How to beat HIV

Scientists have the tools to end the epidemic. They just need better ways to use them.

BY ERIKA CHECK HAYDEN

On the shores of Lake Victoria, Kenyan fishermen spread out their nets on the sand to dry their catch in the sun. At a clutch of tents next to the beach, health-care workers are casting a very different kind of net, one that could help to capture the best approach to eradicating HIV.

The tents draw a steady stream of visitors because the fishermen and their families, as well as farmers, students and others from the surrounding communities, have heard that they can get vitamin A, condoms, and medicines for worms and malaria there. At the same time, they are offered various screening tests — including one for HIV. The hope is that, along with taking advantage of the other medical services, they will agree to be tested and, if necessary, treated for the sexually transmitted virus.

Here in Kenya's Nyanza Province, which has the country's highest rate of HIV infection, this community is part of a groundbreaking study designed to explain a troubling conundrum. Interventions to prevent HIV transmission that work in trial settings — such as rapid on-the-spot HIV tests coupled with effective treatments — often fail to make as much of a dent in the epidemic as they should. The current trial, known as Sustainable East Africa Research in Community Health (SEARCH), has enrolled more than 335,000 people in Kenya and Uganda and is at the forefront of a shift in thinking about how best to deal with HIV. In the past, there was a sense that stopping the HIV/AIDS epidemic would require some radically new biomedical intervention, such as a cure or a vaccine. The growing consensus, however, is that the tools needed to stamp out HIV already exist if they could just be used in the right way.

In trials over the past decade, experimental interventions such as voluntary male circumcision or the use of prophylactic drugs produced head-turning results that earned them funding for broader implementation. But they have not succeeded when rolled out more generally: in some cases because the funding did not last, but in others because the conditions of a clinical trial are not the same as those in real life. SEARCH and efforts like it are intended to explain why. They fall within the domain of implementation science, an emerging multidisciplinary field that seeks to understand and overcome factors — such as human behaviour and economics — that can lessen the impact of interventions that have otherwise proved effective.

Major aid programmes are taking an interest. The US President's Emergency Fund for AIDS Relief (PEPFAR), for example, launched a US$60-million programme in implementation science in 2012. Among other aims, this programme is testing whether integrating the prevention and treatment of HIV infection with other facets of countries' health and social systems — such as family planning, tuberculosis treatment and education — could help to get the HIV epidemic under control.

"A lot of my university colleagues are very good at doing the studies and coming up with a finding, but are clueless about how to get that finding into actual practice," says epidemiologist Farley Cleghorn of the Futures Group in Washington DC, which contracts with governments to conduct aid programmes. "The challenge for implementation science is to diminish that reduction in impact that happens when you move from a controlled environment to the general population."

AMBITIOUS GOALS

SEARCH fits into a bold global strategy for eradicating HIV. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS), based in Geneva, Switzerland, laid out the '90-90-90' target: getting a diagnosis for 90% of people infected with HIV; putting 90% of those on antiretroviral therapy; and getting 90% of those virally suppressed, meaning that they have an undetectable level of HIV in their bodies. Achieving these goals by 2020 would herald an end to the epidemic as a global threat by 2030, with the number of new infections per year limited to about 200,000.

That is easier said than done, however. "To say it's an ambitious target would be an understatement," says Mitchell Warren, director of AVAC, an AIDS prevention advocacy group. Less than half of the people with HIV in some areas of the world, such as southern Africa, have access to HIV tests. In most regions, less than 40% of people with HIV are being treated, and the percentage of people with HIV who are virally suppressed is quite low in many regions (only about 30% in the United States, for example). Worldwide, about 15 million people will have access to antiretroviral treatment in 2015 (see 'Signs of change').

The problem is that individuals drop out at each step of the path that leads to viral

PETER CASAER/MSF

Informal community groups deliver HIV therapy in South Africa.

suppression. Most people with HIV have never been tested. Of those who have, many do not start treatment; and of those who do, many stop for a variety of reasons. Implementation science is finding that some of the best ways to plug the holes in this leaky cascade of care are to make it easier and more rewarding for patients to get the medical attention they need.

The problem is acute in sub-Saharan Africa, which represents 70% of the global total of both new infections and people living with HIV. Eight years ago, doctors with the aid group Médecins sans Frontières (MSF) noticed that, as the number of people being treated with antiretrovirals increased, patients attending an HIV clinic in the township of Khayelitsha in Cape Town, South Africa, were finding it increasingly difficult to get their medication. To pick up their pills, they had to visit the clinic for frequent check-ups and tests of their viral load and T-cell count — indications of the progression of the infection. But at every appointment, they faced hours-long waits to see overburdened nurses. And people frequently left empty-handed owing to a shortage of the drugs. As many as one-quarter of patients who started HIV treatment stopped after one year.

MSF decided to try something different: it set up clubs that met every two months at the clinic, led by trained counsellors, many of whom were patients themselves. The clubs met during slow times at the clinic, and counsellors brought each patient's supply of medicines to the meeting in a pre-packed bag and led a group discussion about the importance of staying on treatment. A nurse visited once a year to take blood samples and measure viral load and T-cell count.

The clubs were a dramatic success: for the patients who received their care in this way, there was a 57% decrease in the number of people dropping out (through either death or giving up treatment) compared with the group that continued to receive care through the previous system at the clinic itself[1]. Such clubs are now seen as a model of how to keep patients in care and have been organized in less formal settings such as private homes after work hours.

The SEARCH trial is building on the idea of adapting the care of people with HIV to their needs. It is taking a broader look at the problem by not only bringing care closer to patients and making it easier for them to get it, but also examining whether integrating HIV care into the overall health-care system can help stop the leaks at each step of the care cascade.

The first step is diagnosis. As few as 40% of Kenyans infected with HIV know that they have it. One problem has been that people eschew targeted HIV-testing campaigns. Another is that those most likely to be infected, such as people who migrate to find work, are least likely to be reached by testing campaigns. So SEARCH is evaluating other ways to attract people — for example, by deploying community health campaigns such as the one in Nyanza Province, where people can access much-desired medical services as well as HIV tests. People who do not attend the community programmes are approached through door-to-door campaigns and are offered HIV tests that they can take in their own homes.

This combination of mobile campaigns followed by home visits has boosted the proportion of adults who had taken at least one HIV test from 57% to 80% in the communities included in SEARCH, Gabriel Chamie, at the University of California, San Francisco (UCSF), reported on behalf of the study at a conference in February.

As the SEARCH trial progresses, it will assess ways to get those who test positive more quickly into care and to keep them there. They are started on antiretroviral drugs rapidly — sometimes on the same day as their diagnosis. The project has enacted a triage system for speeding HIV patients who feel well into and out of the clinic when they attend appointments, and for reducing the number of visits. The project is also trialling appointment reminders and is setting up a telephone hotline to help keep patients engaged in their care. And the project will measure a person's viral load at the start of treatment, six months later, and each year subsequently, to check whether the treatment is working.

"What we've tried to go do is greatly simplify HIV care delivery," says Diane Havlir at UCSF, one of the directors of the SEARCH study.

Researchers are also using implementation science to understand why prevention methods such as circumcision and prophylactic drug treatment have not been adopted as widely as they could have been.

For instance, trials in the mid-2000s proved

that voluntary circumcision for men cut the risk of their acquiring HIV from a female sexual partner by 60%. The World Health Organization recommended in 2007 that circumcision be used for prevention and, with UNAIDS and the Bill & Melinda Gates Foundation in Seattle, Washington, set a target to circumcise 80% of eligible men in Africa by 2016 to prevent up to 3.4 million new HIV infections (see *Nature* **503,** 182–185; 2013). PEPFAR and others provided funding, and 9 million circumcisions have been performed since 2007.

But even this massive campaign has up to now reached only 28% of its target. One problem is that circumcision is a surgical procedure and so requires different expertise and resources from those in current HIV programmes. And setting up stand-alone circumcision programmes diverts resources from existing surgery, which is already under-resourced. "There's a whole lot of logistical and operational issues that are resulting in countries not meeting their targets," Cleghorn says.

A different set of real-world issues has complicated what is known as pre-exposure prophylaxis (PReP) — the concept of taking a dose of antiretroviral medication regularly or around the time of sexual intercourse to prevent infection. In the PROUD study in the United Kingdom, which reported results in February, this has been shown to reduce the risk of infection by 86% in men who have sex with men, and studies of PReP in Africa showed a decrease of 73% in heterosexual couples[2].

But despite these results, PReP is not widely used. One reason is that some people at highest risk of becoming infected with HIV are also those most likely to be in denial about their risk, or unable to access services, and are therefore least likely to take a medicine to prevent infection. And developing countries have enough difficulty distributing antiretrovirals to people already infected to make a serious effort to give them to anyone else. In June, for instance, MSF reported that one in three health facilities in South Africa reported a shortage of medications for HIV or tuberculosis late last year. That makes it hard to face the additional challenge of getting drugs to those who are HIV negative. "They can't wrap their heads around it," Cleghorn says.

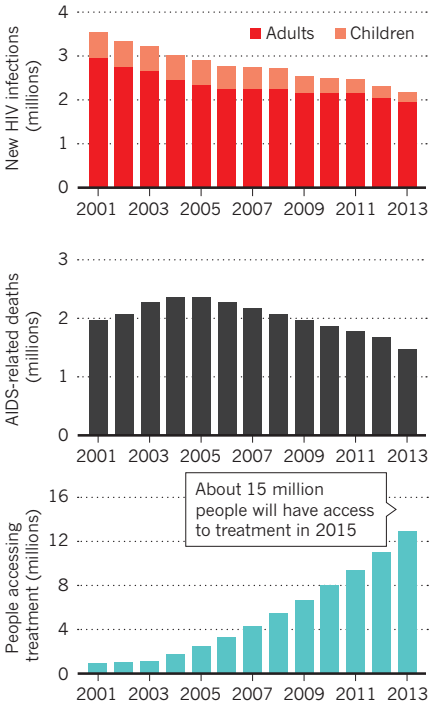
In addition, PReP has consistently failed to protect those arguably most in need of new prevention options — young unmarried women. In most of the poor countries hit hard by HIV, 80% of new infections among adolescents are in girls. Yet PReP has failed in this demographic in trials that used many different delivery approaches, such as vaginal gels containing antiretroviral medication or oral pills taken daily or before and after sex.

The main problem is that many women did not use the products they were given. In one study of 5,000 women in South Africa, Zimbabwe and Uganda, blood tests showed that only 25–30% of participants actually used the medications, even though 88% said that they had. Those questioned in small groups said that they did not use the products because of social factors, such as fear that they would be ostracized or perceived as having HIV already if they were known to possess HIV drugs.

The problem is part of a broader social context that makes girls more vulnerable to HIV than boys of their age. Many date older men, who have a higher prevalence of HIV infection than adolescent boys; some engage in transactional sex to afford necessities; and some are abused.

SIGNS OF CHANGE

The past decade has seen some success against HIV, with the number of new infections and deaths in decline. The progress has inspired more-ambitious targets for the next five years that would herald the end of HIV as a worldwide threat by 2030.



SOURCE: UNAIDS, WHO

IMPLEMENTING SOLUTIONS

Implementation science is trying to find ways to address these broader factors in an attempt to cut the HIV risk in girls. In a meta-analysis published in March, social scientist Nicole Haberland of the Population Council in New York City examined programmes designed to reduce pregnancy, HIV and sexually transmitted disease infection rates in girls[3]. She found that when these programmes included educational components that specifically addressed gender or power — for instance, by including discussions of how girls could negotiate condom use and how gender inequality influenced their own lives — they were more likely to reduce disease risk. Eight of 10 programmes that included such components worked, compared with 2 of 12 that did not address these issues.

Responding to findings such as these, in December 2014, PEPFAR announced the DREAMS initiative which, in conjunction with the Bill & Melinda Gates Foundation and the Nike Foundation, will spend $210 million over two years to provide a combination of preventive interventions targeting young girls, such as HIV testing, counselling and care for rape survivors, and programmes aimed to boost the resilience of girls and their families, such as cash payments for girls who stay in school.

But drawing a direct link between some of these interventions and lowering the risk of HIV infection in girls has been difficult. Two studies that are specifically testing whether cash transfers for children who meet certain academic goals can cut the risk of new HIV infections in South Africa are expected to report their results at the upcoming meeting of the International AIDS Society in Vancouver, Canada, on 19–22 July.

Epidemiologist Audrey Pettifor, who leads one of the trials, says that although such interventions have worked in very poor countries — such as Malawi — they may not apply elsewhere. In her trial, girls and their families were paid the equivalent of $24 per month if the girls attended school, but the youngsters in South Africa have very different expectations from those in much poorer African nations. Along with high levels of poverty, unemployment and HIV prevalence is a desire for luxury goods — the girls in Pettifor's trial named items such as designer jeans, Italian shoes and Blackberry smartphones as necessities. "If we're trying to deter transactional sex, it's going to be a big ask," Pettifor says. It may not work.

Implementation science is still relatively new to the HIV/AIDS field, and it is not yet clear if it will help researchers to hit all of the 90-90-90 goals. "The evidence base is still mixed on programmes or interventions to reach these goals," Pettifor says.

Researchers hope that the field will mature and become more rigorous. The SEARCH trial, for example, is assessing whether streamlining HIV care has knock-on health and economic benefits for the community, such as elevated fishing or farming revenues, or enhanced education rates among children.

The fish catch of a small community on the shores of Lake Victoria may seem far removed from the goal of stopping HIV — but implementation scientists see it as an essential part of the work. "We've set these very aspirational goals," says Havlir. But if they want to reach them, then scientists must get to grips with the complexities of the real world. ■

Erika Check Hayden *writes for* Nature *from San Francisco.*

1. Luque-Fernandez, M. A. *et al. PLoS ONE* **8,** e56088 (2013).
2. Baeten, J. M. *et al. N. Engl. J. Med.* **367,** 399–410 (2012).
3. Haberland, N. A. *Int. Perspect. Sex. Reprod. Health* **41,** 31–42 (2015).