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PERSPECTIVES AND PRACTICE IN ANTIRETROVIRAL TREATMENT

ANTIRETROVIRAL THERAPY IN PRIMARY HEALTH CARE

SOUTH AFRICAN EXPERIENCE

CASE STUDY



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MSF SOUTH AFRICA, THE DEPARTMENT OF PUBLIC HEALTH OF THE UNIVERSITY OF CAPE TOWN,
AND THE PROVINCIAL ADMINISTRATION OF THE WESTERN CAPE, SOUTH AFRICA.



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About This Series

With 42 million people now living with HIV/AIDS, expanding access to antiretroviral treatment for those who urgently need it is one of the most pressing challenges in international health. Providing treatment is essential to alleviate suffering and to mitigate the devastating impact of the epidemic. It also presents unprecedented opportunities for a more effective response by involving people living with HIV/AIDS, their families and communities in care, and will strengthen HIV prevention by increasing awareness, creating a demand for testing and counselling and reducing stigma and discrimination.

The challenges are great. Sustainable financing is essential. Drug procurement and regulatory mechanisms must be established. Health care workers must be trained, infrastructure improved, communities educated and diverse stakeholders mobilized to play their part. *This series, Perspectives and Practice in Antiretroviral Treatment*, provides examples of how such challenges are being overcome in the growing number of developing countries where antiretroviral treatment programmes are under way. The case studies and analyses in this series show how governments, civil society groups, private corporations and others are successfully providing antiretroviral treatment and care to people with HIV/AIDS, even in the poorest settings. In documenting these pioneering programmes, WHO hopes that their experiences will both inform and inspire all those who are working to make access to treatment a reality.

INTRODUCTION

«People no longer accept that the sick and dying, simply because they are poor, should be denied drugs which have transformed the lives of others who are better off.»

-Kofi Annan, UN Secretary General, 26 April 2001

Southern Africa is one of epicentres of the worldwide AIDS pandemic. With more than 5.2 million people infected with HIV, South Africa has the highest number of people with HIV/AIDS of any country in the world. A comprehensive response to HIV/AIDS - including prevention of new infections, prevention of mother-to-child transmission (PMTCT), prophylaxis and treatment of opportunistic infections, dignified end-of-life care, and, critically, antiretroviral therapy (HAART) - is necessary to adequately tackle the epidemic. In South Africa, the government has so far not introduced antiretroviral treatment in its government-run health facilities.

Since 1999, Médecins Sans Frontières (MSF) has been working in the Khayelitsha township, outside of Cape Town, with what was then the only government-supported prevention of mother-to-child-transmission project (PMTCT) in the country. Khayelitsha is a resource-poor township with approximately 500'000 residents. About a quarter of women at Khayelitsha antenatal clinics test HIV-positive. It is estimated that more than 50'000 residents are HIV-positive. More than 50% of the MSF patients are unemployed and the majority is living in informal housing (usually corrugated iron shacks).

In April 2000, in collaboration with the Provincial Administration of the Western Cape (PAWC), MSF set up three dedicated HIV/AIDS clinics within Khayelitsha's primary health care centers. In May 2001, the HIV/AIDS clinics began to offer highly-active antiretroviral therapy (HAART) to people with advanced stage of HIV infection.

OBJECTIVES

The HAART pilot project aims to demonstrate that treatment of HIV/AIDS with antiretroviral drugs in a primary health care setting and in a resource-poor environment is feasible and replicable. In addition, it aims to prove that developing countries can provide affordable HIV/AIDS care with low-cost antiretroviral drugs, whether generic or patent-protected.

THE MSF HAART PROGRAM : BRIEF OVERVIEW

The HIV/AIDS clinics. The clinics provide a comprehensive package of AIDS services that include counselling, support, prophylaxis, treatment of opportunistic infections, HAART and referrals where necessary. The staff in each clinic initially consisted of 1 doctor, 1 professional nurse and 1 lay counsellor. One nurse and one counsellor have since joined the clinic teams, to accommodate the increasing patient load and to develop a nurse-based service model, much more suitable to the reality of health services in Africa. The 3 clinics currently serve over 1'800 HIV clients per month. Clients attend with different regularity according to clinical stage.

Eligibility criteria for HAART. Only patients who attend the HIV clinics regularly and who live in Khayelitsha are considered for HAART. Clinical, biological, adherence and social criteria have to be fulfilled in order for patients to be eligible. In regular clinic visits, a physician assesses the stage of disease. Only patients in stage 3 or 4 — according to the World Health Organization classification — and with CD4 cell counts of less than 200/mm³ are eligible for HAART. Adherence to co-trimoxazole prophylaxis and TB treatment, and regular clinic attendance are used to assess ability to adhere to HAART. After the patient has been counselled about HAART, a clinic worker assesses the social and support structures available to the patient by conducting a home visit. The home visit also verifies the patient's residence and disclosure to at least one person who will act as a treatment assistant. Other relevant social factors include being ready to commit to long-term ARV therapy, expressing a wish to live longer, and being ready to commit to safe sex practices (figure 1).

Figure 1. Selection of candidates for HAART

Regularity: to have attended HIV clinics for least 3 months and been on time for the last 4 visits

Pre-selection
by clinicians

Patients meeting clinical and biological criteria : stage III and IV and < 200 CD4 count

Final selection by community selection committéé

Patients meeting social and asherence criteria : evaluation of home environment, disclose, familly support

Enrolment process. Candidates' anonymous dossiers are presented to a committee of community members, persons living with HIV/AIDS, and clinicians not related to MSF who make the final decision on enrolment, based on the medical, social, and adherence criteria. The presenting clinician is not involved in the final decision about enrolment. In a context where treatment is scarce but urgently needed, this removes some of the burden from the clinician and integrates the community into the process. Preference is given to patients on the basis of their number of dependants (e.g. mother as opposed to single male); health status (very sick compared to one who meets the clinical criteria); income (very poor compared to one who might soon be able to afford treatment), and disclosure / activism (someone who is open about HIV status and/or active in community organizations, as opposed to one who refuses to disclose).

Initiation of therapy. Once selected, the patient is assessed by a physician, who conducts a physical examination and reviews the patient's medical history, including prior ARV use.

Laboratory tests are also performed to determine the most appropriate regimen and to provide a baseline to monitor the response to therapy and adverse events. These tests assess liver function, haematology, CD4 count and viral load.

Treatment regimen. Standardised triple therapy regimens are used. First line therapy includes the combination of zidovudine (ZDV), lamivudine (3TC) and either nevirapine (NVP) or efavirenz (EFV). The choice between Efv and NVP considers if the patient is taking TB treatment, has abnormal liver function (in which case Efv is preferred) or is pregnant (in which case NVP is preferred). The recommended second-line regimen is stavudine (D4T), didanosine (ddI) and lopinavir (LPV) with ritonavir (RTV).

Table 1. HAART regimens for adults

First-line	Second-line
ZDV/3TC/Efv or NVP	D4T/ddI/LPV-RTV

Monitoring of patients. All patients on HAART are assessed clinically, weekly for the first two weeks, then every two weeks until the end of the second month, and monthly thereafter. Once patients are stable on therapy, they can be assessed every two months. All laboratory tests are done at centres from the National Health Laboratory Services. The viral load is measured using the NASBA (Nuclisens(r)) test; a viral load under 124 copies per ml is considered undetectable.

CLINICAL OUTCOMES

A preliminary analysis of patients initiating treatment between April 2001 and late 2002, included 255 adults without prior antiretroviral therapy. The median age of patients at baseline was 32 years (IQR 28-37) and 181 (71%) were women. The median follow-up time was just under 6 months.

Clinical measures at baseline. Median CD4 cell count at baseline was 48 cells/ μ l indicative of many patients initiating HAART at a very advanced stage of disease progression. The mean log viral load at baseline was 5.1. Half the patients had a prior diagnosis of AIDS on initiating therapy.

Treatment regimen. Nearly all patients began ART on zidovudine and lamivudine with the third antiretroviral being nevirapine (40%) or efavirenz (60%).

Weight gain. After one year on treatment, the mean weight

gain was over 9 kg.

Occurrence of opportunistic infections (OIs). The frequency of OIs is dramatically reduced after initiation of HAART. Taking as examples tuberculosis and oral or oesophageal candidiasis, some of the most frequent OIs observed in patients with HIV/AIDS, the incidence rates for new events were reduced two thirds for both conditions comparing the pre-HAART period with the first year on treatment.

Virological response. After 6 months on HAART, 91% of the patients had undetectable viral load levels (below 400 copies/ml). 84% had sustained viral load suppression after one year on HAART.

Immunological response. The mean CD4 cell count at 12 months of treatment was 278 cells/l. The average overall increase of CD4 count was 221 cells/l. Increases were higher in those patients with lower CD4 count at baseline.

Table 2 : Selected Treatment outcomes

Duration on treatment	6 months	12 months
Mean Weight Gain (kg)	+6.4	+9.3
Proportion of those tested with undetectable viral load	91%	84%
Mean CD4 Cell Count Change for those with serial measurements	+141/mmm	+221/mmm
Proportion surviving	86%	83%

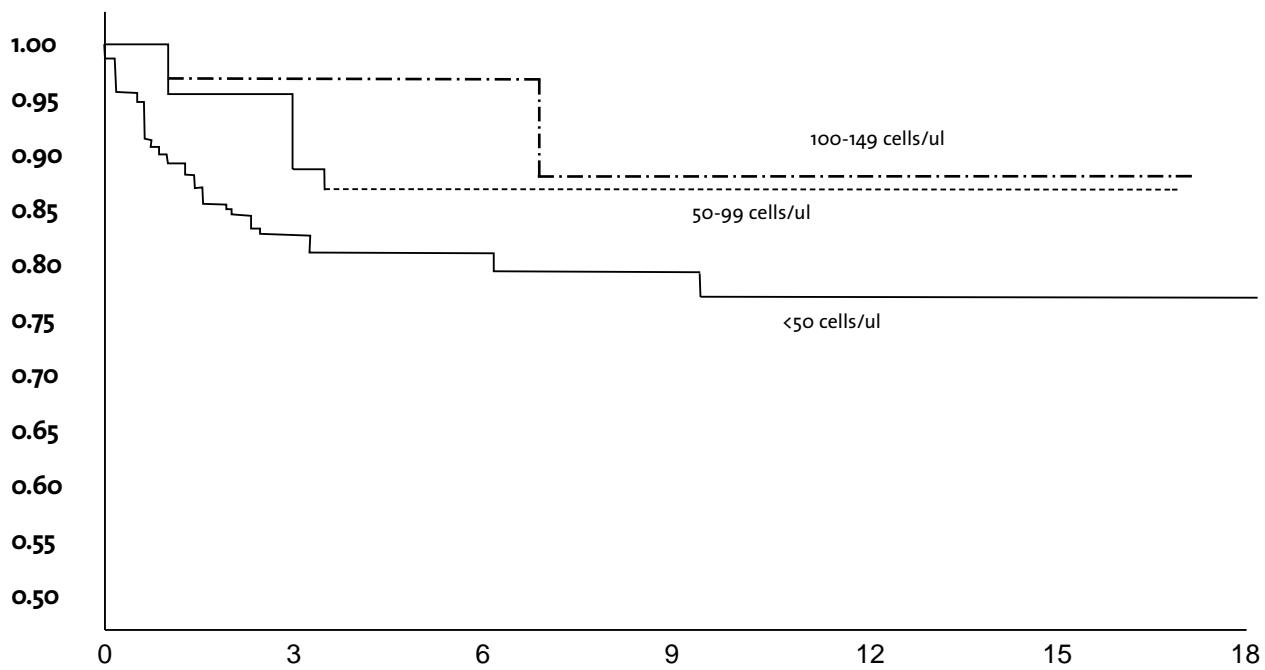
Treatment changes and adverse events. Most patients tolerated the first line regimen well. Approximately 20% of patients changed one of the antiretrovirals because of either side effects or contraindications. The incidence of adverse events severe enough to require a change in treatment was uniformly low, with the highest rate of change for an individual drug due to side effects being 5% at eighteen months for patients on zidovudine. Most of the remaining changes were due to changes between efavirenz and nevirapine due to contraindications. After one year of treatment, approximately 5% of patients had changed to a second line regimen.

Health Related Quality of Life (HR-QoL). An ongoing study is measuring pain/discomfort, anxiety/depression, mobility, self-care, and usual activity in both the MSF clinics

and the general population. At the start of treatment, there was a significant difference in all domains except anxiety/depression between the cohort on HAART and the community sample. Over time, the HRQoL approached that of the community sample in all domains until at twelve months there is no significant differences between the HAART and community populations.

Survival. In the preliminary analysis, survival at 18 months was 83% (95% CI 76- 87). All deaths amongst patients who had started HAART were attributed to AIDS, and none of them to treatment complications. Three quarters of the deaths occurred before 90 days on treatment, with dramatically reduced mortality rates after this time-point regardless of initial CD4 count (figure 2). This is primarily due to the late initiation of treatment as many were already at quite an advanced stage of HIV/AIDS when they arrived at the clinics.

Figure 2. Survival by initial CD4 count after 18 months on HAART



ADHERENCE

Combining simplified regimens with low pill burden, and a comprehensive patient support program, beneficiaries of the Khayelitsha HAART programme show high levels of adherence to the medication.

HAART necessitates good adherence in order to achieve sustained suppression of viral replication, and to prevent the onset of resistance. Because HAART is a life-long treatment, it requires the patient's commitment and responsible attitude. MSF believes that the key to achieve this commitment is to implement a combination of two equally important strategies:

- use simplified and standardized regimens that minimize the burden of pills, the dosages and the risk of side effects,
- ensure a good understanding of the treatment and a strong support system.

The access to simplified regimens is facilitated by the growing availability in the market of fixed-dose combinations of ARV drugs, which can currently reduce the number of tablets to only one twice a day, or three once a day. MSF considers it of utmost importance to accelerate the availability of quality simple regimens in high prevalence countries.

To achieve good understanding of HAART and sufficient support, MSF has developed a patient-centered education programme, which combines different components:

► Individual support: All patients who enrol in the HAART programme are required to identify a treatment assistant (TA). The TA is usually someone living in the household, aware of the patient's status, and willing to assist with medication as necessary. Lay counsellors - trained in HIV/AIDS and HAART - are available in the clinics to help patients with individualized adherence plans that respond to their specific needs. In case of serious adherence problems, a nurse-counsellor performs home visits as needed for more thorough follow-up.

► Peer support: Twice a month, the clinics host support groups attended exclusively by patients on HAART. Participants discuss barriers to adherence, adverse events, disclosure and other psychosocial issues that affect them. A counsellor regularly performs adherence workshops in the support groups.

► **Materials support:** Patients are provided with pillboxes and drug identification charts, daily schedules, diaries and educational materials explaining the risks and benefits of HAART.

With this approach adherence is maximized, as reflected by the high rate of viral suppression. A clinic-based self-reported evaluation of adherence to HAART is currently ongoing, based on a 4-day recall period¹. Preliminary results show 89% of respondents indicating adherence of greater than 95% at three months on treatment (n=73).

THE NEW SOCIAL CONTRACT: «BREAK THE FATALITY AND WE WILL BREAK THE SILENCE»

The public health advances in Khayelitsha in recent years were developed alongside strong civil society pressure and community-based education programs. The Treatment Action Campaign (TAC), a grassroots HIV advocacy organisation, has acted on a provincial and national level, mobilising the community to be aware of HIV as a political issue and pressuring the government to develop a comprehensive response. The TAC's community programs have educated many in the community about HIV/AIDS, prevention, and antiretroviral therapy («treatment literacy»). In Khayelitsha, the education-treatment link can best be described as a «social contract»: the clinics provide effective HIV/AIDS care and life-saving treatment while the community, for its part, breaks the silence, fights stigma and discrimination and, through education, promotes understanding and prevention.

In Khayelitsha, TAC's Project *Ulwazi* («knowledge») has brought HIV-positive people, some on treatment through the MSF program, into schools, clinics, churches, and workplaces, and on radio programs. Through this program, youth have been proactively involved in educating the community, provoking discussion, decreasing stigma, and promoting disclosure. With a «Mobile Exhibition», Project *Ulwazi* volunteers have guided hundreds of school-children, support groups, and community members through a travelling collection of banners, posters, videos, and educational materials showing pictures and live stories of people living with HIV. *Ulwazi* volunteers have also helped to establish AIDS Action Committees in secondary schools to continue in-school education beyond the initial workshops conducted by the volunteers.

¹ A modified Xhosa version of the ACTG questionnaire is being used.

This education and awareness-raising has been critical in preparing the community to accept treatment, especially as the national government continues to offer mixed messages on the benefits of antiretroviral therapy. Treatment, for its part, has motivated people to listen to education messages and has promoted a more open climate for discussion, helping to provoke greater change on a broader scale.

TWO SIDES OF THE SAME COIN : TREATMENT AND PREVENTION

The MSF program in Khayelitsha is part of an increasing number of initiatives in the Western Cape to respond to HIV/AIDS. The government programs range from the expansion of Voluntary Counselling and Testing (VCT) sites, the development of youth clinics to respond to the distinct needs of adolescents, the availability of post-exposure prophylaxis (PEP) for rape survivors in government clinics, and the universal expansion of prevention of mother-to-child transmission (PMTCT) programs in public health facilities. Each of these initiatives has served their direct aim, but has also had an impact on prevention, promoting openness and decreasing the stigma around HIV/AIDS.

In 1999, a provincial initiative on the prevention of mother-to-child transmission (PMTCT) in the Western Cape led

to a dramatic increase in the number of women aware of their HIV status. Before the existence of PMTCT programmes in the province, few were aware of their status and even fewer were willing to disclose. PMTCT, for the first time, provided a motivation for pregnant women to be tested for HIV. In 2000, the opening of the MSF dedicated HIV clinics provoked a similar effect. Through providing effective treatment for opportunistic infections and, for those in the late stages of HIV/AIDS, antiretroviral therapy, these clinics likewise provided an incentive for others to be tested: their own health and survival depended on an acknowledgment that their recurring illnesses were linked to a larger disease.

A 2002 study conducted by CADRE and the South African Department of Health targeted nine commuter sites in South Africa, including Khayelitsha, and found that Khayelitsha residents reported the highest levels of condom use, willingness to use a female condom, willingness to have an HIV test, and desire to join an AIDS club.² Due in part to the availability of antiretroviral therapy and in part to the abovementioned complementary initiatives, the VCT uptake has increased in the district from fewer than 1'000 HIV tests in 1998 to more than 12'000 tests in 2002. The number of HIV support groups in Khayelitsha has also dramatically increased, from 4 in 1998 to 22 in 2002.

The availability of antiretroviral therapy in Khayelitsha has demonstrated that treatment is important for prevention because it :

- ▶ provides a motivation for HIV-positive people to be aware of their status : without treatment as an option, knowledge that one is HIV-positive can be seen as offering little more than stigmatisation.
- ▶ promotes openness and reduces stigma as HIV is no longer an inevitable death sentence.
- ▶ can fuel educational initiatives supported by a pool of HIV-positive people open about their status.
- ▶ improves the efficacy and psychological health of health care workers who are able to offer something beyond temporary treatment for opportunistic infections.
- ▶ helps to keep families intact and economically stable, thereby protecting the most vulnerable (women and children) and minimizing at-risk populations such as orphans and commercial sex workers.

² Centre for AIDS Development, Research and Evaluation, On the Move: The response of public transport commuters to HIV/AIDS in South Africa. 2002.

AFFORDABILITY OF HAART

By using generic ARV drugs and reducing the price of laboratory tests, MSF has cut the cost of HAART from USD 1,366 to USD 536 per patient per year, in January 2002 and April 2003, respectively³.

Aiming in part to demonstrate the affordability of providing HAART in a resource-poor environment, MSF is implementing strategies to minimize costs. The importation of generic drugs from overseas manufacturers dramatically reduced the costs of treatment. As few generic ARVs are registered in South Africa, MSF obtained permission from the South African Medicines Control Council (MCC) under the Medicines Act (Section 21) for the use of unregistered generic ARVs. Authorisation required sufficient evidence about drug quality.

Following a collaboration agreement between MSF and Brazil, MSF started to source generic versions of ARVs for its Khayelitsha project from the Brazilian state manufacturer, FarManguinhos, in January 2002. The price of the first line regimen (ZDV/3TC and NVP) was then USD 1.55 per patient per day. This price was half the cost of the lowest possible price offered by the proprietary companies to government (USD 3.0 per patient per day), and nearly a quarter of the price in the private sector (USD 5.5 per patient per day). Later in 2002, the price of this Brazilian combination dropped further, to USD 1.08 per patient per day.

Recently MSF received MCC authorization to source drugs from different manufacturers worldwide, opening the chances to get the lowest prices. None of the proprietary companies have taken legal action against MSF for the importation of generic ARVs into South Africa.

Simultaneously, MSF has worked with the National Health Laboratory Services (N HLS) to cut the price of laboratory tests, particularly viral load (VL) and CD4 count. The development by the AffordCD4 Initiative of the PanLeucogating (PLG) protocol⁴, and its immediate implementation at N HLS, allowed a price reduction from USD 24/test to USD 8.3/test. Negotiations between N HLS and the proprietary companies that produce viral load kits led to a slight decrease of the cost of viral load testing in the public sector (USD 45/test). MSF believes that the price of viral load testing still can be dramat-

ically cut, when companies apply the offers they have committed to. The target cost for the package of two viral loads and two CD4 counts in the public sector is USD 70/year.

LESSONS LEARNED :

ESSENTIAL COMPONENTS OF AN EFFECTIVE HIV/AIDS TREATMENT PROGRAMME

«The doubters said it was impossible, too expensive, or impractical. Let them say that to our patients who are under ARV treatment and thriving in Khayelitsha. The challenge now is to repeat this and to use successful pilot programmes as a guide to scale up.»

-Dr. Tito August, medical doctor working in the township of Khayelitsha

The experience of the MSF HIV/AIDS treatment programme in South Africa yields several lessons. While individual contexts necessitate different models, an effective HIV/AIDS treatment programme will be defined by its capacity to quickly and effectively treat a substantial number of people living with AIDS.

In the most-affected countries, this can only be achieved if:

1. the entire public health system is mobilised and AIDS treatment activities are integrated into the basic package of care;
2. treatment services are decentralised down to the primary health care level to assure both coverage and community involvement;
3. programmes aim to serve the neediest first, to prevent the entrenchment of existing inequities;
4. treatment and care are part of a «continuum of care,» supported by a facility-linked home based care system and a functional referral system for inpatient needs;
5. ARV treatment is part of a much broader package of care including voluntary counselling and testing, prophylaxis of opportunistic infections, and psycho-social support;
6. large-scale training initiatives target those who supply care: nurses, counsellors, referral public medical officers, and private general practitioners;
7. and, the healthcare capacity of private practitioners, private company health services, trade unions, and NGOs are mobilised to respond where the public sector capacity is deficient.

³ Based on regimen AZT/3TC and NVP, and 2VL/2CD4 tests per year. For comparison purposes, the best offer of proprietary companies to public sector is taken as reference price in January 2002. Cost adjusted by devaluation of USD against the Rand (Jan 2002 : USD1 = R10; April 2003: USD1 = R7.5).

⁴ Glencross et al. Cytometry 50: 69-77 (2002).

The primary technical components of a public sector HAART programme imposes an approach radically different from clinical trials and programmes in the «developed» countries. From the experiences of Khayelitsha, the following characteristics seem essential:

- ▶ primary health care based care within the community, to encourage adherence because of proximity and ease of access; to facilitate initiation of treatment and follow-up; and to minimise costs of care,
- ▶ triple therapy as minimal standard of care, based on accepted medical standards of antiretroviral efficacy,
- ▶ simplified model as much as possible with standardised and simple regimens, and standardised sequencing of drug use and coherent guidelines,
- ▶ multidisciplinary teams: nurse-based care with a major emphasis on psycho-social support, to best utilise available resources and look at HIV/AIDS holistically,
- ▶ a patient-support approach which includes counsellors, support groups, and significant treatment literacy to maximise adherence,
- ▶ a community-based educational programme, incorporating basic HIV/AIDS education and a treatment literacy component explaining the value and use of ARVs,
- ▶ affordable treatment, using generic drugs and inexpensive laboratory monitoring techniques.

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