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COMMENTARY

Protection against HIV Acquisition in the RV144 Trial

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ABSTRACT Differences of opinion regarding whether there may, or may not, have been protective efficacy in the RV144 vaccine trial have important societal implications.

KEYWORDS HIV vaccine, efficacy trials

I am surprised that the leaders of our nation's effort toward a vaccine for HIV/AIDS continue to believe in the protective efficacy claimed for the RV144 vaccine trial (1). See, for example, Corey et al. (2) and a lecture given on 23 March 2015 at the Keystone Symposium (3).

The final statistical analyses, published by leading U.S. investigators of the RV144 trial subsequent to the original *New England Journal of Medicine* (NEJM) report, concluded that the chance for no efficacy in the trial was greater than or equal to 22%; i.e., there was a less than 78% chance that there was protective efficacy in the trial (4). The authors go on further to state that this number "reflects greater uncertainty than has much of the discussion about this trial." Hardly a ringing endorsement for efficacy by the U.S. leaders of the trial.

Next, it is important to examine closely the Kaplan-Meier HIV-1 acquisition curves in the original NEJM report on the RV144 trial (1). In all other efficacy trials of HIV vaccines, the acquisition curves have been nicely linear for both vaccine and placebo groups. In the RV144 trial, the acquisition curve is nonlinear for the placebo group, with a sudden nonlinear increase in acquisition in the placebo arm within the first year of the trial that accounts for most or all of the difference in acquisition compared to the vaccine arm (Fig. 1, left panel). Compare this with the linear acquisition curves from the HVTN505 trial in the report by Hammer et al. (5) (Fig. 1, right panel). Thus, the difference in acquisition does not appear to be due to protective effects of the vaccine but rather to an anomalous increase in acquisition in the placebo arm in the 6-to-12-month time frame. In addition, the "intent-to-treat" analysis and the "per-protocol" analysis revealed no significant differences in HIV acquisition; only with a "modified intention-to-treat" analysis in the initial NEJM publication was a marginally significant difference ($P = 0.04$) in acquisition observed (1). There was no lowering of viral load in vaccinated individuals who became infected.

A "sieving" effect on HIV sequences acquired in the vaccine arm has also been used as evidence for the protective effects in the RV144 trial (6). Certain amino acids present at positions 169 and 181 in the envelope protein were preferentially associated with HIV-1 acquisition in the vaccine arm compared to the placebo arm. The logic here is that immune responses to the sequences in the vaccine can preferentially select for the presence of different sequences at certain locations when HIV infection is acquired. Unfortunately, the amino acid at position 169 in the vaccine was lysine and it was lysine at this position that was preferentially acquired in the vaccine group compared to the placebo group. In addition, statistically significant sieving effects were observed for HIV gene products that were not even included in the vaccine (7). There is no logic to these

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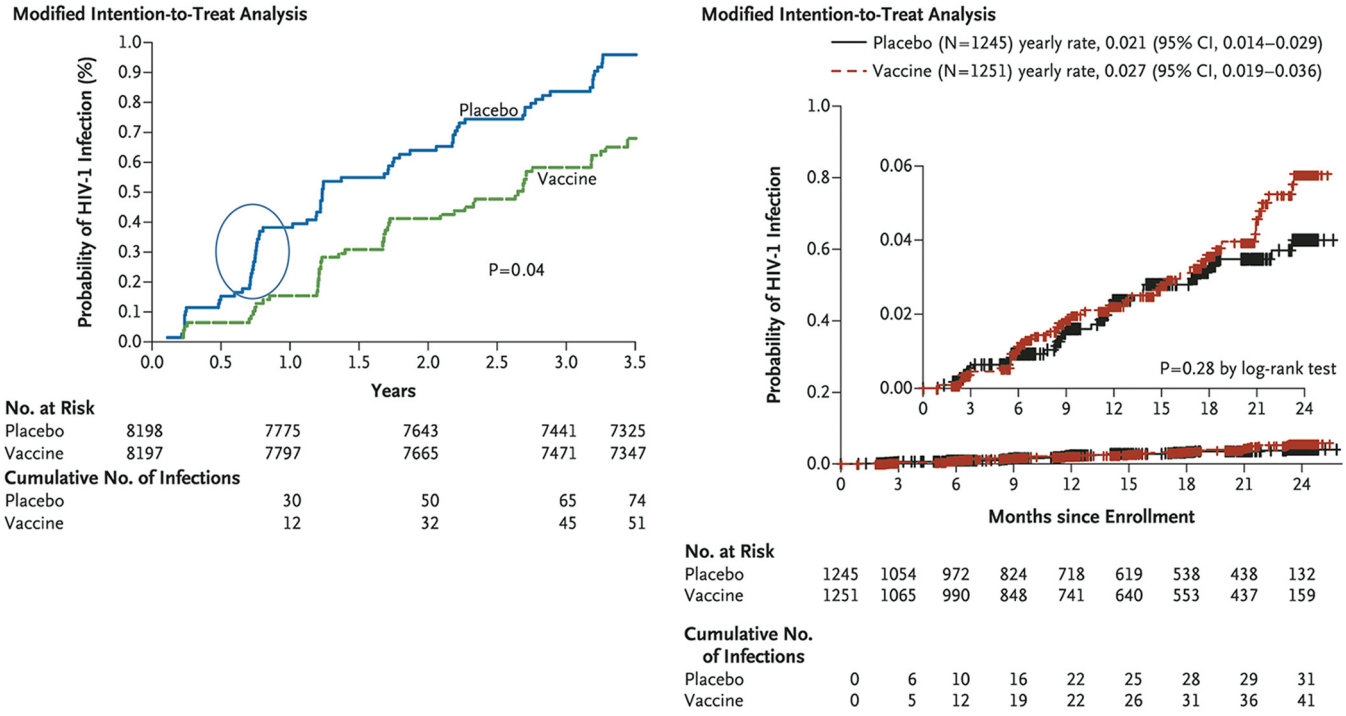

FIG 1 (Left panel) Kaplan-Meier acquisition curve from the RV144/Thai trial. Data are from the one analysis (the modified intention-to-treat group) of three that showed a *P* value of less than 0.05 with the tests used. (Reprinted from *The New England Journal of Medicine* with permission of the publisher [see Fig. 2C in reference 1].) The circled data represent the anomalous nonlinear increase in acquisition in the placebo group in the first year of the trial that was responsible for most or all of the differences in HIV-1 acquisition. (Right panel) Linear rates of HIV-1 acquisition in both the placebo and vaccine groups in the HVTN505 trial. CI, confidence interval. (Reprinted from *The New England Journal of Medicine* with permission of the publisher [see Fig. 2B in reference 5].)

observations; these sieving effects should not be used as an argument to support claims of protective efficacy in the RV144 trial.

An immune correlate of protection has also been presented in support of the claims of protective efficacy in the RV144 trial (8). Close inspection of the immune correlate in this publication reveals a median enzyme-linked immunosorbent assay (ELISA) binding value for V1V2 sequences in Env of approximately 0.36 among infected individuals in the vaccine arm versus 0.40 among uninfected individuals in the vaccine arm, with almost complete overlap in the scatter plots (Fig. 2). It is unclear to what extent a variety of technical issues could have influenced the underwhelming difference in median ELISA values.

Differences of opinion regarding the extent to which there may, or may not, have been protective efficacy in the RV144 trial are not without important societal implications. Those on one side of the fence have called for additional trials to confirm and

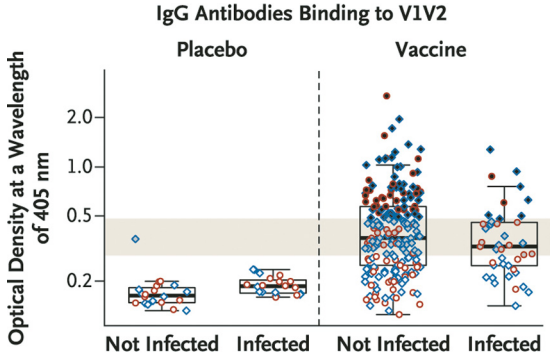

FIG 2 IgG antibodies as a correlate of immunity in the RV144/Thai trial. (Reprinted from *The New England Journal of Medicine* with permission of the publisher [see Fig. 2A in reference 8].)

extend the findings of RV144. In fact, such trials are already under way (9, 10). Quite clearly, efficacy trials are hugely expensive ventures. Those like myself on the other side of the fence see the need for more basic and preclinical research so that approaches can be discovered with a more realistic chance of actual efficacy and a more realistic chance of impacting the worldwide problem. There are certainly some very promising ideas out there that are in dire need of additional research funding.

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