



Ubuntu (means "Togetherness") Integrated HIV/TB Clinic in Khaylitsha, South Africa
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TOO LITTLE FOR TOO FEW

CHALLENGES FOR EFFECTIVE AND ACCESSIBLE ANTIRETROVIRAL THERAPY

BRIEFING DOCUMENT

XVI International AIDS Conference, Toronto, August 2006

IN THE PAST 5 YEARS, CONSIDERABLE PROGRESS HAS BEEN MADE IN SCALING-UP ACCESS TO ANTIRETROVIRAL THERAPY. TODAY, 1.3 MILLION PEOPLE ARE RECEIVING TREATMENT. BUT A HUGE AMOUNT REMAINS TO BE DONE. MORE THAN 40 MILLION PEOPLE ARE LIVING WITH HIV/AIDS AND AN ESTIMATED 5 MILLION OF THESE ARE IN URGENT NEED OF TREATMENT.¹ THIS MEANS THAT 3.7 MILLION ARE GETTING NO TREATMENT AT ALL. MANY OF THESE PEOPLE LIVE IN THE WORLD'S POOREST COUNTRIES WHERE THE SITUATION REMAINS CATASTROPHIC.

MÉDECINS SANS FRONTIÈRES (MSF) CURRENTLY PROVIDES CARE FOR OVER 100,000 PEOPLE LIVING WITH HIV/AIDS (PLWHA) AND ANTIRETROVIRAL THERAPY FOR MORE THAN 60,000 PEOPLE ACROSS 65 PROJECTS² IN 32 COUNTRIES.³ ALTHOUGH MSF PROGRAMMES REPORT VERY GOOD OUTCOMES, IMMENSE CHALLENGES REMAIN.

DRAWING ON DATA AND EXPERIENCES BEING PRESENTED AT THE XVI INTERNATIONAL AIDS CONFERENCE IN TORONTO, THIS DOCUMENT HIGHLIGHTS SOME OF THE STRATEGIES THAT HAVE HELPED MSF TO EXPAND ACCESS TO QUALITY CARE, OBSTACLES CONFRONTED ALONG THE WAY, AND PROPOSALS FOR MOVING FORWARD.

ANALYSIS OF MAJOR CHALLENGES TO PROVIDING TREATMENT

Even after more than 5 years of experience in providing antiretroviral therapy – and substantial commitments of human and financial resources – MSF continues to struggle to overcome day-to-day operational challenges in delivering HIV/AIDS treatment in resource-poor settings:

- Treatment expansion is hampered by an acute shortage of health workers, especially in rural areas, and the high fees that are often charged to patients for medicines and services.
- Too few children are receiving treatment, largely because the tools to diagnose and treat them are inadequate; meanwhile, the number of children born with HIV continues to grow because strategies and efforts to prevent mother-to-child transmission are insufficient.

- Failures of coordination between TB and HIV control programmes and the lack of effective tools to diagnose and treat tuberculosis in HIV patients ensures that this curable disease continues to be the leading cause of death of PLWHA.
- Newer formulations and combinations of antiretrovirals are often not registered or are unaffordable in developing countries. Successful long-term treatment will be unachievable due to lack of access to new drugs and to tools for assessing treatment efficacy, and limited action to ensure this happens.

The above list is not comprehensive, but focuses on barriers that require an urgent public policy response. These problems, encountered by MSF teams around the world, reflect a few of the challenges faced by other actors, governmental and non-governmental, engaged in responding to the AIDS pandemic. They pose a serious threat to all efforts to expand quality treatment coverage and provide long-term care.

¹ AIDS Epidemic Update. UNAIDS, Geneva, December 2005.

² In addition to providing care and treatment (including management of opportunistic infections and antiretroviral therapy), MSF projects provide prevention interventions, in particular prevention of mother-to-child transmission; voluntary counselling and testing; nutritional and psychosocial support; and clinical and other training for local health staff and community health workers.

³ Benin, Burkina Faso, Burundi, Cambodia, Cameroon, China, Côte d'Ivoire, Democratic Republic of Congo, Ecuador, Ethiopia, Guatemala, Guinea, India, Kenya, Laos, Lesotho, Liberia, Malawi, Mozambique, Myanmar, Nigeria, Peru, Republic of Congo, Rwanda, Sierra Leone, South Africa, Sudan, Tanzania, Thailand, Uganda, Zambia and Zimbabwe.

The challenges MSF faces vary from context to context. However, several challenges cut across all contexts in which MSF provides HIV/AIDS care. It is clear that in order to maintain current achievements and support continued expansion of effective and long-term treatment, stronger political commitment is required in at least three areas:

- Making treatment affordable and available to the poorest to maximize their chances of accessing treatment and remaining in care.
- Developing new tools to confront the challenges of HIV in the less-developed world.
- Guaranteeing broader access to affordable medicines.

I. STRATEGIES AND POLICIES NEEDED TO ENSURE THAT TREATMENT IS ACCESSIBLE TO THE POOREST

For successful coverage, governments and donors must commit funding to increase and retain health staff and allow patients to access free treatment and care.

Care must be decentralised and simplified

"If treatment is only available in cities and hospitals, the most vulnerable will suffer."

- Dr Moses Massaquoi, MSF, Thyolo, Malawi

Ensuring that dedicated HIV services are available at the primary health care level is essential in enabling PLWHAs in rural areas to access HIV testing, care and treatment. Faced with severe human resource constraints, MSF has developed strategies to decentralise while maintaining the quality of treatment: specific clinical tasks are delegated from doctors to nurses and clinical officers, and community health workers and PLWHA are trained to assist with adherence counselling and other support activities. Limited access to newer antiretrovirals for use in second-line regimens and the total lack of third-line and rescue therapies means that a deep commitment to adherence support is crucial for long-term successful outcomes.



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Lusikisiki, South Africa
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JULY 2006 DATA

Outcomes from MSF projects confirm the effectiveness of antiretroviral therapy in improving survival over a broad range of contexts.

An analysis of 57,147 adults on antiretroviral therapy (59.7% women) in programmes in 23 countries shows that most began treatment at an advanced stage of disease: 84% were symptomatic (WHO stage III and IV) and 29.6% of all patients had a CD4 count below 50 cells/mm³. The vast majority of patients were treatment-naïve at initiation; 84.5% were started on a generic fixed-dose combination of stavudine, lamivudine and nevirapine. The overall probability of survival was 90% at 12 months and 87% at 24 months of treatment; the probability of remaining in care (excluding death and lost to follow-up) was 81% at 12 months and 74% at 24 months. Mortality and lost to follow-up was highest in the first 3 months. Median CD4 count increased continuously, reaching 251 cells/mm³ at 12 months, 311 cells/mm³ at 24 months and 411 cells/mm³ at 48 months. These results demonstrate that a limited range of ARVs can provide excellent outcomes.

Data from programmes in 14 countries treating children younger than 13 years also show good outcomes.⁴ A total of 3,754 children (mean age 5.7 years, 47% female) were included in the evaluation. More than 40% were severely immunocompromised at baseline. Almost all (99%) received zidovudine or stavudine plus lamivudine plus nevirapine or efavirenz. In the absence of suitable paediatric formulations, most children were treated with adult treatments, which were broken as appropriate. The probability of survival was 87% at 12 months and 77% at 36 months. Significant gains in CD4 count and weight were observed.

⁴ Olson D, Sauvageot D, Ferradini L, Humblet P. Antiretroviral therapy (ART) outcomes in children <13 years of age in resource-poor countries: a Médecins Sans Frontières (MSF) cohort. IAC, Toronto. MOAB0204.

DATA PRESENTED AUGUST 2006

Decentralised care in rural South Africa

In Lusikisiki, a rural district of South Africa (population 150,000), an estimated 2,250 people are in need of antiretroviral therapy. As of March 2006, 1,529 patients were receiving treatment, a rapid scale-up made possible by decentralisation of services and integration into general consultations. Enrolment is increasing faster in the clinics than in the hospital because there are more service points and services are integrated into general consultations rather than being dependent on HIV-specific staff. Immunological and virological outcomes are good in all sites (70% of patients have CD4 >200 cells/mm³ and 91% undetectable viral load after 6 months). Patient retention (minus deaths and loss to follow-up) is better in the clinics (80% still on antiretroviral therapy at 12 months) than in the hospital (69%). This is likely due to the greater proximity to patients' homes.⁵

Efforts needed to address the human resource crisis

"In Lesotho there are about 40 doctors in the entire country, and in the health district we are working in they have lost 18 nurses in 6 months, mainly to the UK and South Africa. We need an emergency response."

- Rachel Cohen, MSF, Morija, Lesotho

Lack of skilled health staff is an overriding constraint to scaling-up treatment, especially in rural areas. Health services are often understaffed and staff motivation suffers from isolation, difficult working conditions and lack of adequate remuneration and support. Recruitment freezes and salary restrictions render the public health sector unattractive. Meanwhile, donors are generally reluctant to provide funds to contribute to recurrent costs, in particular salaries.

It is encouraging that in some countries the human resource crisis is recognised as a crucial hurdle to expanding care and treatment. In Malawi, for example, the government and donor community are working to increase health staff training and deployment in rural areas, and measures have been taken to lift constraints on recruitment and remuneration of urgently-needed health staff.

Without immediate and fundamental changes to address the human resource crisis by governments and donors, decentralisation and scaling-up of AIDS care will be compromised.

Patients need free treatment: charging for treatment costs lives

"By forcing people to pay, you're risking treatment interruptions, and this can make this life-prolonging treatment less effective. If we want large numbers on treatment, we have to ensure access to free care."

- Dr Jens Wenkel, MSF, Lagos, Nigeria

Providing free treatment is essential for optimal access and adherence. However, most countries still require a financial contribution towards AIDS care. Even in those places where antiretrovirals are free, other costs are often borne by patients such as consultation fees, medicines for opportunistic infections, lab tests, and hospitalization.

MSF's experiences in Kenya and Nigeria, where the organisation provides free treatment, show that collecting fees for drugs or other treatment services can result in treatment interruptions, sharing of antiretrovirals and a higher risk of defaulting - all of which can contribute to treatment failure and the development of resistance. In Nairobi, Kenya, MSF runs a free treatment programme in the same hospital as a government programme that charges user fees. Data being presented at the XVI International AIDS Conference in Toronto, August 2006, demonstrate that among paying patients, the percentage lost to follow-up (13.6%) was twice as high as for non-paying patients (6.9%).⁶

II. NEW TOOLS MUST BE DEVELOPED

Diagnosing and treating HIV/AIDS in children

"Our results in treating children are very good, but it's an uphill battle. With better diagnostic tools, treatments that kids will swallow and that their bodies will respond to, many more young children could lead relatively normal lives."

- Dr Rachel Thomas, MSF, Kibera, Kenya



PWA Counselor with patient in the HIV/AIDS Clinic, Thailand
© Kris Torgeson

Nearly 90% of the estimated 2.3 million children living with HIV live in poor countries, mostly in sub-Saharan Africa.⁷

Without treatment, half of all children born with HIV die before they are 2 years old. MSF's experience, among others', shows that children can be treated effectively, but without simple and appropriate tools for diagnosis and treatment, scaling-up will not be possible:

- Diagnosing HIV in newborns is difficult in resource-poor settings because antibody-detection tests commonly used in adults do not work in children under 18 months.
- Appropriate paediatric dosages of antiretroviral tablets are extremely limited, forcing caregivers to split adult tablets. Since these tablets are not designed for partial intake this approach is far from ideal. For children weighing less than 10 kg, even this strategy is impossible; the only treatment options are syrups that are difficult to measure, bitter-tasting and overpriced (up to six times more expensive than adult formulations).

Technical guidance and training to respond to the needs of children are required for caregivers who are more accustomed to treating HIV/AIDS in adults. UNICEF has yet to fulfil its promises to establish and disseminate guidelines in this area, and must do more to push for new and better tools.

While struggling to diagnose and treat children, it is essential that efforts to prevent new infections are not neglected. Preventing mother-to-child transmission of HIV - which is highly successful in wealthy countries - has proven to be a major challenge in resource-poor settings.

URGENT NEED TO MAKE PMTCT WORK

The decline in paediatric HIV infections in wealthy countries is mainly due to the success of programmes to prevent mother-to-child transmission (PMTCT). There are, however, serious operational challenges to implementing PMTCT programmes in resource-poor settings, given the reality that women have little access to antenatal care that could provide the drugs and information women need to prevent mother-to-child transmission. Many institutions and organisations, including MSF, have failed to develop innovative strategies to overcome these constraints. Large-scale, efficient PMTCT programmes that are designed to work with weak health systems should be integrated into emerging antiretroviral treatment programmes at the primary care level. Technical agencies, such as WHO and UNICEF, must take the lead in developing a simple and durable strategy for management of HIV-positive pregnant women that is feasible on a large scale.

Tuberculosis, the most common cause of death among PLWHA

"We must refuse to accept that millions of people will die of tuberculosis simply because we can't detect it. We need a simple, effective tool to diagnose active tuberculosis in HIV patients, and in the meantime, we need a less rigid approach to tuberculosis in high HIV prevalence settings to allow clinicians, including nurses, to ensure early diagnosis and treatment of smear-negative tuberculosis."

- Dr Martha Bedelu, MSF, Lusikisiki, South Africa

Tuberculosis is the most common cause of death in PLWHA. About one-third of the 40 million PLWHA worldwide are co-infected with tuberculosis. In some places where MSF works, such as Lesotho, the HIV prevalence among tuberculosis patients is more than 75%. In such settings, it is essential that these twin epidemics are treated simultaneously and that services for both diseases are integrated. Without proper treatment, approximately 90% of PLWHA die within months of developing tuberculosis.

The inadequacy of current tools makes it difficult to detect tuberculosis in HIV-positive patients. The standard detection method - sputum smear microscopy - detects about only one-third of active tuberculosis in HIV-positive patients. Clinical diagnosis is also difficult because many of the symptoms can also be caused by other infections. If severely immunocompromised tuberculosis patients go undetected, and therefore untreated, the disease progresses rapidly and leads to death.

Anti-tuberculosis drugs and antiretrovirals can interact, rendering some drugs toxic while others become less effective. Even the minor side-effects that both treatments can produce can become intolerable when combined. For this reason, most programmes recommend a shift from the simple standard first-line antiretrovirals to a more complicated and expensive regimen. Access to simple combinations of newer AIDS drugs that are compatible with tuberculosis drugs is needed.

The challenge of long-term management of HIV/AIDS

"You cannot effectively treat a chronic disease with a short-term perspective. We have an obligation to work with others to ensure treatment can be provided for life."

- Dr David Wilson, MSF, Bangkok, Thailand.

Treatment strategies, drug regimens and monitoring procedures for antiretroviral therapy will need to evolve as treatment cohorts mature. The challenges of managing drug toxicity and resistance, inevitable after years on treatment, will be increasingly common. The viral load equipment that is routinely used in developed countries to monitor treatment effectiveness is sensitive to heat and

⁵ Herron T, Bandedzi N, Bedelu M, Reuter H, Mofokeng N. Effective outcomes from decentralizing ARV care to nurse-managed clinics in rural South Africa. IAC, Toronto, 2006. TUPE0246

⁶ Van Ingelgem, Massaquoi M, Jamet C, Ritter H, Zachariah R, Manzi M, Suleh A, Kocholla L, Phillips M, Humblet P. Payment for antiretroviral drugs is associated with a higher risk of "loss to follow-up" among individuals placed on antiretroviral treatment. IAC, Toronto, 2006. MOPE0849

⁷ AIDS Epidemic Update. UNAIDS, Geneva, December 2005.

dust, and requires a stable supply of electricity and highly trained lab technicians. To date there has been little investment in developing monitoring tools that can be used in resource-poor settings and it could be several years before recently-launched initiatives bring needed monitoring tools to market.

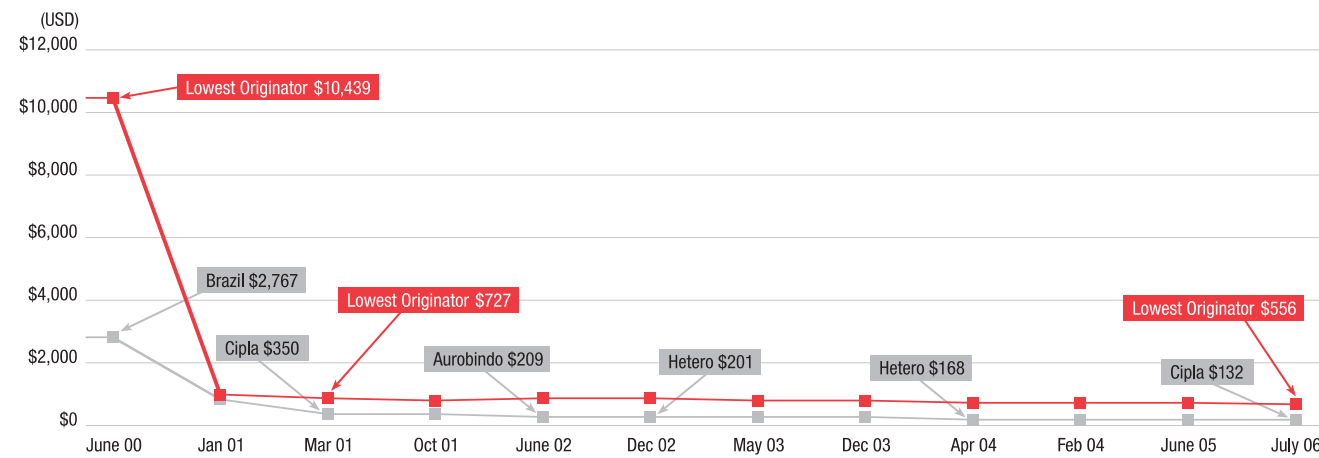
Long-term management of HIV/AIDS calls for access to first-line and second-line combinations with minimal side-effects and tools for simplified virological monitoring to allow accurate detection of treatment failure and identification of the optimal time to switch to second-line. These and other challenges require a shift in research and development efforts to ensure that new tools are designed with specific concern for the problems of providing treatment in resource-poor settings.

III. STRONGER POLITICAL COMMITMENTS NEEDED TO GUARANTEE LONG-TERM TREATMENT

“Affordable generic AIDS medicines have been one of the cornerstones of our ability to keep more people alive.”
- Dr Pehrolov Pehrson, MSF, Manipur, India

Since 2000, thanks to generic manufacture strongly supported by civil society pressure, in countries such as India, Thailand and Brazil the price of first-line regimens has been pushed down by 99% from an average of \$10,000 US to the current price of just \$132 US per patient per year. Today, 50% of people on antiretrovirals in the developing world rely on generic medicines from India. The cost of treatment can and should be pushed as low as possible if scaling-up is to succeed. The most effective way to do this is through generic competition. (figure 1) However, this might become increasingly difficult in the future (figure 2).

FIGURE 1
THE EFFECTS OF GENERIC COMPETITION: June 2000 – June 2006



Sample of ARV triple-combination: stavudine + lamivudine + nevirapine. Lowest world prices per patient per year. Generic competition has shown to be the effective means of lowering drug prices. During the last five years, originator companies have often responded to generic competition.

AFFORDABLE SOURCES OF NEW MEDICINES UNDER THREAT

The progressive implementation of the World Trade Organization's (WTO) patent rules is causing generic sources of new medicines to dry up. Under WTO rules, all new drugs may be subject to at least 20 years of patent protection in all but least-developed countries (but these have little capacity to produce antiretrovirals). An increasing number of developing countries are making use of the Doha Declaration on TRIPS and Public Health to allow the importation of lower-cost generic medicines. In the future however, these countries will be faced with the question of where to find suppliers from which they can import. WTO measures to address this issue do not work.⁸

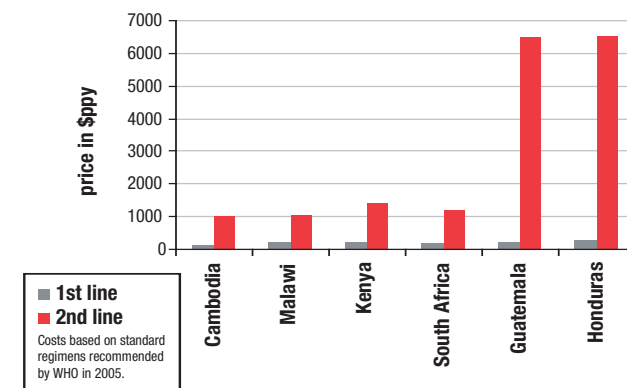
India has been a major source of generic medicines worldwide. Beginning in 2005, India has started to grant drug patents and in the future, generic production may therefore largely depend on compulsory licenses. India's Patents Act has strict patentability criteria, and includes a provision that allows anyone to oppose a patent before it is granted. This provision is being used by PLWHA and civil society groups to oppose the patenting of several key AIDS drugs, including tenofovir, and combivir (zidovudine and lamivudine); if successful, generic production and export of these drugs can continue without facing additional hurdles.



More potent and better-tolerated first-line antiretroviral regimens like those including tenofovir are essential to providing quality AIDS care and must be made affordable and available in developing countries. There is increasing evidence of serious, long-term side-effects from some of the most commonly used first-line antiretrovirals, especially stavudine.⁹ Access to first-line regimens containing tenofovir is an urgent priority.¹⁰ However, tenofovir still remains very costly and unavailable in the majority of developing countries, despite having been registered in the US since 2001.

Access to second-line medicines is also a growing concern. Latest data from Khayelitsha, South Africa, show that one in six patients (16.8%) who had been on treatment for 48 months had had to switch to second-line. But at current prices, treating 58 patients on second-line drugs costs the same as treating over 550 patients on first-line. Lack of affordable second-line treatment is the norm across the developing world (figure 2). In addition, these drugs are difficult to access because pharmaceutical companies often make no serious attempt to register or market them in these countries.¹¹ As resistance inevitably grows, it will become catastrophic if the situation is not addressed.

FIGURE 2
COST OF FIRST- AND SECOND-LINE DRUG REGIMENS



⁹ Boule A, Van Cutsem G, Coetzee D et al. Regimen durability and tolerability to 36-month duration on ART in Khayelitsha, South Africa. CROI, Denver, 2006.

¹⁰ These include the first-ever once-a-day combination of tenofovir, emtricitabine, and efavirenz, recently released in the US, and combinations of tenofovir and lamivudine and either efavirenz or nevirapine, currently being developed by generic manufacturers.

¹¹ Derche C, Pinheiro E, Pascual F. Comparison of prices of first- and second-line antiretrovirals in low- and middle-income countries. What is the relation with the production cost? ICASA, Nigeria, 2005.

CONCLUSIONS

Just five years ago, many argued that providing antiretroviral therapy in resource-limited settings was far too costly and complex for the developing world. The 1.3 million people benefiting from life-prolonging treatment in developing countries today are testament to the dramatic impact it has on people's lives, and highlight the urgent imperative to further increase treatment coverage.

Ensuring treatment reaches those most in need can be achieved only by taking it from capital cities to rural health centres. In the face of the current human resource crisis, this means shifting away from a doctor-centred approach to treatment. At the same time, serious efforts are needed to retain health staff to work in these areas. In addition, treatment must be provided free of charge. Experience has shown that even charging a modest fee for treatment is associated with higher defaulting, poorer adherence and higher mortality. Treatment costs can be driven down by lowering the price of drugs and tests, and by adapting programme approaches. Patients should not be expected to pay.

The challenges of diagnosing and treating HIV in children and addressing tuberculosis as the major cause of death of PLWHA call for a massive innovation through research and development based firmly on the realities and constraints of tackling HIV in the less-developed world. Relying on a system that develops medicines solely with Western markets in mind means accepting to struggle with sub-optimal tools. This again will compromise all efforts to reduce AIDS-related mortality.

Affordable, effective fixed-dose combinations have been the key to scaling-up antiretroviral therapy. But the cost of treatment is rising rapidly as resistance and side-effects mean that patients need to shift to newer, more expensive treatments. Action to ensure sustainable access to second-line medicines is urgently needed. These drugs are priced out of the reach of, or inaccessible to, less-developed countries. This reality underscores the importance of ensuring multiple sources of essential drugs, which can only be achieved through firm political commitment to removing intellectual property barriers that stand in the way of generic competition.

There are many more challenges than the ones covered in this document that need to be confronted in tackling the HIV/AIDS pandemic. But the issues highlighted here are among the most pressing and problematic ones faced every day in MSF programmes across the world. Without urgent political action on these key points, further efforts to scale-up treatment will be limited. Future international commitments to provide universal access will remain as empty as those of the past, made safely in the knowledge that they will never be met.

⁸ Neither expeditious, nor a solution: the WTO August 30th Decision is unworkable. MSF, Geneva/Montreal, August 2006.