

## Fitting AIDS Vaccine Science into the Bigger Picture

For the past year, we've been hearing variations of this sentence: "If PrEP works, AIDS vaccine trials will be impossible." Or, "If MDP 301 shows effectiveness of the microbicide PRO 2000, we won't ever be able to do an AIDS vaccine trial again." Or, "The window is closing for AIDS vaccine trials... once we get a positive result from another biomedical prevention strategy, we won't be able to test a vaccine again."

You can just as easily substitute "microbicide" for "vaccine" in the sentences above. The concerns stem from the simple—and positive—assumption that prevention strategies that show effectiveness in clinical trials will be introduced and used, so that eventually rates of new HIV infections will go down. When incidence goes down, trial size and/or length increases, as does cost. So if new, proven strategies get introduced into communities that are also being considered as partners and participants in trials of other new experimental strategies, these trials could be larger, longer, and more expensive.

But the conversation shouldn't be about whether any specific trial type will become impossible. Instead, the focus should be on the various options for research that might combine AIDS vaccines and other interventions as they emerge. One concern is when and how new interventions become the standard of prevention and get offered to all trial volunteers. Another is the opportunity for testing new strategies in combination with emerging ones, to ask questions like: could a vaccine plus another intervention (e.g., PrEP or microbicide) provide improved protection over that intervention alone?

These two lines of reasoning are obviously closely related, and each impacts the other. If an emerging strategy becomes the standard of prevention and is routinely offered to all participants, then that complicates the design of future trials of single strategies.

On the other hand, it raises the possibility of trials to compare combinations like vaccine plus PrEP or vaccine plus PrEP plus male circumcision versus PrEP alone. Such studies might be large and highly challenging, but they are being considered. Both IAVI and the HVTN are exploring scenarios for evaluating vaccine-PrEP interactions in various ways.

Combining vaccines with other strategies could achieve different goals depending on the vaccine's mechanism of action. A vaccine strategy that reduced viral load setpoint might be evaluated to learn about the level of virologic control offered to people who get infected in spite of PrEP. (PrEP itself might have an impact on post-infection viral load.) Another strategy might be aimed at inducing persistent

defenses at mucosal sites, with the goal of augmenting PrEP- or microbicide-mediated protection against infection.

Although it's critical to plan for new prevention options, we also need to recognize that change won't immediately follow a positive result from a single trial. Additional trials are usually needed to validate and expand on the results. And when they aren't, there's still a set of steps between the initial finding and actually getting programs and products on the ground. These need to happen swiftly and without unnecessary delay. In practice, there is a substantial gap between the announcement of a research result and the introduction of the intervention on a national scale. (For a discussion of the critical role that WHO and UNAIDS play in this process, see the article on page 54.)

Male circumcision provides one example of how prevention trial research teams have already thought through this issue. South African investigators in the Phambili vaccine trial decided that male volunteers should be offered circumcision, even though there was no national policy on the procedure. This decision came about in part because the research demonstrating the effectiveness of male circumcision for HIV prevention had been done in South Africa and so could be assumed to have relevance to the trial population. The teams at the Phambili trial sites ensured that trial participants had access to the service if they wanted it. This effort was supported in part by the HVTN Foundation. Trial sites in other countries have been less active in this regard, providing information and

referrals for male circumcision but not necessarily establishing services.

The male circumcision scenario points to whether there should be a difference between what's done in a community and what's done in a trial setting. Are there certain cases when a research site is obligated to act in advance of national policy? What's the role of community in making these decisions? The emphasis needs to be on specific scenario-planning to identify solutions.✱

“With IAVI’s support, we’ve done clinical trial preparations with men who have sex with men. We’ve also found out that HIV incidence in these men is much higher than in female sex workers. The other significant milestone is in regard to community engagement. While homosexuality is illegal in Kenya, coastal health authorities in partnership with KEMRI and IAVI are now engaging community groups and other district health stakeholders to prepare HIV prevention and behavior change interventions addressing anal sex.”

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