STAYING THE COURSE

Some feared that widespread use of AIDS treatments in Africa would encourage drug resistance, with globally disastrous consequences. But there's no crisis yet, reports **Erika Check**.

The argument was simple, even brutal: there was no point giving anti-AIDS drugs to patients in Africa, because they wouldn't be able to stick with their treatment plans. Worse, the resulting rise of resistant strains of HIV could jeopardize lives elsewhere.

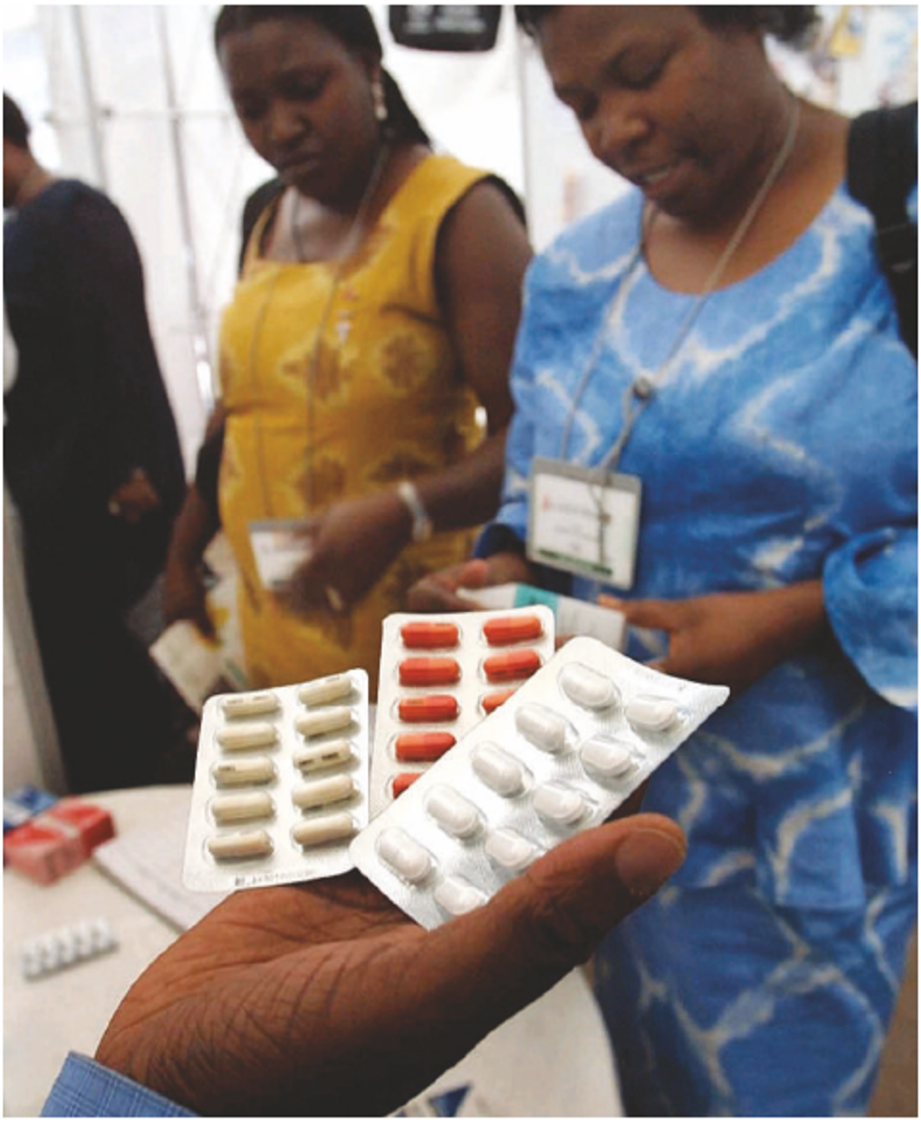
This counsel of despair was first expressed five years ago, after some 17 million people in sub-Saharan Africa had already died of AIDS. It emerged while researchers and politicians debated whether to roll out antiretroviral medications to the millions who needed them in developing countries. Aid agencies and governments found the argument unconvincing, even distasteful, and pressed on. As a result, the epidemic has now reached an important turning point. For the first time, more people are taking anti-AIDS medications in poor countries than in rich ones. They number more than a million — three times the number at the end of 2001 (ref. 1). So, is a crisis looming?

Not so as you'd notice. Despite some important exceptions, there is strong evidence that patients in the poorest countries are just as conscientious about taking their medications as those in the West, and widespread resistance has not yet emerged. But scientists warn that the next step — expanding drug programmes to reach a greater proportion of those who need treatment — will be much more challenging than anything faced so far.

Getting patients to comply with their drug regimens has always been a major issue in the treatment of AIDS. The medications work by blocking HIV during various parts of its life cycle in human cells. But the virus has a notoriously error-prone process of replicating itself, so it can easily mutate to become resistant to treatment. Taking combinations of medicines suppresses the virus and cuts the chances of new, treatment-resistant mutations. But if a patient doesn't take all of his or her drugs on a tight schedule, resistant strains can emerge, and be passed on to other people.

This is already a serious and growing problem in the developed world. A 2005 UK study showed, for example, that, depending on the drug, up to 20% of new patients were infected with strains that were already resistant[2]. Problems with adherence were a factor, but such strains mostly arose in patients taking drugs that were less effective than the combination therapies that later became available.

Back in 2001, Africa was seen as a worst-case scenario when it came to adherence to combination therapies. Even if drugs could be made affordable, poor nations wouldn't necessarily be able to coordinate effective mechanisms to deliver them. Most patients didn't have access to regular medical services. And it was unclear whether they would trust Western medicine enough to stick with a long-term course of medicine with toxic side effects.



S. MAINA/AFP/GETTY

These antiretroviral drugs prolong the lives of people with AIDS. But not all can gain access to them.

Some had more controversial concerns. There were warnings that the very existence of drug programmes in Africa could breed complacency and encourage risky behaviour such as unprotected sex, thus increasing the spread of any resistant strains that arose (see 'Do drugs lead to risky behaviour?'). And most famously, Andrew Natsios, then the director of the US Agency for International Development, argued against giving antiretroviral drugs to patients in Africa, because these patients "don't know what Western time is" and so would be incapable of staying on their treatment plans. Ask patients to stick to a complex regime, Natsios argued, and they "do not know what you are talking about".

Such criticisms might sound prejudiced, if not downright racist, but those advocating them pointed out that if drug programmes in Africa failed, the whole world could come to regret it. "If treatments are not adhered to consistently and correctly, there could be disastrous consequences both for individuals on antiretroviral therapy, and for the HIV epidemic as a whole," wrote social scientists Danielle Popp and Jeffrey Fisher of the University of Connecticut, Storrs, in a 2002 article[3]. "Developing countries could become a veritable 'petri dish' for new treatment-resistant strains," they warned. Such

strains could spread around the globe, rendering antiretroviral drugs useless elsewhere.

Researchers involved in rolling out treatments at the time say they were acutely aware of the dangers. "We were all going into this with our eyes open to resistance issues," says Marc Wainberg, who will co-chair the XVI International AIDS Conference, to be held in Toronto over 13–18 August. Some suggested modelling HIV programmes on principles similar to the directly observed therapy (DOTS) strategy for tuberculosis, in which patients take their medication under the eye of an observer[4]. But this isn't so practical for HIV, because patients have to take drugs every day for the rest of their lives. So researchers who set up some of the earliest sites for antiretroviral treatment in sub-Saharan Africa designed other measures to help patients stay straight.

For example, in 2002, the Botswanan government became the first in Africa to promise AIDS treatment to everyone who needed it. The programme built on a pilot project supported by the government and international funders, including drug companies, universities and the Bill & Melinda Gates Foundation. Patients were asked to nominate a family member or friend as an 'adherence assistant', to help them monitor side effects and stick to their treatment courses.

It seemed to work. Scientists found that nearly 80% of the first 153 patients treated on the programme knocked the virus down to undetectable levels after 48 weeks on drugs — a good sign that they had stuck to their medication[5].

Richard Marlink, director of care and treatment at the Elizabeth Glaser Pediatric AIDS Foundation in Santa Monica, California, and one of the scientists behind the project, sees such results as a stinging rebuttal of those who doubted Africans' ability to stick to complex schedules. "All the indications from studies we've done or anecdotally show that you can obtain levels of adherence you'd attain anywhere else in the world," he says. "And there are some indications that they are better."

Other studies support the idea that patients in even the most challenging environments can manage AIDS treatment regimens. In South Africa, the non-profit group Médecins Sans Frontières has been working since 1999 with local government to deliver HIV drugs to the residents of the Khayelitsha township. In 2004, doctors with the programme reported that of the first 287 patients treated, 70% had undetectable levels of virus after two years of treatment[6]. The results echoed earlier findings from a widely publicized study performed in Cape Town, which found that 66% of patients still on medication after 48 weeks had undetectable virus loads[7]. Other studies have found good, although not exceptional, results in places such as Senegal and Uganda[8,9].

One forthcoming analysis even suggests that, so far, African patients have a better combined record than those in rich nations. Edward Mills and an international group of investigators compared the results of studies on populations in Africa and North America. They were surprised to find that whereas the studies on North Americans reported that 55% of the populations covered stuck to their treatment regimens, 77% of the populations in African studies did so[10]. "The common expectation was that poverty was a risk factor for incomplete adherence," says David Bangsberg, director of the Epidemiology and Prevention Interventions Center at San Francisco General Hospital and senior author on the study. "That's wrong, in retrospect."

> "Poverty was expected to be a risk factor. That was wrong."
> — David Bangsberg

Bangsberg says his team's analysis suggests that other factors may be more important than poverty — such as lack of social support, addiction to drugs or alcohol, bad relationships with the healthcare system and homelessness, which in Western settings have all been shown to make people more likely to stop taking their drugs. "It isn't poverty that's a risk factor for adherence," says Bangsberg. "It's some of the things that go with poverty in North America and western Europe that aren't necessarily part of poverty in southern and western Africa."

Tactics: promoting AIDS awareness is as much a part of the battle as providing the right drugs.

Others aren't sure things are quite so rosy. Last year, Christopher Gill and his colleagues at the Boston University School of Public Health, Massachusetts, released a study in which they surveyed conference abstracts for unpublished reports on adherence in Africa. One abstract reported that only 48% of patients in a Côte d'Ivoire study stuck to their treatments, and although another found 68% adherence in a population in Cameroon, that rate declined over time[11].

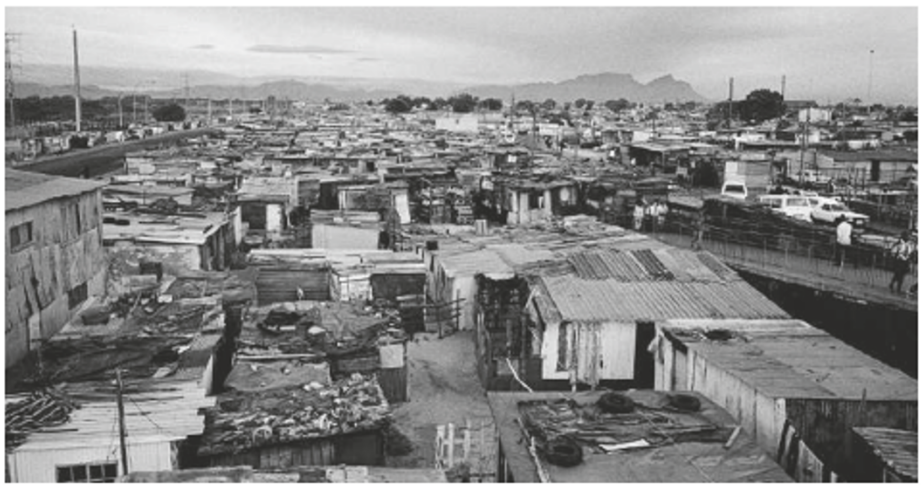
Bad bias

Overall, the authors found that adherence rates were much more variable than those published in the literature, which has led them to ask whether bad news just isn't getting reported. "This would seem to be a classic example of publication bias," says Gill. "People are blowing their horns when things are great, and keeping quiet when things aren't."

Bangsberg, however, argues that the low adherence rates in these unpublished studies often weren't the fault of the patients. He contends that adherence rates in one Senegalese study were poor because patients had to buy their own drugs. So if they ran out of money, they couldn't stick to the regimen. And he says that in the Cameroonian study, the drug supply was interrupted by factors beyond the patients' control[12]. To Bangsberg, these results don't show that patients can't stick to their drugs, but demonstrate the pressing need to strengthen drug-distribution networks.

Indeed, scientists say that fixing such structural problems will be key to keeping adherence rates high, as drug programmes now

P. BONET/PANOS



Model town: residents of Khayelitsha, in South Africa, are successfully keeping to their drug regimes.

S. AZEEM/AP

move beyond pilot projects into the wider population.

Despite progress so far, the majority of patients in sub-Saharan Africa who need antiretroviral drugs still aren't getting them. Botswana is perhaps furthest ahead, but according to conservative estimates, only about half the patients who need treatment there are on it. The rest of the region lags far behind; from South Africa, where about one-third of patients who need drugs are on them, to Zimbabwe, where just 5–10% of those who need treatment can get it. "Sadly, with all the effort and money being put into treatment access, there is still a holocaust going on," says David Katzenstein, drug-resistance specialist at Stanford University, California. He estimates that, globally, 5–10% of the people who will die from AIDS during the next year are actually being treated.

Expanding programmes to reach more people looks likely to be much tougher than anything faced so far. Patients in clinical trials receive many incentives to stay on their treatments, and are carefully followed by specialist teams. But as treatment programmes make the transition from pilot sites to general public-health programmes, not everyone will get such close attention. And the patients who started treatment in the first roll-out programmes may start experiencing problems as the long-term toxicity of some of the drugs kick in. "It's still early days in the roll-out," says Dan Kuritzkes, director of AIDS research at the Brigham and Women's Hospital in Boston. "I'm sure we'll enter a phase two, which is going to be more challenging than the early phase."

A grand plan

Because of this, scientists say it's important to make plans now to monitor the emergence of large-scale drug resistance. In rich nations, doctors are recommended to genotype individual patients' viruses before beginning therapy, to check whether they are resistant to any particular drugs. But such tests cost hundreds of dollars, and it's not feasible to deploy them for every patient starting therapy in sub-Saharan Africa. So a World Health Organization effort called the Global HIV Drug Resistance Surveillance Network has set recommendations for measures countries should take as they scale up treatment — including tracking an easily accessible group of newly infected patients, such as young women pregnant for the first time, and a cohort of patients who stop responding to drugs.

If patients do fail first-line therapy, there's little that can be done, because second-line treatments are still too expensive to be widely available in Africa. So as well as trying to increase access to those second-line drugs, the main concern is keeping everyone adherent. But support costs money, and poor countries will have to make trade-offs, Gill warns. "Do you want to have a good programme for fewer people, or a mediocre programme for a lot of people?" he asks. "Someone has to make that decision."

To stand any chance of success there must be full commitment to providing a robust drug supply and to supporting patients, say scientists, and that means moving on from the idea that Africans aren't capable of taking their drugs properly. "The hard work ahead of us is to go beyond pilot projects, to taking the health of Africa seriously," says Marlink. "It's time to put these concerns about adherence to bed." ■

Erika Check covers the biomedical sciences for *Nature*.

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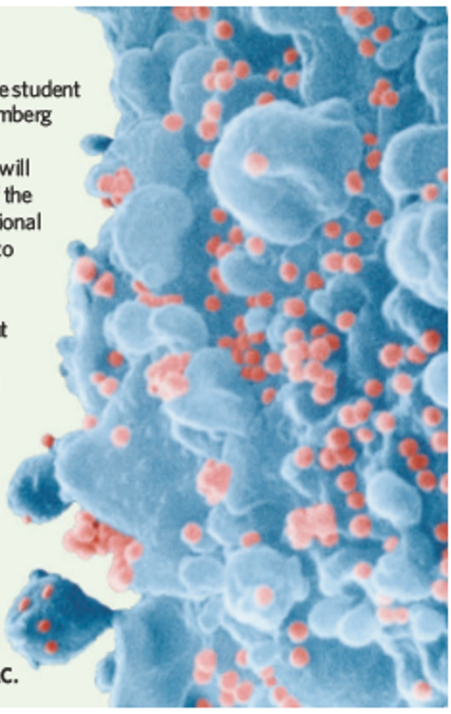
Do drugs lead to risky behaviour?

Thanks to antiretroviral therapy, AIDS is no longer an immediate death sentence in rich nations. That's heartening progress, but there is a downside. Social scientists believe it has also contributed to the phenomenon of 'disinhibition' — increasing rates of high-risk behaviour, for example the rise in unprotected sex that has been observed in some communities of gay men[13].

Before drug therapy was rolled out in Africa, some were concerned that it might cause an increase in risky behaviour there, too. For example, Frank Plummer, director-general of the Centre for Infectious Disease Prevention and Control in Canada, cited evidence that condom use among prostitutes in Nairobi went down when quack cures for AIDS were reported[14].

But so far, the evidence says that access to drugs isn't increasing risky sex — and it may actually help people to be safer. A 2003 study of 711 people with HIV (pictured) in Côte d'Ivoire found that patients not treated with antiretrovirals were more likely to report risky sexual behaviours than those who received treatment[15]. In another study, Ugandans who were treated with antiretroviral drugs were more likely to tell their partners about their HIV-positive status, use condoms with those partners, and seek treatment for other sexually transmitted infections[16]. And when antiretrovirals were provided along with counselling, in a separate study, the rate of risky behaviour in the group dropped by 70% (ref. 17).

"These studies all show the same trend, and it's encouraging," says Caitlin Kennedy, a graduate student at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, who will present a meta-analysis of the studies at the XVI International AIDS Conference in Toronto next week. But the studies done so far aren't highly rigorous, and the treatment programmes are still new. Researchers say it is much too early to draw any firm conclusions. They point out that disinhibition is unlikely to occur in Africa unless treatment becomes so widely available that most HIV-positive people no longer die from AIDS — a point that is sadly far from being reached. **E.C.**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