SOUTH AFRICA'S BID TO END AIDS

The tools exist, but the country's epidemic—the largest in the world—won't yield easily

By **Jon Cohen**, *in South Africa*; *Photography by* **James Oatway**

On a Wednesday morning in April, a line of 600 HIV-infected people snakes through the hallways to the first waiting room of the Themba Lethu Clinic, a wing of the Helen Joseph Hospital in Johannesburg, South Africa. In most places in the country, where clinics are overtaxed, this would presage a wait of up to 10 hours. But here something different is happening. Staffers at computer monitors swiftly log in people and dispatch them for triage or, if they have tuberculosis, a special area away from others. Those who only need their antiretroviral (ARV) drugs walk directly to the pharmacists, who retrieve each patient's electronic medical record and use a robotic system to pull drugs from shelves and fill orders. The average wait time is 30 minutes to 2 hours to complete a doctor or nurse visit and 15 minutes at the pharmacy. A prototype ATM promises to further speed visits by directly dispensing ARV pills; one day, it is hoped, similar pill machines in shopping malls could make some clinic visits unnecessary.

"This is an awesomely efficient place,"

Lesego Kgaladi, 20, who lives in Soweto, South Africa, was infected with HIV at birth. At school, she speaks out about stigma and misunderstandings about HIV.

says Ian Sanne, who heads Right to Care, a nongovernmental organization that runs this and several other clinics in collaboration with the health department. In developed countries, where patients complain about much shorter waits, this boast might seem absurd. But in South Africa, the Themba Lethu Clinic is celebrated as an example of what can be done to care for large numbers of HIV-infected people. This is at once a compliment to the clinic and a hint of the country's overwhelming HIV/AIDS challenge.

South Africa has pledged to ramp up efforts to end its massive HIV/AIDS epidemic, the world's largest. Come September, it will offer every infected person ARVs, which both stave off disease and make people less infectious. The immediate goal is to reach what is known as 90-90-90 by 2020: to have 90% of infected people aware of their status, 90% of known positives start ARVs, and 90% of that group drive the amount of virus in their bloodstream down to undetectable levels. The theory is that as viral levels drop, transmission will, too, leading the epidemic to spiral downward. This 90-90-90 target is the cornerstone of a grand campaign, articulated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and widely embraced by world leaders, to end the AIDS epidemic "as a global public health threat" by 2030.

In a nation estimated to have at least 6.6 million HIV-infected people—18% of the world's total—the drive to hit 90-90-90 by 2020 seems overly ambitious to many experts. And the obstacles faced by South Africa provide a sobering reality check to the lofty, laudable aspiration of ending AIDS, a topic that promises to occupy center stage later this month in Durban at the biannual International AIDS Conference.

SOUTH AFRICA has already made enormous gains against its HIV/AIDS epidemic. When it last hosted this international gathering in 2000, then-President Thabo Mbeki and his health minister questioned whether HIV even causes AIDS, triggering widespread outrage (*Science*, 28 April 2000, p. 590). At the time, only the wealthiest South Africans had access to ARVs, which cost about $5000 per person for an annual supply. But by the end of 2015, the price had dropped to $100, and 3.4 million HIV-infected South Africans were receiving ARVs—more than in any other country in the world. South Africa, in fact, consumes the same amount of the life-saving drugs as Asia and the Pacific, North America, and western and central Europe combined.

As a result, life expectancy jumped 9 years between 2005, when ARVs started to become widely available, and 2014. The country has pioneered innovative ways to deliver the drugs and help people stay on them. And South Africa's strong cadre of HIV/AIDS investigators has made the country a hub of cutting-edge basic research and clinical trials. "Given our resources, we've done amazing things," says Glenda Gray, an HIV/AIDS researcher who heads South Africa's Medical Research Council in Cape Town.

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Yet almost half the infected population today is still untreated. Some have not suffered enough immune damage from the virus to merit ARVs under current government policy. Many other infected people don't know their status or never seek care, and still others who start treatment have difficulty taking their daily pills for years on end. Estimates suggest that because of failures in this "care continuum," only about one in four HIV-infected South Africans has fully suppressed the virus. "We have to ride two horses at the same time," says Fareed Abdullah, who heads the quasi-governmental South African National AIDS Council (SANAC) in Pretoria. "One is to improve our system so that the more than 3 million on treatment are retained in care and properly managed, and we also have to expand to a group that is largely asymptomatic and well."

Adding to those challenges is South Africa's alarming HIV incidence—the percentage of the population that becomes infected each year. The government reports that HIV incidence has dropped from a high of 1.67% in adults in 2005 to 1.22% last year, but that still translates into 330,000 new infections a year. The rate is shockingly high in women under 25, especially in the hardest hit province, KwaZulu-Natal, where incidence tops 6% in some communities.

Health Minister Aaron Motsoaledi, who acknowledges that the country's aggressive HIV/AIDS program got off to a late start because of Mbeki (*Science*, 22 February 2013, p. 898), is confident that South Africa has the willpower and the money to hit 90-90-90. "Can we afford not to treat people?" Motsoaledi asks. "Surely, we're going to pay much more dearly socially, politically, and economically if you can't." To that end, the government, which already spends $1.2 billion a year on HIV/AIDS and receives another $300 million in foreign aid, is adding $65 million annually through 2019.

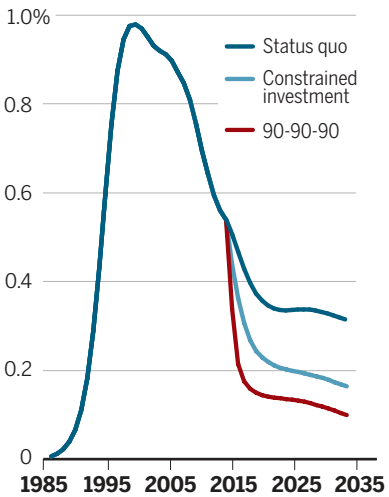
But a new report concludes that meeting the UNAIDS target will require an additional $8 billion over the next 5 years. "UNAIDS is pushing very hard on our health ministry, which doesn't want to be caught short again and wants to make the case that we can reach 90-90-90," says Linda-Gail Bekker, who co-runs the Desmond Tutu HIV Foundation (DTHF) in Cape Town and is one of the co-authors of the report. The cost of drugs is just one part of the equation, she says. Reaching the target will also require massive HIV testing and the costly delivery of ARVs to patients who must be monitored and then helped if they're not suppressing the virus. "I'm really, really anxious about the resources it's going to take."

There are scientific questions, too. The assumption that reaching the 90-90-90 target will end AIDS is based on mathematical models that factor in ARV "coverage" in combination with other proven prevention strategies like male circumcision, condom promotion, and behavior change efforts. Researchers note that in large epidemics like the one in South Africa, which has spread far beyond "concentrated" populations such as men who have sex with men and sex workers, such strategies could prove less effective than expected, allowing HIV to continue spreading at high rates even after the country reaches 90-90-90.

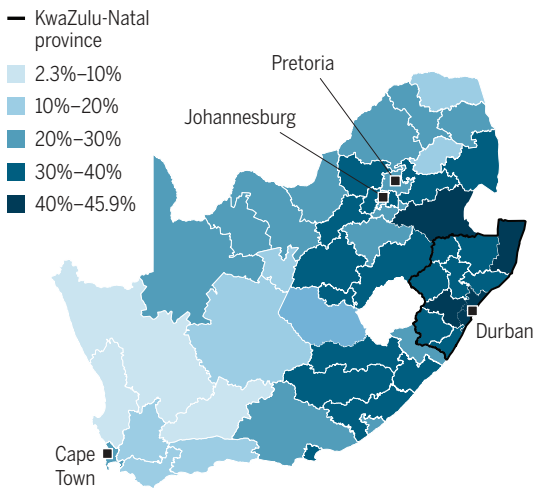
Models and reality

A model predicts how different HIV/AIDS response scenarios would affect new infection rates, or incidence. As seen on the map, some areas of the country have far more HIV than others.

HIV incidence scenarios



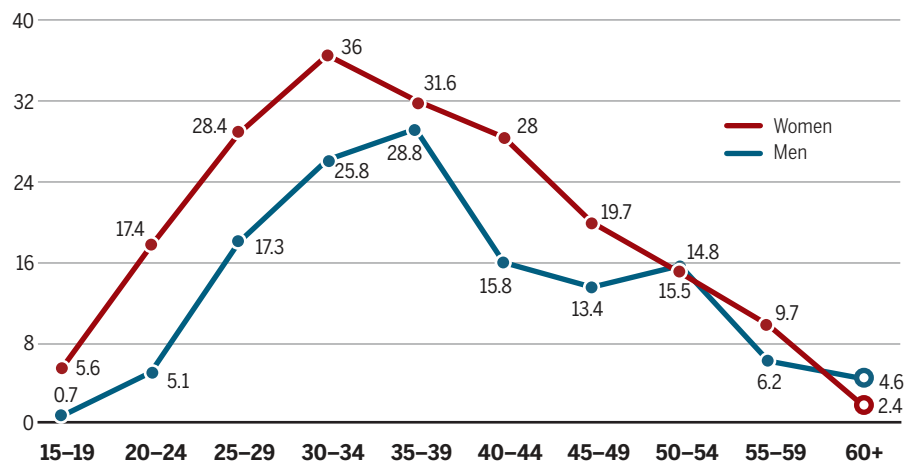
HIV antenatal clinic prevalence (2013)



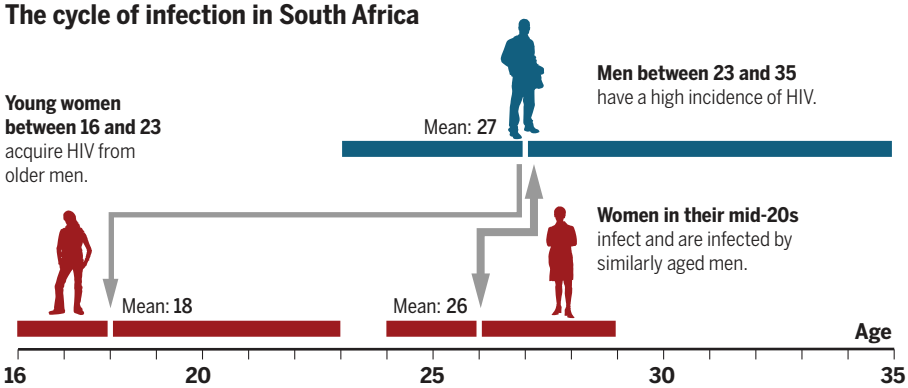
Sex and age

HIV infects far more girls and young women than boys and men of the same age in South Africa. The sex difference shrinks by age 35, then prevalence drops.

HIV prevalence by age groups (2012)



The cycle of infection in South Africa



Epidemiologist Salim Abdool Karim, who runs the Centre for the AIDS Programme of Research in South Africa (CAPRISA) in Durban, points to recent data from Botswana that call into question the model's assumptions. Botswana, which is relatively wealthy and has a tiny population of 2 million, has nearly reached 90-90-90, as shown in a study published online on 23 March in *The Lancet*. But incidence has barely budged, in part because the missing 10-10-10 continue to spread the virus. "For a country that's close to 90-90-90, the incidence is ridiculously high," Karim says. "It's scandalous." A report published by SANAC and the health department further questions the 90-90-90 mathematical modeling. Even if 90-90-90 leads to big declines in new infections by 2030, that report suggests that incidence in South Africa's population of 53 million will not quite drop below 0.1%—the level that UNAIDS says it must reach for an epidemic to end.

The bottom line is that it remains an open question whether the 90-90-90 treatment goal really can stop the spread of HIV in South Africa. Some of the world's largest controlled trials of treatment as prevention (TasP) are underway in the country to try to answer it.

IN AN AREA known as Mfekayi in rural KwaZulu-Natal, two dozen people are sitting on the shaded porch of a plywood shack waiting their turn to see a counselor. The shack is the Egedeni Clinic, and the people are participants in a 28,000-person, multisite clinical trial that will assess the precise relationship between increased levels of HIV suppression in a community and drops in incidence. At Egedeni and 10 other clinics across the province, the TasP study offers ARVs to all infected participants. Another 11 TasP clinics instead offer treatment in keeping with current government recommendations, meaning that people start ARVs only after their immune systems show signs of damage.

One by one, the participants hand bottles of ARVs they received a month earlier to the counselors, who count the remaining pills. This ritual, which is a crude way to monitor adherence, underscores an obvious limitation of the underlying strategy: Even if ARVs make people less infectious, TasP relies on the fickle relationship humans have with taking daily medications.

Run by the Africa Centre for Population Health in nearby Mtubatuba, TasP is the furthest along of four similar large trials in sub-Saharan Africa that are examining the care continuum and the real-world outcome of "universal treatment." Early analysis of TasP results found that fewer than 40% of

CREDITS: (GRAPHIC) A. CUADRA/*SCIENCE*; (DATA SOURCES) PREVALENCE MAP: THE 2013 NATIONAL ANTENATAL SENTINEL HIV PREVALENCE SURVEY SOUTH AFRICA; INCIDENCE GRAPH: SOUTH AFRICAN HIV AND TB INVESTMENT CASE. SANAC AND NATIONAL DEPARTMENT OF HEALTH; PREVALENCE BY SEX: SOUTH AFRICAN NATIONAL HIV PREVALENCE, INCIDENCE AND BEHAVIOUR SURVEY, 2012. HUMAN SCIENCES RESEARCH COUNCIL; CYCLE: G. MICHAEL DELLAR *ET AL*., CAPRISA

the people who tested positive sought care within 3 months, as recommended. This first step still has remained a major stumbling block on the road to 90-90-90.

At the International AIDS Conference later this month, the researchers plan to reveal whether their intervention has reduced incidence. "This will be the first opportunity to assess whether, in fact, the biological rationale is actually true in practice," says Deenan Pillay, a clinical virologist who heads the Africa Centre. But Pillay says the study already has made clear that ending AIDS is not simply a matter of "let's just treat everyone and everything will be OK." In the final analysis, he says, the power of TasP depends as much on human behavior as it does on biology.

JACQUALINE NCUBE, a 19-year-old restaurant worker, first took an HIV test when she was in high school. At the time, Ncube spent many hours after school hanging out at DTHF's Youth Centre, which abuts the struggling township of Masiphumelele outside of Cape Town. The Youth Centre offers teens internet access, holds soccer matches, loans surfboards, and provides care at a health clinic. Kids also earn "Tutus," good for shopping vouchers or food, for everything from helping the community to taking an HIV test. When Ncube got her first results, she was overwhelmed. "I really screamed," she says. She was negative.

Ncube has repeatedly tested negative, and in April 2015 she joined the Youth Centre's Pillsplus, a study of what's known as pre-exposure prophylaxis, or PrEP, in 150 teens. With PrEP, uninfected people take daily ARV pills to prevent infection. Although PrEP is a proven strategy, South Africa recommends its use only in sex workers, and Ncube is one of the first heterosexual teens in the world to take ARVs for prevention. She still uses condoms with her boyfriend, but says she wanted to try PrEP because "no protection is 100%."

DTHF's Bekker, who is heading Pillsplus to assess PrEP's acceptability in teens, contends that PrEP should be provided to all people at high risk of infection. "When I sit opposite a 17-year-old young woman, I have nothing to offer her," Bekker says.

CAPRISA's Karim says using PrEP in young women could be key to breaking the epidemic's back. About 30% of new infections in South Africa occur in young women between 15 and 24 years of age. The new infection rate in men in the same age bracket is more than four times lower. In some districts of KwaZulu-Natal, a woman has a 60% chance of becoming infected by age 34.

To understand the pattern of viral spread, CAPRISA and the Africa Centre mapped out the infection cycle between men and women of different ages in KwaZulu-Natal. The study analyzed the genetic sequences of HIV isolated from 858 men and women, all between 16 and 35 years old, who belonged to the same sexual networks. The viral genetics linked different isolates and indicated which ones were older, allowing the researchers to infer who infected whom. Teenage girls were infected by men who were, on average, 8 years older. After the age of 24, people typically became infected by partners their own age, with transmission more frequently moving from woman to man. "They are trying to find lifetime partners at this age," Karim says. These older men are the same group having sex with the youngest women. "We have to break the chain between men in their late 20s and teen girls," he says.

PrEP can help address shortcomings of TasP, Karim says. In the infection-cycle study, men who infected younger women had extremely high HIV levels, indicating they recently acquired the virus and thus would not appear infected on standard antibody-based tests. "If your strategy is to test and treat these people, you're not going to catch them," Karim says. Men are also less connected to the health care system and often migrate for work, he adds, making it more difficult to help those who know they are infected fully suppress the virus. Giving PrEP to young women sidesteps the male dilemma. "We just have to protect girls for 5 years in that critical risk period until they find their partners," he says.

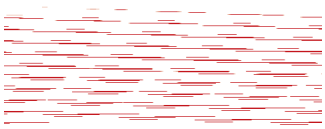
Karim says new biomedical interventions on the horizon may bolster prevention efforts. His group plans to report at the Durban meeting that it has identified an unusual microbe linked to vaginal inflammation in women in KwaZulu-Natal. Treating it could potentially lower their risk of HIV infection. Injectable ARVs that last for 2 months are also being tested in South Africa and elsewhere, and those could eliminate the challenge of taking daily pills—a key problem for both treatment and PrEP. Next fall, South Africa plans to launch the world's only efficacy trial of an AIDS vaccine—the strongest preventive medicine of all.

For now, 90-90-90 is the most powerful tool available to South Africa in its quest to end its epidemic, even if PrEP and other new strategies ultimately are needed. SANAC's Abdullah takes a pragmatic view of meeting the UNAIDS deadline. "I think we should plan for it, because if we don't hit it by 2020, we'll do it by 2022," he predicts. "What we're really after is bringing down new infections to low levels," along with getting as many HIV-infected people as possible on treatment and living longer lives. The virus itself, Abdullah says, "will be with us for the next 100 years." ■

The Pulitzer Center on Crisis Reporting provided support for the reporting in this story.

A robot pulls antiretroviral drugs off the shelf to help Rajan Gudala's pharmacy team at the Themba Lethu Clinic.

PHOTO: JAMES OATWAY



Editor's Summary

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Jon Cohen (June 30, 2016)

Science **353** (6294), 18-21. [doi: 10.1126/science.353.6294.18]

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.