, therefore they require trained technicians and proper bacteriological laboratory facilities — and are relatively expensive. Companies have little incentive to spend the $5-15

[59] Perkins MD. New diagnostic tools for tuberculosis. Int J Tuberc Lung Dis 2000: 4(12):S182-S188.
[60] M Hale Y, Pfyffer GE, Salfinger M. Laboratory diagnosis of mycobacterial infections: new tools and lessons learned. Clin Infect Dis 2001; 33 (6):834-46
[61] WHO/TDR has compiled a confidential database of all groups working on TB diagnostics; TDR is prepared to discuss how MSF could use the database.
[62] Aventis-Pasteur continues to manufacture Mantoux tests.
[63] Scientists develop faster TB test; BBC News Online, Jonathan Amos, reported by Stop TB, October 9th 2002

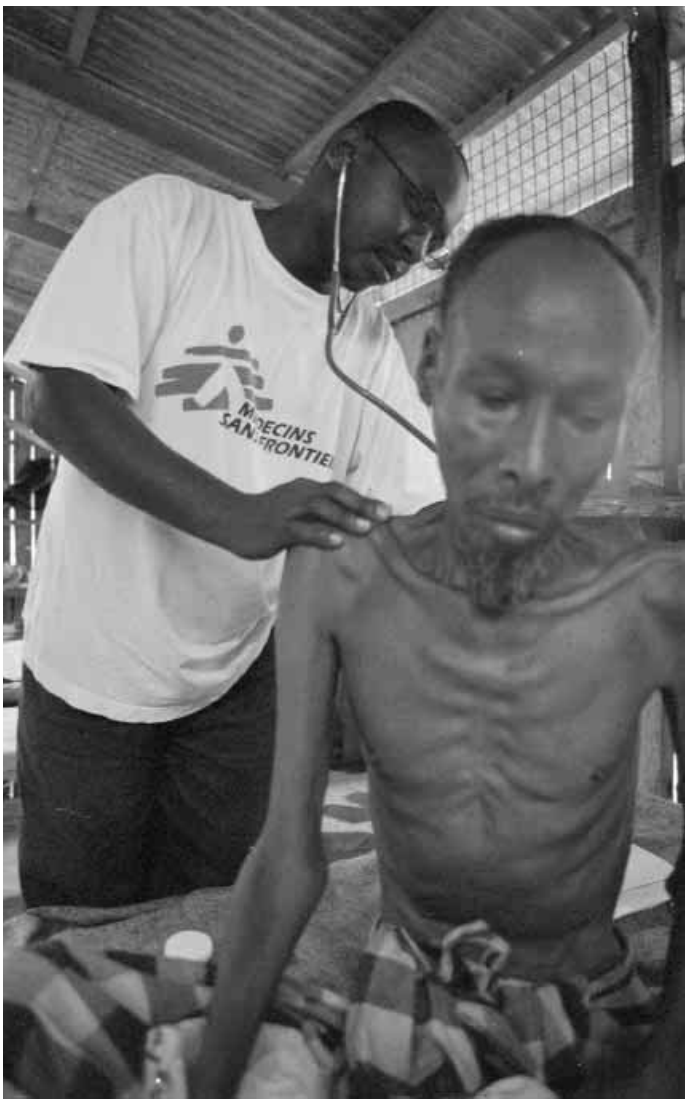


Photo © Robert Malleta / MSF H

million WHO estimates are needed to adapt a test to the conditions of resource-poor settings. But it would be possible to adapt some of the newer tests; particularly interesting are two new tests that might be ready for use within a year's time: the MPB64 Patch Test[64], which detects active TB on skin with the help of a protein, and the "TK medium", a rapid solid media culture for TB[65]. Phage-based tests such as FastPlaqueTB do not require very sophisticated lab skills and can detect 54% of smear negative culture positive cases[66].

DST (Drug Sensitivity Testing) that can determine whether the bacilli reacts to a drug is also commonly used in wealthy country settings. These include rapid and automated systems such as MGIT and Bactec.

The manual MGIT rapid culture test was recently tested by MSF in its Kemerovo Prison project (now closed) in Russia. The test was conducted in an existing, upgraded lab. Results were positive: the direct and indirect MGIT systems provided results with 95-97% accuracy compared to traditional culture and DST. The advantage is in the speed of the results: only nine to 15 days for MGIT compared to two to three months for culture.[67]

In general, there is an urgent need to validate existing diagnostic tests, because unlike drugs or vaccines, diagnostics are very poorly regulated both at the clinical trial and registration stage. The lack of clinical trial standards for diagnostics mean that developers/producers "routinely overstate the significance of trial results or imply clinical impact not demonstrated by their data" and clinical trials are often "little more than marketing tools or academic exercises".[68] However, these highly subjective trial results are nevertheless published and used to market tests in poor countries. It is difficult for physicians to know the real value of the tests. For example, trial-based claims that MycoDot had a sensitivity of 79% in pulmonary TB were subsequently discredited by independent studies showing only 26% sensitivity in smear-positive and 7% in smear-negative patients[69,70]. Doubts have also been cast on initial positive results of clinical trials conducted on the new FASTPlaqueTB in South Africa.

It is also critical that the most promising diagnostic tools for resource-poor settings are prioritised and that their development is properly resourced.

In terms of price of these new diagnostic tools, manual MGIT costs $3-8 per test; FastPlaqueTB $2 per test; and Gen-Probes's Amplified Mycobacterium Direct Test is $25 per test.[71,72]

[64] Nakamura R.M. et al. MPB64 mycobacterial antigen: a new skin-test reagent through patch method for rapid diagnosis of active tuberculosis. Int J Tuberc Lung Dis 1998: 2(7):541-546.
[65] Mark Perkins (TDR/FIND) in a brainstorming on laboratory tests organised by the MSF Access Campaign, Brussels, September 23rd 2003.
[66] Albert H, Heydenrych A et al. Performance of a rapid phage-based test, FASTPlaqueTB, to diagnose pulmonary TB from sputum specimens in South Africa; Int. J Tuberc Lung Dis 2002 6(6):529-537. Also presentations at UIATLD 2002.
[67] Goloubeva V, Lecocq M, Lassowsky P, Matthys F, Portaels F, Bastian I. V, Lecocq M et al. Evaluation of mycobacteria growth indicator tube for direct and indirect drug susceptibility testing of Mycobacterium tuberculosis from respiratory specimens in a Siberian prison hospital. J Clin Microbiol. 2001;39(4):1501-5

3.3. New initiative to develop tests for resource-poor settings

Several publicly-funded groups, including the NIH in the US,[73] have been supporting development of new field-relevant TB diagnostics. The most promising new venture is the Gates-funded Foundation for Innovative New Diagnostics (FIND), launched in May 2003. FIND is designed to develop new diagnostics for poor countries, and will initially focus on TB.

FIND developed out of the former TDR Tuberculosis Diagnostic Initiative (TBDI). TBDI's objective was to coordinate and facilitate existing industry and academic research. Highlights of their accomplishments are as follows:

- Developed a database of all diagnostics in development
  – database has not been released due to commercial confidentiality agreements.
- Set up a specimen bank of over 12,000 samples for use by researchers and manufacturers interested in evaluating new diagnostic tests
  – paediatric and extra-pulmonary specimens not included
- Developing performance guidelines for new diagnostic tests, in consultation with health experts and the pharmaceutical industry.
- Developing and conducting clinical trials for new tests, including the patch test (MPB64).

Photo © Robert Malleta / MSF H

TBDI's progress was limited due to a lack of sufficient funds and industry reluctance to pay to adapt tests. FIND, on the other hand, has been funded with $30 million for an initial five-year period. It is developing a short-list of promising TB diagnostic candidates that could be optimised or developed for use in resource-poor TB endemic settings. The Gates donation will be used to fund co-development of these tests with industry, followed by a formal evaluation of these products in laboratory and field trials, and impact demonstration studies in the field (in conjunction with WHO, other agencies and with national programmes). FIND predicts that they will complete their first development projects during the period 2005-2008.

[68] Perkins, M & Kritski A. Diagnostic testing in the control of tuberculosis; Bulletin of the WHO; 2002, 80(6), 512-513
[69] Small, PM & Perkins MD. More rigour needed in trials of new diagnostic agents for tuberculosis. Lancet. 2000. Vol 356, pp. 1048-1049.
[70] Letsatsi P et al. Tuberculosis serodiagnosis in HIV infected persons, Botswana, 2002. First National HIV/AIDS/STI/Other Related Infectious Diseases Research Conference, Gaborone, Botswana, abstract WBT53-9.
[71] Tassie J-M. Diagnosis of smear-negative and extra-pulmonary TB (in context of HIV/AIDS); draft report by Epicentre, Paris.
[72] Review of TB Diagnostics by Martine Guillerm, MSF Access Campaign, Geneva
[73] The NIH/NIAID provided US$2 million/yr for TB diagnostic research, based on calls for proposals from academia or industry.

4. TB DRUGS

"We need much more emphasis on R&D. Investment in the future isn't into DOTS – it's into new tools. (...) If we can't do better than DOTS 20 years from now, then we're done."

IUATLD staff member

4.1. Why new drugs are needed

The main drawback with existing TB drugs is their weak sterilising activity, which means that the drugs have to be taken at least for six months. Treatment length, probably the single greatest obstacle to controlling TB globally, has not been shortened since the public and private search for new anti-TB drugs has slowed to a virtual standstill, reflecting the decline in tuberculosis incidence in developed countries. Since the late 1990s, there has been some renewed interest in finding new anti-TB drugs following the outbreaks of multidrug resistant TB in the US. With currently available science and technology, researchers are confident that TB treatment times can be reduced to as little as two to five months[74,75]. This would significantly improve TB care by improving compliance to treatment, and thus increasing cure rates, as well as lowering programme costs.

TB drugs need to be taken in various combinations, and although fixed-dose combinations of these medicines exist for adults, formulations adapted for children are not widely available.

4.2. Who is conducting TB drug R&D?

A 2003 Stop TB working group on Drug development update[76] lists over 40 different initiatives and projects involved in TB drug development activities ranging from basic research to regulatory issues. However, only a very small fraction of these can be expected to lead to a new drug being introduced in the market within the next 10 to 15 years.

Development of TB drugs is carried out by the private sector, public private partnerships, e.g., the Global Alliance for TB Drug Development (GATB), public sector institutions, or combinations including several of these actors.

Private sector

The lack of industry investment in TB drugs is linked to the specific dynamics of the global TB drug market. The GATB estimated this market to be $450 million in 2000, expanding to around $640 million in the year 2010[77], far larger as one would expect. Yet two features make this market unattractive to international pharmaceutical companies: the bulk of sales are in developing countries and purchases are normally done by tender. The expected volume of sales in the private sector for TB drugs is only $113 million worldwide, with a projected flat progression in the next decade.

A review of the pharmaceutical industry published in "Fatal Imbalance"[78] (MSF 2001) found that five of the world's Top 20 drug companies self-reported as doing TB drug research, and three self-reported as screening new compounds for anti-TB activity.

Company driven TB ventures/projects:

Novartis opened the new Institute for Tropical Diseases in Singapore in January 2003, with a focus on identifying new drug and vaccine targets for TB and dengue. They simultaneously announced that once they have novel compounds, Novartis will team up with the GATB for further development and these compounds and Novartis will not charge royalties on sales in endemic countries.

GlaxoSmithKline established Action TB, a dedicated TB drug development unit in 1993 and had initially funded it for a five-year period. This unit has now been folded into a drug discovery unit in Tres Cantos, Spain, which is involved in TB. Projects that had been under the ACTION TB umbrella were only funded through 2003.

[74] There have been early animal trials substituting ethambutol with gatifloxacin by Jacques Grosset that showed good 2-month results (presented at the TB Alliance Stakeholders Meeting on 30th October).
[75] Shortening short course chemotherapy: a randomized clinical trial for treatment of smear positive pulmonary tuberculosis with regimens using ofloxacin in the intensive phase. Indian Council of Medical Research. Ind J of Tuberc. 2002; 49,27.
[76] Global Plan to Stop TB: Update 2003 (submitted Sept 16, 2003).
[77] Economics of TB Drug Development, Executive Summary, Global Alliance for TB Drug Development, October 2001, p.12
[78] Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases. MSF and the Drugs for Neglected Diseases working group, 2001, p. 12.

Astra-Zeneca opened a new infectious disease research centre in Bangalore, India, in June 2003, with a focus on TB drug discovery and developing country sales. The company allocated $10 million to build the research centre, and has stated that it spent $39 million in 2002 for TB vaccine research.

Compared to other clinical areas that have lucrative developed country markets, current TB efforts within the multinational pharmaceutical industry are minimal.

Although the relatively "small" TB market may not be attractive to the large pharmaceutical companies, it can be interesting to smaller biotech companies or generic producers building development capacity (e.g. **Chiron** and **Lupin**). Although some of these companies have identified promising new targets, they have insufficient resources to fully develop drugs themselves and need a development partner such as the GATB to take compounds forward.

Public Private Partnerships and Foundations

The Global Alliance for TB Drug Development (GATB) is the only significant public-private partnership for TB. It was launched in October 2000 and is backed by international institutions (WHO/TDR, Stop TB) and public research institutes (CDC, NIAID, Medical Research Council of South Africa) and financially supported by foundations (Gates and Rockefeller), a handful of government donors (Netherlands and US) and a small one-off donation by Bristol-Myers Squibb (BMS).

The GATB's goal is to bring at least one new TB drug through the development pipeline by 2010, through linking pharmaceutical industry expertise and public sector know-how and funds. At its formation, the GATB expressed high hopes to gain rapid access to pharmaceutical industry drug libraries in order to unearth "forgotten" compounds and develop them into new TB drugs. This activity was to be supplemented with general Calls for Proposals, which would capture additional promising compounds being researched in the public or academic sectors[79].

Because they must work closely with industry in order to gain access to their potential stockpile of knowledge/compounds, GATB has been very cautious in pushing for greater industry co-operation. The multinational pharmaceutical industry has shown limited interest in co-operating with GATB. Only one company has donated funds to the GATB ($150,000 from BMS) and none of GATB's pipeline drugs are from the multinational pharmaceutical industry. The first GATB Call for Proposals launched in November 2000 brought in 103 compounds - all were from public or academic sources.[80] The second call issued in 2003 confirmed this trend. Most proposals are from public and academic research at the very earliest discovery and pre-clinical stages of development. This means that it is unlikely that any final product from these leads is registered before 2010.

The Sequella Foundation has some TB development activity around ethambutol analogues. In addition, a plethora of publicly funded groups offer assistance to conduct clinical trials (Phase I-IV) on any new compounds in development.[81]

Public/international sector

The WHO/TDR's work on new TB drug development is now largely folded into GATB activities. The US National Institutes for Health, in particular NIAID, and CDC continue to support both private sector and academic TB drug research, including by providing a free screening service to test compounds for anti-TB activity[82]. A small number of universities and medical schools are involved in both privately and publicly funded TB research activities. In addition, the European Commission recently set up EDCTP, a programme aiming to develop and enhance endemic countries' clinical trial capacity.

In 2000, WHO/TDR wrote that the priority in finding new TB drugs was to "work with industry to evaluate available antibiotics and off-the-shelf drugs" and to "encourage their production by small DC producers". A number of promising families of compounds to be further explored were selected by a group of scientists joined by the GATB Scientific Advisory committee who selected front-runners.

4.3. Promising drugs

Potential new TB drugs fall into two categories. The first is off-the-shelf drugs with anti-TB activity that can be enhanced further. These tend to be far quicker to

[79] GATB website: Catalyzing R&D; A portfolio of drug candidates http://66.216.124.114/3_1_C_CatalyzingRandD.asp
[80] Teleconference w. Joelle Tanguy and Giorgio Roscigno, GATB, March 2003.
[81] Trial assistance is provided by: a) CDC TB Trials Consortium for trials in the US or Canada of new drugs or regimens; b) NIH TB Research Unit for trials outside US; c) Brazil, India and the South African Medical Research Council all have well-developed capacity for TB drug trials; d) the new European Commission DC Clinical Trials Platform; e) Stop TB and TDR also have initiatives to build trial capacity in developing countries.
[82] The NIAID's no-cost screening is on a confidential basis: proprietary rights are protected. If promising anti-TB activity is found, they will work with the owner to conduct additional tests eg. animal studies and can also support clinical trials via NIH to help companies reduce the costs and risk of developing new TB compounds.

develop, but may not be active against MDR-TB. The second category is novel compounds developed specifically for TB. These will take longer to develop: an estimated six to seven years is needed from the start of Phase 1 trials to delivery to patients. Most novel drugs are still on the bench, months if not years from Phase I.

Off-the-shelf

Fluoroquinolones

Already used in treating patients with MDR-TB, these are the most promising as they have the potential to shorten treatment to four months or less. This class includes gatifloxacin (BMS), and moxifloxacin (Bayer), with anti-TB activity four times more potent than other fluoroquinolones. "Older", cheaper fluoroquinolones are already used in the treatment of MDR-TB (e.g., levofloxacin, ofloxacin, ciprofloxacin), and developing country practitioners have also begun using the newer fluoroquinolones, in particular moxifloxacin. Moxifloxacin is only available from the originator and is therefore relatively expensive, whereas both gatifloxacin and ofloxacin are available in less expensive generic form.

- The TB Research Centre in Chennai compared four ofloxacin-containing regimens of either four or five months duration in a cohort of 416 patients and reported between 95 and 97% cure rates with a relapse rate between 2 and 4% in two regimens.[83]

- Bayer AG and the CDC TB Trials Consortium (TBTC) conducted a large Phase II clinical trial throughout North America with sites in Brazil and Uganda to determine the acceptability and short-term efficacy of a moxifloxacin-containing regimen for the initial treatment of patients with newly diagnosed TB.[84] The GATB has convinced Bayer to release moxifloxacin to the CDC TBTC clinical trials. Preliminary results seem positive.

- WHO/TDR and an EU consortium are commencing a 2,000 patient multicentre trial in Africa using generic gatifloxacin as a substitute for ethambutol in an FDC, with both four month and six month arms. This study is aimed at preparing the groundwork for a fixed-dose combination; Lupin (India) is the manufacturing partner. Phase I trials were scheduled for the end of 2003; Phase III will begin in mid-2004 and a final product is expected in 2006-2007.

Rifamycins other than Rifampicin

Rifabutin (Pharmacia/Pfizer) is already used in MDR-TB, since 30% of rifampicin-resistance cases may respond to it, and is the US drug of choice for treating TB-HIV co-infected patients on ARV therapy. It is not superior to rifampicin and is cross-resistant to rifampicin in 70% of cases.

Rifapentine (Aventis, approved by FDA in 1998) is a longer-acting rifamycin. It will not shorten treatment but can be given less frequently, thus reducing DO needs. It is already on the market and has successfully been tested at 600mg. It has shown good anti-TB activity in HIV-negative patients and in patients without cavity.[85,86] A 2002 CDC trial of 150 patients showed that rifapentine 900mg once-weekly "appears to be safe and well tolerated"[87], and CDC says that they are "still very interested in further developing rifapentin" as a once-weekly therapy, possibly with moxiflaxacin as a companion drug.

CDC is currently conducting a large-scale trial (2,000 patients) of rifapentin for latent TB in Brazil and will use further African sites to trial prophylaxis and treatment.

Two other long-acting rifamycins are in development (rifalazil and rifametane) as are some existing older compounds, e.g. rifalazil analogues.

Oxazolidinones:

Linezolid (Pharmacia/Pfizer): These are marketed as broad-spectrum antibiotics and appear to have anti-TB activity[88]. However, oxazolidinones are generally seen as less promising due to their toxicity and high price.

The off-the-shelf compounds listed above are under patent.[89,90] Slow progress in developing existing molecules for TB is due to lack of the political and

[83] Ibid 75, pp. 27-38.
[84] A study of early bactericidal activity in TB is now underway in Tanzania.
[85] Teleconference with Giorgio Roscigno (GATB) who supervised development of rifapentin while at Aventis.
[86] Weiner M et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. Am J Respir Crit Care Med 2003; 167 : 1341-7
[87] Bock NN, Sterling TR et al; A prospective, randomized, double-blind study of the tolerability of rifapentine 600,900 and 1,200mg plus isoniazid in the continuation phase of tuberculosis treatment; CDC, Atlanta; Am J Resp Crit Care Med 2002 Jun 1; 165(11):1526-30
[88] Alcala et al,. In vitro activities of Linezolid against clinical isolates of Mycobacterium tuberculosis that are susceptible or resistant to first-line antituberculius drugs. Antimicrob Agent Chem 2003; 47:416-7
[89] Telecon with Tom Kanyok, Director of New Drugs at WHO/TDR, 25 Jul 03. WHO/TDR first approached two drug companies in the early 1990s asking for access to ofloxacin and levofloxacin for clinical trials, but were refused.
[90] Telecon with Dr Ken Duncan, head of Action TB, GSK, Stevenage, UK; March 03. Despite showing little interest in testing these drugs themselves, drug companies are reluctant to co-develop them with the GATB or to provide them for clinical trials: a TB indication could "muddy the waters" for a drug with much larger profit potential as a general antibiotic in the West.

corporate will and funding to conduct rigorous large-scale clinical trials needed to test these drugs for TB.[91,92] In addition, public health authorities want to reserve these drugs (especially the fluoroquinolones) for use with patients with MDR-TB.

Novel compounds

The GATB has started to build a portfolio and currently has several proprietary compounds in pre-clinical and lead optimisation stages:

The nitroimidazopyran PA-824 is the most advanced and promising: it is novel, bactericidal and sterilizing[93]. This drug candidate which was sitting on the shelf in the lead optimisation stage is now moving successfully through pre-clinical testing[94].

Originally a by-product of 1990s cancer research, PA-824 and its analogues were licensed by the GATB for TB in January 2002 from Chiron. If all goes well, the drug could be registered by 2010. Chiron has agreed to forgo royalties on sale of the final drug in "less developed economies". They have the option to license back their drug to sell in wealthier countries but, if they choose to do so, they must repay the GATB all fees and R&D investments, plus royalties. The GATB retains the licensing rights in the developing world.

A two-year project to synthesize and optimise a group of novel quinolones (late discovery stage) in conjunction with the Korea Research Institute of Chemical Technology; work is also being initiated on analogues of PA-824 in the nitroimidazopyran family.

A compound discovered by Wellesley College was picked up by the GATB in early 2003 and is in the late discovery to pre-clinical stage.

[91] Telecon with Rick O'Brien, CDC, Atlanta, 21 Jul 03The cost of such trials has been estimated at US$2-3 million for Phase II and up to $22-25 million for Phase III if studies are undertaken in a developed economy, or at US$1.6 million for Phase I and US$8.2 million for Phase III in developing countries

[92] GATB "Economics and Drug Development" estimate, op.cit., 2001.

[93] Stover et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature 2000; 405: 962-6

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5. MDR-TB

The true incidence of MDR-TB is unknown. However, a 2000 survey by WHO/IUATLD shows that the highest prevalence of MDR is Former Soviet Union (FSU), Latvia, parts of China and Estonia[95].

MSF's experience corroborates this. MSF has conducted six drug resistance surveys in FSU[96]. The levels of MDR-TB found are dramatic, for example:

- 20% in Kemerovo (prison, Siberia)
- 13% in new and 40% in previously treated cases in Karakalpakstan (general population, Uzbekistan).

To uncover the extent of the problem in Uzbekistan, MSF flew samples to a WHO-accredited supranational reference laboratory (SRL) in Germany and paid $39,000 for the survey. A network of 20 similar nationally financed SRLs equipped to support DST surveys exists, but these facilities are currently not adequately financed by WHO to carry out such work for developing countries[97]. They are necessary because there is a lack of a standardized methodology to assess resistance to second-line TB drugs.

The only readily available test for MDR-TB for resource-poor settings is manual culture and drug sensitivity testing using solid Lowenstein-Jensen medium. The test is affordable at $1.50 but obtaining results takes between six to nine weeks. In addition, the test requires expensive materials, skilled lab personnel and strict precautions including the use of a safety cabinet – often available only in a national reference laboratory (NRL). The absence of such facilities in high-prevalence MDR-TB settings has required MSF to set up or co-develop laboratories[98], and five out of six MSF project sites in the FSU have to send samples to supranational reference laboratories (SRLs) in Europe at great expense.

Once a laboratory is capable of doing manual culture and drug sensitivity tests (DSTs), it does not require much more technical expertise to use rapid DST tests based on liquid media. However, the cost of DSTs is still prohibitive at more than $10 per test (as a comparison, an effective malaria test costs less than $1).

Large-scale trials aimed at assessing MDR-TB diagnostics in the field are in progress[99].

Most MDR-TB patients have no hope of ever receiving treatment within their NTP. Those patients who do manage to get treated must take a cocktail of five drugs – four of which had been previously abandoned because of their side effects and poor bactericidal effect. This explains why MDR treatment is so long (18-24 months) and has low cure rates (around 60%)[100].

These second-line drugs are expensive, with complete treatment costing $2,500-3,500. In 2000, MSF began working with WHO and drug suppliers to dramatically decrease the price of key MDR-TB drugs, in particular the three drugs for which there were no affordable quality sources: cycloserine, capreomycin and PAS – drugs that alone accounted for over 80% of the cost of treatment. The price was negotiated down from $8,000-13,000 to $2,500-3,500. Other drugs in the MDR-TB regime, for example ethionamide, ofloxacin or ciprofloxacin, are available as affordable generics.

WHO has set up a Green Light Committee designed to validate TB treatment programmes and supply them with more affordable second-line drugs. WHO is now recommending second-line drugs be added to programmes that have MDR-TB prevalence above three percent in new cases [101]. However, it is difficult to achieve this objective because of lack of access to appropriate diagnostic tools.

MSF is currently treating a small number of MDR-TB patients in Thailand, Uzbekistan, Karabagh, Abkhazia and Côte d'Ivoire.

[94] The stages of development are: a) basic research: identifies promising targets on the mycobacterium or promising approaches; b) discovery and pre-clinical: assays, screening, lead optimisation (optimising a compound that seems to have good anti-TB activity); c) clinical trials Phase I to III: tends to be the best-supported part of the TB drug development process, the main problem being that there are few compounds to feed into the structure; and d) registration and post-marketing trials (sometimes called Phase IV). These aim to determine optimal use of a drug in field conditions. Also relatively well-supported (eg. European DC Clinical Trials Platform; TDR)

[95] A 2000 WHO/IUATLD survey showed that 46 of the 54 regions surveyed had some MDR-TB, with prevalence of 9% or more in parts of the Former Soviet Union (12-14%), Latvia (12%), several provinces of China (9-15%), and Estonia (18%). Poly-drug resistance was more widespread, with rates of 20% or more in parts of China, Estonia, Latvia, and areas of Russia; and moderately high rates in Italy (9.9%), Iran (9.5%), Mozambique (10%), parts of India (13%), widespread areas of China (12-13%) and Israel (14%). http://www.who.int/gtb/publications/drugresistance

[96] Tuberculosis programmes and drug resistance in 6 Newly Independent states. MSF Presentation at the European Respiratory Society Conference, 2002

[97] Hargreaves S. Time to prioritise tuberculosis laboratory services. Lancet Inf Dis, Vol 3, October 2003.

[98] Two bacteriological laboratories have been implemented: in Siberia, Kemerovo (MSF-B) and in Nukus, Uzbekistan (MSF-H). The former is supervised by the laboratory of the Institute of Tropical Medicine in Antwerp, Belgium, and the latter by the National Mycobacterial Reference Laboratory in Borstel, Germany.

[99] WHO/TDR is conducting a trial in Peru, comparing four methods of DST with a view to determining the best timing for DST and the predictive value of a positive smear test at various stages in treatment. The Antwerp Study, funded by the EU, is evaluating various DSTs in seven different countries in Latin America. Results won't be available before 2005.

[100] Sizaire, V. First results of MDR-TB worldwide. Literature review. MSF. 2002

[101] Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, Baez J, Kochi A, Dye C, Raviglione MC. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA. 2000 May 17;283(19):2537-45

6. CONCLUSIONS AND RECOMMENDATIONS

DOTS expansion is not the only answer to TB. Improving DOTS is key too, if we are going to try to effectively treat the growing number of TB patients.

WHO seems to be in the process of changing its approach to TB, and the inconsistency in their advice to countries reflects this. Stop TB experts still simultaneously say that DOTS is the right approach but that "everything must change".[102] They continue to promote a cost-effective smear-positive focus in their publications, while at the same time advocating treatment for all; and they insist that "global TB control is possible through the DOTS strategy"[103] while noting that TB-incidence rates continue to rise despite increased DOTS coverage and cure rates in Africa.[104]

Likewise, Stop TB say it is now convinced of the need to devote equal attention to development of new tools, yet Stop TB publications state that health systems research, not R&D of new tools, should be the real focus. In their Global Plan to Stop TB, they note that new drugs and vaccines will take many years to develop and will require investments "in the billions of American dollars", while alternative research into health policies and systems "promises significant gains in far less time and at far lower costs". There is, they add, "ample evidence that this approach will succeed" because "existing tools are highly effective".[105]

What seems clear is that vigorous action for improved, more inclusive DOTS and for resources to develop new tools to fight TB is needed.

Médecins Sans Frontières recommends the following points for action:

Revision of the global TB strategy

- WHO should lead the process of revising a global TB strategy that adequately addresses the HIV/AIDS pandemic and its consequences for TB care.
- Access to treatment for smear-negative patients must be ensured: programme objectives need to be revised to eliminate perverse incentives to focus on subsets of patients.
- Innovative means of improving treatment adherence must be found, including reduced need for direct observation.
- More resources to develop new tools to fight TB adapted for resource-poor settings are urgently needed.

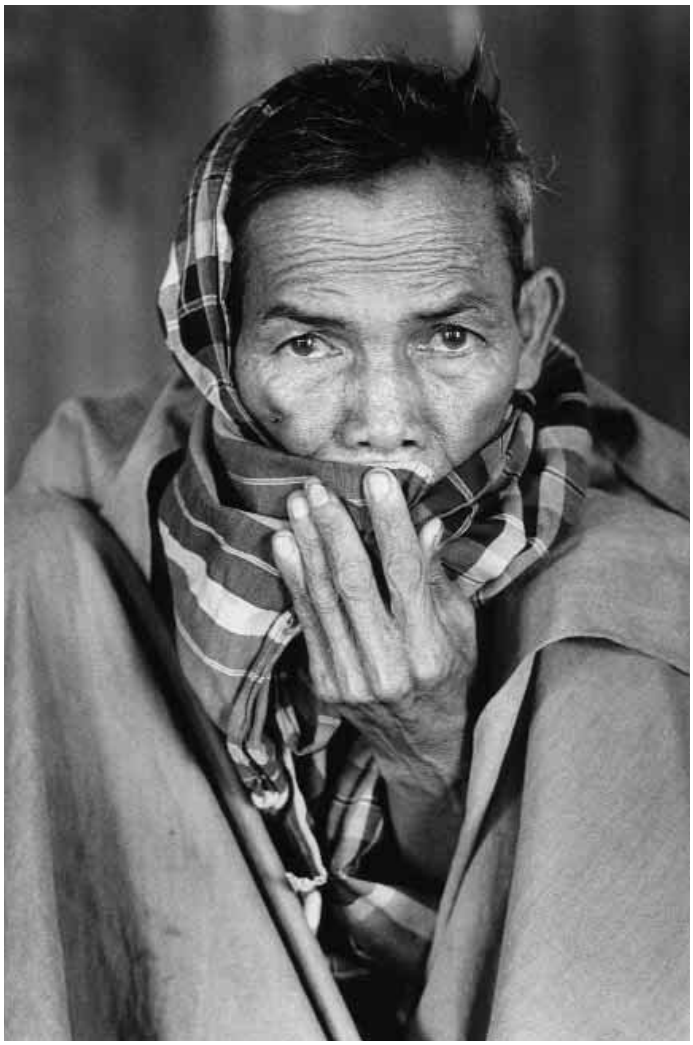
Boost development and validation of new diagnostic tools

- An emergency plan is needed to speed up validation of promising diagnostics.
- Ensure affordability of existing diagnostic and DST (e.g. MGIT).
- More R&D into entirely new TB diagnostic tools (e.g. antigen detection).

Quicken the pace of developing new, easier-to-use drugs and make them available at affordable prices

- WHO and governments must work together to develop and fund an essential TB clinical research agenda, ensuring that needed clinical trials take place. The agenda should consist of developing new TB treatments among:
- TB indications of existing drugs.
- New compounds.
- Governments should insist that companies make compounds with potential activity against TB available to those that are willing to develop them into drugs. When commercial interests hamper the development of a potential TB treatment, governments need to intervene.
- New TB drugs must be affordable to the people who need them.

[102] Meeting with Dr Raviglione, Director of Stop TB, July 3rd 2003
[103] WHO Guidelines op. cit., p.11
[104] WHO Global Plan op.cit., p.54
[105] WHO Global Plan op. cit., p.98



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