

HALTING HIV/AIDS Epidemics

A slew of successes in clinical trials has elated the HIV prevention field, and models now suggest that combining them might virtually stop HIV's spread. But caveats abound

ON 1 DECEMBER, U.S. PRESIDENT BARACK Obama headed a star-studded event, “The Beginning of the End of AIDS,” that attracted heavyweights such as former presidents George W. Bush and Bill Clinton, the president of Tanzania, the head of Coca-Cola, and the rock stars Bono and Alicia Keys. The cause for the occasion held at George Washington University in Washington, D.C., was World AIDS Day, but as Obama noted, this year’s theme was far more ambitious than any in the past. Over the past 2 years, four large-scale studies of interventions to prevent HIV have worked, and for the first time, the goal of ending AIDS epidemics in some locales—and, in time, the world—seems like a possibility, provided, of course, that there’s political will and money. To that end, the Obama Administration a few weeks earlier had declared a global priority of “creating an AIDS-free generation.”

But there’s a vast difference between a study having success and thwarting HIV in the real world. “This is truly an exciting time, but it’s a complicated time,” says Anthony Fauci, who heads the U.S. National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. “If we implement a combination of known prevention modalities, we could probably have a significant impact on the epidemic even before we have a vaccine.” Yet he stresses that the impact of proven interventions might vary from

place to place because the epidemics have different features.

Daunting funding issues face any campaign to ramp up HIV prevention. Just 2 weeks ago, for instance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, low on money, scuttled a round of new grants. But funding aside, it’s a challenge to figure out how best to combine the available interventions. Many mathematical modelers and HIV/AIDS researchers have begun to explore and intensely debate a variety of strategies. “We’re fortunate to have several prevention interventions that are efficacious, but the next step is to factor in the nuances of each of these local epidemics,” says Wafaa El-Sadr, an epidemiologist at Columbia University.

Several large clinical trials under way or in the works should reveal which new prevention strategies best bring down incidence in a population versus simply protecting an individual

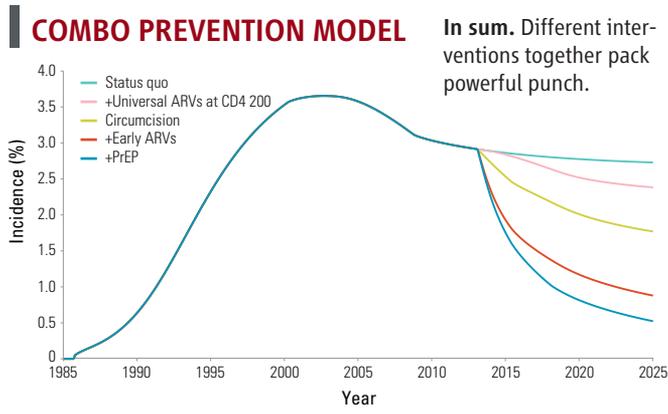
(see map, p. 1340). El-Sadr suggests that, in parallel, countries begin to apply new combinations of proven strategies today with a trial-and-error mindset. “It has to be an iterative process of using the information at hand and being willing to adjust and modify,” she says.

Eric Goosby, who heads the multibillion-dollar U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), says his group is closely analyzing models now. “We see it as a definite opportunity to change the way we do business and move us all toward higher impact interventions,” Goosby says. “We’re taking this as seriously as you can.”

Flood of success

Nearly all of the earliest HIV prevention trials failed badly or yielded confusing results. For instance, efforts to reduce HIV transmission by treating other sexually transmitted infections worked in one large study and failed in others. The first clear success was the demonstration in 1994 that antiretroviral (ARV) drugs could prevent HIV-infected mothers from transmitting the virus to their babies if both received them. So-called harm-reduction strategies, including needle exchange, can protect injecting drug users from HIV. But neither of those interventions slows sexual transmission, the route of spread for most of the world’s 34 million HIV-infected people.

In 2005, a study finally proved unequivocally that a biomedical



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Testing limits. Mass campaigns like this one in Lesotho ambitiously hope to find all HIV-infected people in a locale.

intervention could block sexual transmission: A large, randomized, controlled trial in South Africa found that male circumcision offered 60% protection to uninfected heterosexual men. But it was four subsequent triumphs during the past 18 months that made ending the epidemic seem an achievable goal.

The first was a South African study of a strategy called topical pre-exposure prophylaxis (PrEP), which showed in July 2010 that a vaginal gel laced with an anti-HIV drug could cut transmission to uninfected women by 39%. That November, another trial in six countries of an oral PrEP that combined two anti-HIV drugs taken daily showed 44% efficacy in uninfected men who have sex with men. In May, a nine-country trial known as HPTN 052 had a downright spectacular result. The study recruited “discordant” heterosexual couples. One long-term partner was uninfected at the start whereas the other had a known HIV infection and a relatively intact immune system with 350 to 550 CD4 cells per milliliter (600 to 1200 is normal; fewer than 200 is AIDS). Half of the infected people received treatment immediately; the other half waited until their CD4 counts fell below 250. Earlier treatment reduced the risk of transmitting HIV by 96%. Although observational studies had long suggested that reducing viral levels made a person less infectious, the ongoing HPTN 052 trial proved once and for all that “treatment as prevention” (TasP) works. A different study with discordant heterosexual couples in Kenya and Uganda reported 2 months later that if infected people remained untreated and their *uninfected* partners instead took the two-drug oral PrEP, transmission dropped by 73%.

With these successes has come a dilemma. “We’ve got more things we could spend our money on than ever before but less to spend,” says epidemiologist Timothy Hallett, who has done extensive mathematical modeling of the epidemic with Geoffrey Garnett at Imperial College London (ICL). “It’s a real crunch time.”

Hallett and his ICL colleague Íde Cremin have taken a stab at modeling the impact of combining several proven biomedical interventions. They focused on KwaZulu-Natal, South Africa, which has an annual HIV incidence of nearly 3%. The model assesses the drop in incidence that would occur by 2025

as various interventions are scaled up starting in 2013. First, putting 75% of infected people who have fewer than 200 CD4 cells on ARVs and increasing male circumcision to 65% reduces incidence in the model by 1%. If infected people start treatment an average of 2 years after testing positive instead of waiting for their CD4s to fall below 200, incidence decreases another 1%. If 60% of 15-to-24-year-olds—a particularly high-risk group there—uses PrEP, incidence drops another half-percent. In the final analysis, incidence plummets to almost 0.5% (see graph). “We can cut down the epidemic with 1000 cuts

to apply them in public health programs. Trained specialists who can run diagnostic tests and provide medicines are already in short supply in many low- and middle-income countries. Uninfected people could undermine the effectiveness of TasP, PrEP, or circumcision if they presume they are invulnerable and engage in riskier behaviors. Widespread use of ARVs could increase drug resistance, crippling both TasP and PrEP.

Some say models are being used naively. “People need to get a more realistic view,” says **Sally Blower**, a mathematical modeler at the University of California, Los Angeles.

“Too many think, ‘Treatment as prevention: good. It’s just not right.’”

Loud debates about the limits of TasP have been raging since *The Lancet* published a model 3 years ago that proposed that testing and treating every infected person in the world could “eliminate” the epidemic in 10 years. In a paper published online 26 November 2008, World Health Organization epidemiologist Reuben Granich, Williams, and colleagues used data from South Africa, which has more HIV-infected people than any country, to create a scenario

that involved testing the entire population for HIV once a year and treating every positive individual. Within 10 years, they concluded, the annual rate of new infections would drop from about 2% to below 0.1%.

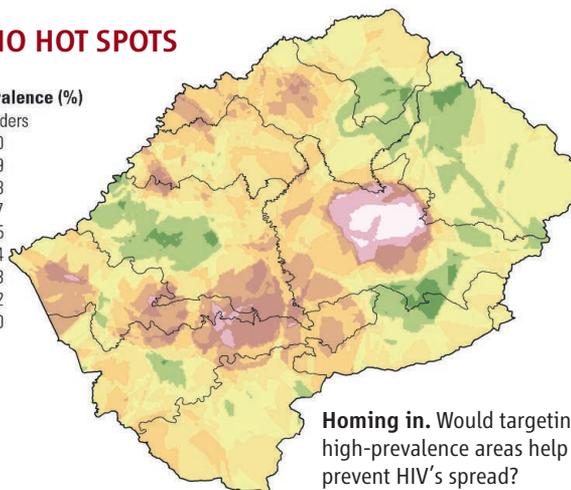
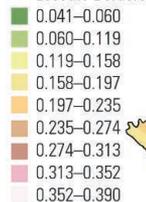
Critics said treating all of South Africa—let alone the world—was unrealistic, both technically and financially. Many questioned the testing scheme, too. Rochelle Walensky, an HIV/AIDS epidemiologist at the Massachusetts General Hospital in Boston, said she found the Granich model “provocative and motivating” but worried that it set benchmarks that no country could meet. A study she led evaluated a **pilot test-and-treat program in Washington, D.C.** Although individuals benefited, “suggestions that a test and treat strategy might be sufficient to eradicate the HIV epidemic create public expectations that cannot be realized,” the study team wrote in the 15 August 2010 issue of *Clinical Infectious Diseases*.

Walensky says it’s extremely difficult to test an entire population, do so repeatedly, then start all positive people on treatment, and see that they take ARVs as prescribed. “We’re nowhere near 100% coverage for testing once,

LESOTHO HOT SPOTS

Male HIV Prevalence (%)

— Lesotho Borders



Homing in. Would targeting high-prevalence areas help prevent HIV’s spread?

rather than one fatal blow,” Hallett says.

Brian Williams and colleagues at the South African Centre for Epidemiological Modelling and Analysis at the University of Stellenbosch looked at the same question but assessed a different outcome: reducing an individual’s risk of infection. According to their calculations, if 60% of men in a given population were circumcised and 80% of infected men and women were taking ARVs, the risk of someone becoming infected would drop by 55%. Reducing risk by 85% would require 90% of infected people on ARVs, 10% on daily PrEP, 80% male circumcision, and 25% of uninfected women using a vaginal microbicide before and after sex. Williams emphasizes that every one of these interventions other than circumcision depends on the person properly using their medication. “The key to success is compliance,” Williams says.

Limitations galore

Variable compliance is but one of many reasons each of the recently proved biomedical prevention interventions may work better in clinical trials—and in models based on them—than when governments attempt

let alone annually,” Walensky says. “When you offer tests, people don’t necessarily take them, and when they get positive results, they don’t necessarily start treatment.”

Myron Cohen of the University of North Carolina, Chapel Hill, who heads HPTN 052, raises another caveat. **Cohen contends that a disproportionate amount of transmission occurs from recently infected people who have high viral loads but do not yet produce the antibodies that standard HIV tests detect.** Even if a program managed to start all HIV-positive people in a community on ARVs, it would miss the acute or recent infections. A model that Cohen and co-workers described in the 16 July issue of *The Lancet*—using behavioral and viral load data collected in Lilongwe, Malawi—calculated that acutely infected people were high transmitters for up to 5 months after becoming infected, accounting for 38% of the transmissions. “If the contribution of acutely infected people to incidence is very

Online on 11 October in the journal *AIDS*, Blower and Columbia’s El-Sadr applied HPTN 052’s design in a model, targeting discordant couples in Malawi, Lesotho, Ghana, and Rwanda. The number of infections prevented varied dramatically according to population size. Malawi, population of 15.3 million, benefited the most; Lesotho, with only 2 million, the least. The rate of new infections, a different measure of effectiveness, also varied considerably among countries. Because Lesotho had the highest HIV prevalence and the greatest percentage of discordant couples, it benefited the most. “One really needs to be very specific and look at the population at hand in order to figure out where does this strategy fit,” El-Sadr says.

Blower says it does not make sense for countries to target discordant couples with TasP. She says the best strategy is to test and treat in geographic hot spots that have the highest prevalence (see Lesotho map).

TasP—including compliance, repeated testing, and drug resistance—could be mitigated by male circumcision. But for it to work, men must first choose to be circumcised, and the procedure has to be properly done. A study published 29 November in *PLoS ONE* asked 241 applicants to the Lesotho Defence Force whether they were circumcised. Trained clinicians examined the 64 who said yes. Of these, 50% either were not circumcised or had portions of foreskin left—an HIV-infection risk. The men who misreported their status were seven times more likely to have been cut by a “traditional” circumciser as part of an initiation rite, which the researchers stress is common in sub-Saharan Africa.

Blower says each country will ultimately have to figure out the best combination of interventions for its population. The “mantra” is that the more interventions we use, “the more synergy we get,” Blower says. “It isn’t true.” If the measures are simply redundant, “synergy might not occur for decades, or you might not get it at all.”

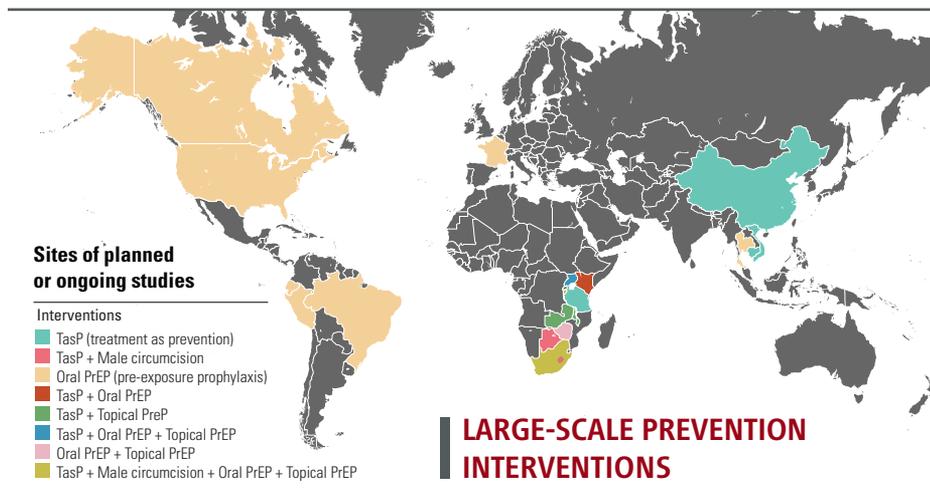
The road forward

Whatever the limitations of the overall scheme, each component of combination prevention makes solid scientific sense. And the abundant enthusiasm on display at the World AIDS Day event in Washington shows that ending AIDS has become something of a movement. But as many speakers at that event stressed, the research successes being celebrated come in the midst of a financial crisis that has many countries worrying whether they can maintain, let alone expand, the HIV/AIDS programs they have in place.

PEPFAR and other programs have begun to look for smart ways to transfer already-allocated funds to support the new opportunities, and they’ve turned to modelers such as South Africa’s Williams to identify the most cost-effective interventions. Williams says male circumcision should be used as widely as possible. “It’s a no-brainer,” he says. “It’s very cheap, and you do it once and it’s for life.” Giving uninfected people ARVs as oral PrEP, on the other hand, he says, would have the most bang for the buck with groups at the highest risk of infection. Treating infected people to prevent spread, he argues, would have the greatest impact: “If you want to stop transmission, the core of it has to be treatment as prevention.”

Models only point out routes to ending AIDS, and many will surely differ from the one proposed by Williams. But for the first time since AIDS surfaced 31 years ago, many researchers believe the destination itself is no longer a mirage.

—JON COHEN



large, we might be very disappointed by the results of combination prevention,” Cohen says. **Hallett and co-workers at ICL showed with a model in *AIDS and Behavior* in May that acute infection likely has a major impact on a community’s prevalence if many people have overlapping, or “concurrent,” sexual partners,** as is common in parts of sub-Saharan Africa and in communities of men who have sex with men. In their model, increasing concurrency from 10% of the population to 12% led HIV prevalence to jump from 3% to 11%.

In the past, some dismissed the Granich model because TasP had never proved its worth in a rigorous study. HPTN 052 ended that argument. But Blower and others have now turned their sights on the limits of HPTN 052.

Scaling up use of oral PrEP, another part of the combination package, raises its own issues—the first being who has priority? Some 7.6 million HIV-infected people in the world need ARVs for survival but have no access to the drugs. Scientists and policymakers alike agree that infected people should receive the lifesaving drugs before the uninfected.

It’s also unclear how much oral PrEP protects women: Two studies have shown it reduces transmission, and two studies have shown no effect. “I really don’t know whether it works in women,” Cohen says. Confusion similarly surrounds topical PrEP, or microbicide-laced gels: On 25 November, a large study reported that it had no effect, putting a question mark on earlier positive data from South Africa.

Several potential flaws dogging PrEP and