Testing HIV Prevention Tools: Other Ways Up the Alley

Condoms (and maybe PrEP) can complicate prevention trials. But there may be solutions.

March 14, 2013 By Anna Forbes and Jim Pickett

Yes, we have condoms. But what else works to prevent HIV? This question drives research into pre-exposure prophylaxis (PrEP, when HIV-negative people take HIV meds to keep from contracting the virus), microbicides (gels and other products applied to the vagina or rectum that contain meds to prevent infection), vaccines and other HIV prevention strategies.

While we place a lot of focus—and hope—on these new prevention strategies, it is time to reconsider how we test these tools to see if they work. Is it possible that the trials, themselves, are creating roadblocks to prevention breakthroughs? For example, trial participants receive condoms and condom counselling because, ethically, researchers have to do everything they can to reduce participants' risk of acquiring HIV. It is the right thing to do. But these new prevention tools are needed most by people who do not use condoms regularly. So isn't there some ethical way to test the products under conditions that are more like real life?

Researchers and advocates have been asking these questions—and raising the related ethical concerns—as they explore ways to improve the testing process. But before delving into the details and the future of prevention trails, the need for this discussion must be reiterated: We can no longer ignore the fact many people don't use or don't like condoms. If they did, the number of new HIV infections in the United States every year would have decreased as condom promotion increased. It hasn't.

In fact, the National Institutes of Health (NIH) reports that only "25 percent of men and more than 20 percent of women reported using a condom during their most recent sexual experience." Among U.S. women at highest risk for HIV, that figure is 18 percent. While a lot more gay men are using condoms, 54 percent reported having unprotected anal intercourse in one survey by the Centers for Disease Control and Prevention (CDC). Male condoms are readily available in most places, and female condom access and use is increasing. But the bottom line is still that most people aren't using condoms. We need more choices.

Future of prevention research—more complicated, more costly

Alternatives have been identified, but determining how well each one works is very complicated. Since the safety of the participants in clinical trials testing PrEP, microbicides and vaccines is paramount, trial participants receive the best prevention package and care currently available to help them reduce their HIV risk. At present, this generally includes HIV testing, free condoms (male and hopefully female too), condom counselling and testing for sexually transmitted infections (STIs) and treatment as needed.

Last summer, in a first, the U.S. Food and Drug Administration approved HIV med Truvada for use as PrEP (it's prescribed as a daily pill). In the near future, PrEP may also be added to the mix for participants wishing to use it.

Imagine how adding PrEP might play out in a clinical trial testing a new microbicide. All trial participants would receive free condoms and be regularly urged to use them. They would also be offered PrEP and, if they accept, would be reminded to take it consistently and correctly.

In addition to the prevention package, participants in one arm of the trial would get the candidate microbicide (containing active ingredients) and those in the other arm would get a placebo (something that looks just like the test product but does not contain the active ingredients). The researchers would then watch to see how many sero-conversions occurred in each arm. The candidate microbicide would only be judged effective if fewer new infections occurred in the test product arm, indicating that the product added to the amount of protection received by people who already had other effective prevention methods at hand.

You can see how a microbicide would have to be highly effective in order to show any additional benefit in this scenario. In the CAPRISA 004 trial in 2010, all trial participants received condoms and counselling. The women in the test product arm had 39 percent fewer new HIV infections than the woman in the placebo arm, so the test microbicide (a gel containing tenofovir, an ARV drug) was shown to be moderately effective. Is 39 percent reduced risk lower than the protection provided by consistent condom and/or PrEP use? Yes, of course. Do women still urgently want access to this gel? Yes! If their male partners won't use condoms, women want at least some protection if they can get it. In fact, "Where the hell is the gel?" demonstrations have broken out at international conferences since CAPRISA 004.

So the prospect of adding PrEP to the clinical trial prevention package raises a difficult conundrum. On one hand, there is the imperative to "first do no harm" to trial participants. They must have tools to reduce their HIV risk. On the other hand, there is the challenge to show that any test product is superior—or at least not inferior—to such a strong baseline prevention package. The stronger the package, the more participants have to be enrolled in order for researchers to have enough data to make any statistically valid comparison between the level of protection in the test product arm and the control arm. Using the current prevention package (condoms and counselling), trials must recruit several thousand participants to get valid measures of effectiveness. If PrEP is added to the baseline prevention package, researchers will likely have to enroll 10,000 to 20,000 people to get meaningful results. The added expense and complexity of this would likely result in far fewer effectiveness trials being conducted.

Hold “run-in” auditions before trials to recruit appropriate volunteers

We need to design prevention trials that ask, “Is this test product better than nothing?” rather than, “Is this test product better than the best available prevention combination we have?”

One way may be using a “run-in” period to select who should enroll in a particular clinical trial. Run-in periods are relatively common in treatment research. Participants with high blood pressure, for example, may be invited to enroll in a trial for a hypertension medication if their condition is not responding adequately to current standard treatments.

If they meet the eligibility criteria, they may first be asked to take a particular drug or intervention during the run-in period to see if their bodies respond to it. Those who respond in one way are invited to enroll in the actual trial, in which a test treatment or intervention is provided. Those who respond in another way are not enrolled. This allows researchers to get effectiveness data from a cross section of people whose bodies do respond to the drug and not from those who don’t.

A run-in period is kind of like an audition for the actual trial. It is not part of the trial, and it lets researchers select trial participants from among those who audition. The selected volunteers who still want to participate and give their informed consent are enrolled and randomized (assigned randomly to one of the trial arms). Randomization removes the chance that trial results will be biased.

Recruit people who don’t regularly use condoms? Here’s why—and how.

Run-in trials have never been used to sort participants on the basis of their frequency of condom use, though it was briefly considered in connection with the MIRA diaphragm trial. This trial was done to see if using a vaginal diaphragm and gel provided additional protection from HIV beyond that provided by the prevention package. No additional protection was detected, but principal investigator Nancy Padian and her team pointed out that they might have learned more about the effectiveness of the diaphragm “if we [had] excluded those who were able to use condoms consistently after a short run-in.”

What could a prevention trial run-in look like? Presumably, those auditioning would be provided with condoms and intensive condom counseling at every visit. At the end, researchers would collect data on reported rates of condom use. Those who said that they didn’t use condoms consistently (even though they were freely available and strongly recommended) would be invited to participate in the trial. Condoms would still be provided to all trial participants. But the odds that these participants were using the condoms would be different because of the pre-selection of volunteers who had already indicated low condom use.

This idea of using a run-in period to identify and recruit participants who acknowledge that they were unlikely to use condoms regularly was raised at a January 2013 meeting called “Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues.” There were objections from several researchers and funders present, one of whom flatly said, “NIH would never fund a trial

like that.” Others pushed back on that resistance, noting there was ethical space between the obligation to help reduce trial participants’ HIV risk to the greatest extent possible and the urgent public need for additional prevention tools.

Those eligible for the study at the end of such a run-in period would go through an intensive informed consent process to firmly establish their understanding of the following four things: (1) their knowledge that condoms are an extremely effective tool for protection from HIV if used consistently and correctly; (2) that condoms would always be available to them free of charge throughout the study; (3) that the study staff fully would support their condom use; and (4) intensive condom counseling would not be provided at each trial visit, as it had been during the run-in period. To help ensure participant safety, free condoms would still be available at each visit.

This model was also discussed in connection with future trials that might offer PrEP as a part of the prevention package. Some study participants might be unable or unwilling to use PrEP during a run-in, for whatever reason. Those declining PrEP at the time of enrollment might then be invited to join a prevention trial testing in which PrEP was offered as part of the prevention package.

Protecting the safety of trial participants is ethically fundamental. But how does it interact with the participant’s right to autonomy? If people are properly informed and consented, and make decisions of their own free will to not do something—is that unethical?

Problems with relentless condom promotion

Some meeting attendees raised concerns about the intense promotion of condoms in clinical trials. Repetitive, intense condom promotion could:

1. Discourage individuals who don’t regularly use condoms from participating in the trial, because they know that they won’t be able to “follow the rules.” Their under-representation could detract from the trial’s ability to assess the test product’s impact on the very people in greatest need of condom alternatives.

2. Cause temporarily increased levels of condom use that are unsustainable after the trial ends.

3. Induce participants to lie to researchers about their condom use and possibly to misreport other behaviors as well (such as their use of the test product) because they want to make the study staff happy.

4. Inhibit realistic discussions of the full range of safer-sex behaviors by prioritizing condom use over other protective behaviors. If trial participants decide not to use condoms because they are engaged in other protective behaviors, will they then be honest in reporting this decision to researchers?

5. Assume participants cannot make a deliberate, informed choice about condom use.

What is ethical? What is unethical?

Is it unethical to offer people the option of participating in a trial in which condoms are supplied for free and discussed with all participants—but in which it is understood that many of those participants do not or cannot use them and that they are aware of the associated risks?

What trials will be pursued if each proposed prevention tool has to prove its superiority to an existing, expanding prevention package? How can we prove if anything new “works” if we recruit people into trials who are consistent condom users and consistent PrEP takers?

There are also serious ethical issues associated with reaching the point at which research to measure the effectiveness of low-cost, easily distributed, potentially non-prescription prevention tools (such as non-ARV-based microbicides) cannot be done because we simply can’t afford to of find out if they are better than existing, expensive, prescription-only prevention tools.

What is the best way to involve trial host communities and advocates in decisions around trial design? Should they be involved in deciding whether or not it is ethical to use a run-in period as a basis for selecting participants? To play an informed role in shaping these decisions, host communities and governments will need education about the challenges associated with doing these trials and the ethical and logistical implications of any proposal to move away from intense condom (and possibly PrEP) promotion.

Distributive justice and individual rights

At the Forum meeting in January, Deborah Donnell reminded us of the principle of distributive justice—the benefits and risks of research should be fairly distributed. She noted this can be interpreted to mean research studies should address areas of the greatest unmet need. Whether viewed within discreet populations (gay men seeking condom alternatives) or globally (women who lack the autonomy to insist on condoms), the need for new ways to prevent HIV is undeniable.

The ethical imperative to protect individuals enrolled in HIV prevention trials is also unarguable. But how they are protected, and how they wish to be protected, needs to be reconsidered in light of their own right to autonomy and the demands of distributive justice.

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