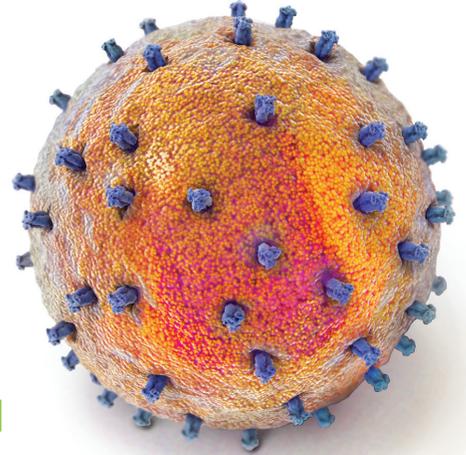


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The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

## Wringing out HIV

Results from efficacy studies of a new approach to HIV prevention were the biggest news to emerge from this year's Conference on Retroviruses and Opportunistic Infections. *By Michael Dumiak*

Last summer more than 2,500 women from Malawi, South Africa, Uganda, and Zimbabwe completed their participation in a three-year clinical trial designed to show whether a vaginal ring—a silicone 'o' containing an experimental antiretroviral (ARV) that is inserted into the vagina—could reduce a woman's risk of contracting HIV. This was the larger of two simultaneous efficacy studies to determine whether this approach to pre-exposure prophylaxis (PrEP), the use of ARVs in healthy individuals to ward off HIV infection, would work.

Results from these two studies were presented recently at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, one of the largest annual meetings of HIV scientists and clinicians. The results show that a vaginal ring containing an ARV known as dapivirine (DPV) does prevent women from acquiring HIV, but how well it works depends on how compliant the volunteers were and this varied greatly by age in both studies.

Overall, behavioral issues related to PrEP loom large and they were a major topic of discussion at CROI. Other approaches that aim to circumvent adherence issues also received top billing, including studies involving direct injection of anti-HIV proteins known as broadly neutralizing anti-

bodies as a means of HIV prevention and the development of long-lasting ARVs that may be applicable for both treatment and prevention of HIV infection.



### Aspiring to protection

The two efficacy trials of the DPV-containing vaginal rings were: A Study to Prevent Infection with a Ring for Extended Use, or ASPIRE trial (MTN-020), and what's called The Ring Study. ASPIRE, led by the National Institutes of Health (NIH)-funded Microbicide Trials Network, was the larger trial with 2,629 volunteers enrolled at 15 study sites: nine in South Africa, three in Zimbabwe, two in Malawi, and one in Uganda. This trial took place from August 2012 to June of 2015. The Ring Study was led by the International Partnership for Microbicides (IPM) and

involved 1,959 women volunteers in South Africa and Uganda.

DPV-containing vaginal ring development dates back to 2002 with the founding of IPM, which holds the global license for DPV. The experimental ARV was never licensed for HIV treatment. Volunteers in both trials were counseled to use the ring continuously and return each month for collection of the spent device, to obtain a fresh one, to be tested for pregnancy, HIV, and other sexually transmitted diseases, and to receive HIV prevention and risk-reduction counseling. Follow-up was for a minimum of one year.

Results from ASPIRE and The Ring Study differed only slightly in their overall protection rates, with ASPIRE showing an overall 27 percent reduction in HIV infection and The Ring Study showing a reduction of 31 percent. But the trials showed vastly differing rates of protection when analyzed by age. In ASPIRE, women aged

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18 to 21 showed no overall reduction in HIV risk, whereas in The Ring Study it was only 15 percent. However, there was a 56 percent reduction in risk for women ages 22 to 26, and a 51 percent reduction among women ages 27 to 45 in the ASPIRE trial. The Ring Study showed 37 percent efficacy in women older than 21.

The main reason the protective effect varied so greatly was adherence. Adherence was significantly lower among younger women who happen to be at the highest risk of contracting HIV. “We really wanted those numbers to be higher. We were disappointed, too, originally,” says Annlene Nel, IPM’s Paarl, South Africa-based chief medical officer. Even so, the researchers behind the studies say the results are compelling enough to pursue licensure of the DPV ring for HIV prevention in women.

To receive regulatory approval, the group needed two pivotal trials showing statistically significant efficacy. “We’ve got that,” says Nel. “It is modest efficacy. We know that, very much so. But look at the burden of disease in the communities where we are conducting this trial. It is significant. If you can prevent a third of women from contracting HIV, over 10 years you prevent thousands of women from becoming HIV positive. Long term you can really change the incidence.”

Development of the ring itself comes directly from the effort to improve adherence—insert the ring and forget about it, as opposed to oral PrEP, which requires women take a pill on a daily basis. But adherence is still an issue with the ring.

Nel and other researchers suspect non-adherence had to do with volunteers being leery about the safety and efficacy of the product. “There may also be rumors in the community. A negative influence really spreads. And when there’s a change of partner, there’s

a fear component where they will not disclose and then they might just remove the ring.”

Sheena McCormack, a clinical epidemiologist at the Medical Research Council Clinical Trials Unit at the University College of London, says the rings are a new beast altogether, and there are issues around vaginal practices that may influence their use. “Women do like to wash after sex. It’s possible they take the ring out to do that. It might be something that doesn’t fit with their culture, doing that with the ring in,” she says.

But even though adherence remains an issue, many researchers are optimistic about the DPV ring as an additional HIV prevention option for women. Robin Shattock is an immunologist and mucosal infection expert at the Imperial College of London who is researching combination prevention approaches. This includes ARV-based gels or rings as well as the use of broadly neutralizing monoclonal antibodies. He suggests there are some things that may help improve upon the results of the two ring trials. “When the ring was being designed, they could have put more drug into the ring. I think more drug probably would have given higher efficacy in women that used it,” he says. “That can be improved.”

A combination of drugs may also provide better protection. Shattock says combining the ring with a contraceptive, as IPM plans to do, would be a no-brainer. “Women may then be using it for the convenience of contraception, and to have a contraceptive ring that also provides some level of protection against HIV may be more appealing than thinking, ‘I’m at risk and need to have something that will stop me from getting HIV.’” For any of the PrEP regimens, adherence is the key to efficacy. “For these things to work, people need to use them,” Shattock says.

Bruce Walker, an immunologist and director of the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology (MIT), and Harvard, says tools need to be independent of behavior. “We need things that are going to work in women at the most vulnerable periods of their lives. The fact the ring didn’t really work in women before age 25 is a disappointing finding. I’m less optimistic about that being part of a solution for HIV infection,” he says. “The more you can take behavior out of the equation, the more successful these interventions are going to be.”

Three of the 15 clinics in the ASPIRE trial were located in Zimbabwe, serving 678 of the study volunteers. Nyaradzo Mgodzi of the University of Zimbabwe served as clinical researcher directing the study. “In Zimbabwe we have a saying, home is a woman. We want to take care of women because this is how you make steps in promoting public health. I’m happy about the results,” Mgodzi says.

She thinks that in Zimbabwe a ring has a better shot of being used, even given the adherence questions. “Most young women in Zimbabwe are unemployed. Some of them have secondary education. They are homemakers, they take care of their family and extended family,” Mgodzi says. “Any day they may be asked to go to rural areas to look after a sick relative, or attend a funeral, or go to a church conference.” Mgodzi recalls the VOICE trial that tested oral PrEP in sub-Saharan Africa. “The volunteers used to say they would forget sometimes to take their tablets. They want something which is less user-dependent, so I think this will be good.”

IPM is pushing ahead with an open-label, follow-on study of Ring Study volunteers, and is also in discussions for a similar open-label study for ASPIRE participants. Open-

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label studies may positively influence adherence, according to the University of Washington's Jared Baeten, who led the ASPIRE study. Baeten says what is important now is to understand who are the populations that would use a pill, and who are the populations that would not use a pill but might use a ring. Meanwhile, the group is compiling data for a submission dossier which, if things go as planned, should be delivered to the European Medical Association and regional southern African regulators either by the end of this year or in the first quarter of 2017.

## Researchers to antibodies: Stick around

Another realm of prevention research discussed at CROI centers on the hundreds of anti-HIV proteins or antibodies researchers have isolated in recent years. These antibodies are capable of knocking out a broad swath of HIV strains circulating around the globe, earning them the moniker of broadly neutralizing antibodies (bNAbs). These antibodies are the types that vaccine researchers ideally wish to induce through immunization.

In the meantime, researchers including John Mascola, director of the National Institute of Allergy and Infectious Diseases' (NIAID) Vaccine Research Center, want to determine whether directly injecting these antibodies into people may be able to protect them from HIV infection, an approach referred to as passive administration. To optimize the antibodies for this purpose, researchers are attempting to improve their potency and staying power so that less antibody is necessary to protect and it sticks around for a longer time.

Within the next couple years, Mascola says, antibodies targeting four major sites on the virus are likely to be in passive-administration studies. The question now is what amount of antibody is sufficient to prevent HIV infection. To determine this, researchers are now enrolling volunteers in a Phase IIb study, known as the Antibody-Mediated Prevention (AMP) Study. "Can a passively infused antibody prevent HIV in humans?" Mascola asked. "That's what needs to be studied and answered." AMP will be a placebo-controlled study of an antibody identified by NIAD researchers. The antibody, known as VRC01, will be

administered every two months in 2,700 men who have sex with men and transgendered people in North and South America, and 1,500 women in sub-Saharan Africa.

Mascola says there are many reasons to pursue passive administration: there's a reasonable chance it will work; that because the antibodies are human antibodies they are likely to be well-tolerated; and that a single shot could potentially deliver long-term protection against HIV, reducing some of the reliance on adherence that is required for oral PrEP or even the vaginal rings. The ultimate goal, he says, is a subcutaneous injectable antibody that could be given every three to four months and safely and effectively protect high-risk individuals from HIV infection. "That's where the field is trying to go," Mascola says.

To do so, any eventual product needs to meet specific targets: it will need to cover 98 to 99 percent of all HIV strains, which may require a combination of bNAbs, cost about as much as ARV-based PrEP, and be injectable every three to four months. These elements, Mascola says, are already achievable in the lab.

## Long-lasting inhibition

Another long-lasting approach to HIV treatment and prevention involves a new generation of incredibly durable ARVs. Jay Grobler, director of infectious disease biology at pharmaceutical company Merck, presented data at CROI on a long-acting, experimental drug known as MK-8591, which the company licensed from Japanese company Yamasa. Grobler said the drug has the potential for once-weekly oral administration as well as much longer-acting parenteral administration that could persist for up to a year. The drug is being explored for both HIV treatment and prevention.

Grobler reported results from Phase I studies of MK-8591, which he says showed the drug persisted even longer and had better antiviral activity in humans than in either laboratory studies or animal experiments. Following a single oral dose, Merck researchers saw a very rapid uptake of the drug, with high concentrations reached in blood within an hour.

Merck considers the drug an ideal candidate for low-dose parenteral formula-

tions, either by injection or patch, which release effective drug levels for up to 180 days. There is potential for the long-acting ARV to even provide coverage for up to a year's time. This would greatly reduce the burden of therapy.

David Margolis, director of drug development at ViiV, the HIV joint venture between GlaxoSmithKline and Pfizer, has been overseeing another long-acting HIV therapeutic—in this case, combining two licensed ARVs (cabotegravir and rilpivirine) that were developed as once-daily pills. In the LATTE program, for which Margolis presented the second round of study results at CROI, researchers are testing the combination as an injectable, long-acting HIV treatment.

LATTE 2, a 32-week study aimed at establishing safety and efficacy of the combination and to set a dosing schedule for future trials, involved 286 volunteers randomized to receive gluteal shots of the ARVs either every four weeks or every eight weeks. A third group took oral doses of the two drugs daily.

Volunteers with the highest level of virologic success were in the group that received shots every eight weeks (95% as compared to 91% in the daily oral dosing group). Volunteer satisfaction was also higher for the injection than the oral dosing. The next step, Margolis says, is a 48-week dose-selection for upcoming Phase III trials.

The long-acting ARV combination outlined by Margolis could be a "game changer" for treatment and prevention once implemented, according to Steve Deeks, a clinician at the University of California at San Francisco who specializes in HIV inflammation. However, in Deeks' view the data with MK-8591 could be an even more exciting approach to treatment and prevention. "It is potent and can be formulated for very long-acting delivery methods, due to the limited amount of drug needed to block HIV," the San Francisco clinician says. "This data was a complete surprise and quite novel." ■

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# Understanding the Gut Microbiome and HIV

Why are HIV researchers interested in the bacterial and fungal environments present in the human digestive system? *By Michael Dumiak*

Our bodies are not really ourselves: at least not completely.

Trillions of bacteria, fungus, and viral organisms make their homes throughout and on the surface of the human body in a series of mini ecosystems. Scientists refer to this as the human microbiome. The creatures that live in the microbiome are the microbiota.

Researchers are particularly interested in the microbiota and the composition of the microbiome in the intestinal tract in the stomach or gut. It is there that the microbiome seems particularly lively and where researchers suspect that altering or modulating the multitude of microorganisms that live there can have either ill or beneficial effects upon the health of an individual. One simple example of modulating the quantity of microorganisms in the gut is taking probiotics, such as those in yogurt, which are the types of good bacteria that can aid digestion. Viruses, like HIV, can have a negative impact on the gut microbiome, and there may be links between the gut microbiome and other diseases as well, including Malaria.

## HIV and the gut

Scientists have known for some time that HIV is first and foremost a virus associated with the gut. From the moment after it establishes initial infection, HIV wreaks havoc in the gastrointestinal tract. The virus primarily attacks immune cells known as CD4<sup>+</sup> T cells and the majority of these cells exist in the tissues that line the gut. As HIV infects these cells, it results in inflammation. As the virus progresses and becomes a persistent, chronic presence, it disrupts the regulation of the immune system in the intestines and the mucosal barrier that lines them, allowing bacteria to escape the gut. The alterations in the gut mucosa that occur as a result of HIV infection may also affect the microbiome. In recent years researchers have linked the malfunctioning of the intestinal immune barrier to an imbalance in gut bacteria, with much more ‘bad’ bacteria being pres-

ent than ‘good’ as a result. This imbalance can spark chronic inflammation and overstimulation of the immune system, one of the hallmarks of HIV and a long-term problem, even in individuals on effective therapy.

Last April the US National Institutes of Health, among others, sponsored the first HIV Microbiome Workshop, drawing more than 100 researchers and participants. A second, larger workshop will be held in November, signaling the increasing interest in studying the microbiome in the context of HIV research. This topic was also one of many discussed earlier this year at the annual Conference on Retroviruses and Opportunistic Infections.

Efforts are underway to describe and understand the gut microbiome and its apparent involvement in the progression of HIV disease. Researchers hope that one day it may even be possible to change the makeup of a person’s gut microbiome to reconstitute immune function in those living with HIV. This could reduce virus-related chronic inflammation which affects all HIV-infected individuals even if their virus levels are kept in check by antiretroviral therapy. By reducing inflammation, it would help ease some of the health burdens associated with chronic HIV infection such as heart disease, increased risk of stroke, and accelerated aging.

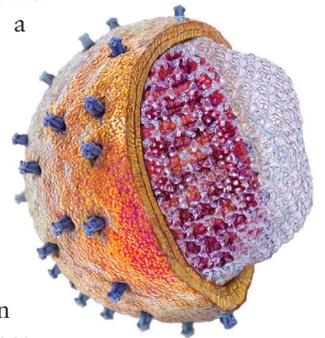
One such effort underway by researchers at the University of California in San Francisco (UCSF) involves fecal microbial transplantation, in which the poop containing healthy or particularly calibrated microbiota is transferred to a patient’s colon. UCSF gastroenterologist Ma Sansouk says it is possible that administration of different types of good bacteria could boost the effects of therapies aimed at curing HIV. He says it could also help restore the very damaged gastrointestinal tract of someone with HIV infection. This strategy is successful in treating another infection but it is still early days in using fecal transplantation to reverse the damage from HIV. Further research and experi-

mentation is necessary to see if this will be a feasible approach.

## Understanding the microbiome

It is an age of discovery for the microbiome, but it is also rather complicated. There are trillions of different microorganisms that reside in the gut and it is difficult to tease out exactly what is happening there. Unlike blood samples that can easily be obtained to track the progression of HIV infection, gut biopsies are harder to come by.

There are also vast differences in the microbiomes of different people as a result of geography and diet. A person growing up in the west may have very specific differences in their gut microbiome from someone in rural Africa, whose diet varies greatly.



Jesús-Mario Luévano, Jr., a medical student at Harvard Medical School and a member of Doug Kwon’s mucosal surfaces lab at the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology, and Harvard, analyzed 140 fecal samples from volunteers in Boston and 110 from Ugandan volunteers. He found a clear difference in the samples taken from Boston volunteers who were HIV infected and those uninfected. But this difference based on HIV-infection status was not evident in samples from Uganda. However there were clear differences in the composition of the microbiomes between Ugandan volunteers and those in Boston regardless of whether they were HIV infected. This variation illustrates how difficult it may be to determine precisely what effects HIV has on the microbiome. ■

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