

TODAY'S TRIAL LANDSCAPE: NOT AS SIMPLE AS I, II, II

The past few years have seen a blossoming of new terms to describe efficacy trials, including test-of-concept, proof-of-concept, and Phase IIb. More recently, IAVI has introduced a trial design it calls STOC, for “screening test-of-concept,” into its plans.

Different names aside, these trial designs have a lot in common. The main components of a design, for these purposes, are the number of people enrolled, the projected incidence—or rate of new infections—in the population, and the number of HIV infections or other “endpoints” needed within the study population for the trial to have sufficient statistical power to answer its question or questions.

In general, test-of-concept trials are smaller than full-scale efficacy studies, and they may have fewer endpoints. Each of the two test-of-concept studies of Merck's Ad5 candidate aims to enroll around 3,000 people and is looking for 100-120 endpoints. However, size is not always an accurate indicator. The ongoing Thai prime-boost trial, the largest AIDS vaccine efficacy study ever undertaken, is also a test-of-concept trial, according to its investigators, who say that the data from the 16,000-person study will have to be further explored in additional, follow-up trials.

Someone hearing these numbers for the first time would likely ask: How is it possible to enroll 16,000 people and still need more data? Or to design a study that indicates that a candidate might have a benefit, but does not confirm it?

One answer has to do with incidence. The Thai study is being conducted in a relatively low-incidence population—so it has to be quite large to detect any kind of vaccine-related effect.

In the specific context of AIDS vaccines, another critical answer has to do with what we expect from the current candidates. All of the current test-of-concept studies are designed to find out whether the experimental vaccine strategies have an impact on viral load setpoint in people who receive the vaccine and later become infected. (In the course of natural HIV infection, a person's viral load climbs to a very high level shortly after infection and then drops down to settle at what is known as the “setpoint,” where it can remain relatively stable for some time.) These trials are also measuring whether the vaccine strategy reduces risk of becoming infected in the first place.

The MRK-Ad5 trials are designed to detect a 0.5 log reduction in viral load setpoint in vaccine recipients, compared to participants in the placebo arm. The Thai prime-boost study is designed to detect a 0.4 log reduction.

The main reason for looking for this type of reduction is that in observational studies of natural HIV infection, lower viral setpoint is linked to slower disease progression. So a vaccine that dropped a person's viral load setpoint could help him or her remain healthier longer and possibly delay the time to starting treatment. At this point, no one knows how much of a reduction would give a clinical benefit, although natural history and animal studies suggest that it could be in the realm of 1.0-1.5 logs.

But while there is a scientific rationale for looking at viral setpoint, the truth is that we don't know whether a vaccine-induced change in viral load will be enough of a benefit to make the strategy a viable part of the HIV-prevention tool kit. At the end of these relatively brief (2-3 year) test-of-concept studies, we won't know how long this reduction in setpoint lasts or how it affects individuals' clinical outcomes (their overall health). We also won't know whether it reduces a person's likelihood of passing the virus to sexual or needle-sharing partners or to the person's children.

All of these questions will need to be explored in additional studies and in follow-up of trial volunteers from the original studies. It could take years, and significantly larger trials, to determine whether the reduction in viral load setpoint has a clear and lasting benefit.

That's one reason why these studies almost all use the term *concept*. They are an initial test of an idea: in this case, the idea that a vaccine strategy, which primarily induces cell-mediated immunity, can have a beneficial effect—either reducing risk of HIV infection or reducing viral setpoint.

These trials leave a lot of gray areas, including questions such as, how much of a reduction in viral load is enough to warrant follow-up studies? Clearly, the answers from the first trials will prompt more questions and more years of research. There is a long road ahead of us. And if we do not communicate this reality to all of the audiences who are watching the AIDS vaccine field and wondering how their money is being spent, then we risk losing credibility at the precise moment—the end of a test-of-concept trial—when we need it the most.