New HIV Prevention Research

After the discovery of HIV in the early 1980s, the best available methods to prevent sexual transmission of the virus were condoms and behavioral counseling. In recent years, the picture has changed dramatically with the finding that anti-HIV drugs (antiretrovirals) can protect HIV-negative people from acquiring the infection—an approach called pre-exposure prophylaxis (PrEP). Effective antiretroviral treatment can also prevent people living with HIV from transmitting the virus to sexual partners by reducing the amount of virus in the bloodstream to undetectable levels (a message communicated by the Undetectable = Untransmittable or U=U campaign).

These advances have greatly improved HIV prevention efforts, but they also complicate the scientific search for additional biomedical prevention options, such as vaccines.

Researchers determine if new experimental HIV prevention options work by conducting large-scale **efficacy*** trials. Typically, these trials enroll people who are particularly vulnerable to acquiring HIV and randomly assign them to either receive the experimental intervention or a dummy version known as a placebo (the group not receiving the intervention is known as the control arm of the trial). Researchers then compare how many people acquire HIV in each group during the trial and use statistical calculations to assess whether the intervention significantly reduced the risk of acquiring HIV.

Research ethics require that everyone in biomedical prevention efficacy trials be offered the best available HIV prevention methods, known as the standard of care. In the era where the HIV prevention standard of care included only condoms and counseling, efficacy trials could be conducted knowing that the number of people acquiring infection would likely reach the threshold needed to show if the experimental prevention intervention worked.

Now that the availability of PrEP has greatly improved the standard of HIV prevention care, this historical approach to efficacy trials is being reevaluated. If everyone in an efficacy trial of an experimental HIV prevention intervention accepts and adheres to PrEP, very few HIV infections are likely to occur, making it difficult or impossible to figure out if the new approach worked better than the placebo.

This is a good problem to have. It's important to recognize that researchers don't want anyone to acquire HIV; the reason for doing these types of trials is that current prevention options don't suit everyone, and new options are needed. But it means that researchers and other stakeholders—including community-based prevention advocates—are having to consider different, innovative trial designs to demonstrate that new HIV prevention strategies are effective.

New approaches to HIV prevention efficacy trials include "noninferiority" designs that assess if an experimental intervention works at least as well as an existing, approved approach. These trials can be used if the interventions are similar; for example, comparing a new antiretroviral drug to the licensed drug Truvada for PrEP.

Another more complex approach involves conducting efficacy trials that focus on enrolling people at risk of HIV infection who choose not to use PrEP. The challenge for this type of trial is ensuring that potential participants have made what researchers call an authentic choice to decline PrEP.[1] Some proposals involve a lead-in period before a trial during which people interested in participating would try available PrEP options in order to decide if those options are right for them. People would enroll in the trial only if they did not find available PrEP acceptable.

Researchers and even regulators, like the U.S. Food and Drug Administration, are also talking about using "external" or "historical controls" to help evaluate new prevention options. In one approach under exploration, bacterial sexually transmitted infections (STIs) are being viewed as a way to estimate the number of HIV infections averted in a clinical trial (based on evidence that the incidence of rectal gonorrhea is typically predictive of the incidence of HIV infection among men who have sex with men).[2] Another method might be to use historical **incidence**** data to create an external control arm. The idea behind both is to estimate how many participants would have gotten HIV in the absence of effective prevention options, to sidestep

the ethical issues around providing the standard of prevention. The challenge here, however, is making sure that the methods are rigorous and provide reliable information; it would be a problem if the true efficacy were under- or over-estimated.

New ideas for conducting efficacy trials have already moved from theory into the real world. The strategy of enrolling people who choose not to use PrEP is being employed in an HIV vaccine efficacy trial named Mosaico, which began in 2019.[3] This makes it important for community members interested in HIV prevention research advocacy to become familiar with how new trials are being conducted, so they can provide meaningful input into whether the designs are ethical and appropriate.

*** Efficacy/Efficacious and Effectiveness**
Efficacy and efficacious are terms that refer to how well an intervention works in the controlled context of a clinical trial. Effectiveness refers to how well an intervention works in the real world, outside of a clinical trial.

**** HIV incidence**
HIV incidence is a measurement of how many people are diagnosed with HIV infection during a given period of time.

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[3] https://www.mosaicostudy.com/