

Joining forces

No single strategy alone is likely to thwart HIV's spread. Researchers are turning to 'prevention packages' of two or more approaches, **Cassandra Willyard** reports.

Developing a vaccine against HIV has proven infinitely complex, but designing alternative methods of prevention has not been any easier. Of the handful of strategies tested in recent years, only male circumcision has been an unequivocal success. Older strategies, such as condoms and needle exchange, all sounded more promising than they turned out to be.

After decades of disappointment, researchers are turning to antiretroviral therapy — the one tool proven to stop the virus in its tracks. Trials are under way to test whether oral antiretroviral pills or gels laced with the drugs can prevent infections. Researchers are also testing whether treating infected individuals early can make them less infectious (see sidebar on page S12).

"We are in a new antiretroviral-based prevention generation," says Mitchell Warren, director of the AIDS Vaccine Advocacy Coalition, a New York-based non-profit organization aimed at accelerating HIV-prevention research.

Scientists are also assessing combinations of two or more of the strategies — for example condoms, needle exchange, male circumcision and antiretroviral drugs. "Because no new prevention intervention will be a silver bullet, we must understand the optimal combinations of interventions," says Stefano Bertozzi, HIV director for the Bill & Melinda Gates Foundation's Global Health Program.

The ideal prevention strategy is cheap, effective and easy to use. Although condoms meet these requirements, many men are reluctant to use them. In the early 1990s, researchers began thinking about strategies that women could control. They estimated that a microbicide that is 60% effective at preventing HIV infection could prevent 2.5 million infections in just three years¹.

Unfortunately, the microbicide field has been plagued by failures. Scientists have developed dozens of candidates, and led at least six into clinical trials. Despite promising preclinical data, however, each has failed to prevent infection. Alarmingly, a couple even

appeared to increase women's risk of contracting the virus.

In December, researchers reported the most recent failure: a gel called PRO2000, which had shown promise in a small study, but had no effect on HIV transmission in a trial of 9,385 African women.

Preventive pills

These disappointing results were not a major setback, says Sharon Hillier, professor of obstetrics, gynaecology and reproductive sciences at the University of Pittsburgh in Pennsylvania. "We had already moved on to the next generation of products, which are much more potent."

The new generation of microbicides, two of which are in clinical trials, are laced with potent antiretroviral drugs. Results from the first trial, a 900-person test of a vaginal gel containing tenofovir, are expected to be announced in July at the International AIDS Conference in Vienna.

The preventive power of antiretroviral pills has been harnessed before, to block transmission of the virus from mother to unborn child. For example, a single dose of the antiretroviral nevirapine, given to the mother during labour and to the infant after birth, cuts HIV transmission by more than 40%.

Scientists reason that the pills might also prevent the virus from taking hold in uninfected adults. This pre-exposure prophylaxis (PrEP) strategy is being tested in at least five independent trials. The first results are expected later this year. "We are going to get our first glimpse at whether these new approaches with antiretrovirals work," Warren says.

For such methods to be effective, they must be used regularly — daily or before every risky sexual encounter. That might be feasible in the controlled setting of a clinical trial, but impractical in the real world, notes Robin Shattock, professor of cellular and molecular infection at St George's, University of London.

Some researchers are devising ways to make these methods easier to use. For example, a



This Chinese device, a ShangRing, holds the foreskin in place, allowing it to be snipped away quickly with no stitches required.

vaginal ring — much like the ones used for contraception — could deliver low doses of the drug for a month or more. Researchers at Weill Cornell Medical College in New York have designed a ring that delivers both antiretroviral drugs and contraceptives, although it has not been tested outside the laboratory².

Similarly, antiretroviral injections that last for several months, like the contraceptive injection Depo-Provera, might be preferable to a daily pill. "The less you have to think about it, the more likely it will be adopted," Shattock says.

Aggressive strategies

Scientists have known for more than a decade that people who have low viral loads are less likely to pass on the virus. Some studies have shown that treating HIV-infected individuals early decreases their risk of infecting their partners. One research team is testing this approach — dubbed 'treatment as prevention' — in a clinical trial of 1,750 couples.

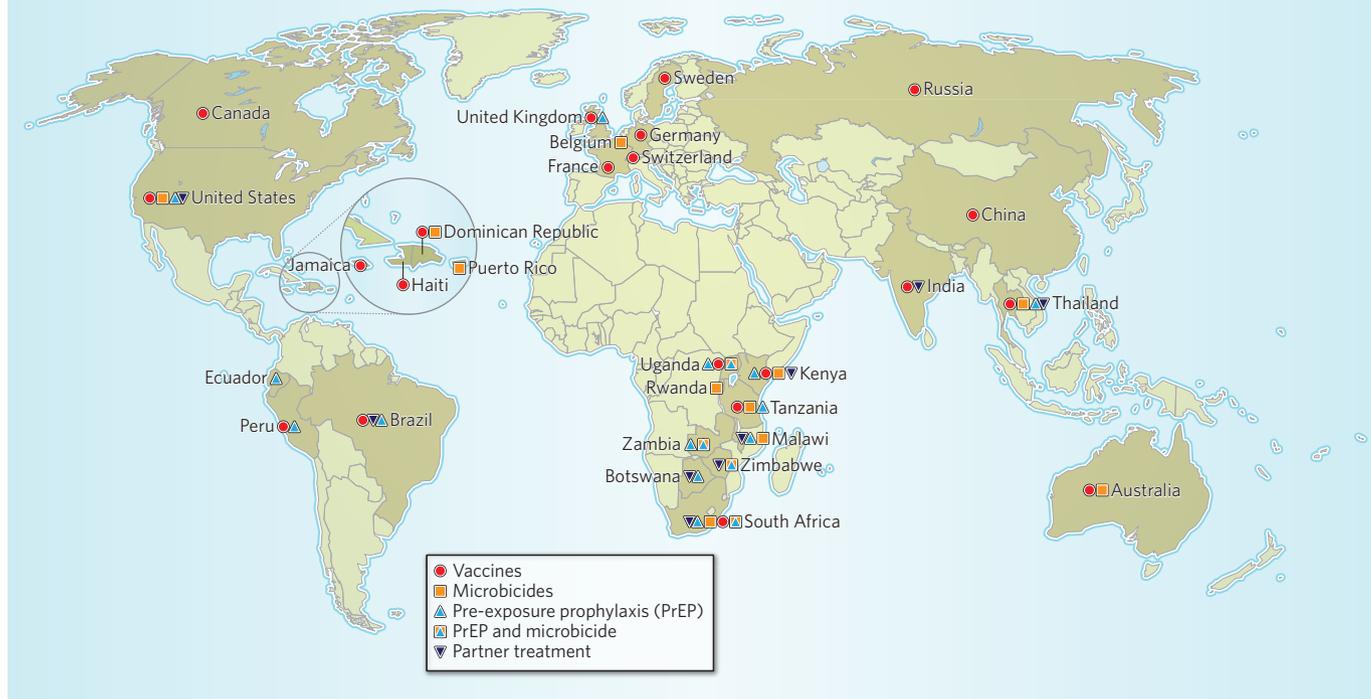
Last year, the World Health Organization (WHO) proposed that an aggressive global strategy of yearly universal HIV tests and immediate antiretroviral treatment for those infected could dramatically slow the spread of HIV within a decade, and reduce prevalence to 1% within 50 years³.

Many experts argue, however, that this 'test and treat' approach will be difficult to implement. "I think it will be a challenge even in the US, let alone in places with a much higher HIV burden," says Connie Celum, director of the University of Washington's International Clinical Research Center in Seattle. "How do you think about test and treat when it's such a long way to go to even treat those who will die in a few years if they don't get [antiretrovirals]?"

The US National Institutes of Health (NIH) is planning to test a less-regimented strategy in Washington DC and New York City's Bronx neighbourhood. The three-year study, set to

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ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



Scientists are testing every preventive approach available, including microbicides, vaccines and antiretroviral pills, alone and in combination.

begin in June, will rely on local health centres. The researchers plan to encourage HIV testing through media campaigns, and to help those who test positive to find doctors to prescribe treatment. “We really want real-world data,” says David Burns, branch chief for HIV prevention research at the US National Institute of Allergy and Infectious Diseases.

Some interventions take longer to gain traction than others. In the case of male circumcision, for example, lack of political will, limited resources and even cultural mores have deterred some communities from adopting the procedure. “Nothing gets to the heart of social cultural issues as much as a man’s penis and his foreskin,” Warren says.

Three independent clinical trials showed, in 2005 and 2006, that circumcision cuts men’s risk of contracting HIV by about one-half. Consequently, the WHO, in 2007, began recommending male circumcision for HIV prevention, and the strategy is slowly gaining ground.

At least 8 of the 13 African nations identified as priority countries in 2007 by the WHO and the United Nations Joint Programme on HIV/AIDS (UNAIDS) are scaling up male circumcision services. Kenya, which launched its campaign in 2008, has made the most progress. As of February 2010, doctors there had circumcised 90,000 men. The government aims to reach a million men — nearly all those uncircumcised in the country — by 2013. South Africa, in April, launched free male circumcision services as part of its national HIV campaign. The country’s ministry of health aims to help 2.5 million men by 2015.

Cutting edge

In many countries, there is a dearth of trained professionals who can perform the surgical procedure. Some research teams have set up training camps, and others are investigating ways to make the procedure easier and safer to perform.

One clinical trial, organized by researchers at Weill Medical College of Cornell University in New York, is testing a Chinese device called ShangRing, which consists of two plastic rings that sandwich the foreskin, allowing it to be snipped away quickly. A typical circumcision takes about 20 to 30 minutes, but ShangRing cuts that down to about 5 minutes — with no stitches required. However, the device must be left in place for ten days to allow the wound to heal.

Even if millions of men sign up, circumcision neither eliminates their risk of infection nor directly benefits women. “It can’t be considered as the sole method of prevention,” says Maria Wawer, professor of population, family and reproductive health at Johns Hopkins University.

In fact, no single strategy — not even a vaccine — is likely to be 100% effective. In some cases, “two interventions applied together can be greater than the sum of their parts,” says Timothy Hallett, a research fellow in the department of infectious disease epidemiology at Imperial College London. There are few hard data, however, on which combinations might be best for a given population.

Last year, the NIH funded six groups to design “prevention packages” for specific populations — including injecting drug

users in Eastern Europe, men who have sex with men in the Americas, and households in Uganda. The institute plans to fund several more this year.

Celum, who is designing a package for Uganda, is investigating the feasibility of sending health workers door-to-door to test for HIV. Based on the results, they could develop an on-the-spot “prevention prescription,” she says.

Real-world tests of these combinations are not always feasible. Clinical trials would cost hundreds of thousands of US dollars and take years to yield results. What is more, says Burns, “it quickly becomes a very complex research design.” The NIH projects will be assessed using small pilot studies, with successful strategies tested in larger clinical trials.

Mathematical models offer a quick and inexpensive way to skip some cumbersome steps. “You can simulate the impact of an intervention,” says Hallett, who is working with Celum on the Uganda project.

These new approaches require unprecedented levels of collaboration between immunologists, virologists, modellers, and behavioural and social scientists.

“People are moving beyond the [attitude that], ‘There’s only my approach that’s going to work,’” Celum says. “The move towards combination prevention is breaking down some of those divides.”

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1. Watts, C. & Vickerman, P. *AIDS* **15**, S43–S44 (2001).
2. Saxena, B. B. et al. *AIDS* **23**, 917–922 (2009).
3. Granich, R. M. et al. *Lancet* **373**, 48–57 (2009).