Giving it a Try: A Guide to Clinical Trials

Studies of new treatments, prevention tools, comorbidity management and cure strategies are key to better quality of life for people living with or at risk for HIV.

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Most of what we know about HIV prevention, treatment and care comes from clinical trials. There are many types of research studies, and they all add to our knowledge in different ways. Joining a trial can be a good way to gain access to cutting-edge therapies and contribute to science, but it's important to weigh the pros and cons.

"We really need rigorous clinical trials," says Jeanne Marrazzo, MD, MPH, director of the National Institute of Allergy and Infectious Diseases (NIAID). "They're not perfect, and they're not the real world. They don't always give us the answers we want, but I do think they give us the answers we need."

Trial Basics

The gold standard for research is the double-blind randomized controlled trial. In these studies, participants are randomly assigned to receive an experimental intervention or a comparison—for example, current standard care or a placebo. This minimizes bias and helps ensure that the groups are otherwise similar. Double-blind means neither the researchers nor the participants know who is in which group; if these assignments are known, the study is open-label.

Randomization means that any given participant might not be initially assigned to the experimental group. But modern antiretroviral therapy trials do not include inactive placebos, and often, participants will be offered the new treatment once the randomized part of the study ends.

For ethical and practical reasons, some studies can't use randomization, controls or blinding. Observational studies—such as the large Multicenter AIDS Cohort Study and Women's Interagency HIV Study, which were combined in 2019—also yield valuable information. These studies don't test specific interventions but rather monitor real-world outcomes over time.

A good trial design ensures that a study can provide useful data. Trials should include enough participants and last long enough to produce statistically significant results, meaning that the findings are unlikely to be due to chance alone. What's more, it's important to include participants who reflect the full population that will use an intervention in the real world, including people with more advanced disease or coexisting health problems and people of all genders, ages and racial and ethnic groups.

New Treatment Trials

The most familiar clinical trials assess new treatments in a stepwise manner (see "Clinical Trial Stages" below). The process of developing new medications is lengthy and expensive, and only a small fraction of experimental therapies ever make it from the laboratory to pharmacy shelves. The fact that a new drug shows activity in a test tube or a mouse doesn't necessarily mean it will work in humans.

Early in the epidemic, AIDS activists were instrumental in speeding up access to new therapies. Thanks to these efforts, the Food and Drug Administration (FDA) can grant accelerated approval of experimental drugs based on surrogate markers, such as viral suppression, rather than waiting to see whether study participants get sicker or die.

In the early years, treatment trials were riskier. Scientists often didn't know whether investigational drugs would work or what side effects they might cause. Nonetheless, people with no good options were eager to enroll. Once effective combination antiretroviral regimens were developed in the mid-1990s, the focus turned to reducing side effects. Today, many trials aim to make treatment easier—for example, by testing drugs that can be taken less often.

Now that many people with HIV are doing well on treatment, there's less incentive to join a trial to find something better. But some people still need other options, such as those who can't take daily pills and long-term survivors who tried less effective medications and developed extensive drug resistance. For the latter group, new options include the HIV entry inhibitors ibalizumab (Trogarzo) and fostemsavir (Rukobia) and the HIV capsid inhibitor lenacapavir (Sunlenca), which work differently than other antiretrovirals and remain active against highly resistant virus.

Nelson Vergel, who was diagnosed with HIV nearly 40 years ago, found himself in this situation, struggling to achieve viral suppression. In 2013, he joined a clinical trial of ibalizumab, a monoclonal antibody that blocks HIV from entering CD4 cells. Within two months, his viral load became undetectable for the first time. "I was able to restart my life again," he previously told POZ.

But looking back, Vergel is more wary. “I joined too many studies in the past that used functional monotherapy, and on each one, I developed more resistance. But I didn’t have many options,” he says. “Everybody should be told that if you join a study, you may not be eligible for other interventions down the line. Now that we have more options, we have to be more transparent about what people give up when they join studies.”

Treatment Strategies

Clinical trials don’t end when new drugs are approved. Some studies look at treatment strategies to learn how best to use them.

When HIV medications were less well tolerated, some experts thought starting antiretrovirals later or taking periodic treatment breaks might reduce toxicity. But two large treatment strategy trials put these ideas to rest. The START study showed that people with a CD4 T-cell count above 500 who were randomly assigned to start antiretrovirals immediately had a lower risk for AIDS-related events, serious non-AIDS complications and death than those who delayed treatment until their CD4 count fell below 350. Likewise, the SMART study showed that participants randomized to stay on continuous treatment had better outcomes than those who took medication breaks when their CD4 count rose above 350. These and other studies helped inform current guidelines that recommend continuous treatment starting as soon as possible after HIV diagnosis.

Once drugs are approved, researchers can conduct pilot studies to try out innovative strategies. For example, long-acting Cabenuva (injectable cabotegravir and rilpivirine) is currently approved only as a switch option for people with an undetectable viral load. Researchers at San Francisco General Hospital’s Ward 86 HIV clinic conducted a pilot study of Cabenuva, given in the context of extensive support, for people who were unable to maintain viral suppression on daily pills. Of the 57 people with a detectable viral load who received Cabenuva injections, all but two achieved viral suppression, many for the first time. Based on these findings, the International Antiviral Society–USA recently updated its treatment guidelines to say that Cabenuva may be considered for some people with detectable virus who are unable to take oral meds consistently.

“For those of us treating HIV on a daily basis, we know that some patients have challenges taking pills, including substance use, housing and food insecurity and stigma,” says Ward 86 medical director Monica Gandhi, MD, MPH. “We saw high success rates that were equivalent to those in clinical trials.”

Prevention Trials

Clinical trials for new prevention methods, such as pre-exposure prophylaxis (PrEP) and HIV

vaccines, follow a similar pathway, but the safety bar is higher. While side effects may be acceptable for HIV-positive people whose health would worsen without treatment, PrEP is used by a large number of healthy HIV-negative people.

Beyond testing specific prevention tools, large trials can also shed light on the bigger picture. The PARTNER studies, for example, showed that people with an undetectable viral load do not transmit HIV via sex (see "Heroes").

As with treatment trials, it is important for prevention studies to include all populations that will use an intervention in the real world—and the FDA can take a hard line if they don't. Tenofovir alafenamide/emtricitabine (Descovy) was approved as PrEP for men and transgender women in 2019, but it has not yet been approved for cisgender women and others exposed to HIV through vaginal sex because they weren't included in a pivotal trial.

While both men and women respond similarly to antiretroviral treatment, studies of HIV prevention methods have yielded more variable results. Initial studies suggested that daily tenofovir disoproxil fumarate/emtricitabine (Truvada or generic equivalents) did not protect cisgender women as well as gay men and transgender women. Further analysis shows that protection depends on adherence, not biology. A recent analysis of real-world data from post-marketing studies found that daily PrEP pills were highly effective for women who took at least four doses per week—but less than 40% achieved this level of adherence.

"Oral PrEP is working for women, but uptake remains very low, and HIV incidence hasn't really budged," Marrazzo told POZ. "Women want different choices. Whether that's a longer-acting product, a vaginal product, a shot—those are things we still need to look at. There's a big gap between what we have and what we need."

In contrast to the remarkable success of antiretroviral treatment and PrEP, large vaccine trials have led to a string of disappointments, as study after study has failed to show that traditional vaccines can prevent HIV. But according to Larry Corey, MD, of Fred Hutchinson Cancer Center, these trials shouldn't be considered a failure: "We did get an answer, but it wasn't the one we wanted," he says.

What's more, the benefits of clinical research are not confined to a single field. "Advances in HIV vaccine science have literally paved the way for SARS-CoV-2 vaccines," says former NIAID director Anthony Fauci, MD. "What goes around comes around, and I expect this to feed back into HIV vaccine development."

Indeed, researchers are now studying more sophisticated HIV vaccine approaches in small trials, including some that utilize the same messenger RNA technology as COVID vaccines. But testing HIV vaccines has become more challenging now that highly effective oral and injectable PrEP is widely available. Ethics require that study participants be offered the best available existing prevention tools, and it will be difficult to show that vaccines add to the already high level of protection provided by PrEP.

Comorbidity Studies

Clinical trials can help people with HIV lead healthier lives beyond new antiretrovirals. In the era of effective treatment—and given that more than half of HIV-positive people are now ages 50 or older—HIV care has largely shifted to managing coexisting health conditions.

Compared with the population at large, studies have shown that people living with HIV are at greater risk for many chronic conditions, including cardiovascular, liver and kidney disease and certain cancers. Comorbidity trials may evaluate new types of treatment for these conditions, novel care strategies or behavioral interventions, such as exercise or smoking cessation.

The REPRIEVE trial, for example, tested pitavastatin (Livalo) for HIV-positive people at low to moderate risk for cardiovascular disease, a group that ordinarily would not be prescribed statin medications.

The study showed that people randomly assigned to receive the statin had a 35% lower risk for heart attacks, strokes and other major cardiovascular events. Based on these findings, the Department of Health and Human Services recently updated its treatment guidelines to recommend statins for HIV-positive people ages 40 to 75 who are at low to intermediate risk for cardiovascular disease.

While testing the statin, REPRIEVE also shed new light on cardiovascular disease in people with HIV. Nearly a third of the participants were women, enabling the study to see how cardiovascular disease manifests differently in the two sexes. One finding was that traditional cardiovascular risk scores for the general population underestimate risk for HIV-positive people, and this is especially true for women. (REPRIEVE participant Alicia Diggs describes her experience in the “Heart of the Matter”).

Another trial showed that doxyPEP—a single dose of the antibiotic doxycycline taken within 72 hours after sex—lowers the risk of chlamydia and syphilis for gay men and trans women, though it was less effective against gonorrhea, and a similar study of cisgender women did not see the

same benefit. Other recent comorbidity studies have shown that weight-loss drugs appear to work well for people living with HIV, and that screening and early treatment can reduce the risk of anal cancer among HIV-positive people.

Cure Trials

HIV cure trials can be more complex and may involve greater risks. Unlike new antiretrovirals, researchers are not so sure whether interventions such as therapeutic vaccines, broadly neutralizing antibodies or gene therapy will work or what adverse events they might cause.

To determine whether a cure strategy leads to long-term remission, participants may need to interrupt antiretroviral therapy, which could lead to disease progression and HIV transmission. What's more, while these studies add to our understanding and may help other people with HIV down the line, they generally are not expected to cure current trial participants.

Here, too, the inclusion of women is crucial. Some research suggests that women may be more likely to be elite controllers or to achieve long-term HIV remission after stopping antiretrovirals, perhaps due to differences in their immune response.

"We are still in the exploratory phases of cure research. This will be a very tough nut to crack—but one that is essential to see the end of the HIV pandemic," says Sharon Lewin, MD, of the Peter Doherty Institute at the University of Melbourne. "Participation in early clinical trials is absolutely essential to understand what might or might not work. I tell potential participants that it's very unlikely that they personally will have any benefit from an early phase cure trial. However, their participation will have a major impact on the field."

Joining a Trial

If you are thinking about joining a clinical trial, HIV care providers, advocates, support groups and the National Institutes of Health's ClinicalTrials.gov website are good sources of information about available studies.

When considering a trial, learn all you can about the intervention being tested, what other options are available and the potential risks and benefits (see "Trial Pros and Cons," below). Don't be afraid to ask questions! Before agreeing to join a study, participants must sign an informed consent document, but this is not a contract—you have the right to withdraw at any time for any reason.

Studies of new antiretroviral medications, prevention methods, comorbidity management and cure strategies don’t offer guarantees, and researchers can’t rule out unforeseen adverse events. But despite this uncertainty, clinical trials can be a gateway to better care for people living with or at risk for HIV, now and in the future.

Clinical Trial Stages

Preclinical: Laboratory and animal studies are done prior to human trials.

Phase I: Early feasability trials, typically including 10 to 100 participants, assess safety and collect pharmacokinetic and dosing data.

Phase II: Mid-stage trials, typically including a few hundred participants, evaluate safety in a larger group and gather preliminary efficacy data.

Phase III: The largest and longest trials, typically including hundreds or thousands of participants, evaluate efficacy and side effects in a population reflecting patients who will use a new therapy.

Phase IV: Post-marketing studies conducted after approval and commercial availability assess how well a therapy works in the real world.

Trial Pros and Cons

Pros:

- Early access to new therapies
- Free drugs and health monitoring
- Expert doctors and leading medical centers
- Financial incentives
- Satisfaction of helping others
- Advancement of science

Cons:

- Time commitment
- Associated unreimbursed costs
- May need to stop or forgo other treatments
- Might not receive experimental therapy
- Intervention might not work
- Potential side effects
