

EDITORIAL



HIV Vaccine Trial Results — An Opening for Further Research

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HIV-AIDS has emerged as an enormous, worldwide public health problem over the past 25 years. An estimated 33 million persons are infected with human immunodeficiency virus type 1 (HIV-1), and more than 7000 new infections occur every day.¹ Although major advances have been made in the treatment of HIV-1 infection and in certain behavioral approaches to the prevention of HIV infection, ultimately, control will most likely depend on the development and application of a safe and effective HIV vaccine.

Substantial effort is being expended to develop an HIV vaccine through a variety of approaches.² However, disappointing results have emerged from the only three large-scale efficacy trials previously carried out in humans.³⁻⁵ In this issue of the *Journal*, Rerks-Ngarm et al.⁶ report the results of a clinical trial of a vaccine regimen (ClinicalTrials.gov number, NCT00223080), describing the first findings of possible prevention of HIV-1 infection in humans. This is of potentially great importance to the field of HIV research. The two analyses specified in the protocol, the intention-to-treat and per-protocol analyses, showed vaccine efficacies of 26.4% ($P=0.08$) and 26.2% ($P=0.16$), respectively. A modified intention-to-treat analysis, in which subjects who had HIV-1 infection at the time of randomization were excluded, showed a vaccine efficacy of 31.2% ($P=0.04$). Although the merits of each type of analysis can be debated, all three yielded a possible, albeit modest, effect of the vaccine in preventing HIV infection, although only the findings from the modified intention-to-treat analysis reached statistical significance at the traditional $P<0.05$ level. Despite its possible effect on acquisition of HIV-1 infection, the vaccine did not have any effect on the early HIV-1 viral load

or CD4+ T-cell counts in vaccinated subjects who eventually became infected. The study was well designed and carefully conducted, and the demographic characteristics and risk factors for acquisition of HIV-1 infection appeared to be well balanced between the vaccine recipients and the placebo recipients. Information on other potential risk factors, such as circumcision status and serologic status for herpes simplex virus type 2, should be sought during follow-up.

The reported findings will be surprising to many investigators in the field because of the disappointing clinical and laboratory data previously reported in similar vaccine candidates. A glycoprotein 120 (gp120) B/B vaccine (AIDSVAX B/B) failed to show efficacy in two previously conducted clinical trials.^{3,4} The canarypox vector vaccine (ALVAC-HIV, vCP1452), after considerable study, was deemed by the HIV Vaccine Trials Network not to be sufficiently immunogenic to proceed to an efficacy trial.⁷ That unfavorable view was shared by a number of leading investigators in the field.⁸ In contrast, a phase 2 study in Thailand of the ALVAC-HIV (vCP1521) vaccine boosted with a gp120 B/E vaccine (AIDSVAX B/E) was believed to show sufficient immunogenicity⁹ to proceed to the efficacy trial undertaken by Rerks-Ngarm et al.

Despite the large size of the study by Rerks-Ngarm et al. (16,402 subjects and 52,985 person-years of follow-up), it was not designed or powered sufficiently for a number of additional subgroup analyses. Nonetheless, several interesting and potentially important observations are worthy of consideration. First, the population in the current trial was made up largely of persons at low risk (47.5%) or moderate risk (28.4%) for HIV infection, rather than those at high risk,

and the means of infection was deemed to be primarily heterosexual sex. In contrast, the previous efficacy trials of a gp120 vaccine were conducted in high-risk populations: men who have sex with men³ and intravenous drug users.⁴ The recent efficacy trial of an HIV vaccine containing an adenovirus type 5 vector, which failed to show efficacy, was also conducted in high-risk men who have sex with men.⁷ Perhaps the requirements for protection against transmission in low-risk, heterosexual persons are considerably different or less stringent than those in high-risk subjects, as suggested by the data in Table 2 of the report by Rerks-Ngarm et al. This observation may be important in the design of future clinical trials as well as direction for increased research activity.

Rerks-Ngarm et al. also were not able to determine the duration of the possible vaccine effect. The results are reported after a 3-year follow-up period, but there is a suggestion that more of the effect might have occurred during the first year. The duration of the vaccine's effect should be addressed by follow-up of the participants in the current study as well as by future trials.

Another important topic raised by the trial is the relative contribution of each of the vaccine components to the observed effects. Does the possible protective effect require the prime-boost combination or just one of the components? What is the relationship between HIV strains represented in the vaccine and the circulating strains that infected the vaccine recipients?

The possible vaccine efficacy observed was modest and indicates that the vaccine regimen studied is unlikely to be a public health control measure for HIV-1 infection, as the authors themselves acknowledge. The most important contribution of the study is most likely the opportunity to investigate possible host-response correlates of protection against infection. The establishment of such correlates is the central question in HIV vaccine development and will have a profound effect on the designs of vaccines and clinical trials to assess their efficacy. Given the lack of detection of conventional immune responses in earlier studies of these vaccine components, as well as the divergence between the vaccine's effect on the infection and the effect on viral load, the correlates of protection may, indeed, reflect new concepts of host

response. This should be the focus of intense research using the most current research techniques. Ultimately, it is the results of such studies that will most likely determine the significance of this clinical trial to the field of HIV vaccine development.

The clinical trial reported here represents an enormous effort by investigators, sponsoring institutions, and participants in the community. The findings raise a number of questions that have important implications for future directions in vaccine research. The answers to these and related questions will require the application of a balanced and coordinated research approach to the complex and difficult problem of the development of an HIV vaccine. This balanced approach includes fundamental laboratory and experimental-model studies, as well as rigorously designed and conducted clinical trials, such as the one reported on here.

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