

**Optimal priming of poxvirus vector (NYVAC)-based HIV vaccine regimens requires 3 DNA injections.
Results of the randomized multicentre EV03/ANRS Vac20 Phase I/II Trial**

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Background. DNA vectors have been widely used as priming component of prime/boost vaccine regimens in combination with poxvirus or adenovirus vectors. Two or three DNA primes have been used in previous smaller clinical trials, but the number required for optimal quantitative and qualitative vaccine-induced T-cell responses has never been assessed in adequately powered clinical trials. The EV03/ANRS Vac20 phase I/II trial investigated this issue using the DNA prime/poxvirus NYVAC boost combination, both expressing a common HIV-1 clade C immunogen consisting of Env and Gag-Pol-Nef polypeptide.

Methods: 147 healthy volunteers were randomly allocated through 8 European centres to either 3xDNA plus 1xNYVAC (weeks 0, 4, 8 plus 24; n=74) or to 2xDNA plus 2xNYVAC (weeks 0, 4 plus 20, 24; n=73), stratified by geographical region and sex. T cell responses were quantified in a single laboratory using the interferon γ Elispot assay and 8 peptide pools; samples from weeks 0, 26 and 28 (time points for primary immunogenicity endpoint) were considered for this analysis. The magnitude of a response at a particular time point was calculated as the sum of spot-forming units (SFU) per 10^6 cells from all peptide pools with a positive response.

Results: 140 of 147 participants were evaluable at weeks 26 and/or 28. 64/70 (91%) in the 3xDNA arm compared to 56/70 (80%) in the 2xDNA arm developed a T cell response to at least one peptide pool ($P=0.053$). 26 (37%) participants of the 3xDNA arm developed a broader T cell response (Env plus at least to one of the Gag, Pol, Nef peptide pools) versus 15 (22%) in the 2xDNA arm (primary endpoint; $P=0.047$). At week 26, the overall magnitude of responses was also higher in the 3xDNA than in the 2xDNA arm (similar at week 28), with a median of 545 versus 328 SFUs/ 10^6 cells at week 26 ($P<0.001$): for Env, the median magnitude was 539 versus 294 SFUs/ 10^6 cells ($P<0.001$); for Gag, Pol and Nef together it was 180 versus 109 SFUs/ 10^6 cells ($P=0.12$). Both regimens were safe and sufficiently well tolerated.

Conclusions. This large clinical trial demonstrates that optimal priming of poxvirus-based vaccine regimens requires 3 DNA injections and further confirms that the DNA/NYVAC prime boost vaccine combination is highly immunogenic. Analyses of the qualitative profile of the vaccine-induced T-cell responses are ongoing.