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### Commentary

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# Simplified steps to heterologous prime-boost HIV vaccine development?

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**The RV 144 HIV vaccine efficacy study showed a reduction in HIV-1 infection risk in Thai volunteers who received two priming vaccinations of vCP1521 ALVAC (attenuated recombinant canarypox virus expressing HIV group-specific antigen, polymerase, and envelope genes) followed by two additional ALVAC vaccinations and coadministration of purified bivalent gp120 proteins (AIDSVAX B/E). In this issue of the *JCI*, Roupheal et al. build on these results by substituting a DNA plasmid cocktail expressing HIV-1 subtype C group-specific antigen, polymerase, and envelope antigen genes (DNA-HIV-PT123) for ALVAC in a phase 1b safety and immunogenicity study. The results indicate that the vaccine regimen is safe, elicits promising cross-subtype humoral and cellular responses, and opens up potentially simplified approaches to HIV-1 vaccine development.**

## Attempting to improve a vaccination strategy with demonstrated efficacy

The Thai HIV vaccine efficacy trial RV 144 evaluated an approach that combined an ALVAC vCP1521 (a canarypox-vectored HIV expressing group-specific antigen, polymerase, and envelope antigen-encoding genes [*gag/pol/env*]) prime with an AIDSVAX B/E (bivalent gp120 monomeric Env protein) heterologous boost (1). To date, this prime-boost regimen is the only strategy that has demonstrated efficacy in preventing HIV acquisition in humans; however, the overall protection was relatively modest (1). In this issue, Roupheal et al. extend upon the RV 144 trial and evaluated the effect of substituting a DNA vaccine for ALVAC vCP1521 in four study arms of a phase 1, randomized, double-blinded, placebo-controlled safety and immunogenicity study performed at multiple study centers (2). The vaccine

regimen in the benchmark RV 144 study included ALVAC vCP1521, which expresses HIV-1<sub>LAI8</sub> *gag/pol* sequences (subtype B) along with HIV-1<sub>92TH023</sub> gp120 *env* (subtype circulating recombinant form 1\_AE [CRF\_01AE]) with a partial extension into the transmembrane domain of gp41, and was given four times (at baseline and then at months 1, 3, and 6). AIDSVAX B/E, which is composed of purified gp120 Env proteins from HIV-1<sub>MN</sub> (subtype B) and HIV-1<sub>A244</sub> (subtype CRF01\_AE) variants adsorbed to alum, was given at the same time as ALVAC vCP1521 in separate injections in the ipsilateral deltoid muscle of volunteers at months 3 and 6.

The study design of Roupheal and colleagues included four independent arms with vaccinations given at 0, 1, 3, and 6 months (2). AIDSVAX B/E was administered in the same dose and route as was used in RV 144; however, the ALVAC vCP1521 boost used in RV 144 was

replaced in the current study by a cocktail of three DNA plasmids, DNA-HIV-PT123, which consists of equal amounts of plasmids expressing HIV-1 subtype C sequences: HIV-1<sub>ZM96</sub> *gag*, HIV-1<sub>ZM96</sub> *gp140*, and HIV-1<sub>CN54</sub> *pol-nef*, delivered at a total dose of 4 mg administered intramuscularly via needle and syringe.

Subjects in the first study arm (T1) were primed with AIDSVAX B/E followed by DNA boost without coadministration, and subjects in the second study arm (T2) received the same vaccines, but in reversed order (2). Thus, T2 includes the use of the AIDSVAX B/E boost at the month 3 and month 6 vaccination visits after priming with a DNA-based vaccine, as was done in RV 144. In the third study arm (T3), subjects were given DNA-HIV-PT123 as the prime at the first and second vaccination visits followed by coadministration of DNA-HIV-PT123 and AIDSVAX B/E at the third and fourth vaccination visits. The T3 arm was the most homologous to the RV 144 regimen, which used vCP121 ALVAC vaccinations at all four vaccination visits and coadministration of AIDSVAX B/E (albeit in different anatomical locations) at the third and fourth vaccination visits. The fourth study arm (T4) included coadministration of DNA-HIV-PT123 and AIDSVAX B/E at all four vaccination visits. Immunogenicity was broadly assessed by Roupheal et al., and their analysis included HIV-1 Env antibody binding stratified by IgG subclass and V1V2 scaffold binding, neutralizing antibody (nAb) assays, and antibody-dependent cell-mediated cytotoxicity (ADCC). Cellular immunity was assessed by intracellular cytokine staining and the computational biology-based T cell polyfunctional assay, the combinatorial polyfunctionality analysis of single cells (COMPASS) assay. Notably, measures of cellular immunity were found to correlate with risk of HIV infection in RV 144 (3) three years after the V1V2 antibody signal was originally identified as the primary correlate of reduced risk of

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HIV-1 infection in RV 144 (4). Rouphael et al. did not observe any significant reactivity to any of the vaccine treatments in the study volunteers, implying a favorable safety profile. DNA-HIV-PT123 priming appeared to provide similar immune responses compared to those seen with ALVAC vCP1521 priming in RV 144 (4). Early coadministration of vaccines, as in the T4 arm, was superior in terms of the kinetics of development of Env- and V1V2 scaffold-binding antibodies, nAbs able to neutralize tier 1 viruses, which are relatively easy to neutralize, and ADCC. Together, the results of this trial provide three important lessons for the field of HIV vaccine development.

### Lessons learned and future directions

First, Rouphael et al. effectively contrasted the differences in immunogenicity between the RV 144 regimen and correlates of risk of infection from Haynes et al. (4), viral sieve analysis first reported by Rolland et al. (5), and the gravamen of the work done from 2012–2019 in the RV 144 family of collaborating laboratories that was recently critically summarized by Zolla-Pazner and Gilbert (6). Importantly, the observation that the DNA vaccine prime, which expressed a subtype C Env protein rather than a subtype CRF\_01AE Env, as well as Gag and Pol antigens, gave remarkably similar humoral responses to those generated in response to the RV 144 regimen, which included the vCP1521 ALVAC vector, which expresses CRF\_01AE Env and subtype B Gag/Pol protein, bears introspection, as these results raise the possibility that priming with HIV-1 subtype C Env/Gag/Pol antigens followed by heterologous Env protein boosting could be a step towards a simplified set of HIV vaccines with global coverage of major HIV-1 subtypes. The development of vaccine strategies that protect against multiple virus subtypes is currently an area of intense focus in vaccine development not only for HIV (7) but also for influenza (8), flaviviruses

(9), and other infectious diseases of public health importance.

Second, Rouphael and colleagues have defined a pathway to build on the only HIV vaccine study to date associated with signs of clinical efficacy using a genetic vaccine type that is far more readily available to a wide range of investigators than the development of complex viral vectors that are frequently restricted by manufacturer protection of their product development portfolios. While individual DNA plasmid expression backbones may also be constrained by these provisions, the general availability of these vectors allows for a broader base of investigator-initiated preclinical studies (10), directly underpinning the vital innovation that comes from academic investigators.

Third, while many in the field remain skeptical about the possibility that HIV vaccines that fail to elicit potent, broadly cross-reactive nAbs could ever be an effective public health tool to control the HIV pandemic, additional approaches to drive heterologous prime-boost vaccines that generate both functional T cell (11) and nonneutralizing humoral responses (12) potentiate a permissive environment to simultaneously test efficacy in iterative, randomized clinical trials with HIV acquisition and enhanced immune responses as primary endpoints (13, 14). Moreover, two, and soon a third, such clinical trials, to evaluate vaccine regimens whose preclinical correlates of risk of acquisition did not include nAb mechanisms, are currently ongoing, speaking powerfully to the point that non-nAb approaches may provide meaningful prevention (15).

Taken together, the results of the clinical investigation by Rouphael and colleagues pivots from the familiar territory of RV 144 to potentially open new and innovative ground in HIV-1 vaccine development. Moreover, this study indicates that the road to a globally effective vaccine may not involve quite as many steps as envisioned.

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