HIV vaccine trials in India

To the editor:

As CEO and president of the International AIDS Vaccine Initiative (IAVI; New York), I am writing to protest against a news brief "HIV vaccine controversy" in your March issue[1], which I regard as both tendentious and inaccurate.

First, it is impossible for a phase 1 vaccine trial—like the one of the AIDS vaccine candidate tgAAC09 that IAVI co-sponsored in Belgium, Germany and India—to establish that a candidate "had failed to protect trial participants." A phase 1 trial generates safety and initial immunogenicity data on a vaccine candidate; it does not test efficacy. The volunteers in a phase 1 AIDS vaccine trial are low-risk individuals unlikely to ever be exposed to HIV, so it is not possible to asses protection against HIV infection.

At issue was one trial with two arms: one in Europe, one in India. Because vaccinations began first in Europe, some preliminary data became available from Europe soon after vaccinations began in India. Those data suggested tgAAC09 was safe and well tolerated. As part of a safety trial, researchers also measure volunteers' immune responses to a vaccine candidate to help determine the appropriate dose and schedule for further testing. The preliminary data from Europe showed tgAAC09 elicited only modest immune responses, but this was no reason to discontinue the Indian arm of the trial, as your news brief suggests. Typically, when vaccinations are halted in a phase 1 trial, it is because of evidence that a candidate is not safe or is poorly tolerated by volunteers; there was no such evidence in this case. The trial protocol was designed to include 80 volunteers, 30 of them in India, and without data from the cohort in India the phase 1 trial results would have been incomplete.

India was included in the multi-country design of the trial in part because the vaccine candidate was matched to the subtype of HIV prevalent in India, clade C; in Europe, clade B HIV is prevalent. TgAAC09 was considered promising because it performed well in preclinical studies; had the candidate eventually proven effective in human trials, having data from India and other places in the world where clade C HIV is common would be important. Thus, it was valuable to test the candidate in a part of the world where the vaccine, if effective, might eventually have done the most good, to lay the groundwork for possible future licensure. Also, the trial was designed as an international study in part to determine how the vaccine candidate would behave in different populations. The safety and immunogenicity data from Indian and European volunteers might have differed owing to environmental or genetic factors that can affect immune responses.

According to your account, the Indian Council of Medical Research (New Delhi), which, like IAVI, co-sponsored the phase 1 tgAAC09 trial in India, "stopped the trial in December, saying the vaccine gave 'poor' immune responses." In fact, the trial was not stopped; it was completed as planned in January 2007.

When data from all arms of the phase 1 trial of tgAAC09 were collected and analyzed, researchers were able to confirm that the vaccine candidate was safe and well tolerated in all populations tested. The candidate produced an immune response in 17% of trial volunteers at the highest dose tested. This information served precisely the purpose for which immunogenicity data in a phase 1 trial are intended: it indicated that a higher dose might be necessary.

In a subsequent phase 2 trial of tgAAC09 conducted in three countries in Africa, a higher dose of the vaccine candidate was used, and this also proved safe and well tolerated. Unfortunately, even at the highest practical dose, the candidate, in IAVI's view, did not generate sufficiently robust immune responses to justify further testing as a stand-alone vector.

The reality of vaccine development is that the vast majority of experimental vaccines and other pharmaceutical candidates do not advance past phase 1 and 2 trials. But from every properly conducted trial, whatever its result, comes new knowledge that helps to illuminate the search for more effective candidates.

Your report finally claims that IAVI is "stuck in an ethical quagmire" because participants in the trial now "test seropositive for HIV" and cannot convince their employers that this is because they were immunized as part of an AIDS vaccine trial. This is completely erroneous; given the nature of the vaccine candidate, not a single volunteer in the tgAAC09 trial in India tested positive for antibodies against HIV. Such a scenario has occurred in other trials of vaccines against AIDS and other diseases. When it happens in AIDS vaccine trials, volunteers are offered a certificate that explains to an employer or any other interested party that their HIV antibodies are due to participation in an AIDS vaccine trial and not to actual HIV infection.

IAVI's conduct throughout testing of tgAAC09 was consistent with its model to work with in-country partners to ensure the highest ethical and operational standards, and we remain committed to developing a safe, effective AIDS vaccine for use throughout the world, especially in those regions in greatest need.

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1. Jayaraman, K. *Nat. Biotechnol.* **26**, 256 (2008).