



**HIV/AIDS treatment in developing countries:
The battle for long-term survival
has just begun**

CAMPAIGN FOR	
ACCESS	
TO	
ESSENTIAL MEDICINES	

Introduction

Over three million people living with HIV/AIDS in the developing world receive antiretroviral therapy (ART). However, the medicines and diagnostic tools available are inadequate to respond fully to their needs. In addition, seven million people are in need of treatment and are still waiting for access.

The public health approach to treatment in resource-limited settings has enabled significant scaling-up of treatment - thanks to fixed-dose combinations and to the lower prices of first generation treatments. But this approach has also come at the cost of compromise. For example, stavudine-containing regimens, no longer recommended in well-resourced settings because of side effects, are still widely used in resource-limited settings. In addition, clinical algorithms and CD4 counts are still common methods to diagnose treatment failure even if these have proven to be unreliable.^{1,2} In most resource-poor settings, since viral monitoring is not available, patients and medical staff are only alerted to resistance when patients suffer from opportunistic infections. This is no longer acceptable medical practice.

It is now time to invest in improving the public health approach. Treatment scale up must continue so that more people in need receive treatment and care. Support for universal access to treatment has been repeatedly confirmed by the international community.³ Clearly, the promise of universal access cannot be abandoned when only 30 percent of those in need have been reached.

At the same time, ambitions must be expanded for those already on treatment to increase their chances of long-term survival. If we do not respond to evolving medical practice with improvements in drugs and monitoring, we will be guilty of maintaining a sub-optimal status quo.

In-depth look at Khayelitsha, South Africa – five year results

Khayelitsha, home to 500,000 people, is a township located on the outskirts of Cape Town and has one of the highest HIV prevalence rates in South Africa. The country has the greatest number of people living with HIV/AIDS in the world. The majority of the population lives in informal housing and there are alarming rates of poverty, unemployment and crime, including sexual violence. Antenatal HIV prevalence stood at 22.0 percent in 2001, and at 32.7 percent in 2007.⁴ The TB incidence rate reached nearly 1,600 per 100,000 in 2006 and TB/HIV co-infection is nearly 70 percent.⁵

By the end of 2007, AIDS treatment was being provided in Khayelitsha as a routine government service, with limited support from Médecins Sans Frontières (MSF). Between 2001 to 2008, 12,000 people with HIV/AIDS started on ART. This is one of MSF's longest running AIDS treatment projects.



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The Khayelitsha AIDS treatment programme benefits from the relatively strong healthcare infrastructure in South Africa and has an extensive monitoring and data collection system.

Patients are prescribed either nevirapine (NVP) or efavirenz (EFV), with stavudine (d4T) and lamivudine (3TC) as a first-line regimen. A CD4 count is taken at the initiation of treatment and every six months thereafter. Viral load is done at six months and every six months after that.

An analysis of 7,323 people on ART from 2001-2007 shows relatively good long-term results. The cumulative estimate of mortality based on clinic-held data was 15.5 percent at five years.

Patients still on treatment were tested at one, three and five years, and found to be virologically suppressed at rates of 87.5 percent, 88.1 percent and 83.8 percent respectively. At five years, 16 percent of patients had thus failed first-line treatment. Patients who switched to second-line treatment earlier were less likely to be virologically suppressed, with almost 25 percent failing at two years.

In this analysis, failure was defined as two viral load measurements above 5,000 copies per ml. The most common reasons for failure were treatment interruptions, exposure to nevirapine from prevention of mother-to-child transmission, and low baseline CD4 count. Of those failing virologically, fewer than 20 percent had a drop in CD4 count and would thus not have been detected by CD4 count alone.⁶

The Khayelitsha project shows that as more people live longer on antiretroviral drugs, inevitably a substantial number of patients will develop resistance and subsequent treatment failure. These people need timely diagnosis of treatment failure and treatment options that respond to their needs.

1 Calmy A, Ford N, Hirschel B et al. HIV Viral Load Monitoring in Resource-Limited Regions: Optional or Necessary? *Clin Infect Dis* 2007; 44(1): 128-34

2 Reynolds SJ, et al. Failure of immunological criteria to appropriately identify antiretroviral treatment failure in Uganda. *AIDS* 2009; 23 (6): 697-700

3 For instance at the UN General Assembly in 2001, and again at the G8 summit in 2005 in Gleneagles.

4 Western Cape Government Department of Health. Antenatal HIV and Syphilis Prevalence Survey, 2006.

5 MSF / City of Cape Town / Provincial Government of the Western Cape Department of Health: A patient-centred approach to drug-resistant tuberculosis treatment in the community: a pilot project in Khayelitsha, South Africa, March 2009.

6 MSF internal data.

Newer first-line drugs can ensure long-term survival

Resistance is an inevitable element of long-term antiretroviral treatment. However, it can be delayed by using drug combinations with fewer and less severe side effects so that adherence is easier, and can be limited by changing treatment soon after viral suppression begins to wane.

Most patients in developing countries on antiretroviral treatment receive a combination of three drugs: lamivudine (3TC), stavudine (d4T), and nevirapine (NVP). However, in 2006, the World Health Organization (WHO) recommended that the first-line treatment in developing countries be based on tenofovir disoproxil fumarate (TDF) or zidovudine (AZT), rather than stavudine, because of side effects attributed to the drug. Stavudine has a common side effect of lipodystrophy that causes fat loss in the limbs and face and fat gain around the stomach, shoulders and neck. The drug also can cause peripheral neuropathy, or nerve damage, that can make it difficult to walk. Stavudine can cause lactic acidosis which, in rare cases, can lead to death.

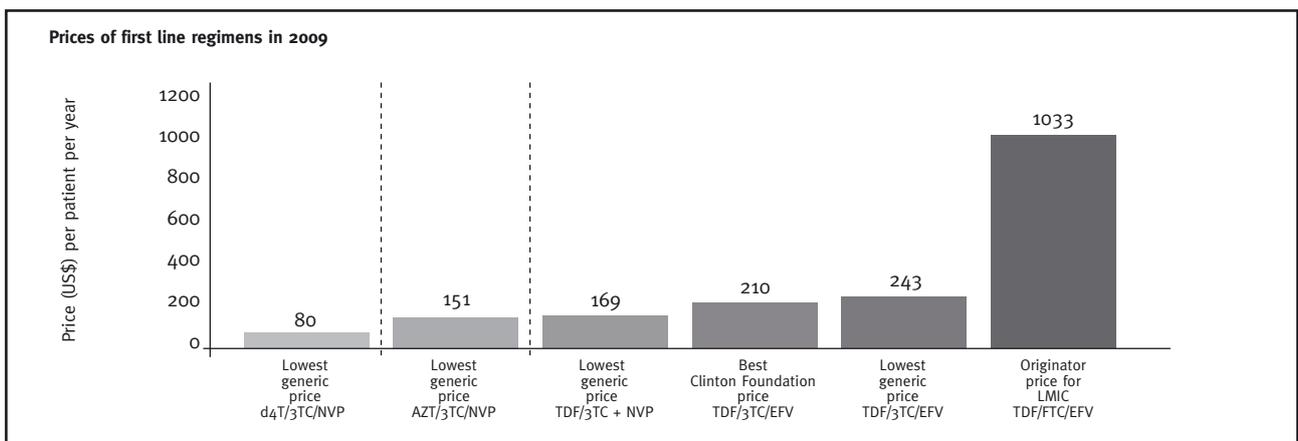
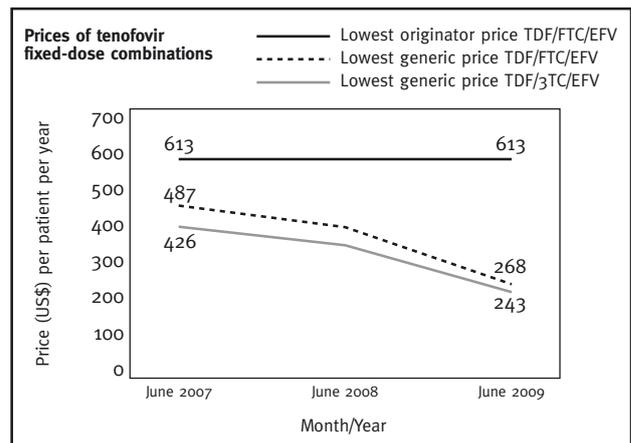
So far, the move to tenofovir has been stymied by price. However, tenofovir is now available at significantly lower prices than before. The price of a tenofovir-based regimen now ranges from US\$ 169 to US\$ 243 per patient per year, still two to three times higher than a more toxic stavudine-containing regimen. The price is likely to fall further with increased volume of purchases.

One study showed that savings on toxicity management of stavudine alone can offset part of the higher price of tenofovir, and that a tenofovir-based regimen would be highly cost-effective in South Africa at the lowest generic price.⁷

Considerations other than price need to be taken into account, most importantly the long-term benefits for patients. Tenofovir has been part of the WHO recommended first-line treatment for three years, it is time to make the change.



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7 Rosen S, Long L, Fox M, Sanne I. Cost and cost-effectiveness of switching from stavudine to tenofovir in first-line antiretroviral regimens in South Africa. J Acquir Immune Defic Syndr. 2008 Jul 1;48(3):334-44.

Diagnosing Treatment Failure: The Need for Viral Load Testing

Until now, the primary focus has been on rapid and simplified scale up of first-line treatment. Most national AIDS programmes still lack the ability to detect treatment failure and to switch drug combinations in a timely manner.⁸ Even where viral load technology is available, the cost and the complexity of testing (which requires skilled technicians at a referral laboratory and complicated sample transport) severely limit the ability to perform these tests on a routine basis.

What is needed is a simplified viral load assay, which can determine if a patient's viral load is above a pre-determined cut-off level. A tool with improved access, that could be used to provide clinicians with help diagnosing treatment failure at set time points, would improve chances for long-term survival.

Clinical examination and CD4 count leaves medical staff in the dark

In the absence of viral load tests, WHO guidelines recommend that clinical signs, such as opportunistic infections, and CD4 cell count be used in order to decide if a person needs to change drug regimen. However, both these tools have serious limitations: changes in CD4 counts are difficult to interpret because of individual variations in immunological response to ART, and clinical failure comes much later than virological failure.

Studies have shown that a combination of routine clinical examination, pill count monitoring, immunological (i.e. CD4 cell count) and other forms of adherence monitoring, will miss the majority of patients having inadequate viral suppression.

In one study in Uganda, 1,133 participants were followed over 44 months to determine the ability of CD4 to detect treatment failure, compared to viral load (the current gold standard). Of the 112 patients failing treatment according to viral load (with failure defined as two tests > 400 copies/ml), only 26 would have been detected by CD4 count.⁹ In another study, it was found that only eight out of 100 people failing treatment (defined as virological failure) would be identified through the WHO recommended CD4-based method. Conversely, whereas 100 people were identified as failing treatment according to CD4 cell counts, only eleven were actually failing. Based on CD4 counts alone, without viral load testing, these 89 patients would therefore have been mistakenly identified as failing ART and prematurely switched from their primary antiretroviral regimen – when in fact it was effectively controlling viral replication.¹⁰ Similar problems were reported from a further study in South Africa.¹¹

MSF's experience in Khayelitsha illustrates similar experiences. As mentioned above, of those who failed treatment as measured by viral load monitoring, only 20 percent would have been identified through a CD4 count alone.

Most MSF programmes have no access to viral load monitoring. Data analysed on 67,616 MSF patients in 31 MSF projects in 14 countries show that only 1.4 percent of patients receiving antiretroviral treatment are on second-line regimens – a switch rate of 8.9/1,000 person-years on treatment. This figure is probably lower than it would have been had there been access to viral load. Without the possibility of viral load measures, healthcare workers are usually not able to identify treatment failure until patients develop opportunistic infections.

In short, the current clinical and CD4 count-based monitoring may not accurately identify treatment failure, leading clinicians to delay switching from a failing regimen or causing them to switch away too early from a regimen that is still effective.

Further, viral load has been identified as a useful tool to detect treatment failure and trigger adherence support that can preserve patients for longer on a first-line regimen before a switch is required.

In Khayelitsha, 71 percent of patients with detectable viral load at six months were undetectable after adherence support.¹² Similar results were found in a Thai study, with 80 percent of patients who initially had a detectable viral load becoming undetectable after targeted adherence counselling.¹³

Access to adapted viral load monitoring is critical

Increasing data on the limitations of CD4 and clinical staging count should lead national AIDS programmes, donors and WHO to make access to viral load monitoring a key priority. Viral load testing is an investment to spare available treatment combinations and ensure that a patient's regimen is changed neither too early nor too late.¹⁴

An increasing number of countries do have some access to testing. The simplification and validation of new viral load tests is an urgent priority that is currently hampered by insufficient political will and funding.



8 Gupta R, Hill A, Sawyer A et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. *Lancet Inf Dis* 2009; 9: 409-417
9 Reynolds SJ, et al. Failure of immunological criteria to appropriately identify antiretroviral treatment failure in Uganda. *AIDS* 2009; 23 (6): 697-700
10 Moore DM et al. J Acquired Immune Deficiency Syndrome 49 :477-484, 2008
11 Mee P, Fielding KL, Charalambous S et al. Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa. *AIDS* 2008; 22(15): 1971-7
12 Van Cutsem, MSF Internal data
13 Wilson D, et al. HIV-1 viral load monitoring: an opportunity to reinforce treatment adherence in a resource-limited setting in Thailand. *Trans R Soc Trop Med Hyg* 2008; doi:10.1016/j.trstmh.2008.11.007
14 Calmy A, Ford N, et al. HIV Viral Load Monitoring in Resource-Limited Regions: Optional or Necessary? *Clin. Infect. Dis.* 2007; 44 (1): 128-34.

History repeating itself: New drugs out of reach

Mother of two, Thembisa Mkhosana, from Khayelitsha, Cape Town, South Africa, discovered she was HIV positive in 2001. Through an HIV/AIDS programme supported by MSF, she started on antiretroviral drugs in 2003 and became well enough to work and care for her children. But now Thembisa is showing drug resistance to second-line treatment and she currently has no other options. Unlike in Europe and the US, there is currently no third-line of treatment available in South Africa.



"I'm so worried now because I don't know what is going to happen to me. If there's no such thing that can help me – I know that I'm going to die. And then who's going to look after my children?"

Thembisa Mkhosana, mother of two, patient at Ubuntu HIV/TB clinic



"As a nurse, seeing a patient that you have been treating since 2003 and now this patient is failing on her second combination, you feel, as a nurse, you are a failure. We are feeling like our hands are tied. There is nothing we can say to Thembisa because it's she who needs answers from us."

Sister Mpumi Mantangana, Unit Manager, Ubuntu HIV/TB clinic

As data from long-term ART programmes shows, more and more patients will need access to additional drug combinations.

In a demand forecast by Clinton Foundation, it is estimated that the number of those receiving second-line antiretroviral drugs in developing countries is to rise to more than a quarter of a million by 2011.¹⁵ The actual number of people needing second-line treatment will be much higher.

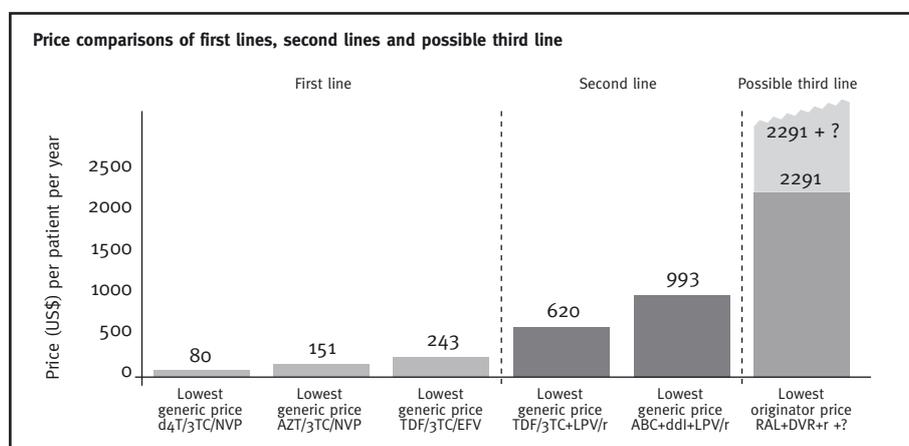
But the prices of these newer medicines are dramatically higher: in some countries, switching a patient from a first- to second-line regimen increases the cost of treatment as much as seventeen-fold.¹⁶

For first-generation antiretroviral drugs, the absence of patents in manufacturing countries like India and Brazil made competition and resulting price drops possible.

But today, more and more countries need to comply with the World Trade Organization's TRIPS agreement (Trade-Related Aspects of Intellectual Property Rights). This means that most countries with the capacity to produce generic drugs grant pharmaceutical patents for a minimum period of 20 years, during which generic companies are prevented from entering the pharmaceutical market and selling medicines more cheaply. This severely limits generic production and thus low-cost drug options for developing countries.

Although India's new patent law contains valuable public health safeguards that limit patentability of drugs and allow civil society organisations to oppose patents, many of the newer antiretroviral drugs will be patentable in India, and several – such as raltegravir, maraviroc or etravirine – already are.

Therefore, treatment providers are once again faced with a situation where drugs could be priced out of reach.



¹⁵ The All-Party Parliamentary Group on AIDS: The treatment time bomb, Report of The All-Party Parliamentary Group on AIDS into long-term access to HIV medicines in the developing world, July 2009, p.12.

¹⁶ Untangling the Web of Antiretroviral Price Reductions, 11th edition, July 2008. MSF – Campaign for Access to Essential Medicines. Available from www.msfastcess.org

Overcoming price barriers

Overcoming these price barriers will require a range of different solutions:

The restriction of patentability criteria – such as Section 3d and other public health safeguards contained in India's 2005 Patents Act – is an essential tool to keep the door open for generic competition. Countries have the right to define, in accordance with their public health needs, what deserves a patent and what does not. Overbroad patentability criteria limit the number of drugs that generic companies can produce and restricts their ability to drive prices down to affordable levels. Countries also have the right to authorise civil society groups or other actors to oppose a patent application before the patent is granted, or challenge it once this has happened. These processes, known as pre-grant or post-grant oppositions, are important safeguards to ensure the national patent offices only grant patents that meet national patent criteria.

Once drugs are patented, there are still means of enabling competition. Originator companies can allow generic manufacturers to produce affordable versions of drugs by agreeing

to voluntary licences. If originator companies refuse to grant voluntary licences or grant them with unacceptable restrictions, countries can also override patents – in an entirely lawful manner – by issuing what is called a compulsory licence. This can be done without the permission of the patent holder, who must nevertheless be paid royalties.

One example is Thailand. Until recently, two patented AIDS drugs – efavirenz and lopinavir/ritonavir – were available in Thailand only from the patent holders, and at high prices. In late 2006 and early 2007, the Thai Ministry of Health issued compulsory licences authorising the governmental pharmaceutical organisation to import the drugs from Indian generic manufacturers, at a fraction of the price of the patented drugs. Countries must feel supported in their right to use these and other TRIPS flexibilities.

There are other ways to overcome patent barriers, for example through the collective management of intellectual property. Patent pools – such as the one for HIV medicines that the international drug financing agency UNITAID is establishing – are one new systematic solution with the potential to allow access to affordable medicines.

Why crucial AIDS medicines must go into the patent pool

In 2008, the international drug financing agency UNITAID took the groundbreaking decision to establish a patent pool in principle. The idea behind a patent pool is that companies, researchers or universities license the patents on their inventions to one entity: the patent pool.

In this way, any company can get a license from the pool, under pre-determined licensing terms, in exchange for the payment of royalties. It could then produce generic versions of the patented inventions and export them to countries covered by the licence. Originator companies get rewarded, generic companies can produce, and patients and treatment providers get access to more affordable drugs from day one.

The patent pool must go beyond just first- and second-line drugs. Newer drugs, such as raltegravir, etravirine and darunavir, are potent, safe and are now well known and part of treatment recommendations in developed countries. Other new medicines, still in development, such as rilpivirine, have the potential to be co-formulated, low dose and affordable and can be used either in treatment-experienced or naïve patients. Also, new booster medicines such as GS-9350 and SPI-452 are needed to avoid the current monopoly by one company on ritonavir. These medicines can save lives of patients who have been exposed to all existing WHO treatment lines, but can also be the cornerstone of innovative first-line regimens.¹⁷

MSF calls on patent owners to support the UNITAID pool and commit to putting their patents in the pool.

But in addition to ensuring lower prices for new drugs, there is also a need to ensure that drugs are registered in a timely manner. Patent pools will have to be accompanied by a mechanism to register drugs, so that companies participating in the patent pool agree to register their drugs in developing countries.



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Funding for Universal Access to Treatment

Despite the potential of new mechanisms to lower the price of drugs, there will still be an urgent need for donors to cover the cost of more expensive treatments. Especially in the short-term, before economies of scale are reached, there will be an urgent need to increase budgets to cover the costs of new treatments.

Yet financing for HIV/AIDS is stagnating. People living with HIV/AIDS in developing countries rely on financing of their governments as well as of international institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the U.S. government-funded President's Emergency Plan for AIDS Relief (or PEPFAR). The Global Fund is facing a shortfall of at least US\$ 3 billion needed to fully fund existing programmes and maintain and finance programmes for 2010. The U.S. government commitment to PEPFAR has stagnated despite earlier promises of a US\$ 1 billion increase in desperately-needed funds.

The risks of this funding shortfall are evident. A UNAIDS/World Bank survey found that 11 percent of respondents in 71 countries reported that the global economic crisis has already affected their country's antiretroviral treatment programmes;

31 percent anticipated an impact on treatment this year. Some healthcare providers in Uganda have stated that they do not intend to enrol new patients on treatment. Tanzania has reported significant cuts its HIV/AIDS budget, and Botswana recently announced that it would cease enrolling new patients by 2016.¹⁸

Unless financing increases, treatment achievements and lives saved are at risk.



Conclusions and Recommendations

The chances for long-term survival for people who need treatment and those already accessing it will be improved if the following steps are taken:

National programmes must provide a more robust first-line regimen containing tenofovir so that people can stay on their first regimen as long as possible and with fewer side effects.

- National treatment protocols need to be revised to recommend a tenofovir-based first-line regimen.
- Donors such as the Global Fund and PEPFAR must make it clear that they will support countries who make this change with necessary financing.

There must be increased access to viral load testing to detect treatment failure before high viral load causes irreversible damage. Progressive introduction of viral load monitoring should support the public health approach to antiretroviral treatment provision.

- Viral load surveys should be considered, in order to generate reliable data on the proportion of patients with treatment failure to guide programming.
- Some capacity to run viral loads in all countries should be established.
- Limited viral load testing for patients that are suspected of treatment failure, or have reached a certain time point on treatment, should be incorporated into treatment, programmes urgently.
- WHO, national governments and donors should prioritise ongoing efforts to develop simpler viral load technologies that can be incorporated into a public health treatment approach.

Countries must begin ensuring access to second and third-line treatment combinations.

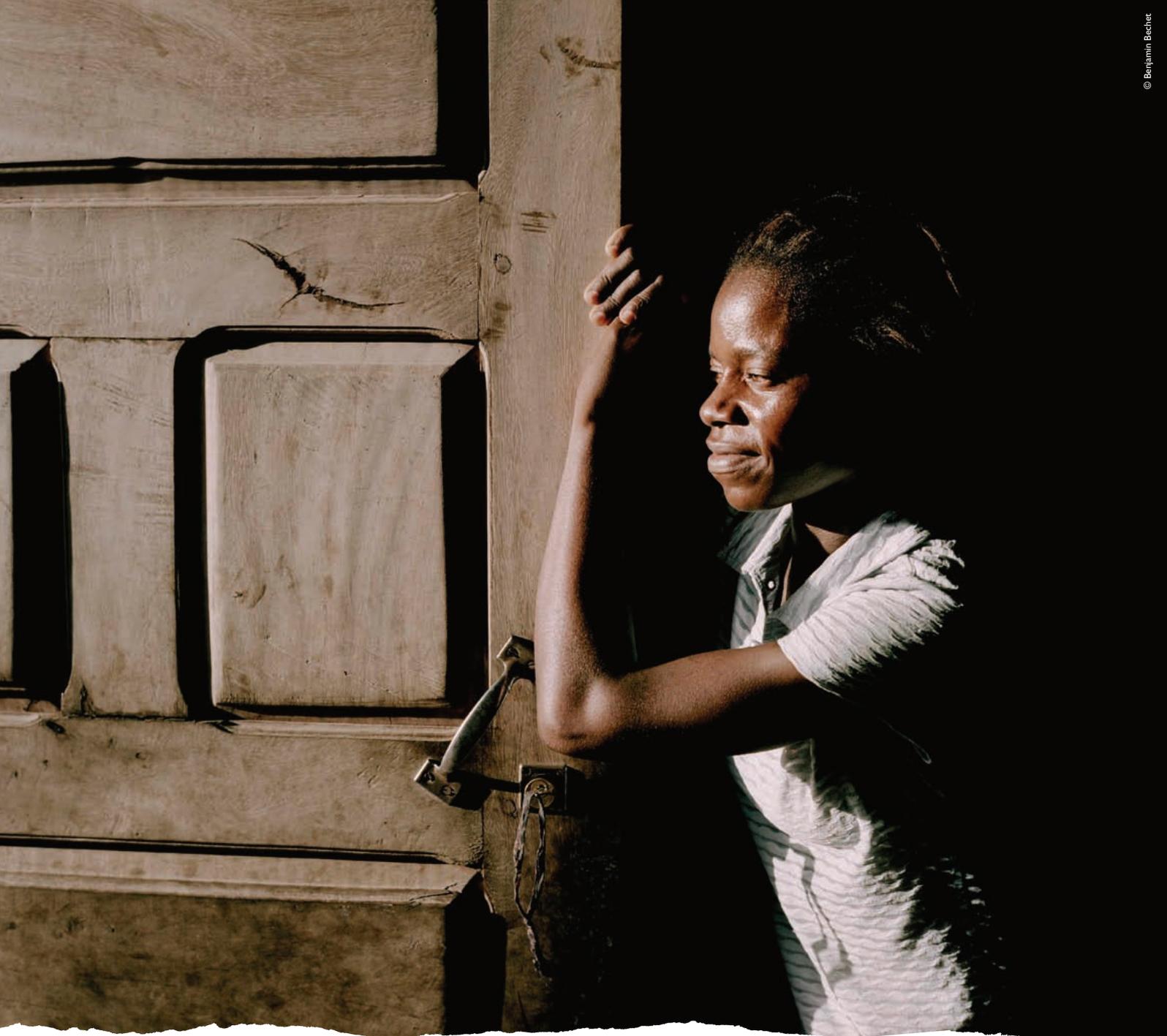
- In its next guideline review, WHO should add treatment options for those failing second-line.
- Donors need to ensure sufficient funding to buy more expensive second and third-line drugs.
- Originator companies need to carry out speedy registration of new drugs such as raltegravir, darunavir, etravirine in developing countries.
- Originator companies must commit today to put their patents into the patent pool that is being set up by UNITAID.
- Countries should ensure generic competition through use of TRIPS flexibilities when needed.

Funders and national governments must honor their commitments to fund universal access.

The lesson learned over the last decade is clear: an international commitment to global health targets can actually achieve measurable and life-saving results. Three million people are on treatment today despite the fact that many had said it was impossible to treat in resource-poor settings. At this critical juncture, the international community must re-affirm its commitment to providing treatment and care for people living with HIV/AIDS.

Further, international financing must increase to support other important and neglected health priorities. The answer to the global abrogation of responsibility for global health more generally cannot be to redistribute the existing insufficient resources. Stagnation of external aid for HIV/AIDS is not an option.

¹⁸ Peter Mugenyi, director of Uganda's Joint Clinical Research Centre, said: "It is a recipe for chaos as patients start to share doses or skip treatment altogether. I fear that we will soon start to see more drug-resistant strains of HIV and rising death rates."



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