

Alive at Five: Lessons Learned from AIDS Treatment in Resource-poor Settings

Médecins Sans Frontières has been providing antiretroviral (ARV) treatment to people living with HIV/AIDS in developing countries for nearly five years now.

With over 57,000 patients on ARVs in a variety of resource-poor settings, MSF is constantly re-evaluating and evolving its approach to AIDS treatment. We strive to reach more people by simplifying treatment, rethinking treatment strategies, and relying more on paramedical staff as treatment providers. But the accomplishments to date have led to a series of new clinical and political challenges.

First, a lack of adapted diagnostic tests and treatments for babies and young children means that caregivers and medical staff struggle to provide adequate care for the growing number of children needing ARVs.

At the same time, some of the adult patients who have been on treatment for a few years now are finding their drugs are no longer working. The nature of the HIV virus means that patients cannot stay on one single regimen indefinitely, and experience from developed countries shows that it is indeed unrealistic to expect this. More and more individuals will need to be switched to so-called second-line treatment – yet medical teams don't know at what point it is best to make this change. Part of the problem is that there is as yet no simple and affordable means to monitor the presence of the virus in the person's blood, the best indicator of whether or not treatment is still working.

When the decision is made to switch a patient, care providers will need one or two practical standardised second-line combinations. Since many people will have been on a first combination for years and may have accumulated resistant virus before being switched, the second-line treatment will need to be robust: it will need to work despite resistance to the first-line combination. The ideal combinations could be stored at room temperature and would have few side effects. Today's second-line regimens do not fulfil these criteria; what's more, they cost up to 20 times more than the first-line medicines, a fact that will need to change dramatically.

But it may be that the strategies we have used to promote access to first-line treatment will be insufficient to cope with the new challenges. These include the full implementation of the World Trade Organisation's patent rules through the TRIPS (Trade-related Aspects of Intellectual Property Rights) Agreement, which has consequences for the availability and affordability of medicines.

The stakes in the global fight against AIDS are high – they far exceed the current funding commitments to the Global Fund to Fight AIDS, tuberculosis and malaria, for example. Government funding for AIDS is nothing short of insufficient. This is evident in the area of AIDS research: from direct experience, MSF staff know that there is an urgent need to do clinical and operational research that would benefit people living with HIV/AIDS in developing countries. But is the research conducted in Africa today really designed to respond to the needs of people with AIDS on the continent, or will its benefits only be felt where patients or their health systems can afford state-of-the-art solutions?

There is no easy answer to how we can expand treatment to more people who need it. We are currently only touching the tip of the iceberg, and will need to find strategies to cope with the ever-growing queues of people waiting to be treated. How will we, or any treatment group or government programme, reach and care for all patients in need of ARVs in a particular location, for example?

Let's face it: collectively, WHO, national governments, donors and non-governmental organisations have not reached the objective of providing the best treatment for people living with HIV/AIDS. AIDS is a complex chronic disease about which medical professionals have more questions than answers. But the international political environment is constantly evolving, and priorities change. A recent case in point is the avian flu, which has opened governments' eyes about not letting patents stand in the way of protecting lives. This potential threat has suddenly mobilised hundreds of millions of dollars, whereas AIDS, a pandemic that kills eight thousand people a day, is not getting the attention it deserves.

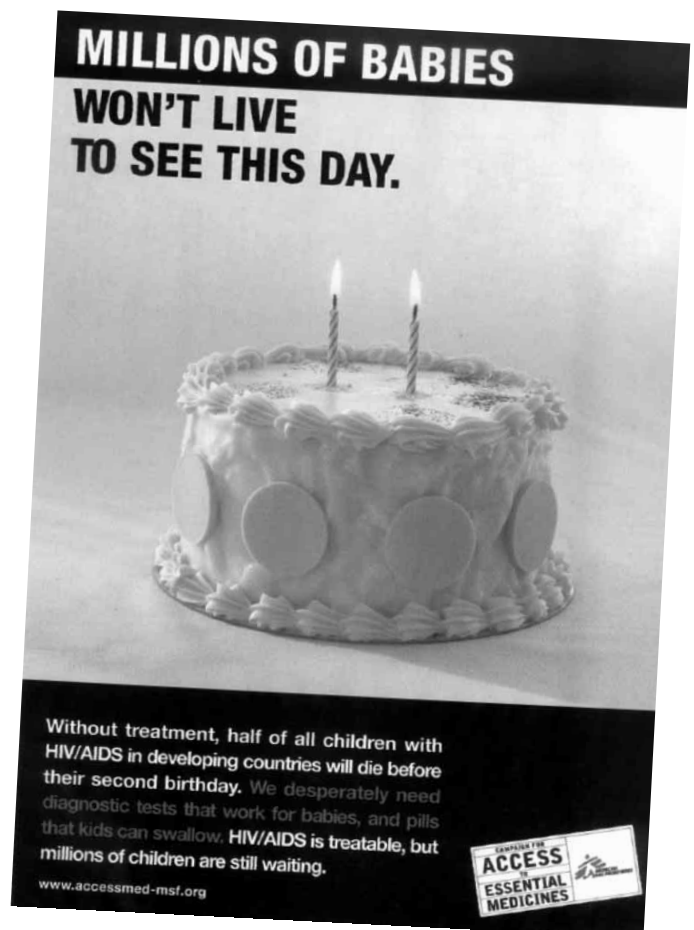
While we debate the best strategies for the future, we mustn't lose sight of a crucial question: when will we be able to celebrate the second birthday of the children born with the HIV virus?

■ Alexandra Calmy

Dr Calmy is advisor to MSF's Campaign for Access to Essential Medicines and works in Sydney, Australia.

Summary

- 1 Editorial Alive at Five: Lessons Learned from AIDS Treatment**
Still a Struggle: Treating Children with HIV/AIDS
 - 2 A Paediatrician's Perspective on HIV/AIDS**
 - 3 AIDS Drugs and Diagnostics The Sorrows of Single Source Supply: GSK in Honduras**
 - 4 The HIV-TB Deadly Duo: Integrating HIV and TB Care**
Lessons from AIDS Advocacy: Pushing for a Global TB Movement
- The Second Wave of the AIDS Drug Pricing Crisis: Action Needed At WTO**
Diagnostic Wish Lists: From the Field to the Lab and Back



Still a Struggle: Treating Children Living with HIV/AIDS

Millions of children with HIV/AIDS die every year because there are no appropriate diagnostic tools and paediatric antiretroviral [ARV] formulations that are affordable. 95% of these children live in poor countries. In the West, infections from mother to child can be effectively prevented, and ARV therapy gives children born with HIV an excellent chance of reaching adulthood. Yet in the developing world, the lack of treatment experience and the difficulties in providing ARVs to children mean that only a tiny proportion of those in need get treated.

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Continued from front cover

In Kenya, only one percent of the approximately 120,000 children with HIV receive ARVs. But despite the enormous challenges involved, MSF is intent on increasing the number of children in its programmes. Situated on the outskirts of Kenya's capital Nairobi, Kibera is Africa's largest slum. An estimated 1.2 million people call this maze of corrugated tin shacks home.

Five-year-old Johanna is one of 200 kids who has to pay regular visits to the MSF clinic. Johanna was diagnosed with HIV and put on ARVs when she was two. She needs to come in for regular check-ups to have her opportunistic infections treated. Adherence to treatment is extremely important, and her mother has to make sure Johanna takes her daily doses correctly. But this is a real challenge for caregivers and health workers alike. Unlike adults, who can take a cocktail of medicines in one pill (known as a fixed-dose combination, or FDC), there are no adapted formulations for kids. This means there's no choice but to crush adult tablets. Each day, Johanna's mother wraps the pill in a little plastic bag and crushes it into a fine powder. "Crushing the pills is hard," she explains, "sometimes, you lose a bit of the powder, it's complicated and it's difficult to make sure that you have the right quantity of the medicine."

In a poor setting like Kibera, this simple method is the only way to obtain a child's dosage. Other options do exist but they are just as impractical. "Some of the drugs available come in syrup forms that taste horrible and children don't like taking them. If they are in powder form, they have to be mixed with water. This means that you need a source of clean water, and if you live somewhere like Kibera, it's very difficult," explains MSF medical coordinator, Dr. Rachel Thomas.

What makes Johanna's treatment even more complicated is that there are no clear guidelines or dosage charts for kids. As a child grows and gains weight, the dosage

they need changes. "Adequate dosing is crucial," stresses Dr. Thomas. "Mistakes can have a severe impact: over-dosing can result in increased side effects and toxicity while under-dosing often leads to resistance." Developing resistance to a drug would mean that a child like Johanna would no longer respond to the first-line drugs. And since there are virtually no adapted second-line treatments for kids, Johanna would have no chance to survive in the longer term.

Yet for now, Johanna is doing well. She is one of the lucky few actually receiving treatment. In the small counselling room next door, MSF counsellor Aggrey Momo is faced with an even bigger challenge: mothers who bring very young babies for testing. There is no simple and affordable diagnostic tool to determine whether babies under 18 months are infected or not. The routine test detects antibodies to the virus, but since newborns acquire their mother's antibodies, it is impossible to determine whether they are really infected. "With the test kit we have here, we cannot confirm if babies are HIV positive or not. So we have to tell the mothers to wait until the baby is 18 months old to take the existing test." But many children cannot afford to wait that long. Half of those infected with HIV never reach their second birthday.

To change this, MSF has started treating children according to their clinical signs. Yet throughout the developing world, the lack of adequate diagnostic tools continues to prevent babies from getting treatment that could save their lives. "The people who can change this situation are governments and international agencies who are all based in rich countries," stresses Dr. Thomas. "We need a greater commitment and response from pharmaceutical companies to design paediatric formulations that can be used in poor settings. We need affordable simple HIV tests that can diagnose children under 18 months. And this commitment needs to come very fast."

■ Véronique Terrasse

A Paediatrician's Perspective

Interview with Felipe Garcia de la Vega, a paediatrician who first worked with MSF in Peru in 1997, followed by missions in Burma and Mozambique. Since May 2005, he has been the HIV/AIDS & TB Advisor to MSF's Campaign for Access to Essential Medicines in Geneva.

■ **What is MSF's position and role regarding paediatric HIV/AIDS?**

Across the globe, MSF currently treats over 57,000 patients with anti-retroviral therapy [ART], but only six percent are children. Because we don't have appropriate diagnostic tools and medicines adapted to children's needs, the majority of our patients are over one year of age. Only once we felt confident enough treating adults did we begin to look into the problems of the younger population. It has been a good start but many challenges remain.

■ **You worked as a paediatrician in Mozambique – how was the situation in terms of treating and diagnosing children with HIV/AIDS?**

In Mozambique, MSF Switzerland has two HIV programmes. When I arrived in 2003, few children were being offered ART for various reasons: Health staff is generally not confident handling children with suspected or confirmed HIV infection, as they have growth problems and recurring infections, and there are few tools to facilitate the staff's work. As a paediatrician, it was incredibly frustrating not to be able to treat all the children that needed this life-saving treatment. Children's lives change completely once they receive ART: they start to grow, the recurrent infections and skin lesions gradually disappear, and they can return to school and normal life. As our team in Mozambique gained confidence in treating adults, we began to treat more and more children, and the number receiving ART has gradually increased to more than 200 children today.

■ **What other challenges did you face regarding children and HIV/AIDS?**

Adherence to treatment is a big problem. As with adults, it is crucial that children take their medicines their whole life without missing a day, in order to delay the onset of resistance. If asking adults to stick to their regimen for life is hard, imagine how hard it is with children and their caregivers. Factors that reduce adherence in children include lack of a liquid formulation for some drugs and the large volume of medications they need to take.

■ **Why has it been so hard to put paediatric HIV/AIDS high on the international health agenda?**

The answer is simple. There are very few children infected with HIV/AIDS in rich countries, and the millions of children infected with HIV/AIDS in developing countries don't represent a lucrative market for pharmaceutical companies.



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■ **What are the new developments regarding paediatric HIV/AIDS?**

So far, there have been very few. We have mostly seen adaptations of the tools used for treating adults. Scientists at Cambridge University are currently working on adapting viral load technology to make it available in resource-poor settings, but these projects require strong funding.

■ **UNICEF is launching a campaign to support paediatric HIV/AIDS. What is MSF expecting from this?**

Putting children on the agenda is always welcome at MSF. Adequate healthcare and treatment for children is not only an ethical imperative, but a right recognised by the countries that signed the UN Convention on The Rights of The Child. We want UNICEF to strongly push for the inclusion of more children on ART, and to address the problem of unaf-

fordable paediatric ARV formulations in relation to both originator and generic companies. We want them to be more active in pushing for the prequalification of second-line paediatric formulations, as well as in the development of dosing tables adapted to resource-poor settings.

■ **Pedimune, a new generic paediatric combination, is expected to become available quite soon. How will this change the situation?**

Pedimune is a paediatric adaptation of a FDC tablet used in adults. As it will be produced in smaller doses, it will allow doctors to treat more children, starting at three kg babies – right now, when FDCs are crushed, it is only possible to treat children that weigh more than 10 kg. Adherence will also be made easier, with just two pills or two drinks per day if a dispersible formulation is also developed.

AIDS Drugs and Diagnostics...

The Sorrows of Single Source Supply: The Honduran Case

Over two thousand Hondurans on antiretroviral [ARV] treatment had just over one month of pills left when the drug company GlaxoSmithKline [GSK] announced that they wouldn't be able to deliver their next drug shipment on time. In a letter addressed to the AIDS drug procurement agency IDA [International Dispensary Association], GSK wrote that due to "increased demand" for its AIDS drugs, it was experiencing a shortage and would have to delay delivery of pending orders. This meant that the Honduran people on the ARV Combivir, a fixed-dose combination of AZT+3TC, would be left without their lifeline drugs for over two months. GSK blamed others for their own shortcomings, stating that generics producers had "either failed to meet World Health Organization pre-qualification standards, or had found the registration of their products slow," contributing to the shortage.

This is a classic example of the dangers of relying on one source to supply essential drugs. When a shortage occurs, patients can be left in the dark. The Honduran government picked up the phone and called MSF, which had been a partner in providing ARV treatment in the country since 2002. Though it had handed over its ARV project to the Honduran government this fall, and is now only monitoring AIDS projects across the country, MSF agreed to jump in and lend 75,000 pills [three weeks of treatment] of generic AZT+3TC from its Guatemalan project to the Honduran Ministry of Health, to help fill in the gap and avoid 'stock out.' With a gentle nudge from MSF, the Honduran government agreed to buy an emergency stock of the cheaper generic version of the drug manufactured by Cipla. Up until then, the government had only bought AZT+3TC from GSK, even though an independent investigation found that GSK's patent on the drug was not valid in Honduras. The stock from Cipla will last until early next year. It remains to be seen whether after this experience the Honduran government will again begin buying this drug from GSK.

■ Sheila Shettle

Tackling the Second Wave of the AIDS Drug Pricing Crisis: Action needed at WTO

As the World Trade Organization's (WTO) ministerial meeting prepares to convene in Hong Kong, MSF warns that urgent action is needed to ensure a continuous supply of affordable medicines to those who need them. Patents on medicines are a matter of life and death for people in poor countries. MSF calls on the WTO to examine whether the measures to remedy the negative effects of drug patents are robust enough to address today's problems.

Following the full implementation of the WTO TRIPS (Trade-related Aspects of Intellectual Property Rights) Agreement in India and other developing countries in January this year, access to affordable new drugs is expected to become more difficult. In the future, all new drugs may be subject to at least 20 years of patent protection practically everywhere but least developed countries.

Generic competition has brought down the prices of first-line AIDS drugs from US\$ 10,000 to as little as US\$ 150 per patient per year over the past five years. Local production in India, Thailand and Brazil – possible because medicines were not patent protected there – has had effects far beyond the borders of those three countries. National AIDS programmes in Brazil and Thailand have been successful because key pharmaceuticals could be produced locally at much lower costs.

"But after hard-fought progress, we are now seeing the 'second wave' of the AIDS drug pricing crisis," says Ellen 't Hoen, director of policy advocacy with MSF's Campaign for Access to Essential Medicines. "The prospects of competition are diminishing because patent rules are being implemented by all but least developed countries. For example, second-generation AIDS medicines are up to 20 times more expensive than older drugs, and when patients inevitably need to be switched to new regimes, their drug bills will shoot up."

Originator companies have shown very little willingness to further lower the prices of their drugs in developing countries, despite requests by international organisations such as UNAIDS and the World Health Organization. MSF has first-hand experience trying to access existing ARVs at discounted prices given to some countries by companies. Some companies do not offer discounts to middle-income countries – this is the case of lopinavir/ritonavir (Kaletra, manufactured by Abbott Laboratories) in Thailand, Latin America and Ukraine, where MSF programmes pay US\$4,000 to 6,000 per patient per year for this one drug alone. To put these prices

in perspective, MSF currently pays less than US\$250 per patient per year for WHO-prequalified first-line triple combinations sourced from Indian generic producers.

Patent rules may also hamper the development of fixed-dose combinations – the three-in-one pills that have helped simplify patients' lives – when patents on the different compounds are held by different companies. Although these pills are currently what approximately 70% of all MSF's patients take as first-line treatment, patent rules in India will make such combinations difficult, if not impossible, to produce in the future.

But the patent system clearly has not resulted in a mechanism nurturing essential health research and development that would benefit the most vulnerable populations. "The TRIPS Agreement has failed to address the needs of patients in developing countries," says Ellen 't Hoen. "MSF is urging WTO member states to ensure that existing products remain affordable, and that new therapies are developed and made available to patients in poor countries." The TRIPS Agreement has provisions to set patents aside, and countries should use these. One such flexibility is compulsory licensing, which allows the production and importation of generic medicines.

■ Laura Hakoköngäs

Diagnostic Wish Lists: From the Field to the Lab and Back

Lack of access to appropriate diagnostics limits the quality of medical care

When it comes to diagnostic tools, there is a wide gap between what patients need and what is actually available for resource-poor settings. In wealthy countries, a lab workup is a standard part of patient care. But in most of the settings in which MSF works, patients don't have such access. Often this is because the existing tests are prohibitively expensive, are not adapted to use in the field, or simply do not exist. This is seen very clearly in HIV clinics. Information on patient CD4 levels is considered a major improvement over clinical staging alone. But such tests are slow in being adopted because the technology is complex and requires expensive and sensitive machinery.

High costs are not the only issue. Companies tend not to develop new diagnostics for markets they perceive as unprofitable. On top of that, a major access barrier to appropriate diagnostic tools is the fact that test developers and biotech companies often do not know or understand the true needs of the field.

MSF's Access Campaign is carrying out a diagnostic needs assessment to address the knowledge gap that is limiting the quality of medical care in our projects. We are discussing with MSF field doctors and their colleagues to find out what their most important requirements are for diagnostics, and exactly what information these tests should provide. So far, we have visited MSF projects in Cambodia and Kenya, and will follow up the initial findings with further field and stakeholder consultations.

Our goal is to produce a "wish list" of tests that we can use to fuel discussions with researchers, biotech companies, other test developers and funders. We want to use the field needs as a basis to stimulate the development of diagnostic tools that are adapted to field use and to local conditions. Although HIV care is a major focus, we are considering all field needs, and plan to assess both the immediate, urgent needs and more forward-thinking ideas that will help develop innovative ways to improve the standard of patient care. We are still at the information gathering phase of the assessment and would welcome any comments or input: Martine.usdin@paris.msf.org or Martine.Guillerm@paris.msf.org.

■ Martine Usdin

Research scientist with MSF's Access Campaign



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Treating the Deadly Duo: Integrating HIV–TB Care in South Africa

The shape of the TB epidemic has been dramatically affected by HIV. Today, TB is the leading cause of death among people living with HIV. Despite this fact, few countries have programmes to provide TB treatment alongside HIV care.



Twin epidemics, HIV/AIDS and tuberculosis (TB), are spreading illness and death in southern Africa. Today, an estimated 12 million people are co-infected with these diseases and more than two-thirds of them live in sub-Saharan Africa. With the world's highest rate of HIV/AIDS infection and an ongoing TB epidemic, South Africa's people are at the epicentre of the crisis.

MSF has been spearheading efforts to integrate care for people living with TB and HIV/AIDS in Khayelitsha, South Africa, a poor urban township near Cape Town. In 2003, in cooperation with the Provincial Administration of the Western Cape and the City of Cape Town, MSF started a pilot project at Khayelitsha's Site B Ubuntu clinic. The clinic's "one-stop" services, quick referrals and careful monitoring of both TB and HIV patients have made it the busiest clinic in the Western Cape for both TB and ARV treatment.

Word has travelled quickly that patients can now get care for both illnesses at the same place and the waiting room is full every morning at 8:00. "The patients are coming," says Gilles van Cutsem, an MSF physician working at the Ubuntu clinic. "This clinic is seeing more patients than others. Integration is working for patients. They know it makes it easier to get care."

Integrating TB and HIV/AIDS care has not been easy as treatment for both illnesses have historically been provided through separate programmes in the Western Cape region run by different health authorities. Plus, the WHO's commitment to daily directed observed TB treatment hampers efforts to introduce more flexible and adapted treatments. "MSF is one of the few organisations working to make integration a reality in South Africa," says Marta Darder, coordinator of MSF's Access Campaign in South Africa. Places like the Ubuntu clinic show that on a small scale, integration is working, but a lot still needs to happen. Ubuntu is one of only a handful of South African health centres that are offering integrated care for TB and HIV patients and all of these efforts pale in comparison to the immense need for them.

MSF believes South Africa and other countries hit by the dual epidemic will have to push for integration based on their own national health situation and political climate. "People keep trying to block integration," concludes Darder, "but MSF keeps pushing because medically it makes sense."

TB is more difficult to detect in HIV-positive patients as they tend to contract less common, more difficult-to-diagnose types of the disease. The fact that in many countries different health staffs and departments handle diagnosis and treatment for these two illnesses means that many patients found to have one disease may not be treated or even tested for the other. Even when they are referred for testing or care, many patients must visit multiple health centres to get the care they need. Health care providers also face frustrating obstacles in getting sick patients tested and started on treatment because of the separate systems.

"ARVs are my life"

Ruben, a 44-year-old HIV and TB patient at the Ubuntu clinic, has been taking ARVs for four years. He was diagnosed with HIV in 1998 after he was admitted to a Cape Town hospital feeling very sick and weak. After a few months of care he began to feel better and transferred to the Khayelitsha clinic, which is much closer to his home. There he was diagnosed with TB as well and given treatment. In 2001, he began ARV treatment. Then in December, he fell ill again.

"I didn't feel alright. I couldn't walk. I had shortness of breath. I thought, What is wrong now? I went to the HIV nurse, she brought me to the TB doctor who sent me for an x-ray. At the x-ray, the man said, "No, you've got TB." I think: What? Where is TB coming from now? He told me, "Oh, you are HIV-positive, an infection comes easy to you because your immunity level is low." So in December I started the treatment for TB again. I'm getting the TB treatment here and the HIV treatment there. Now I am feeling very, very well, very powerful. Before, I couldn't go from there to the corner. I was just doing that and then I would have to sit down and catch my breath. But now I am alright, I can go! The treatment for TB is working. I feel the drugs are working. Maybe next month I'll finish the TB treatment, and then it will be just HIV. That's my life! I am going for ARVs for my life, I know that."

■ Lisa Hayes

Lisa Hayes was MSF International Editor until November 2005, and is now Communications Advisor for MSF-Holland

Lessons from HIV/AIDS Advocacy: Pushing for a Global TB Movement

Treatment Action Group is an organisation fighting to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. As tuberculosis is the leading opportunistic infection in people with HIV/AIDS, the organisation is pushing to get more people from HIV-affected communities to work on TB issues.

Mark Harrington, TAG's Executive Director, talks about how TB advocacy can benefit from the experiences of campaigning on HIV/AIDS.

■ How do you see the difference between the HIV/AIDS and the TB advocacy efforts?

HIV was a new disease, and it was very, very scary. It affected communities in rich countries and in poor countries, so the possibility of mobilising a social response was greater. HIV/AIDS is not curable, so once a person is infected, it changes their identity for the rest of their life. So it's possible to develop an identity around being HIV positive.

TB is a disease of the marginalised and the poor. It is curable, so in some ways it doesn't seem as scary to society as a whole. And because TB is curable, it's not like something that changes your identity forever. People haven't traditionally had an identity as a TB survivor and then turned that into political advocacy. And disease is intrinsically isolating, as opposed to something that brings people together.

■ How can the experience gained from the activism of people with HIV/AIDS contribute to shaping the international response to TB?

Even before there was effective treatment for HIV/AIDS, there was broad mobilisation among communities affected by the disease to demand that society pay attention and that resources be mobilised. That led to greater funding, which in turn led to effective diagnostics and treatments, although not overnight. It only took 15 years, all told, from the discovery of the disease to the development of effective, but not curative, treatment.

If you look at the amount of resources devoted to AIDS research in those years, it just massively dwarfs what is being spent on TB research. That isn't to say that AIDS research gets too much, but rather that TB gets too little. So massively increased research is needed if we're going to get new diagnostic tests, new drugs or new vaccines for TB.

■ In what way do you think greater community activism on the TB or HIV-TB front could translate into concrete solutions for TB R&D?

One way is by working on mobilising and educating HIV community leaders from countries around the world, particularly countries with high burdens of HIV–TB to understand the issues about TB and then to begin to participate in decision-making in national TB programmes and TB advocacy. Another way is getting involved in trying to really push research. That means becoming educated about the research issues and then meeting with the research agencies and trying to get them to work faster and get more resources. It's going to be a complicated process, but the larger TB community needs to think more ambitiously than they have in the past about TB not being a problem just for public health systems, but for society as a whole.

For further information:
www.aidsinfoync.org/tag/tbhiv/tbhiv.html