Access to antiretroviral drugs has improved the quality of life of millions of people in South Africa: this woman could not walk before receiving treatment.

BRENT STIRTON/GETTY

A NEW ERA FOR HIV

South Africa *has developed the biggest programme of antiretroviral therapy in the world. Now scientists are exploring the long-term consequences of the drugs.*

BY LINDA NORDLING

Sixteen years ago, a sickly eleven-year-old became the human face of the AIDS epidemic that was sweeping South Africa. Standing up to speak in front of thousands at the International AIDS Conference in Durban, the diminutive Nkosi Johnson pleaded with the South African government to start giving the drug azidothymidine (AZT) to pregnant women with HIV so that they would not transmit the virus to their babies. "Don't be afraid of us — we are all the same," he told the tearful audience. Johnson, himself HIV-positive from birth, lent a moment of high emotion to a tense week that had been dominated by clashes between scientists, activists and AIDS denialists. The president of South Africa, Thabo Mbeki, had sparked international condemnation when he opened the meeting with a speech that failed to acknowledge HIV as the cause of AIDS.

That week in Durban was a watershed moment for the global AIDS response. As the first international AIDS conference ever held in a developing country, the meeting turned the spotlight on the epidemic in Africa, where the disease was raging worse than anywhere else. In developed countries, antiretroviral drugs (ARVs) had given hope to those living with HIV, but in poor nations, AIDS was still a death sentence for anyone unable to afford the astronomical cost of the medication: about US$10,000 per person, per year. In the week of the conference alone, an estimated 2,500 South Africans died from AIDS — one-quarter of them children. Johnson died little under a year after giving his speech.

Next week, the International AIDS Conference returns to Durban — but to a radically changed outlook. The government's AIDS denialists have quietened, and international funding has

poured in. Today, around half of the country's 7 million people with HIV are on ARVs — the biggest such programme in the world. Expanded access to the drugs is largely responsible for a leap in South Africa's average life expectancy at birth, from 53.4 years in 2004 to 62.5 in 2015 (see 'HIV in South Africa'). Mother-to-child transmission has fallen from a high of 30% in the early 2000s to just 1.5%. "It's a miraculous achievement that shows the world what can be done," says Steffanie Strathdee, associate dean of Global Health Sciences at the University of California, San Diego, and one of the headline speakers at this month's conference.

But enormous challenges remain. South Africa still has the largest HIV epidemic in the world, and the rate of new infections remains depressingly high, especially among young women. At the epidemic's epicentre, the province of KwaZulu-Natal, a 15-year-old girl in some communities has an 80% risk of getting HIV in her lifetime. Epidemiologists struggle to fully understand the situation here for the simple reason that those infected are difficult to track. The massive ARV programme is putting immense pressure on the stretched public-health system — and yet the country has just signed up to a major expansion that could double the number of people taking the drugs.

For doctors and medical researchers, the age of ARVs has thrown up new puzzles. They are just beginning to understand how long-term exposure to the drugs and to HIV itself could affect health. Some are exploring what happens to people who reach middle or old age after decades on the treatments. Others are trying to work out whether children who are exposed to HIV and ARVs in the womb might face health problems even if they do not contract the virus.

These results could prove important for the rest of the world, where ARVs could soon be rolled out on an unprecedented scale. The global AIDS-strategy body, UNAIDS, has set a target known as 90-90-90: by 2020, 90% of people living with HIV should know their status; 90% of those diagnosed should be on ARVs; and 90% of those on ARVs should have undetectable levels of the virus. South Africa has been a testing ground — to see whether ARV programmes can be ramped up in developing countries, and to see what happens to the population when they are. "South Africa's success in defeating AIDS is key to the global effort to end AIDS," says Salim Abdool Karim, director of the Durban-based Centre for the AIDS Program of Research in South Africa.

LIFE AFTER HIV

The face of HIV in South Africa today is a young woman called Thembisa Mbhobho. A 15-metre-tall mural of her greets motorists as they turn off the N2 highway to enter Cape Town's Khayelitsha township; it bears the slogan 'There is life beyond HIV'. Mbhobho knows all about that, being one of the millions of South Africans taking daily ARVs to keep the virus at bay. "You can live for more than 50 years if you take your medication correctly," she says. Mbhobho volunteered to be on the mural, which was painted by local artists for World AIDS Day last year, with backing from Médecins sans Frontières (MSF, also known as Doctors without Borders).

"I was diagnosed in 2008. I started taking ARVs in 2014," says the 26-year-old, whose first name means 'promise' in her mother tongue, Xhosa. Today, the virus is so well suppressed in her body that it doesn't show up in blood tests, reducing her likelihood of passing it on. She enjoys it when people recognize her from the mural, or from the television advert that she featured in to encourage people to find out their HIV status. "They motivate me, they say I must keep it up." Her five-year-old son is uninfected, thanks to the drugs Mbhobho was given while pregnant and in labour. She hopes that one day he'll be a pilot, or a lawyer.

South Africa's road to widespread ARVs has been bumpy. Its first community treatment programme started in 2001 in Khayelitsha, but because of the HIV-denialist ideas subscribed to by Mbeki and other leading politicians, the programme — along with many others in the early days — was labelled as a 'feasibility study'. Some people in the international medical community doubted that ARVs could be effectively administered in Africa. In 2001, the head of the US Agency for International Development, Andrew Natsios, gained notoriety for saying that treatment would not work there because many people in Africa "have not seen a clock or a watch their entire lives", and so would be unable to take their pills on time.

He was wrong. The early studies showed that adherence and treatment outcomes were, in fact, better in African cohorts than in the United States[1]. In 2004, when South Africa started to offer free access to ARVs through the public-health system, just under 50,000 citizens received treatment. By 2007, the number was more than 380,000, and today it's well over 3 million.

But the programmes have had different outcomes in South Africa than in high-resource settings in Europe and North America. "In Europe, when ARVs came along, the hospital wards emptied of people who were severely ill," says Gilles van Cutsem, medical coordinator for MSF in South Africa. "When we started our HIV programme in Khayelitsha, the waiting room was full of sick people in wheelbarrows. There is less of that now, but people are still coming in very sick." Despite the information campaigns, and free drugs, many people still wait too long to get tested and treated, he says.

Keeping track of the ARV roll-out has been challenging. The data centre of the Southern Africa International Epidemiological Database to Evaluate AIDS at the University of Cape Town has tracked treatment enrolment and retention since the initiative was established in 2006. But even those simple data have been difficult to collect and interpret, says Morna Cornell, a senior researcher and project manager at the centre. Sometimes the same person turns up in several different records — having moved, perhaps, and started going to a different clinic. Many others are enrolled, but are 'lost to follow-up'. For a long time, the centre's HIV-clinic data showed a low number of AIDS deaths and a high loss to follow-up. But when the data were integrated with the country's death register in the late 2000s, it emerged that more than 30% of those reported as lost were actually dead.

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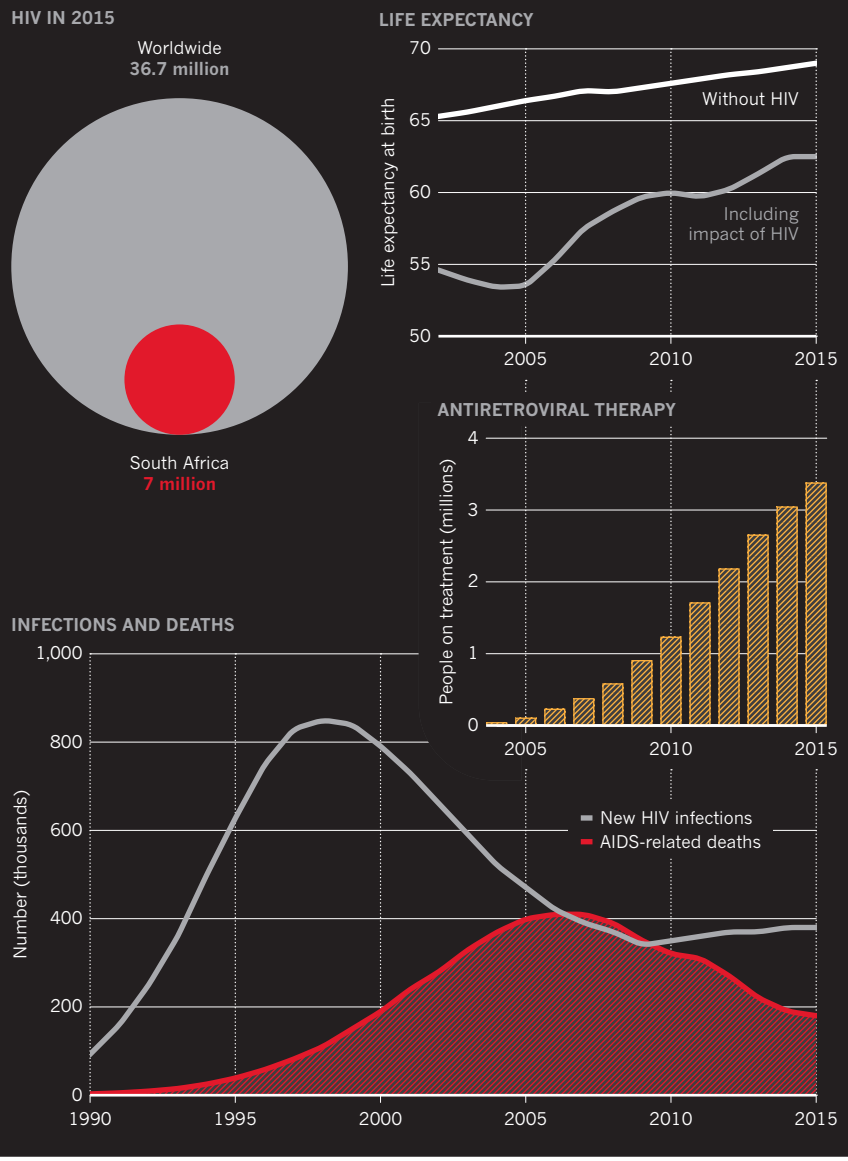
Monitoring should get easier with the planned introduction of unique patient identifiers, says Cornell. She thinks that better data will help South Africa to improve its HIV programmes and assist in future research. Many scientists would like to see much more detailed clinical data collected, so that they can find out what happens when large populations take ARVs in the long term. There is a wealth of research on the health effects of the drugs, but much of it comes from Europe or North America, where patient populations are much smaller, and the medical resources are vastly bigger.

COMPLICATING FACTORS

Drug resistance is a looming issue. In rich countries, resistance testing is routinely done on every person diagnosed with HIV to ensure that they are given drugs that will work. But in South Africa, only a few of the available ARV drugs are provided free through the country's health system, and resistance tends to be poorly managed. "People think drug

HIV IN SOUTH AFRICA

The country has made huge progress in fighting HIV; access to antiretroviral drugs has soared and life expectancy has risen. But South Africa still has the largest HIV epidemic in the world.



SOURCES: UNAIDS AND STATISTICS SOUTH AFRICA

resistance isn't a problem any more. But the place where resistance is going to emerge again is here. You can't throw so much drug out there and not experience it," says Deenan Pillay, a virologist and director of the Wellcome-Trust-funded Africa Centre for Population Health near Durban.

The Africa Centre holds more than 15 years' worth of longitudinal data, gathered from a community of about 100,000 households in the rural district of uMkhanyakhude, about 2 hours' drive north of Durban, in KwaZulu-Natal. Sure enough, the data show that resistance is a burgeoning problem. Between 2010 and 2012, the proportion of new HIV cases that were already drug resistant rose by 7% — and Pillay suspects that it will grow further. "People sit on failing drug combinations without getting help. That's a big risk," he says.

South Africa's ageing population of people on ARVs is another focus of research. The fraction of HIV-infected people who are older than 50 is predicted to triple in the next 30 years[2]. Some studies have found that certain cancers are more common in people taking ARVs, and long-term use of the drugs has been linked to increased risk of hypertension, diabetes and obesity[3] — although it's difficult to establish whether this is caused by the drugs or by HIV itself. To find out, researchers are now looking at the possible effects of ARVs on metabolism. The life-saving benefits of the drugs outweigh these potential risks, but public-health researchers are nevertheless anxious to know what the future holds for a colossal ARV-taking population.

In Europe and the United States, people ageing with HIV tend unsurprisingly to fare worse health-wise than do those who do not have the virus. But there was a surprise in store for Janet Seeley, a social scientist based at the London School of Hygiene and Tropical Medicine, when she and her colleagues took a close look at data for several hundred people over the age of 50 in Uganda and South Africa. They found that people with HIV who were taking ARVs had better quality of life and were more able to perform daily activities than were their HIV-negative peers[4].

"My first thought was 'this must be wrong', but it's logical really," she says. Care for people with HIV isn't always great, but at least they see a health practitioner on a regular basis. In South Africa, older people who received HIV therapy were more likely to be on treatment for other chronic conditions than were people in the comparison group who were HIV-negative.

Researchers are also exploring what happens to children who are born to mothers with the virus but are not infected themselves. Clinicians have found that these 'uninfected exposed' children tend to have worse health — such as lower birth weight and bone density — than do those born to mothers without the virus. But the evidence is conflicting: a systematic review published earlier this year[5] found some studies indicating that uninfected exposed children are at increased risk of death, hospitalization and under-nutrition, and others that saw no such evidence.

Even if the effects are marginal, the fact that around 30% of children born in South Africa fall into this category is cause to take the issue very seriously. Mark Cotton, head of infectious diseases at Tygerberg Children's Hospital in Cape Town, is convinced from what he has observed in the clinic that these children fare worse than others. The challenge lies in working out why. "There are theories that HIV-positive women might be sicker, or poorer, or that there might be more TB in these homes. But we think it could go beyond that," he says.

Clive Gray, an immunologist at the University of Cape Town, is investigating the possible effects of *in utero* HIV and ARV exposure on the developing fetus and on an uninfected child's long-term health. With funding from the Canadian Institutes of Health Research, he and some colleagues are investigating 500 mother–baby pairs — including mothers both with and without the virus — in Nigeria and South Africa. The study is not complete, but Gray and his colleagues have already spotted that HIV-negative children born to infected mothers have impaired immunity in their first year of life.

As to whether HIV or the ARVs are the cause, Gray says, that is

difficult to tease out. And he's not sure it's the most important question to answer. "These children are sick, and whether that is because they are exposed to HIV or to the drug, or to the combination, it doesn't matter from a public-health point of view." Ultimately, the work might point to alternative ways to handle HIV in pregnant women. And, Gray says, the research might also help to explain why women with the virus often go into preterm labour — another confounding factor, because it is known to negatively affect child development.

BREAK THE CYCLE

But perhaps the most pressing question is how South Africa's massive rollout of ARVs will affect infection rates. People who have a suppressed viral load are less likely to transmit the virus to others — a fact that led the World Health Organization (WHO) to recommend last year that all people who test positive for HIV immediately go on ARVs, rather than waiting until their CD4 count — an indicator of disease progression — fell below a certain level. In May, South Africa's health minister, Aaron Motsoaledi, announced that the country would adopt these guidelines from September, a strategy that could double the number who receive ARVs. Motsoaledi also said that his department would supply prophylactic treatment to sex workers, who have a very high risk of contracting HIV.

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Even patchy ARV coverage can slash infection rates. A study by the Africa Centre found that someone living in a community where 30–40% of HIV-infected people are on treatment is 38% less likely to get infected than is someone living in a community where fewer than 10% are on treatment[6].

In practice, however, ARV therapy is unlikely to ramp up quickly. A major difficulty lies in getting people tested in the first place, and another is getting those who test positive to accept treatment — because many of them will not feel sick — and to stay on it.

To reach those people, the country has to rethink its HIV programmes, van Cutsem says. Research by MSF has found that allowing people who manage their HIV well to attend fewer clinics helps to take the strain off the facilities and health workers. He also supports the introduction of self-testing kits. These can already by bought over the counter in South African pharmacies, but are not promoted in the public-health sector. "There was an initial concern in South Africa that it would lead to self-harm or domestic violence. But frankly, there is no evidence saying the risk would be bigger than if you test with a counsellor," van Cutsem says.

There is no shortage of scientists to study the evolving epidemic. Since South Africa hosted the International AIDS Conference in 2000, many world-class research centres have emerged to develop vaccines and therapies that might, one day, supersede ARVs. And later this year, the country will start a large trial of an HIV vaccine candidate that has shown promising results in Thailand[7]. It would be the first major vaccine trial in years and one that, if successful, could make a big difference, especially to women with the highest risk of infection.

For many of the researchers returning to Durban next week, the trip will remind them of how far they've come. "Before ARVs, HIV was the same around the world, in that everybody died who got it," says Carlos del Rio, a global-health researcher at Emory University School of Medicine in Atlanta, Georgia, and one of the keynote speakers in Durban this year. "But after 1996, people stopped dying in the developed world. It was that meeting in Durban that made us believe that the impossible would be possible. Now people live in South Africa with HIV who would otherwise have died."

But the conference also makes del Rio reflect on how far there is to go. A huge number of African people are reaching reproductive age, and encouraging them to understand and manage their HIV risk will be crucial to sustaining the continent's momentum. Some would not have seen the epidemic at its chilling peak, and could become complacent about the need to protect themselves and others. "We run a massive risk that if we fail with that generation, the epidemic could get even worse."

"Are we at the end of AIDS?" says del Rio. "I don't think so. I think we're at the beginning of the end of AIDS. But not keeping up investment, not keeping our eyes on the ball, could be potentially devastating." ■

SYDELLE WILLOW SMITH/MSF

Thembisa Mbhobho, who is HIV-positive, is depicted on a mural near Cape Town's Khayelitsha township.

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