Within a couple of years’ time, we may know if two crucial new HIV prevention approaches will work. If they do, what then? Who will pay for them, who will use them, and will their use have a positive or negative impact on the epidemic? A debate at the International AIDS Society (IAS) Conference in Cape Town in July, sponsored by the IAS and the AIDS Vaccine Advocacy Coalition (AVAC) looked at how to prepare for microbicides and pre-exposure prophylaxis (PrEP).

To remind you, a microbicide is a substance that can be incorporated into a lubricant, gel or barrier such as a diaphragm that will stop HIV transmission during sex. And PrEP is the concept of HIV-negative people taking anti-HIV drugs in advance of sex (or needle-sharing) to prevent HIV.

Over the next three years or so, crucial trials of these new prevention methods will announce their results. In 2010, we’ll have results from the biggest microbicide trial to date, the Microbicides Development Programme trial of PRO2000 gel, followed by results from a US trial, too small to produce a definitive result, of PrEP in gay men.

By 2011 we’ll know about tenofovir PrEP in Thai drug users, tenofovir/FTC PrEP in South American gay men, and tenofovir gel as a microbicide in South Africa. 2012 will offer PrEP results from men and women in Africa, and from a comparison trial of tenofovir as a microbicide and PrEP. And 2013 will see the end of HPTN052, a lengthy trial aiming for a definitive answer on whether treating everyone with HIV would stop onward transmission.

New prevention methods in HIV have had setbacks in the last few years, after the Merck HIV vaccine and a microbicide (cellulose sulphate) actually increased the risk of acquiring HIV. But following a promising result for the microbicide PRO2000 announced earlier this year, prevention advocates are daring to believe that positive results could be on their way. UNAIDS’ chief epidemiologist, Catherine Hankins, commented: “I’ve got more of my chips down for PRO2000 than I did. We need to anticipate success and plan a very careful communication strategy.”

Hankins was speaking at an AIDS Vaccine Advocacy Coalition (AVAC) seminar, which preceded the recent IAS conference in Cape Town and brought together leaders in HIV prevention technologies.

Carl Dieffenbach, director of the AIDS Division of the US National Institute of Allergies and Infectious Diseases (NIAID) laid out an apparently straightforward development strategy.

“The first thing we have to do is to prove that these concepts work,” he said. “Then, with the current agents, we have to develop alternative dosing schedules using pharmacological data to maximise adherence.”

This refers to the fact that PrEP and microbicide trials have featured continuous use of the products to try to get the most convincing result. But no one expects this is how people will use PrEP, let alone a microbicide, in real life.

Dieffenbach added, “We need to engage our partners in social marketing programmes that are also pieces of operational research. How are we going to market these products?”

“We also need to keep working on new agents,” he said. This was echoed by Yasmin Halima, the new director of the Global Campaign for Microbicides, who said: “I am really worried about the lack of a drug pipeline for PrEP. If tenofovir doesn’t work, we’re stuffed.”
Others responded that the original question of ‘proof of concept’ was not a simple one. What level of efficacy would be regarded as a success? The PRO2000 trial was powered to demonstrate a protective effect of 30%; its consistent use protected only three out of ten people exposed to HIV. Most panel members said that if the second trial demonstrated this, it would not be enough efficacy to take the product forward.

What would be enough? A straw poll indicated that most audience members would be happy with efficacy of 40 to 60% (roughly comparable to male circumcision), but some would want the product to stop at least four out of five infections (80% efficacy, comparable with real-world condom use).

Sharon Hillier, Director of the Microbicides Trials Network, defined this as the problem of the ‘partial yes’. She foresaw that people would need to use a variety of different prevention methods, rather than putting all their faith in one.

“We need to identify approaches that are going to be used by a wide variety of people,” she said, “which they are going to want to use and have available. We need …funders … willing to buy them and regulators willing to register them. We need to make sure our successes are not just clinical.”

She criticised what she called the hitherto ‘siloiised’ approach in the field, with PrEP and microbicide researchers not co-ordinating research, and rectal microbicide development only slowly being incorporated. “We will need all of these approaches,” she said.

Stephen Becker of the Bill and Melinda Gates Foundation, which has been one of the prime private-sector sponsors of new prevention technologies for HIV, was concerned about the slow progress: “We can’t wait until clinical proof of concept has occurred,” he said. We need to investigate delivery channels, how we engage with policy makers, and how we will market these approaches now.”

He reminded delegates that the current trials of such novel concepts were not sufficient for registration purposes by regulators such as the US Food and Drug Administration. Successful trials might require novel regulatory processes.

Catherine Hankins and other delegates contrasted PrEP with microbicides. Although complementary, they may have to be prescribed and marketed in very different ways. Prophylaxis pills would always have to be prescribed and countries would need to consider strategies for PrEP availability.

“If we are certain PrEP will work, we need to strengthen the knowledge of countries as to where their next 1000 HIV cases are going to come from. For whom would PrEP be a useful product? Which groups do I give it to and in what way? To sex workers in exchange for a monthly HIV test? To gay men in exchange for counselling?”

Some countries’ experience of HIV drug side-effects might make PrEP unpopular: “If you are going to introduce it in a country with widespread experience of lipodystrophy related to the use of d4T, you will find widespread resistance to it.”

In contrast, some delegates said that they suspected that if PrEP trials came up with a positive result, widely publicised, a black-market culture would start. Morenike Ukpong of Nigeria’s New HIV Vaccine and Microbicide Advocacy Society said: “I tell you, if a result is announced at a conference, PrEP will be on the market in 24 hours.”

Professor Helen Rees, Executive Director of the Reproductive Health and HIV Research Unit (RHRU) at the University of Witwatersrand in South Africa, agreed: “If PrEP works, we can’t waste a lot of time debating registration, because people will vote with their feet and start to use it. There are several studies in Africa to show that people are secretly taking it already, with findings of drug in people’s blood and so on.”

She emphasised the urgency and importance of finding out if PrEP was safe and whether it would differently affect populations excluded from the trials such as pregnant women and adolescents.
Like many delegates, she also stressed the urgent need to do trials of intermittent use (a study comparing intermittent versus continuous use in heterosexual couples has just begun in Uganda).

With microbicides, the potential still exists, especially if PRO2000 produces a positive result, that they could eventually be sold over the counter.

Dr Francois Venter, also of the RHRU, described himself as a microbicide sceptic. Delegates should not dismiss the effect of the public’s perception of “a lot of failed trials – the field is vulnerable. We do need varied prevention approaches, but this is an expensive approach. There is a lot of rhetoric around about how women are dying and need protecting: they do, but I’m sceptical about how in a country like South Africa, you decide who is high risk enough to need it, and how you tell them that. How are you going to ensure that people who go home deciding to have sex that night will use a microbicide?”

Delegates answered by citing microbicide acceptability studies. These showed that people liked microbicides: for the first time, we have an HIV prevention intervention that could potentially make sex more rather than less enjoyable.

Sharon Hillier commented: “Maybe if they’re going to make sex fun, people who don’t consider themselves at risk and who wouldn’t take a medicine might use a microbicide.”

She said it was important to find out how people thought. For instance, in one trial in Uganda, the microbicide had an unexpected double effect: firstly, women said it made sex fun and then, because of that, their male partners were more faithful. When the trial stopped, their men started looking for other girls. “Prevention interventions may have completely unexpected additional positive and negative effects,” she said.

Nonetheless, Francois Venter maintained, it was going to be an extremely hard job persuading funders to pay for approaches with only partial efficacy. It’s not just about whether these interventions will work and can be promoted ethically; can cash-strapped health systems pay for them?

Dr Yogan Pillay, Director of Strategic Health at South Africa’s Health Ministry, agreed, commenting that it was challenging enough “pay[ing] for the cost of HIV treatment today and paying for TB and opportunistic infections too. Don’t ask me to be on a panel discussing paying for PrEP!”

Pillay and others drew parallels between the new technologies and circumcision. Three conclusive randomised, controlled trials showing that circumcision prevented about 60% of infections in men had not translated into national programmes.

Patrick Ndase, regional physician for the Ugandan PrEP trial, said that partial efficacy had been a stumbling block of circumcision programmes. “We need to do convincing modelling studies of efficacy and cost-effectiveness so that these options become really attractive to people who are already trying to fund HIV or TB treatment. We need to cost this approach before it comes to our doorstep.”

“We need to be deciding what language we need to use with the ministries and the funders that is going to make them decide to support an approach with 50% efficacy.”

Yasmin Halima said that this was why an ongoing development pipeline for biomedical prevention was so important: we would not, in all likelihood, be able to stop at the first approach licensed and say it was good enough. Jim Rooney of the tenofovir manufacturers Gilead agreed, saying his company was looking at approaches such as a long-term injectable formulation of their new HIV drug rilpivirine (TMC278).

Zeda Rosenberg, Director of the International Partnership for Microbicides, summed up the feeling of the meeting. “We’re used to scepticism,” she said. “The sceptics used to say ‘it won’t work and women won’t use it’. Now they say ‘You won’t be able to fund and deliver it to the people who need it’. That’s progress!”
References


Conference news
• Overall HIV prevalence stabilises at 11% in South Africa, with decreases in younger age groups
• Elvitegravir ‘Quad’ pill performs well, new booster cobicistat works as well as ritonavir
• Increased testing leads to decrease in viral load and infections in San Francisco, and in late diagnosis in Washington

Women and HIV news
• Preventing cervical cancer: good outcomes from screening programme for HIV-positive Zambian women
• Pregnancy rates rise in women after beginning ART
• Progestogen-only hormonal contraception linked to metabolic problems in HIV-positive women

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