EDITORIAL REVIEW

Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling-up

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Introduction

Access to antiretroviral (ARV) therapy for patients in developing countries has become an increasing global public health and political concern in recent years. Both donor governments and those of high-burden countries agree that treating AIDS is a major priority. Efforts are underway in many countries to increase the numbers receiving ARV treatment, and the level of international funds committed to assist this effort has increased significantly, albeit insufficiently. In 2002, this led the World Health Organization (WHO) to launch an ambitious '3×5' plan to place three million people on ARV by 2005 [1].

While numbers benefiting from ARV therapy in the developing world have increased over the last few years, the need for scaling-up is as urgent as ever: over two-thirds of the six million people in the developing world who are in urgent need of ARV therapy live in sub-Saharan Africa, but less than 2% of these have access to this treatment. It is estimated that around 6500 people are dying of AIDS each day in this region [2].

Treating AIDS in the developing world means working in a context of poor health-care infrastructure and limited financial and human resources, most of which are concentrated in capital cities. Health-care providers in the developing world are faced with patients who have different characteristics to those seen in clinics in Western countries: half of all cases in developing countries are among women of childbearing age; there are much higher proportions of children affected; patients tend to be in a more critical condition as they are diagnosed late in the course of the disease; and they are commonly afflicted with one or more complex comorbidities, such as tuberculosis, malaria and malnutrition.

In moving towards providing sustainable access to treatment for the majority in the developing world, models of care must be adapted to the realities of these regions. Current treatment models have been developed in Europe and North America, are based on the availability of more than 20 ARV drugs, assume the routine use of sophisticated laboratory tools by specialists, and address viral strains that predominate in wealthy countries. Simplification and decentralization of treatment are therefore essential components of a successful strategy to extend ARV therapy.

The concept of simplification covers the whole process of providing ARV drugs: inclusion criteria, management of side effects, choice of a drug regimen (first line, alternative first line and salvage therapy), when to

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switch, and so on. Simplification of the drug regimen is a crucial strategy in facilitating adherence, which is a key condition to optimize the chances of long-term success for the therapy [3]. Clearly, this is not just important for resource-poor settings: for example US guidelines state that 'regimens should be simplified as much as possible by reducing the number of pills and therapy frequency' [4].

Simplification of the first-line regimen has been the cornerstone of the treatment strategy in developing countries since triple therapy started to become available in 2001. While treatment cannot rely on one single combination alone, the availability of an affordable and easy-to-use first-line regimen is the starting point from which other strategies can be usefully explored.

This editorial draws on the experience within Médecins sans Frontières (MSF) to date, based on treating 21,000 people in 27 countries worldwide, together with information gathered through a series of expert consultations [5]. It is intended to provide a brief overview of priorities in adaptation and simplification in developing-country settings.

Simplifying AIDS treatment in the developing world

The use of ARV drugs for HIV commenced in Western countries with the launch of zidovudine in 1987. Highly active antiretroviral therapy (HAART) has been in widespread use in these countries since 1996. Treatment protocols were developed in countries with high standards of care and few limitations in terms of monitoring, access to drugs and human resources; such protocols are complex and require high levels of technical diagnostic support. There has been little effort applied to standardizing the first-line regimen, except through academic research [6].

Widespread treatment in developing countries became a realistic goal in early 2001, when companies producing generic drugs reduced the price of treatment by announcing they could provide triple therapy at an annual cost of US$ 300 [7]. At the same time, it was clear that it would not be possible to replicate the Western approach if large numbers of patients were to be reached. New models were needed that took into account limited human resources [8], limited availability of drugs and lack of access to monitoring tools. Through practical experience and operational research, MSF and ministry of health partners have been moving towards a rationalization of available resources and simplification of strategies. This process has focused on patient entry criteria, choice of therapy, drug supply management and delivery of care.

Simplification of entry criteria: who to treat?

Quite aside from the complex ethical dilemmas associated with achieving fairness in situations of limited resources [9], there are fundamental practical constraints to setting inclusion criteria in resource-poor settings.

Health insurance schemes and access to free public care are very limited in many developing countries, and the cost of accessing care is placed upon the patient. In these cases, the only way to ensure access is to offer free HIV care. MSF has chosen to offer free access to ARV treatment. In this situation, medical criteria rather than ability to pay guides decisions about rationing care.

Laboratory tests that are routinely used for the decision to begin treatment in wealthy countries are inaccessible to most people in developing countries. Until accessible and affordable means of measuring CD4 cell count (or proxies such as total lymphocyte count) and viral load become widely available, the decision to start treatment must rely on clinical staging, which means prioritizing symptomatic (WHO stages III and IV) patients. Such triage can be done by clinical officers and nurses provided that they are sufficiently trained.

The process of decision making is important and should incorporate perspectives of both provider and receiver in a manner that is perceived as fair by the different stakeholders. In MSF's experiences, putting those with greatest risk of death first is most in keeping the notion of fairness held by people living with HIV/AIDS.

In most developing-country settings, prioritization is not a choice but a practical necessity. It can be argued that giving priority to the sickest will reduce the chances of success of treatment. In our experience [10], severely sick patients can benefit from a significant increase in life expectancy (Table 1). Most patients arriving at MSF clinics are already sick, with low CD4 cell count (40% of patients treated by MSF programmes in Africa have CD4 cell count $< 50 \times 10^6$ cells/l), and present with opportunistic infections. Nevertheless, the overall probability of survival is at 85%. The majority of deaths occur in the first trimester, which is probably a consequence of under- or late diagnosis of opportunistic infections.

The selection process should not become a bottleneck to scaling-up. As the WHO puts it: 'It will be crucial to recognise that there may be no right answers, and from an ethical perspective, there may be some answers that are troubling, and even violative of basic conceptions of fairness.' MSF has made the choice in some programmes to disband selection committees, instead referring patients meeting clinical criteria directly to counsellors for orientation and support for treatment.

Table 1. Baseline characteristics and survival probability of 12 058 patients starting antiretroviral therapy in Médecins sans Frontières' programmes worldwide[a].

Demographic characteristics	
Female (%)	56
Median age [years (IQR)]	34 (29–40)
Median CD4 cell count [$\times 10^6$ cells/l (IQR)][a]	71 (22–143)
Percentage of patients with CD4 cell count ($\times 10^6$ cells/l)	
< 50	40.4
50–200	49.2
$\geqslant 200$	10.4
Median follow-up [months (IQR)]	5 (2.1–10)
Percentage followed for > 6 months	42.8
Outcome	
Probability of survival at 24 months (IQR)	0.85 (0.84–0.86)
Probability of survival at 24 months taking into account deaths and lost to follow-up (IQR)	0.73 (0.71–0.75)

IQR, interquartile range.[a]Data up to March 2004.[b]Available for 8487 individuals.

Simplification of treatment: protocols

The ideal first-line treatment would be potent, easy to use, well tolerated and without major side effects, contraindications and adverse drug interactions. Such a therapy would have the advantage of limiting the need for monitoring for side effects. In addition, it would be suitable for pregnant women and children. No existing first-line regimen currently fulfils all these criteria.

Current guidelines recommend the combination of two nucleoside reverse transcriptase inhibitors with a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor. Considering all ARV drugs currently available, there are around 1333 possible three-drug combinations, and over 150 treatment protocols are in use [11]. However, in resource-poor settings, standardization of first-line therapy is essential because of the limited availability of medicines and the need to provide clear recommendations that can be easily followed.

The most practical choice today is the WHO-recommended fixed-dose combination of stavudine/lamivudine/nevirapine [12]. This combination is affordable, easy to use (one pill twice a day) and is also indicated for pregnant women. A recently published study from Cameroon demonstrated the excellent efficacy and safety of this fixed-dose combination [13]. It is well tolerated, requires minimal monitoring and shows comparable efficacy to the other widely used non-nucleoside reverse transcriptase-based combination: lamivudine, stavudine and efavirenz [14].

A major advantage of the nevirapine- over the efavirenz-based regimen is that the former is not teratogenic (a significant number of patients in sub-Saharan Africa are women of child-bearing age) and it is available as fixed-dose combination pill: this reduces pill burden, encourages adherence, limits the risk of wrong doses (thus limiting the risk of resistance development) and facilitates drug supply management [15]. Quality of suppliers has been validated by the WHO pre-qualification process [16].

Results from MSF HIV/AIDS programmes using this fixed-dose combination in over 6800 patients (as of March 2004) are excellent [17]. Of a cohort of adults followed for over a year, 70% were still on the fixed-dose combination, 12% had died (62% in the first 3 months after initiation of treatment), 7.3% had to stop this combination and 10% were considered lost to follow up. Clinical and immunological outcomes were comparable to Western standards, even in severely ill patients.

While this first-line therapy has broad applicability, there are limitations. Around 7% of patients in the MSF fixed-dose combination cohort had to switch from a nevirapine-based fixed-dose combination regimen to one that did not contain nevirapine and was not available as a fixed-dose combination pill. The main reasons for the switch were tuberculosis (25%) and nevirapine-attributed hepatotoxicity and cutaneous rash (50%). Other limitations include peripheral neuropathy (five cases reported), lactic acidosis (no case reported) or lipoatrophy (two cases reported). Possible adverse drug interactions (nevirapine and rifampicin), suboptimal efficacy on certain virus groups (group O) and types (HIV-2), and the risk of rapid development of drug resistance (especially to nevirapine) were also a major concern. In our experience, those patients who had to stop nevirapine did so within 28 days [interquartile range (IQR), 19–114], whereas those who had to stop stavudine did so after 215 days (IQR, 157–287).

In all, it is expected that approximately 10% of patients will need access to an alternative non-nevirapine-based

first-line regimen. These alternative regimens are based on the most commonly required drug substitutions: efavirenz for nevirapine and zidovudine for stavudine. However, these alternatives are much more expensive, do not exist as fixed-dose combinations and also have significant side effects (central nervous system toxicity with efavirenz; anaemia with zidovudine).

New first-line regimens need to be developed. The use of once daily atazanavir has potential in a robust and less-toxic first-line approach, but for pharmakokinetic reasons, ritonavir must be added which requires refrigeration. Unfortunately, several studies do not favour the use of triple nucleoside analogue regimens [18]. Once daily efavirenz/didanosine/lamivudine or tenofovir/lamivudine/efavirenz could also be advantageous, but no fixed-dose combination is in the pipeline. There is a clear role for the pharmaceutical industry to engage in the development of new drugs and combination for first-line therapy.

Work to improve first-line treatments is needed, and is all the more pressing as second-line treatments are more expensive, more complex to administer, and more complex [19]. Given that the expected failure rate after 1 or 2 years is 20–30%, there is an urgent need to ensure that affordable and highly effective second-line treatment can be provided to patients showing clinical, immunological, or virological failure to first-line regimens.

Currently, there are no fixed-dose combinations for second-line therapy (patients move from one pill twice a day to up to 15 pills daily), and the price can be as much as 10–20 times higher than a generic first-line regimen: in Cameroon, for example, first-line therapy costs US$ 277, while second-line therapy is over US$ 4000 [19]. Quality generic production of second-line fixed-dose combinations needs to be supported.

The treatment of children with AIDS poses a particular challenge. Because of lack of commercial interest (few paediatric cases in western countries), some manufacturers of ARV drugs do not produce paediatric formulations at all; some molecules are marketed without ever having been tested for use in children (e.g., tenofovir) and those paediatric formulations that are produced are generally more expensive. While the fixed-dose version of stavudine/lamivudine/nevirapine for adults is available for about US$ 200 per patient per year, the best price for the same drugs in paediatric formulations is approximately US$ 1300 (oral solutions and syrups). There are no paediatric fixed-dose combinations. For the second-line regimen of zidovudine/didanosine/nelfinavir, the adult yearly price is US$ 1228; the same regimen in paediatric powder and syrup formulations costs US$ 2846 per person per year [20,21].

Some paediatric formulations are sold as syrups, which are difficult to use, or in powder, which require clean water (a constraint in resource-poor settings) and are difficult to distribute and store. The main recourse for doctors in the field is to break adult tablets. However, few drugs are manufactured as scored, breakable tablets, nor have they been specifically studied for use in children. The only companies taking an interest in paediatric formulations are those generic companies based in the developing world: breakable tablets are produced by companies in India and Thailand, and the Thai Generic Pharmaceutical Organization is currently developing a fixed-dose paediatric combination (lamivudine/stavudine/nevirapine).

Simplification of laboratory testing: minimum requirements

Lack of capacity for laboratory monitoring should not be a barrier to starting treatment for patients in clear medical need, but monitoring will be crucial for diagnosing treatment failure before the manifestation of clinical signs. Unfortunately, tools for diagnosis and monitoring are subjected to the same market dynamics as medicines: developed primarily for sale in rich countries and patent protected.

The price, complexity and running requirements of biological tests used to measure CD4 cell count or viral load, or to monitor drug side effects, pose significant technical and financial obstacles to project implementation at the community level. The first priority for improving clinical care is access to a practical and affordable means of measuring CD4 cell count, in particular to facilitate treatment decisions for asymptomatic patients and pregnant women. Current means of measuring CD4 cell count all have their limitations.

Relying on 'open' flow cytometry systems and promoting use of generic reagents could reduce the price of these tests by at least 50%, although use of the flow cytometer machine itself remains expensive and will be largely limited to referral centres. Alternative machines are being deployed on the field but some of them await independent evaluation. A recent evaluation of the Cyflow (PARTEC, Münster, Germany) by MSF in Malawi is encouraging [22]. Costs per test are 3–10 times cheaper than the next alternative (Facscount; Becton Dickinson, San Jose, California, USA).

However, even if generic reagents are used and funds are found to buy machines, running requirements such as steady electrical supply, temperature control and the need for periodic servicing means that current technology will be of limited use away from large cities. There are two ways to overcome this: development of a system of transporting samples to reference centres (this is currently possible) or development of rapid tests that do not require sophisticated machinery.

Assessing treatment failure is also a challenge that must be met. Waiting for clinical failure before changing drugs will mean higher failure rates. Clinical failure is often only apparent many months after the first quantifiable increase in viral load. Relying on CD4 cell count criteria has a considerable impact on survival rate, reducing the effectiveness of salvage therapy by up to 50%. This average failure rate varies according to the nature of the first- and second-line regimens, and is even greater if clinical criteria alone are used.

There is a need for a semiquantitative, simple and inexpensive rapid test to detect early virological failure and optimize the response to second-line therapy. Until rapid tests are available and affordable for use in rural settings, the most practical solution will be to transport blood samples on filter paper for polymerase chain reaction. This method is stable within a wide range of temperatures and humidities.

Innovative and accessible tools are also needed to monitor toxicity and support diagnosis of opportunistic infections. Diagnosing tuberculosis, for example, is difficult: depending on the number of specimens examined, Ziehl–Nielsen detects 30–60% of the culture-positive tuberculosis suspects [23]. Moreover, as the degree of immunosuppression increases, the frequency of extrapulmonary tuberculosis and mycobacteriaemia increases, leading to difficult diagnostic challenges in places where culture and biopsy are not readily available [24]. There is also no easy means of diagnosing tuberculosis in HIV-positive children [25,26]. (Clinicians must rely on a combination of clinical score and rafiography to diagnose pulmonary tuberculosis.)

Simplification of the drug delivery pipeline

One of the main challenges in treating a chronic disease like HIV/AIDS is to maintain continuity in the drug supply. Interruptions in drug supply have been put forward as a major cause of non-adherence [27]. The use of a fixed-dose combination pill does help to ease pressure on the supply chain, but few such combinations are available and their further development and use is being threatened by increasing patent protection and political pressure against generic manufacture [28].

A constant stock of alternative first-line drugs is needed to enable substitution in case of drug toxicity or adverse reactions: efavirenz 200 mg/600 mg, nevirapine 200 mg and the dual-combinations zidovudine/lamivudine and stavudine/lamivudine (also needed for the first 15 days during nevirapine dose escalation). This means that a minimum of five different drug presentations is needed even for standard adult first-line therapy. This illustrates why simplification and standardization of protocols is necessary to improve drug supply management.

The need to refrigerate medicines can be a major limitation in the tropical world and is an important reason why the use of ritonavir-boosted protease inhibitors is limited in MSF programmes. This again highlights the need for the development of new medicines that take the developing world context into account.

Simplification of care through integration and decentralization

Integration of treatment delivery within HIV clinic services and programmes for prevention of mother-to-child transmission and tuberculosis, and even within hospital wards, is key for improving access to ARV treatment. Health workers need to be made aware of opportunities for identifying eligible people for ARV treatment. Such treatment could be integrated within programmes for prevention of mother-to-child transmission, especially in settings where CD4 cell count testing is already available for identifying asymptomatic mothers with significant levels of immune depression (CD4 cell count $< 350 \times 10^6$ cells/l).

Special attention is needed to the integration of ARV treatment within tuberculosis treatment programmes. In Malawi, MSF has noted that tuberculosis programmes are mostly decentralized while ARV treatment initiation and follow-up is often still very centralized, resulting in relatively low uptakes for ARV treatment among HIV-positive patients with tuberculosis (WHO stage III or IV). Most patients with tuberculosis who are also HIV positive are too weak and cannot afford to return for additional consultations for ARV treatment initiation and follow-up while taking tuberculosis treatment. Therefore, there is a need for new models where ARV treatment and follow-up is integrated into tuberculosis programmes and gradually decentralized.

For scaling-up to be successful, treatment programmes must be decentralized from urban centres to the community primary health-care setting. Patients cannot be expected to travel tens of kilometres every month to receive life-long treatment, and ARV drugs have to be delivered as close as possible to where people live in order to ensure good adherence. Even in resource-poor and understaffed settings, this could be implemented at least for the follow-up of stable patients who have initiated ARV treatment in clinics.

A critical barrier to scaling-up is lack of human resources. Most resources are focused in the cities, and a much greater responsibility needs to be given to nurses, medical assistants and clinical officers in consultations, particularly in rural areas. MSF's experience in decentralizing care and ARV treatment through a mobile team in the district of Chiradzulu in the south of Malawi has been very positive. Local nurses and

medical assistants are now being trained to become involved in diagnosis and treatment of opportunistic infections, follow-up of HIV-positive patients stable with HAART and in counselling and adherence support. In this way, it was possible to triple capacity in under a year, from 1000 patients in May 2003 to 3122 patients in March 2004 (of which 2194 were taking ARV therapy) [8,29].

Simplification of patient follow-up for ARV treatment should be sought in order to increase clinic capacity for offering access to treatment and to facilitate decentralization of treatment follow-up, while maintaining an acceptable quality of care. MSF's experience in South Africa [30], Thailand [31] and elsewhere has shown that careful preparation of patients, by providing education on treatment and adherence support, is essential to good compliance and successful treatment. Patients and their peers play a central role the provision of treatment. The head of the WHO 3×5 initiative at the *XV International Conference on AIDS* in Bangkok [32] emphasized the central role for community-based care delivered by health workers providing fixed-dose combinations, with doctors dealing mainly with complications.

What needs to be done

Progress has been made in recent years towards treating HIV infection in the developing world. At the time of the *XIII International Conference on AIDS* in Durban, 2000, the lowest yearly cost of treatment was still more than $US 1500 (in Brazil); prices in developing countries were generally several times higher than this, and it was impossible to imagine widespread access [33]. Today, thanks to generic competition, that price has dropped to under US$ 200 [34] and an increasing number of developing countries have started to provide treatment. However, much more needs to be done to ensure treatment reaches those in greatest need.

Cost of treatment: a low-cost first-line fixed-dose combination

Through a combination of bulk purchasing and generic competition, an annual treatment cost of $US 50 is a realistic aim. Affordability is crucial to good adherence [35] and the goal should be to ensure that treatment is provided to patients at as little cost as possible, ideally free. New combinations for first-line therapy are needed. However, continued political pressure to block the use of patented medicines threatens to stifle progress in making simple and affordable treatments more widely available. The simplicity of fixed-dose triple combinations makes them attractive for both developed and developing world settings, but patent holders are unwilling to cooperate in producing these combinations, and they are only available through generic producers to developing countries. Their use has been discouraged by the US government, which recently raised false concerns about their quality and safety [28] despite the fact that several fixed-dose combinations have been prequalified by the WHO and their safety and efficacy is proven through extensive use in the field [17].

Affordable second lines: an absolute necessity

The cost of second-line regimens remains prohibitive [19]. Differential pricing and generic competition must be encouraged to bring down the price of these medicines. Otherwise, many of the patients who are currently benefiting from treatment will be left without an alternative in case of failure to first-line treatments. Optimal second-line therapy will require good viral monitoring, as second-line regimens will be less effective among patients whose failure has to wait to be determined clinically.

With the full implementation of the WTO TRIPS Agreements in 2005, access to new drugs and diagnostics is a pressing concern. All new drugs will be subject to at least 20 years of patent protection in most countries, which can drive prices up and block coformulation. Patents must not be a barrier to accessing the simplest and most affordable treatment, and public health safeguards in patent law must be used to the full to ensure that affordable new treatments are available to all who need them [36].

Diagnostics: a new battle

Recent negotiations have led to price drops for diagnostic reagents. In April 2004, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the World Bank, UNICEF and the Clinton Foundation announced agreements that secured lower-priced diagnostic reagents. Such negotiations must continue. However, much lower prices would be possible using simplified protocols and generic reagents. In general, the need for feasible and affordable diagnostics is largely overlooked. Diagnostics should move up both the donor agenda to help develop and purchase diagnostics and WHO's agenda so that clear recommendations are made and manufacturers prequalified.

Who will develop new tools for neglected patients?

Experience across the developing world over the last few years has demonstrated the feasibility and efficacy of providing ARV drugs in resource-limited settings. A recent WHO consultation sought to develop emergency technical and operational recommendations to guide the scaling-up of ARV therapy in resource-limited countries [12]. While efforts like these must continue to help to adapt and simplify treatment, the

task of the health-care providers would be made easier with the development of appropriate and affordable tools. Training needs are enormous and should be addressed in all plans.

However, work is needed to adapt and to simplify the process of delivering treatment to those in greatest need. More tools are needed to respond to the needs of neglected patients such as children, patients coinfected with tuberculosis, and pregnant women.

There is a need for new medicines and diagnostics tailored to the developing world. Successful innovation will likely require new approaches to treatment, including therapeutic vaccines. Who will develop these tools? The Western-based pharmaceutical industry has been effective in rapidly bringing a range of therapeutics for HIV infection onto the market [37], but huge gaps remain in meeting the needs of people in developing countries because of poor prospects for profit [38]. This failure of the market has led some to call for AIDS to be considered as a neglected disease [39].

This is a political challenge that cannot be sidestepped. The public sector must be willing to take responsibility for ensuring the development of new medicines and diagnostics for neglected diseases and neglected patients. International organizations and funding initiatives such as the Global Fund and WHO should integrate a research component into their strategy.

Today, however, donor funds are insufficient to sustain even current programmes, let alone provide funds for research and development. All multilateral initiatives, including the Global Fund [40] and the WHO 3×5 [41], are critically underfunded. The international community has finally woken up to the urgency of AIDS, but resources are still inadequate to meet the needs. This is a critical moment in deciding whether that awakening includes a practical determination to stem the devastation of one of the worst epidemics the world has ever faced.

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