Reply to Richie and Villasante

To the Editor—Richie and Villasante [1] pose thoughtful questions about the implications of our recently published analysis of the Step Study data with extended follow-up time [2]. Although some of the points are well taken, we would like to clarify several questions raised about the study methods and conclusions.

First, Richie and Villasante note that, in the subgroup analyses of the vaccine effect on risk of human immunodeficiency virus (HIV) infection within 18 months of follow-up, a statistically significant hazard ratio (HR) was observed only for the subgroup of adenovirus serotype 5 (Ad5)–seropositive, uncircumcised men. They state that these are post hoc subgroup analyses of a hypothesis that the trial was not designed to test and that, “[w]hile making recommendations based on suboptimal trial design may be prudent to ensure safety, appropriate caveats explaining the scientific limitations should be included ….”

It should be pointed out that our conclusions and recommendations were not based solely on the subgroup analyses. The trial was designed to test the risk of HIV infection among vaccinees versus placebo recipients, anticipating a reduction in incidence among vaccinees or no vaccine effect. In the analysis presented, we found a statistically significant increase in risk among all vaccinees over all follow-up time (HR, 1.44; 95% confidence interval, 1.05–1.97). This result was statistically significant (P = .03), using a 2-sided P value (see Inferential Analysis Results in our article [2]).

They also note that enrollment was opened to Ad5-seropositive individuals after the trial had begun. This does not pose a scientific limitation to the results...
on vaccine-associated risk because the subgroup HRs presented always compare vaccine to placebo recipients within strata defined by circumcision and Ad5 status.

Second, they question the use of 1-sided P values. The salient question of interest is less about 1-sided versus 2-sided P values and more about the level of evidence needed to make a recommendation to not use a product in a subgroup. One-sided P values were used to provide the level of evidence specifically for 1 direction of concern (ie, the potential increased risk of HIV infection with vaccination). However, the resulting P values can be readily converted to 2-sided P values. For example, a 1-sided P value of .025 reflects the same degree of evidence as a 2-sided P value of .05.

Third, Richie and Villasante question the extension of a recommendation based on the statistically significant increase in risk seen among uncircumcised, Ad5-seropositive men to men with only one of these risk factors. During the first 18 months after enrollment, the vaccine-to-placebo HR was highest among men who were both uncircumcised and Ad5 seropositive and was elevated, although not statistically significant, among men with one of these 2 factors. The possibility of elevated risk among vaccinees who are either uncircumcised or Ad5 seropositive is supported by the trend toward higher HR in these two groups (Table 2 in our article [2]) and by the biologic plausibility of increased risk associated with Ad5 seropositivity suggested by the dose-response relationship between vaccine-associated HIV risk and Ad5 titer (Figure 3 in our article [2]).

Failure to detect a statistically significant association in uncircumcised, Ad5-seronegative men or in circumcised, Ad5-seropositive men may simply be due to the small sample size in the subgroups. It is prudent to place importance on the point estimate, as well as the 95% confidence interval of the relative risk, in such small groups.

Finally, Richie and Villasante go on to state that our recommendations regarding Ad5-vectored vaccines should apply only to individuals who are exposed to HIV, since “increased risk … requires exposure to HIV transmission.” Although this is certainly true, a critical caveat is that an individual may be exposed to HIV without their knowledge. In many regions where HIV vaccines are most needed, such as sub-Saharan Africa, many individuals are at risk for HIV acquisition from their primary sex partner, whose HIV status is often unknown to them. In these populations, it seems prudent to avoid use of vaccines that might potentially increase the risk of HIV acquisition. Our data suggest a relationship of Ad5 titer to vaccine-associated risk of HIV acquisition (Figure 3 in our article [2]), which likely could occur regardless of the vaccine insert. Thus, our recommendation was that, until more data are available, Ad5-vectored vaccines should not be used in populations potentially at risk.

In planning future studies, the issues under discussion relate to risk-benefit ratios, which may vary over time and by region. For example, if an Ad5-vectored vaccine has been shown to be effective in Ad5-seronegative persons, then the extension of such potential benefits to Ad5-seropositive persons at potential risk for HIV acquisition may be reasonable.

Richie and Villasante correctly state that many hypotheses could explain the Step Study findings. Current data do not allow us to distinguish among them or to project with certainty what might occur in different populations or with different prime-boost regimens or vectors. Importantly, the results presented in Figure 3 from our article pertain to the Step Study population and vaccine and cannot be generalized further without additional data.

The considerations mentioned above notwithstanding, it may be possible in a clinical trial setting such as that discussed by Richie and Villasante to select individuals whose risk of HIV exposure is known and low. In such settings, Ad5 vaccines could be safely tested. For example, our analysis presented in Figure 3 estimated at most a 4% increased risk of HIV infection in the first 18 months associated with vaccination among individuals with the highest levels of baseline Ad5 titers. On the basis of this estimate, if a phase 1 trial of 50 Ad5 vector vaccinated individuals with these high Ad5 titers were conducted, with 1 year of follow-up and 0.5% annual HIV incidence, then 0.01 additional (vaccine-associated) HIV infections would be expected \((0.01 = 50 \times 0.005 \times 0.04)\). This represents an upper bound of vaccine-associated risk, as the phase 1 study population would include individuals with lower baseline Ad5 titers. This type of calculation may be useful for weighing the risks and benefits of studying Ad5 vector vaccines in phase 1 trials, which may be tailored to account for specifics of the trial design in sample size, anticipated HIV incidence, and distribution of baseline Ad5 titers. Indeed such studies may provide the additional insights needed for further development of these important vaccine vectors.

**Note**

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