

ANNIVERSARY ISSUE

Demystifying antiretroviral therapy in resource-poor settings

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FEW areas of public health have generated as much debate, controversy and protest in recent years as the drive to expand access to antiretroviral therapy – the drugs that have transformed AIDS from a death sentence to a chronic condition – in developing countries. Several years ago, it was a futile discussion: with a yearly cost of US\$10,000 per patient, there was little possibility of widespread access in developing countries. But, largely as a result of a potent combination of generic competition and activism, prices have plummeted, with triple therapy now being available for as little as US\$209 a year¹, causing a huge shift in the debate about availability.

Today, the debate centres on if antiretroviral therapy is possible in severely resource-constrained environments, and, increasingly, on the best ways to deliver these drugs. In a poor township 30 kilometers outside Cape Town, South Africa, Médecins Sans Frontières set out to grapple with both of these issues. Khayelitsha has around 500,000 inhabitants – a figure swollen by a steady influx of economic migrants from rural areas – of whom 50% are unemployed and more than 70% live in shacks. HIV seroprevalence rates at antenatal clinics are above 24%, having risen with shocking rapidity over the past 10 years.

The provincial government of the Western Cape decided to launch South Africa's first government-run programme to prevent mother-to-child transmission (MTCT) of HIV in Khayelitsha. Zidovudine (AZT), first became available in the township's two maternity wards in early 1999, and the programme has subsequently become one of the continent's biggest, with more than 20,000 women having accepted testing, and over 3,000 having received antiretroviral therapy. Médecins Sans Frontières began supporting this MTCT programme in 1999, before opening clinics to offer treatment to the mothers, their infected children, and others with HIV from the broader community at three government primary health care centres in April 2000. Despite catering solely to those with HIV, the centres were called "infectious disease clinics", out of a fear that labelling them HIV clinics would generate stigma and deter people from accessing services. This concern turned out to be entirely misplaced, as the community quickly branded them AIDS clinics, and nonetheless the queues steadily lengthened. Treatment was initially limited to opportunistic infections – the conditions that arise with increasing frequency as HIV erodes the immune system's capacity to ward off infections. But in May 2001, this was broadened to include antiretroviral therapy, making the project the first to use antiretrovirals in government health facilities outside the context of clinical trials.

This step was motivated by both humanitarian and public health principles: despite receiving quality care and prophylaxis for opportunistic infections,

patients were getting sick and dying at unacceptable rates and so needed access to the only drugs that have been proven to suppress HIV infection and thus extend life. Further, there was a clear need to develop models for the delivery of antiretroviral therapy in South Africa. Thus the project was intended to demonstrate that the use of antiretroviral therapy at primary health care level was feasible, affordable and replicable.

Impressive survival rates

Preliminary analyses recently presented at the XIV International AIDS Conference in Barcelona provide strong indications that poor black women and men can indeed derive considerable benefit from antiretroviral therapy without undue toxicity. To date, 180 patients have been placed on this therapy, selected from among the 3,000 patients who have attended the MSF clinics in Khayelitsha (Box 1 gives details of the selection process). These patients were extremely sick when they began therapy, having a median CD4⁺ T cell count of 43, with as many patients initiating therapy with under 10 CD4⁺ T cells as above 100. In contrast, a typical CD4⁺ T cell count in a seronegative person would be in the range of 800–1200, and it is well-established that the risk of death increases significantly as the count drops below 50. Thus if untreated, the prognosis of this

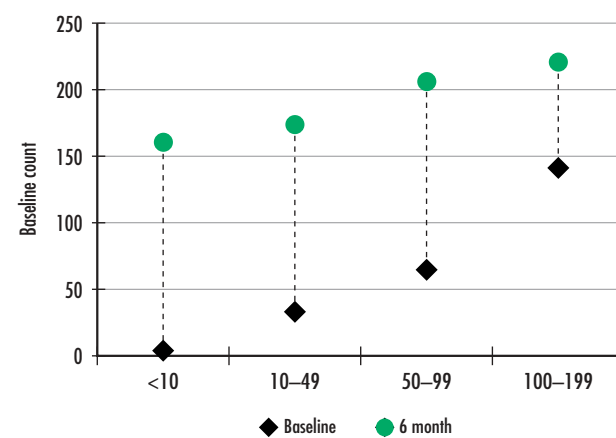
group of patients would be extremely poor, with death within a year the sad reality for most.

However, on antiretroviral therapy, their survival was impressive. After nine months of treatment, 88% of the patients were alive. The reason for this dramatic improvement is simple: patients with immune systems weakened by HIV infection are prone to get sick with infections that people with healthy immune systems can normally fight off. On antiretroviral therapy, the rates of these opportunistic infections were significantly reduced (see Graph 1). The reduction was particularly striking for tuberculosis, which is one of the major killers of people with HIV/AIDS in South Africa.

Reduction in opportunistic infections is largely attributable to the considerable improvements seen in immunologic status. After six months on therapy, the mean increase in CD4⁺ T cell count was 143. This meant that while 54% of patients had below 50 CD4⁺ T cells at the start of therapy, only 2% were still below this level after six months; in contrast, none were above 200 at baseline, while at six months 53% had climbed above this important threshold. Interestingly, even patients with severely compromised immune systems at initiation of therapy experienced large improvements after beginning antiretroviral therapy, as shown in Graph 2.

These improvements were possible because antiretroviral therapy effectively suppressed viral replication in the large majority of patients, thus allowing the immune system to recover, instead of having to concentrate its energy on fighting off HIV infection. This success was evident whether measuring using the

Graph 2
Median CD4⁺ T cell count counts at baseline and six months, stratified by baseline count



“gold standard” of undetectable levels of viremia (less than 125 copies in the test available) or using a higher level that some have suggested is more appropriate to developing country contexts, as shown in Graph 3.

These encouraging results occurred with very few serious adverse events. There were no deaths related to drug toxicity, and while 46% of patients reported at least one side-effect, most of these were minor, scoring only a 1 or a 2 on the AIDS Clinical Trials Group grading of adverse events, with 1 being the most mild and 4 the most serious (64% were grade 1, grade 2:19%, grade 3:11% and grade 4:6%).

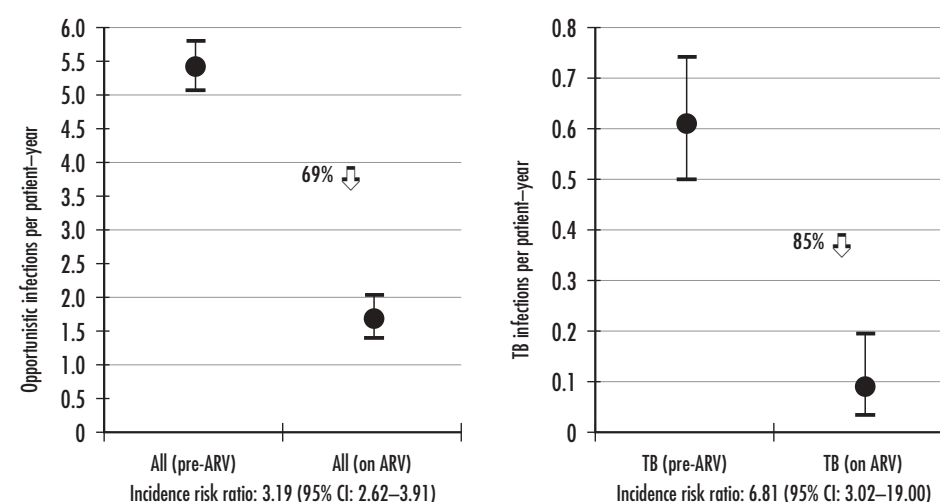
Three key factors

In analysing the programme's success to date and assessing the possibilities to use it as a model in other settings, three key aspects stand out.

First and most fundamentally, the drugs must be affordable. In this case, it meant beginning with brand-name drugs which, although considerably cheaper than in developed countries (or, indeed, in South Africa a few years earlier), were still much more expensive than generic versions produced in countries such as Brazil, India and Thailand. These alternatives were not registered in South Africa, but after authorisation to use Brazilian generic antiretrovirals was received from the South African Medicines Control Council, a change to Brazilian drugs has allowed twice as many patients to be treated.

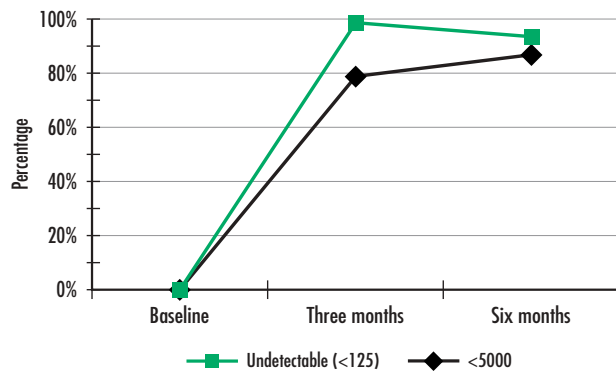
The second key to success was the involvement of the community. This was facilitated by giving all treatment at primary health care level, rather than at a large reference hospital. Additionally, the community was integrally involved in the process of selecting patients for therapy, which played a major role in guaranteeing local ownership over the project as a whole (see Box 1 for more on the selection process).

Graph 1
Impact of antiretroviral therapy on incidence rates of opportunistic infections (all and TB only)



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Graph 3
Viral load (HIV RNA) at baseline, three and six months



Finally, the involvement of the patients themselves has been essential. They are genuine partners in the project at a number of levels:

- At the political level, when politicians have questioned the validity of using antiretroviral therapy in resource-poor settings, it was the patients who responded, writing letters to newspapers and speaking out in the media.
- At the community level, they play an important role in the support groups run for patients on antiretroviral therapy, with those who have been on therapy for longer periods of time helping mentor those beginning. Also, a number of patients work with a South African NGO, the Treatment Action Campaign, on a major community education initiative.
- At the individual level, patients have educated themselves on the importance of adherence, allowing them to take responsibility for their own therapy, making it unnecessary to use medical staff to observe them taking their pills (see also Box 2).

The lessons

The project has revealed a number of important lessons:

First and foremost, antiretroviral therapy can be safely and effectively used in resource-poor settings, and the time has come to scale up from pilot projects to widespread access.

Managing patients on antiretroviral therapy is often easier than managing patients not taking antiretrovirals. Patients in advanced HIV infection are frequently ill with a variety of opportunistic infections, many of which are difficult to diagnose and treat, particularly at a primary health care level. In contrast, patients on antiretroviral therapy typically experience rapid improvements in their health, and, particularly after the first few months on antiretroviral therapy (when the bulk of side-effects occur), they can be followed by nurses. In Khayelitsha, this was facilitated by the development of standardised tools to assist in the assessment and management of adverse events.

The availability of antiretroviral therapy bolsters the entire health system. South Africa – and many other sub-Saharan African countries – is experiencing a major loss of medical staff, in part as a result of poor working conditions and low morale engendered by the enormous

influx of patients with HIV, many of whom are dying, despite the best efforts of the staff. When antiretrovirals are available, the staff's role shifts back from care of the dying to being able to help patients return to good health, with an obvious improvement in morale.

Additionally, access to antiretroviral therapy provides an important reason for patients to stay in the medical system: in Khayelitsha, not a single patient on antiretroviral therapy has been lost to follow up, in marked contrast with the

general experience in this highly mobile township. Finally, the significant decreases in opportunistic infections (and the resultant need for hospitalizations) suggest that those who argue that antiretroviral therapy is unattainable, based on crude calculations of the cost of drugs, are missing a fundamental aspect of the provision of antiretroviral therapy. That is that a considerable percentage of the costs incurred by drug purchases can be offset by drops in hospitalizations and opportunistic infections. This has been demonstrated in Brazil², and is quite likely to be true in South Africa, a country that spends an estimated R4 billion (approximately US\$400 million) on care and treatment of people living with HIV/AIDS.³ Research is ongoing in Khayelitsha to quantify the magnitude of this offsetting effect.

Finally, in contrast to those who argue that treatment and prevention are inextricably opposed and competing for resources, in Khayelitsha the synergy

"People must know that a poor person like me living in a shack can take these drugs properly. They are my chance to live."

Patient on antiretroviral therapy in Khayelitsha, South Africa.

between treatment and prevention has been striking, with the availability of treatment providing a powerful incentive to learn one's status. It was thus no surprise that a recent survey of nine sites around South Africa found that Khayelitsha had the highest rates of HIV testing, and desire to be tested among those who had yet to be tested, as well as the highest levels of condom use.⁴ □

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Box 1

Selecting patients for antiretroviral therapy

Patient selection is one of the more difficult aspects of setting up a programme, as the need inevitably outstrips the supply of drugs available. However, it is important to note that, contrary to popular perception, not all people with HIV should immediately be placed on antiretroviral therapy. In Khayelitsha, the biological and clinical criteria used to select patients include:

- ◆ a CD4⁺ T cell count of less than 200, and a WHO disease stage of 3 or 4, both in line with WHO's recently-released guidelines on antiretroviral therapy in resource-poor settings;
- ◆ patients must live in Khayelitsha;
- ◆ patients must have regularly attended the clinics for at least three months (instituted in light of the highly mobile nature of Khayelitsha's population).

These requirements plus the fact that some patients chose not to take antiretroviral therapy mean that the number of patients who were ultimately candidates to be started on therapy has not overwhelmed the resources available.

Nonetheless, a system was introduced that involved the community in the process of selecting patients. A number of community representatives – typically people with experience with people with HIV (and including those with HIV themselves) – met regularly to assess candidates and determine who would ultimately be placed on therapy. Deliberations are based on a number of factors, such as the health of the patient, their income level, the social support available to the patient and her/his openness about HIV infection, and if other members of the same family are already on antiretroviral therapy. Although the process is time-consuming, it has proven a valuable way to fairly and equitably allot spots in the treatment programme, as well as an important means of ensuring community ownership over the programme.

Box 2

Patient-centred approaches to adherence

The issue of how to ensure that antiretroviral therapy is taken regularly and appropriately has generated considerable discussion and controversy. Some even suggest that the use of antiretroviral therapy in poor countries will only lead to the widespread development of resistance. They advocate either that resources are not put into making the drugs available or that they are only administered under strictly controlled conditions, such as in the presence of medical staff (along the lines of the DOTS model for TB, although the comparison is complicated by the greater frequency of dosing of antiretroviral therapy and the fact that it is life-long rather than of a limited duration). However, in Khayelitsha, an approach centred on educating patients and empowering them to be actively involved in the treatment programme has yielded very positive results.

This begins with the careful selection of a regimen that is easy to take – for example a combination of nevirapine and co-formulated AZT/3TC, which amounts to two pills twice a day – and setting the health care facilities within easy reach of the patients (for example, at primary health care level). Once patients begin therapy (after an educational process), a tripartite programme supports adherence:

- ◆ Individual support is available in the form of trained counsellors available during clinic hours to answer questions, and, more informally, through "treatment assistants," a household member or neighbour whom each candidate for therapy is requested to identify who can provide support on adherence;
- ◆ Peer support comes in the form of support groups run solely for patients on antiretroviral therapy, and which serve both as valuable spaces for patients to discuss barriers to adherence with others sharing similar experiences and as a forum for ongoing education;
- ◆ Educational materials are provided to help patients fully appreciate the risks and benefits of antiretroviral therapy, and understand the importance of adherence.

Research is ongoing to quantify the levels of adherence, but the dramatic improvements in the surrogate markers of changes in viral load and CD4⁺ T cell counts strongly suggest that adherence is good.