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# First-line antiretroviral therapy: not as simple as we'd like it to be

First-line antiretroviral therapy is now reaching over 3 million people in low and middle-income countries, [according to statistics released](#) by the World Health Organization on June 2<sup>nd</sup>.

Five years ago there were many sceptical voices, including those who said it couldn't be done without state of the art tests and highly trained doctors, both in short supply in sub-Saharan Africa. Others said it would never be affordable.

Five years of experience in the field have proved the sceptics spectacularly wrong. Drug prices have fallen, nurses are now starting patients on treatment and monitoring them in some countries, and in many treatment programmes patients are adhering to drugs even better than their counterparts in wealthy nations. Death rates are also beginning to fall, according to early data from [Malawi](#) and rural South Africa.<sup>1, 2</sup>

But there is still a long way to go. Global coverage is between 27 and 34%, due in part to low rates of HIV diagnosis but also to lack of predictable long-term funding, weak health systems and a chronic shortage of health care workers.

But as well as these problems, countries are faced with two dilemmas about first-line treatment that will determine how quickly they achieve universal access to treatment. One challenge is which drugs to use, the other is when to start treatment. Both were discussed at the 2008 HIV Implementers' Meeting in Kampala, Uganda in early June.

## National guidelines - not keeping up with the neighbours?

A survey of national treatment guidelines in the 15 PEPFAR focus countries presented at the meeting found that half of the countries had not updated their guidelines to take into account new recommendations made by WHO in 2006.

Those recommendations advised a switch away from a 40mg d4T dose in first-line therapy [due to the high rates of toxicity](#) that emerged as d4T-based fixed dose combinations came into wide use in resource-limited settings. High rates of peripheral neuropathy became quickly apparent, along with lactic acidosis. Lipoatrophy (fat loss in the limbs and face) began to emerge in increasing numbers of patients after the first year, just as it had done in Europe, North America and Australia after ART came into use in the mid-1990s.

Countries were [advised](#) either to switch to a reduced dose of d4T (30mg twice daily), to use AZT instead of d4T, or if they could afford it, to use tenofovir, due to its better tolerability, its strong record of viral suppression, and its minimal cross-resistance with other nucleoside analogues.

The survey of guideline concordance, carried out by the US Centers for Disease Control Global AIDS Program, found that five countries still recommend d4T/3TC as the preferred nucleoside analogue backbone, while all those countries that have updated their guidelines since the 2006 WHO revision now recommend AZT (six countries) or tenofovir (three countries).

Tenofovir is less likely to compromise second-line treatment options, since it does not give rise to broad-spectrum resistance to nucleoside analogues, although its resistance profile when patients

experience extended periods of treatment failure is not fully understood.

In contrast, data from South Africa show that when patients are left on failing first-line therapy based on d4T, they develop high level resistance to nucleoside analogues in one-third of cases, and may lose sensitivity to tenofovir too.<sup>3</sup> Similarly, a virology sub-study of the DART study, looking only at patients with virologic rebound after 48 weeks of treatment with AZT, 3TC and tenofovir found that 36% had at least four thymidine analogue mutations, potentially compromising the use of tenofovir or abacavir in second-line therapy.<sup>4</sup> A study of patients failing treatment in Nigeria [presented at this year's HIV Implementers' Meeting](#) showed that 53% of patients of a sample of patients who had been receiving d4T-based treatment through a PEPFAR-funded clinic for around 630 days – and in many cases receiving antiretrovirals previously through the Nigerian government programme – had no active nucleoside analogues available for use in second-line treatment.<sup>5</sup>

The dilemma facing many countries, [as reported last year](#) from the HIV Implementers' Meeting, is the trade-off between using a drug that may be better tolerated (tenofovir) and using drugs that are considerably cheaper (D4T or AZT) in order to be able to offer treatment to more people. For example, Zambia reported that while d4T/3TC/nevirapine costs \$96 a year, tenofovir, emtricitabine (FTC) and nevirapine costs \$343 a year, while using efavirenz instead of nevirapine would push the price up to \$ 430 a year per patient treated – just for drugs.

On the other hand, Dr Ishmael Katjitae from Namibia told this year's HIV Implementers' meeting that *Truvada* (tenofovir and FTC combination tablet) is now actually cheaper than *Combivir*, the branded form of AZT/3TC – but for the time being Namibia continues to use a first-line regimen of AZT/3TC/nevirapine, with efavirenz reserved for patients who also need TB treatment, and tenofovir reserved for patients with hepatitis B coinfection.

## Kidney toxicity

The other factor complicating the use of tenofovir is the risk of renal toxicity, which although a low risk is most likely to occur in people with impaired kidney function.<sup>6</sup> The incidence of renal toxicity in people taking tenofovir in resource-limited settings is still unclear.

A [retrospective analysis](#) of a large cohort from Zambia – 25,249 patients starting antiretroviral therapy at 18 PEPFAR funded sites in Lusaka between May 2004 and September 2007 – found that one-third had some degree of renal insufficiency as measured by Cockcroft-Gault score, mostly mild, and that renal insufficiency at baseline predicted a 40-70% increased risk of death in those with mild renal insufficiency. It should be noted that the elevated risk was not associated with tenofovir treatment; the drug only began to be used in the last two months of the period analysed.<sup>7</sup>

An analysis of creatinine clearance among all 3316 participants in the DART study (underway in Uganda and Zimbabwe) similarly showed that 45% had mild renal insufficiency as measured by estimated glomerular filtration rate, 7% moderate and 0.2% grade 3, or serious, renal insufficiency. During 96 weeks of follow-up, serum creatinine increased over the first 60 weeks (probably reflecting weight gain and improved health). Fifty-two individuals with normal, mild or moderate renal impairment at baseline subsequently developed grade 3 or 4 renal impairment, and there was no significant influence of tenofovir treatment on the development of renal insufficiency across the study as a whole (patients were randomised to receive nevirapine, tenofovir or abacavir with AZT/3TC).<sup>8</sup> Although not statistically significant, the

authors of the study note that all 11 deaths from renal disease during the study occurred in patients who started treatment with tenofovir.

However, the estimated glomerular filtration rate (eGFR), a measure of kidney function, did decrease slightly in those who received tenofovir or abacavir when compared to nevirapine, and this difference persisted to 96 weeks.

The authors of the review of renal dysfunction in the DART study concluded that "patients with grade 3 or 4 impairment should begin treatment with other antiretrovirals, whereas our data suggest that those with mild or moderate impairment may do well with a regimen of tenofovir DF, at least over the short to medium term. If monitoring is being performed, then eGFR should be used to adjust the dose of tenofovir DF or to indicate drug substitution."

In Zambia creatinine monitoring is being carried out in all patients, and anyone with renal insufficiency is not eligible for tenofovir treatment. In Zambia, investment in laboratory equipment and sample courier services enables any clinic to have rapid access to serum creatinine measurements, but this may not be practical in all places. Then again, countries that can afford to use tenofovir in the first place are also likely to be those most able to make the investments in laboratory and health system capacity needed to use the drug safely.

There are still some unanswered questions about renal screening in resource-limited settings, such as whether to use actual or ideal weight when calculating creatinine clearance. Using a patient's body weight at the time they present for treatment may give a misleading picture of their kidney capacity, since severe weight loss can lead to a decline in creatinine clearance that is reversible when body mass returns after antiretroviral therapy proves successful. Using actual body weight at baseline may exclude from treatment those who could benefit from tenofovir – but how safe is it to treat people with transient renal insufficiency?

It's also unclear whether serial measurements are necessary once treatment has started; this is standard practice in wealthy nations, but how much value does the additional information provide, and if longitudinal measures are needed, how frequently is it necessary to assess creatinine clearance in patients taking tenofovir in resource-limited settings?

"I think we're going to have to think hard about what we do about renal disease in Africa as we go forward," commented Dr Francois Venter, president of the Southern African HIV Clinicians Society, during the closing session of the 2008 HIV Implementers' meeting.

### Switching to tenofovir – not as easy as it looks

But even if countries decide to switch to tenofovir, or raise the threshold for starting treatment, the process can be complicated and drawn-out. Zambia, for example, made the decision at Ministry of Health level to start using tenofovir in June 2006, but the first patients didn't begin to receive the drug until July 2007.

Before patients could receive tenofovir new national guidelines and clinic protocols had to be drawn up. For example, it was not standard practice to record the weight of patients coming in for antiretroviral therapy, but this information is essential in order to calculate creatinine clearance. Health systems capacity had to be reviewed: were laboratories equipped to do serum creatinine measurements for the huge numbers of patients starting treatment each month, and would those labs be accessible to all treatment sites? (Zambia had to purchase biochemistry analysers for 160 sites to meet this need.)

Where would the *Truvada* tablets be purchased, how would they be distributed, and were logistics systems good enough to predict demand and stock usage so as to avoid drug stock-outs? Partners and donors had to be briefed on the changes, and providers had to be trained. Finally a system for monitoring and evaluation had to be set in place to monitor patient responses – particularly adverse events – and to spot problems in the transition, particularly with stock management.

As it happens, stock management proved a particular challenge as patients flowed into clinics to ask for the new and better tolerated drug. Almost double the expected amount of *Truvada* had been dispensed by March 2008 due to patients stable on a 30mg d4T dose being switched to tenofovir, Albert Mwango, Zambia's national ART coordinator, told the HIV Implementers' Meeting.<sup>9</sup> (A similar upsurge in demand for tenofovir occurred in South Africa after a character in a popular soap opera switched to the drug without experiencing any side-effects.)

The process of changing protocols was an opportunity to spring-clean the national treatment guidelines, he said. The new Zambian guidelines can be downloaded at [www.zambiahivguide.org](http://www.zambiahivguide.org)

The Zambian example may partly explain why some countries have not revised their guidelines – changes can have big implications for over-stretched health systems.

### Tenofovir and hepatitis B

One issue often overlooked in the discussion about first-line treatment is the extent to which hepatitis B coinfection complicates treatment. Although hepatitis B is perceived in the wealthier parts of the world as a coinfection confined to injecting drug users and gay men, cross-sectional studies from several African countries show a substantial prevalence of hepatitis B coinfection in HIV-positive people.<sup>10, 11</sup>

Reporting on occult hepatitis B in a large urban clinic population in Johannesburg, Cynthia Firnhaber told the HIV Implementers' Meeting that out of a volunteer sample of 502 antiretroviral-naïve patients attending the Themba Lethu clinic at Helen Joseph Hospital, 4.8% were hepatitis B surface antigen-positive, while 10.6% were positive for hepatitis B core antibody alone. That is a substantial number, but further investigation using hepatitis B DNA testing in 43 of the 53 core antibody-positive samples showed that 91% had detectable hepatitis B DNA (sensitivity limit 50 copies/ml). In one case a patient who was surface antigen-negative had a hepatitis B DNA load of more than 1 million copies/ml. Thus, in total, 13% of patients in the cohort had evidence of hepatitis B coinfection.<sup>12</sup>

Given this level of coinfection and the lack of capacity to diagnose occult HBV infection due to the absence of HBV DNA testing in many settings, first-line treatment for all with tenofovir and 3TC or FTC may be preferable, suggested Cynthia Firnhaber.

Although HBV replication can be controlled with 3TC, resistance is quick to develop. This is problematic given that first-line regimens in resource-limited settings are dependent on 3TC; antiretroviral therapy may control HIV but could make hepatitis B more difficult to treat in the long-term if the regimen does not contain a drug that is both active against hepatitis B and less prone to resistance than 3TC. Tenofovir has shown a sustained effect in controlling HBV replication in people with HIV and hepatitis B coinfection [in several small studies](#), reducing the long-term risk of liver cancer.

## Efavirenz or nevirapine?

There's no doubt that without nevirapine, the scale-up of antiretroviral therapy would not have been so successful. The drug is cheap, easy to coformulate with other antiretrovirals and relatively well tolerated.

Its main drawbacks are a potential interaction with rifampicin that makes TB treatment alongside nevirapine-containing ART a problem, and an increased risk of severe hepatotoxicity in women with CD4 counts above 250 cells/mm<sup>3</sup> and men with CD4 counts above 400 cells/mm<sup>3</sup>.

Efavirenz was initially viewed as an alternative to nevirapine, its use to be confined to patients who could not tolerate nevirapine or who needed to take rifampicin too. Its greater cost made widespread use unaffordable in most settings. But as time has gone on, the perception has arisen that efavirenz is more potent than nevirapine, driven in large part by guidelines in Europe and North America where it is now the preferred NNRTI due to a widespread consensus that it is more potent than nevirapine. Although the 2NN study showed similar efficacy, the upper bound of the confidence interval overlapped the protocol-defined confidence limits, leading some to conclude that the study showed a hint of nevirapine's inferiority.<sup>13</sup>

Efavirenz is also attractive because it is becoming available in coformulations with *Truvada* (as *Atripla*) or with tenofovir and 3TC – the first one pill, once a day antiretroviral drug combination.

But efavirenz also has its drawback: it is not recommended for use in the first trimester of pregnancy due to the suspicion that it may cause birth defects. Proving whether or not the drug is a cause of birth defects is impossible without long-term surveillance, so a blanket prescription of efavirenz is a problem in settings where more than 60% of patients may be women of child-bearing age, the majority of whom do not have access to contraception, or who want to conceive.

## Raising the threshold for starting treatment

The other issue challenging national treatment programmes is the question of when to start treatment. Guidelines in [Europe](#) and [North America](#) have recently moved to a recommendation that treatment should start when the CD4 count falls below 350 cells/mm<sup>3</sup> in the light of accumulating evidence that an earlier start reduces the risk of death from non-AIDS defining illnesses (see, for example, [recently published data](#) from the SMART study).

In South Africa the Southern African HIV Clinicians' Society [has also recommended](#) that treatment should begin at a CD4 count of 350 cells/mm<sup>3</sup>, and is petitioning ministers to change guidelines for the public health system. Patients who receive treatment in the private sector are likely to see a more immediate benefit from the guidelines change.

In the developing world [the World Health Organization recommends](#) treatment for anyone with stage 4 disease, and anyone with stage 3 HIV disease and a CD4 cell count below 350 cells/mm<sup>3</sup>. Treatment should also be considered for any patient with stage 1 or 2 HIV disease when the CD4 cell count is below 350 cells/mm<sup>3</sup>. Yet the reality, according to the CDC-GAP survey of PEPFAR focus countries, is that few are able to put that into practice yet: only two currently initiate treatment in patients with WHO stage I or II disease when the CD4 cell count is below 350 cells/mm<sup>3</sup>.

James Shepherd of CDC-Botswana described the dilemma facing Botswana on the question of when to start treatment.<sup>14</sup> Botswana

has raised the treatment threshold from 200 cells/mm<sup>3</sup> to 250 cells/mm<sup>3</sup>. Even the current revision will result in 20,000 people suddenly eligible for treatment in a country of 1.7 million. "That's a huge bolus of humanity suddenly entering a system that's still in chronic emergency mode," said Dr Shepherd. There are still long waiting times for the first ART prescription in the existing system, and there will have to be widespread referral of stable patients out of the more technically advanced facilities in order to accommodate the new patients.

Had the threshold been raised to 350 cells/mm<sup>3</sup>, a total of 50,000 people would have been eligible. The human resource implications of initiating this number of patients on ART in a health system with a chronic shortage of qualified staff may have acted as a disincentive to raising the threshold, Dr Shepherd believes.

However Botswana has particular constraints that may not apply to all countries in sub-Saharan Africa. Antiretroviral therapy must be prescribed through a limited number of accredited clinics, unlike countries like Malawi, where prescribing is being devolved to primary health clinics with the supervision of visiting physicians.

In Namibia the raising of the threshold to 350 cells/mm<sup>3</sup> is being considered, said Dr Ishmael Katjitae, but three factors need to be addressed: the cost, the risk that asymptomatic patients will be less motivated to adhere well to treatment, and the infrastructure and extra personnel needed to accommodate the extra patients on treatment.

## Treatment need underestimated

In addition, countries will need to think very carefully about the resource implications of a move to earlier treatment, since current estimates of the numbers of symptomatic people with HIV – those in WHO stages 3 and 4 and therefore already eligible under most national guidelines – may need to be raised as a result of recent refinements of HIV prevalence estimates.

Previous estimates of the numbers requiring treatment were based on a life expectancy estimate of two years after becoming eligible for antiretroviral treatment. The UNAIDS Reference Group on Estimates, Modelling and Projections recommended that this period should be increased to three years, and that the time from seroconversion to death in the absence of antiretroviral therapy should be revised from 9 years to 11 years, and that the time from seroconversion to antiretroviral therapy eligibility should be revised from 7 years to 8 years.

Prof. Charlie Gilks told the HIV Implementers' Meeting that the numbers eligible for treatment according to current guidelines are likely to be 30% higher than previously estimated despite the declines in HIV prevalence estimates for some African countries that were also a result of the epidemiology review, and an increase in the threshold for starting treatment to 350 cells would see the numbers in need of treatment grow by 50%. Countries currently showing strong progress in achieving high treatment coverage could post less encouraging results in the future.

"You will see your coverage dropping by 50% [if the threshold for treatment is raised to 350]. This will be catastrophically undermining unless you prepare your president, your minister of health, your press," he told the meeting.

The World Health Organization is currently engaged in revision of its treatment guidelines, and part of that process will be scenario modelling of the costs of different national approaches, using varying thresholds for treatment and first-line drug regimens.



He said that more information on the quantifiable advantages of treatment at 350 cells/ mm<sup>3</sup> would be needed in order to persuade policy makers of the need for change at national level.

A modelling exercise comparing the effects of starting treatment at a CD4 count of 350 or at the current thresholds laid out in South African guidelines, using a d4T-based regimen, found that treatment costs would be increased by \$13 billion over five years, but that indirect costs (GDP lost due to early loss of life) would fall by \$61 billion, and that earlier treatment was highly cost-effective for the South African economy.<sup>15</sup>

A [mathematical modelling exercise](#) by researchers at Imperial College, London, suggests that CD4 cell monitoring and initiation of treatment at a threshold of 350 cells, together with a much greater frequency of HIV diagnosis, would have the most substantial impact on mortality in sub-Saharan Africa. However the study also found that earlier treatment would have significantly less impact on mortality if it was not accompanied by a much higher rate of HIV diagnosis.

Speaking during the rapporteur session at the close of the HIV Implementers' Meeting, Dr Francois Venter suggested that the short-term effect of changing the threshold would benefit only a limited number of patients at first.

"Starting CD4 cell counts are usually very, very low, so in fact, increasing the threshold is unlikely to make a huge impact in terms of the number of people or what CD4 cell count they actually are initiated at," he told the conference.

Offering treatment to those already in care but not yet eligible for treatment may be the best way to retain those people in treatment, and a number of speakers at this year's HIV Implementers' Meeting expressed concern about the ongoing difficulties that treatment programmes face in retaining untreated people in care.

"The hidden part of loss to follow-up is the people who are eligible for all other care but antiretroviral therapy," said Diane Noble of the Clinton Foundation. Loss to follow-up in this patient group is not as well quantified as in those who have started treatment, and those lost to follow-up are not flagged as in need of investigation in the same way as those already on treatment.

## Prevention advantage to earlier treatment

One benefit of earlier treatment might be the reduction in new infections as a result of larger numbers of people with HIV having suppressed viral load. Analysis of HIV incidence in the Ugandan Home Based AIDS Care (HBAC cohort), [presented by Rebecca Bunnell of CDC-Kenya](#) at the Fifteenth Conference on Retroviruses and Opportunistic Infections in February showed an estimated 90% reduction in new infections over three years when compared with a historical control, attributable to antiretroviral therapy and, crucially, systematic attempts to identify serodiscordant partnerships and counsel about the need for safer sex.

It's also worth noting that the median baseline viral load in the HBAC study population was high – 226,000 copies/ml across the population as a whole. The higher the baseline viral load in the untreated population, and the more of those people who are in HIV-discordant relationships - especially concurrent partnerships - the greater the prevention benefit of antiretroviral treatment is likely to be.

Conversely, the greater the increase in unprotected sex in the population as a whole after ART is introduced, the smaller the benefit is likely to be.

The population-level benefit of antiretroviral therapy as a means of reducing new infections when given in asymptomatic HIV disease

is still unknown, although a large modelling study, using data from British Columbia, suggests a substantial reduction in HIV incidence as a consequence of using a treatment threshold of 350.<sup>16</sup> A large randomised study ([HPTN 052](#)) in Brazil, Malawi, Zimbabwe, Thailand and India, is evaluating the effect on HIV incidence of starting treatment at a CD4 count between 350 and 550 compared with treatment initiation at a CD4 count of 200 or AIDS. HPTN 052 is not expected to report until 2013.

## CD4 cell monitoring

The other big barrier to earlier treatment is the lack of CD4 cell counting machines. It's relatively easy to use clinical guidelines to initiate antiretroviral therapy – you just need to train staff to recognise the symptoms of stage 3 or 4 HIV disease – but the use of CD4 cell counts in asymptomatic patients requires laboratories equipped to carry out the test, laboratory staff trained to carry out CD4 cell counts, systems for getting blood to laboratories in a state that will enable CD4 cells to be identified, and systems for getting results back to treatment centres in a timely manner.

In its 2006 revision of antiretroviral treatment guidelines the World Health Organization urged national treatment programmes to invest in the capacity to monitor CD4 counts.

Nevertheless, "for the majority of people starting treatment, we believe clinical staging rather than CD4 counts remains the threshold for starting treatment," said Prof. Charlie Gilks.

Even where CD4 counts are available, delays in getting results back to treatment centres are likely to result in delays in initiating treatment. When Brazil first started its antiretroviral treatment programme in the mid-1990s, viral load tests and CD4 counts were carried out at regional centres, and it took up to four months for results to be returned to clinicians, Prof. Gilks noted. Testing has subsequently been decentralised, but the scale-up of laboratory capacity in a country treating nearly 200,000 patients has taken time and huge resources.

Efforts to make it easier to carry out a CD4 count are underway. The Bill and Melinda Gates Foundation is supporting a research programme, coordinated by the CD4 Initiative at Imperial College, London, that aims to develop a point-of-care CD4 cell test. The CD4 Initiative aims to have one test ready for use in the field by 2010, assuming that field studies due to start in 2009 validate at least one of the assays currently in development.

Point of care assays are likely to be relatively insensitive, perhaps showing only whether a patient is above or below the level at which treatment is recommended. The first generation will probably prove less useful in measuring accurately the degree of change in CD4 cell counts on treatment; for example, the assays may not be able to consistently distinguish between a 10% or 50% decline in CD4 cell count in someone on treatment.

Groups are also working on low cost solutions for results delivery, even where testing continues to be carried out at centralised laboratories, such as using cell phone technology to SMS test results to nurses at remote clinics.

## Drug costs

The other big barrier to earlier treatment, of course, is cost.

"Even minor differences in cost become accentuated when you scale up," said Elliot Raizes of the CDC Global AIDS Program.

National treatment programmes will need to become increasingly alert to variations and trends in drug prices, but need more timely information in order to do so.

The Global Price Reporting Mechanism for antiretroviral drugs, which compiles data on the prices paid for drugs by Global Fund grant recipients, PEPFAR programmes and others, shows wide variations in the prices paid for products by different countries. This is not driven by patenting, according to Brenda Waining of Boston University, but by inadequate information about the prices that are being paid by other purchasers, and by the fact that people who pay their bills on time get better prices.

Further research from the Boston University team, commissioned by the United Kingdom's Department for International Development, indicates that if procurement efficiency was increased at current prices, so that all countries were paying prices in the lower end of the spectrum currently paid (below the 25th percentile), \$186 million could be saved in the first year, enough to treat 472,000 extra patients with a first-line regimen of tenofovir, 3TC and efavirenz – or 1.96 million with a first-line regimen of d4T/3TC/nevirapine.<sup>17</sup> Even ensuring that everyone currently paying above the global median price pays no more than the median would save \$106 million a year.

In comparison, further reducing the price of efavirenz – to \$120 a year – would save just \$14 million a year.

But declines in drug prices will also be limited by technical constraints.

The potential for a very substantial decline in the price of tenofovir, so that it costs the same as AZT, or even d4T, is limited by the fact that the drug is a more complex molecule, and requires more production steps and a larger volume of raw materials than d4T.

## Equity

The drive towards earlier treatment with more expensive drugs that may require greater monitoring capacity raises issues of equity, Prof. Gilks told the HIV Implementers' meeting. "We may end up benefiting only those people who can access the clinics where this is more widely available and fall into that typical development trap that all the development benefit is concentrated in few numbers of families and communities that have far better access to services," he said.

The fear of creating islands of excellence in a sea of deprivation has not held back treatment scale-up so far – after all, one has to start somewhere.

But there are worrying signs that the flow of resources to combat the AIDS epidemic is not going to keep growing at the pace set by the past five years, especially if the global economy faces lean years due to rising commodity prices and inflation. Debates about national priorities for treatment will only become more complicated as time goes on and the numbers requiring treatment grow.

Nevertheless, as the experience in Zambia and South Africa shows, awareness of improvements in the standard of care is quick to spread, and if the history of treatment scale-up teaches us one thing, it is that awareness of treatment and its potential stimulates demand. How long will national governments and donors be able to dig in their heels against demands for the same standard of care as that available in wealthy nations?

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