

## testing aids vaccines in people

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**MOST AIDS VACCINE TRIALS** so far have been *Phase I* studies that enroll small numbers of volunteers and test a vaccine candidate's safety, along with its ability to induce *immune responses (immunogenicity)*. But studies with small numbers of volunteers can't tell us whether or not a vaccine prevents HIV infection or disease. For this we need to carry out large-scale *clinical studies* called *efficacy* trials, or (in their traditional form) *Phase III* trials.

So far there have been only two completed Phase III trials of an AIDS vaccine, and a third is ongoing—altogether involving nearly 24,000 volunteers and costing hundreds of millions of dollars. But with many vaccine candidates now in early phases of clinical testing, there will hopefully be several promising ones ready for efficacy trials within a few years.

Yet the huge commitment of people and funds required for a single Phase III trial has led many AIDS vaccine developers to consider testing some candidates in smaller, shorter “proof of concept” (*Phase IIb*) trials, which give preliminary information about a vaccine's efficacy. The first IIb study of an HIV vaccine started in late 2004 (see chapter 8).

As complicated as these studies are to carry out, the idea behind them is simple: Compare the rate of HIV infection (or some sign of disease) in people given the real vaccine with those who got only an inactive substance called a *placebo*. If the vaccine is effective, the vaccinated group should have significantly fewer infections or disease markers than the group that got placebo. Statisticians then analyze the data to make sure that the difference isn't just a fluke, but is due to the vaccine.

This approach works only if some of the volunteers expose themselves to HIV (for example, through unprotected sex) over the course of the study—even though the trial staff provide risk-reduction counseling at every study visit. (No study ever deliberately exposes volunteers to HIV.) High quality prevention services during efficacy trials are crucial (as well as morally and ethically necessary), since the vaccine may not work, and because some people get only a placebo. But counseling is rarely 100% effective. If there are few or no infections in the placebo group, it's impossible to tell whether the vaccine is working. And the converse is also true: the higher the rate of new infections, or *incidence*, in the study population, the easier it is to detect a vaccine effect, which means that the trial will need fewer volunteers and/or a shorter follow-up period.

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This is why AIDS vaccine efficacy trials need to be done in high-risk populations—which, in turn, is a big part of what makes these trials complicated. High-risk populations are concentrated mostly in countries hit hardest by the epidemic (nearly all in the developing world) and among groups that are often marginalized and discriminated against—such as gay men, injecting drug users and racial/ethnic minorities.

Doing clinical research that involves vulnerable participants—especially when it also involves a stigmatized disease like AIDS—raises lots of sensitive issues, which are the subjects of many chapters in this book. On the other hand, these highly affected populations are among those who stand to benefit most from a successful vaccine.

Besides a high incidence, it's also important that the study population (or *cohort*) in Phase III trials reflects a diversity of people who will use the future vaccine. That's because it's possible that one particular subgroup in the cohort (for example, a certain racial group, or women only) might respond differently to the vaccine—and if there are too few volunteers in this subgroup, such trends can't be detected, as the first Phase III trial by VaxGen vividly showed (see chapter 22). Although a single trial can't analyze the vaccine separately in all possible subgroups of a cohort, it can spot trends in one or two key subgroups if the trial is designed to do so.

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### preparing for efficacy trials

Before vaccine developers can design an efficacy trial in a given population, they need to have some key information in hand—such as HIV incidence, and a good sense of what other diseases and health issues are common in the community. Often these data are gathered in a “vaccine preparatory” study that enrolls healthy HIV-negative volunteers and follows them for one or a few years. These studies may also look at peoples' knowledge about vaccines, their willingness to participate in vaccine trials, and at practical matters such as how to best recruit and retain participants. They can also help cement referral networks for care of people who become infected during the trial (or are found to be positive at screening) and can deepen the working relationship with a community.

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### conducting efficacy trials

Volunteers who have gone through screening and *informed consent* and then enroll in the trial are *randomly assigned* to either the vaccine or placebo group. Neither the trial staff nor the volunteers know who received vaccine or placebo until the study is over. Throughout the trial, volunteers receive regular HIV tests and risk-reduction counseling, which reinforces the message that they should not consider themselves to

be protected. Those who nevertheless become infected are monitored for at least the rest of the trial period to see whether the vaccine affects their *viral load* (the amount of HIV in the blood) or their *CD4+ T-cell* counts, both of which indicate how the disease is progressing.

Once completed, the study is “*unblinded*” and scientists look for differences in infection rates between the vaccine and placebo groups and, in infected participants, in viral load and CD4+ T-cell counts. If differences are detected, *statistical* tests can determine whether they are due to the vaccine or to coincidence.

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### hedging your bets: phase IIb trials

Phase III trials are the gold standard for testing efficacy and, if the vaccine shows some efficacy, for generating data that can be used in applying to national regulatory authorities for licensing the vaccine. Depending on a trial's size and design, it could also reveal trends (of higher or lower efficacy) in one or two subgroups within the overall cohort.

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Phase IIb trials, on the other hand, are best suited to weeding out ineffective candidates and identifying relatively high-efficacy ones. But they can't estimate efficacy with nearly the same accuracy as a Phase III study, nor would they yield licensable results in most cases (except perhaps for a blockbuster vaccine with very high efficacy). So candidates identified as promising in a IIb trial will probably still need to undergo Phase III testing.

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### multiple trials in multiple populations

Rather than conducting one large trial to see if an AIDS vaccine is protective, vaccine developers may plan multiple trials of the same (or closely related) vaccine(s). One reason for this strategy is that there are several different ways that

people can become infected with HIV: through unprotected sex, breastfeeding from an HIV-infected woman or use of a needle that has been contaminated with HIV-infected blood, for example through needle-sharing among people who inject heroin.

The ultimate goal is to develop an HIV vaccine that protects people no matter how they are exposed. But since the different infection routes bring HIV up against a different set of immune defenses, we can't assume that vaccines which work against one route will work equally well against the others. The only way to find out is to test vaccines in populations of HIV-negative people exposed to HIV through different routes—for example, gay men exposed through anal sex, and injecting drug users through sharing needles. This strategy was used in VaxGen's two large-scale Phase III trials (see chapters 22 and 23).

Another reason for carrying out HIV vaccine trials in multiple populations is to test the vaccine against the *diverse* HIV *strains* (called *clades*) circulating in different regions of the world. No one knows whether a vaccine based on one HIV clade will protect against infection with others (see chapter 10). Last but not least, the efficacy of a vaccine might be influenced by differences among populations, such as other *pathogens* they are exposed to, the diseases they live with, and genetic differences, which are known to influence how well the immune system responds to particular *antigens*.

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#### trial success and failure

A TRIAL THAT FINDS solid evidence of vaccine efficacy is obviously a clear success. But even if it doesn't, the trial shouldn't be viewed as a failure—if it clearly resolves that the vaccine doesn't work (thus settling an important question) and if it advances our understanding of what's needed to make a vaccine that's more likely to protect.