In their recent Policy Forum (1), Burton et al. state that phase III trials alone are required to establish the efficacy of HIV vaccines; we fully agree. However, we disagree with the position of the authors regarding our sponsorship of a recently initiated HIV vaccine efficacy trial in Thailand. For nearly 20 years, HIV vaccine development has posed a formidable challenge. No laboratory assay or animal model has yet been validated as a predictor of the efficacy of HIV vaccines in humans. Identifying correlates of protective immunity and improved immunogens is critical; however, with five million new infections each year, the luxury of time is absent. A comprehensive development strategy also requires testing bona fide hypotheses in human efficacy trials, simultaneously if necessary, until a laboratory or animal correlate is validated and vaccine efficacy is established.

The first HIV vaccine efficacy (phase III) trials began in 1998 and 1999 tested similar candidates based on recombinant gp120 envelope proteins (VaxGen’s rgp120 AIDSVAX B/B and AIDSVAX B/E). In 1999, evaluation of a combination vaccine regimen, referred to as “prime-boost,” was initiated in Thailand. In 2003, the VaxGen trials showed that T cell helper and antibody responses induced by AIDSVAX alone had no protective effect against HIV. In September 2003, the Thai and U.S. governments undertook RV144, a phase III efficacy trial of the prime-boost combination. Nearly 1000 volunteers have enrolled in the study.

RV144’s prime-boost combination includes Aventis Pasteur’s canarypox vector, ALVAC-HIV (vCP1521) as a prime, and VaxGen’s rgp120 (AIDSVAX B/E) as a boost. Both are derived from strains of HIV that circulate in Thailand. The trial’s objective is to prevent HIV infection and/or to control HIV replication in breakthrough infection.

In the phase II study in Thailand (2), vCP1521 + AIDSVAX B/E generated immune responses comparable to earlier studies of ALVAC-HIVs + envelope protein. Depending on the laboratory assay used, ALVAC-HIVs + envelope protein typically induced cytotoxic T lymphocyte (CTL) responses in 25 to 45% of recipients; lymphocyte proliferative responses in 50 to 100% of recipients; and T cell line–adapted neutralizing antibody responses in 50 to 100% of recipients (2). Responses induced by the prime-boost combination are different from those induced by each component alone: quantitative augmentation of lymphoproliferative response; qualitative changes in CD4+ T cell response; and induction of antibody-dependent cellular cytotoxicity (2, 3–6). Based on phase II results and supported by the observation of ALVAC-induced protection in nonhuman primates (NHP) (7, 8), a decision was made in January 2002 to proceed with a prime-boost efficacy trial in Thailand. Subsequent NHP studies have continued to support the potential efficacy of this combination (9, 10).

The National Institute of Allergy and Infectious Diseases (NIAID) and its HIV Vaccine Trials Network (HVTN) planned an efficacy trial in the Americas to evaluate a similar prime-boost regimen and to determine if CD8+ T cell responses, as measured by an enzyme-linked immunosorbent spot assay (ELISpot), correlated with protection. The frequency of ELISpot positivity needed to conduct this evaluation was not achieved, so this could not be evaluated as a correlate of protection. The overall immune response data were consistent with previous prime-boost studies and NIAID and HVTN elected to support the further advanced RV144 trial as the most cost-effective and efficient means to assess prime-boost’s efficacy (11, 12).

For nearly 2 years before its initiation, RV144 was widely and publicly presented. It was reviewed and endorsed by 11 international governmental and academic scientific, ethical, and regulatory review bodies in Thailand and the United States and by the World Health Organization and the Joint UN Programme on HIV/AIDS (WHO–UNAIDS).

Nonetheless, questions remain (1). Given that AIDSVAX failed in two efficacy trials, why should it be included as a component of prime-boost? The reasons are both scientific and practical: (i) the efficacy of AIDSVAX given alone is not known to predict its contribution to the prime-boost combination; (ii) although arguably modest, immune responses induced by the addition of AIDSVAX are augmented relative to ALVAC alone; and (iii) advancing the underlying vaccine hypothesis of cell-mediated plus antibody-mediated immunities requires ALVAC and AIDSVAX. In November 2002, a special WHO-UNAIDS consultation concluded that “because of its independent scientific rationale,” efficacy evaluation was appropriate irrespective of potential null efficacy of AIDSVAX alone (13); this recommendation was affirmed by the full WHO Vaccine Advisory Committee.

Although there is a real chance that this candidate vaccine may not be efficacious, there is a very high probability that information gained will advance HIV vaccine development. RV144 will be independently monitored to determine whether continuation of the trial is scientifically and ethically justified, or whether the trial should be terminated early.

When agreed-upon milestones in vaccine development are met, and unless the underlying hypothesis has been debunked, commitments must be honored lest we undermine the confidence of, and potentially halt partnerships with, industry, other governments, and communities. Equally important is the moral obligation to volunteers who have participated in this iterative process.

Clinical trials are expensive, but expenditures are always relative. The cost of RV144 represents about one five-thousandth of the annual U.S. National Institutes of Health HIV R&D budget.

In summary, established scientific principles and appropriate processes supported the decision to proceed with this efficacy trial. The ongoing prime-boost trial in Thailand is scientifically justified, morally correct, and strategically important.

References and Notes