

First-in-Human Evaluation of a Hexon Chimeric Adenovirus Vector Expressing HIV-1 Env (IPCAVD 002)

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Background. We report the first-in-human safety and immunogenicity assessment of a prototype hexon chimeric adenovirus (Ad) serotype 5 (Ad5) vector containing the hexon hypervariable regions of Ad serotype 48 (Ad48) and expressing human immunodeficiency virus (HIV) type 1 EnvA.

Methods. Forty-eight Ad5 and Ad48 seronegative, HIV-uninfected subjects were enrolled in a randomized, double-blind, placebo-controlled, dose escalation phase 1 study. Four groups of 12 subjects received 10⁹ to 10¹¹ viral particles (vp) of the Ad5HVR48.EnvA.01 vaccine (n = 10 per group) or placebo (n = 2 per group) at week 0 or weeks 0, 4, and 24. Safety and immunogenicity were assessed.

Results. Self-limited reactogenicity was observed after the initial immunization in the highest (10¹¹ vp) dose group. Responses in vaccinees included Ad48 neutralizing antibody (nAb) titers higher than Ad5 nAb titers, EnvA-specific enzyme-linked immunosorbent assay titers, and EnvA-specific enzyme-linked immunospot assay responses, and these responses generally persisted at week 52. At week 28 in the 10⁹, 10¹⁰, and 10¹¹ vp 3-dose groups, geometric mean EnvA enzyme-linked immunosorbent assay titers were 5721, 10 929, and 3420, respectively, and Ad48 nAb titers were a median of 1.7-fold higher than for Ad5.

Conclusions. Ad5HVR48.ENV.A.01 was safe, well tolerated, and immunogenic at all doses tested. Vector-elicited nAb responses were greater for Ad48 than Ad5, confirming that Ad-specific nAbs in humans are primarily, but not exclusively, directed against the hexon hypervariable regions.

Clinical Trials Registration. NCT00695877.

Keywords. HIV vaccine; adenovirus 5 HVR48; safety; immunogenicity; dose escalation.

Development of a preventive human immunodeficiency virus 1 (HIV-1) vaccine is a global health priority, but to our knowledge only 4 vaccine concepts have been

evaluated in field trials to date [1–7]. Adenoviruses are potent vectors [8], and although recombinant adenovirus (Ad) serotype 5 (rAd5) vectors have been studied as preventative HIV-1 vaccines both alone and in conjunction with DNA priming, they have not been efficacious [1, 7]. Potential limitations of Ad serotype 5 (Ad5) vectors include the high level of preexisting antivector immunity, particularly in the developing world [9, 10], as well as qualitative features of the immune responses elicited [11].

To overcome these potential limitations, adenoviruses with lower seroprevalence have been proposed as vectors [12]. Alternative serotype Ad vectors have notable biologic differences from rAd5 in terms of baseline seroepidemiologic findings, receptor usage, tropism,

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innate immune profile, adaptive immune phenotype, and protective efficacy in the simian immunodeficiency virus (SIV)/macaque model [13–16]. Several alternative serotype Ad vectors, including Ad26 and Ad35, have advanced into clinical trials as potential vaccine vectors [17–20].

An alternative approach to retain favorable immunologic features of Ad5 vectors while reducing the potential impact of pre-existing Ad5 antibodies is to develop chimeric recombinant Ad vectors in which the key Ad5 neutralization epitopes have been removed. Because Ad5-specific neutralizing antibodies (nAbs) are directed primarily against the Ad5 hexon major capsid protein [21], specifically against the 7 hexon hypervariable regions on the hexon surface, we developed chimeric rAd5 vectors in which the hexon hypervariable regions were swapped with the corresponding regions from the rare Ad serotype 48 (Ad48) [22]. These chimeric vectors use the same cellular receptor as Ad5 and effectively circumvented dominant Ad5-specific nAbs directed against the hexon hypervariable regions [22]. Furthermore, a single injection of an Ad5HVR48 chimeric vaccine expressing SIV Env/Gag/Pol/Nef was immunogenic and led to improved peak and plateau viral loads after SIV challenge in macaques [23]. In this study, we report the first-in-human safety and immunogenicity evaluation of an Ad5HVR48 vectored HIV-1 vaccine, and we evaluated the capacity of this chimeric vector to induce nAbs against both Ad5 and Ad48.

METHODS

Vaccine

The Ad5HVR48.ENVA.01 vaccine was produced in complementing HER96 cells by Crucell Holland BV, Leiden, the Netherlands. A replication deficient (deletion in the early region 1/early region 3[Δ E1/E3]) rAd5 with hexon hypervariable regions from Ad48 was constructed with an HIV-1 clade A Env gene encoding a modified envelope gp140 protein [24, 25] (see [Supplementary Material](#) for details). The placebo was final formulation buffer.

Participants and Study Design

This study was a single center, randomized, double-blind, placebo-controlled, dose escalation trial to evaluate the safety and immunogenicity of a 3-dose regimen (weeks 0, 4, and 24) of Ad5HVR48.ENVA.01 at 10^9 , 10^{10} , or 10^{11} viral particles (vp) and a single-dose (week 0) regimen at 10^{10} vp in healthy HIV-uninfected volunteers. The 2 groups receiving 10^{10} vp allowed a comparison of 1 versus 3 vaccinations. Study subjects were Ad5 and Ad48 seronegative and at low risk for acquiring HIV according to standard criteria [26]. The protocol was approved by the institutional review board and biosafety committee and written informed consent was obtained from each subject. The study was registered at ClinicalTrials.gov (NCT00695877).

Groups 1, 2, and 3 received 3 inoculations of 10^9 , 10^{10} , 10^{11} vp, respectively, and group 4 received a single inoculation of 10^{10} vp.

Each dose group had 12 subjects, 10 vaccinees and 2 placebo recipients, for a total sample size of 48. The placebo recipients in each group were pooled into an 8-subject placebo group for analysis (2 placebo recipients received 1 injection rather than 3). All vaccines were given by needle and syringe in the deltoid muscle.

Immunogenicity Studies

Immunogenicity assessments were performed on samples collected at weeks 0, 4, 8, 24, 28, and 52. Week 28 samples were not analyzed in group 4. All immunogenicity assays were performed in a blinded fashion under good clinical laboratory practices conditions. Luciferase-based Ad neutralization assays were performed to assess Ad5- and Ad48-specific nAbs, as described elsewhere [14, 16]. Direct enzyme-linked immunosorbent assay (ELISA) was performed with serum samples to assess EnvA-specific binding antibodies against the vaccine immunogen [13]. Interferon γ enzyme-linked immunospot assay (ELISPOT) was performed to assess EnvA-specific cellular immune responses using a pool of overlapping EnvA peptides [13]. Criteria for positive Ad5 and Ad48 nAb responses were titer >16 and for Env ELISA responses, titer ≥ 100 . Criteria for ELISPOT assay positivity were ≥ 55 spot-forming cells (SFCs)/ 10^6 peripheral blood mononuclear cells (PBMCs) and ≥ 3 times background; ELISPOT responses that were <10 SFCs/ 10^6 PBMCs after subtraction of medium-only responses were considered baseline and imputed to 10. The EnvA protein and peptides were provided by the National Institutes of Health (NIH) Vaccine Research Center, Bethesda, Maryland.

Statistical Methods

All analyses are based on the intent-to-treat principle including all subjects in the group to which they were randomized. Summaries of responses are presented as geometric mean titers (GMTs) for the antibody data and medians for the HIV-1 ELISPOT data. Differences in proportions were tested with 2-sided Fisher exact tests. The Kruskal–Wallis nonparametric analysis of variance was used to test for differences among the groups. When a significant overall difference in the Kruskal–Wallis test was identified at a given time point, pair-wise tests of all possible treatment pairs were performed using the Mann–Whitney–Wilcoxon nonparametric test. Spearman correlations were used to assess the correlation between Ad5 or Ad48 nAb titers and the magnitude of EnvA-specific T-cell responses or ELISA titers for vaccinees for the 2 assays being compared. Tests with a 2-sided P value $< .05$ were considered significant. No adjustments were made for multiple comparisons.

RESULTS

Subject Characteristics and Demographics

Of the 585 subjects screened for Ad5 and Ad48 seropositivity between February 2009 through November 2011, 278 (47.5%)

were positive for Ad5 nAb and 49 (8.4%) were positive for Ad48 nAb. Of the 48 subjects enrolled, 31 (65%) were female, 35 (73%) were <31 years old (median, 24 years; range, 18–50 years), 15 (31%) were nonwhite, and 4 (8%) were Hispanic. The mean body mass index was 23.8 kg/m² (range, 16.9–34.9 kg/m²). The overall retention rate was 98%, and 119 (99%) of the 120 planned vaccinations were given (99 of 100 for active vaccine and all 20 for placebo injections).

Safety and Tolerability

The Ad5HVR48.ENVA.01 vaccine was safe and generally well tolerated at all doses studied (Supplementary Figure 1A and 1B). Minimal reactogenicity was observed in the 10⁹ or 10¹⁰ vp dose groups. Some systemic reactogenicity was observed after the initial immunization with the 10¹¹ vp dose and consisted of a constellation of moderate to severe symptoms including malaise, myalgia, headache, and/or chills in 9 subjects, which typically began on the evening of vaccination and spontaneously resolved within a day. The reactogenicity pattern with the initial injection of the 10¹¹ vp dose is significantly different from that in the other dose groups ($P = .01$), but there were no significant differences among dose groups with the booster inoculations.

Local reactogenicity was relatively common in all dose groups with all 3 inoculations and consisted of mild to moderate erythema, induration, pain, tenderness, or itchiness at the inoculation site, which generally resolved within 4–7 days, either with no treatment or with over-the-counter analgesics. Local reactogenicity symptoms did not differ among the groups after the initial or second inoculation but were greater than in the placebo group after the 6-month booster injection ($P = .01$). Additional safety information and comparisons between antivector and anti-insert immune responses are presented in the Supplementary Material.

Ad5 nAb Responses

All subjects were seronegative for Ad5 at baseline. All placebo recipients had negative Ad5 nAb titers throughout the course of the study. Figure 1 shows the kinetics of the Ad5 nAb responses by dose group. Twenty-eight subjects (70%) had detectable Ad5 nAb titers by day 28 after first vaccination and all subjects who received a second injection seroconverted (titer >16) by 8 weeks except 1 subject in the lowest dose group. At week 52, the Ad5 nAb titers remained positive in all subjects who had received ≥1 booster vaccination, whereas only 40% of subjects (4 of 10) who received a single 10¹⁰ dose still had detectable Ad5 nAb at 1 year.

No clear dose-response trend was observed in the Ad5 nAb titers at week 4 after the initial immunization; GMTs were 66, 176, 78, and 89, respectively, in the groups that received 3 doses at 10⁹, 10¹⁰, or 10¹¹ or 1 dose at 10¹⁰ (hereafter 10⁹ × 3, 10¹⁰ × 3, 10¹¹ × 3, and 10¹⁰ × 1; $P < .02$ for all groups compared with placebo). At week 8 there was an increase in Ad5 nAb GMTs in

groups 1–3 (4 weeks after second vaccination) but, as expected, not in group 4: 169 (10⁹ × 3 group), 229 (10¹⁰ × 3 group), 172 (10¹¹ × 3 group), and 42 (10¹⁰ × 1 group). A 32% decay in Ad5 nAb titers was noted at week 24 (before the third vaccination), but significant boosting was observed after the third vaccination (week 28) to 346 (10⁹ × 3 group), 1234 (10¹⁰ × 3 group), and 996 (10¹¹ × 3 group). At week 52, Ad5 nAb titers persisted with GMTs of 175, 612, and 538 in the 10⁹ × 3, 10¹⁰ × 3, and 10¹¹ × 3 groups, respectively, with a trend ($P = .08$) toward higher Ad5 nAb titers in the 2 higher-dose groups.

Ad48 nAb Responses

All subjects were seronegative for Ad48 at baseline. All placebo subjects were Ad48 nAb negative throughout the study except 1 subject who had a low titer response at week 52. Figure 2 shows the kinetics of the Ad48 nAb responses by dose group. Ninety-eight percent of the subjects (39 of 40) had a detectable Ad48 nAb titer by day 28 after first vaccination, and the single vaccinee (in the 10¹⁰ × 3 group) who did not respond to the first dose had a detectable titer by week 24. At week 52, the Ad48 nAb titer remained positive in most subjects who had received ≥1 booster vaccination (26 of 29; 90%) and in all 10 subjects who received a single vaccination.

An increase in Ad48 nAb titer was observed as the dose was increased from 10⁹ to 10¹⁰ or 10¹¹ with GMTs at week 4 of 123, 601, 484, and 462 in the 10⁹ × 3, 10¹⁰ × 3, 10¹¹ × 3, and 10¹⁰ × 1 groups, respectively, at week 4 after the initial immunization ($P < .02$ for all groups compared with placebo). These responses were not significantly increased after the second vaccination, at week 8, in the 10⁹ × 3, 10¹⁰ × 3, and 10¹¹ × 3 groups but declined by about 32% by week 24. A significant increase in Ad48 nAb titer was observed after the third vaccination compared with the preboost GMTs, with increases from 129 to 382 (10⁹ × 3 group), 330 to 1321 (10¹⁰ × 3 group), and 496 to 2395 (10¹¹ × 3 group). At week 52, Ad48 nAb titers persisted in all groups: 171, 547, 673, and 77 in the 10⁹ × 3, 10¹⁰ × 3, 10¹¹ × 3, and 10¹⁰ × 1 groups, respectively.

Taken together, these data show that Ad5HVR48.ENVA.01 consistently elicited vector-specific nAbs that increased with a subsequent boost immunization at 6 months (but not with the 1-month boost) and could be detected for ≥1 year after a single inoculation. Higher titer and more durable nAb immune responses were elicited against Ad48 than against Ad5 and with 3 doses compared with a single dose. An analysis of all the vaccinees at peak immunogenicity time points (week 28 for the 10⁹ × 3, 10¹⁰ × 3, 10¹¹ × 3 groups and week 4 for the 10¹⁰ × 1 group) showed that they had a median 2.2-fold higher Ad48 nAb titer compared with Ad5 nAb titer ($P = .02$). Furthermore, 69% of vaccinees (27 of 39) had higher Ad48 than Ad5 nAb titers ($P = .01$). This is a striking finding, because the chimeric Ad5HVR48 vector contained >99% Ad5 sequences with <1% Ad48-derived sequences.

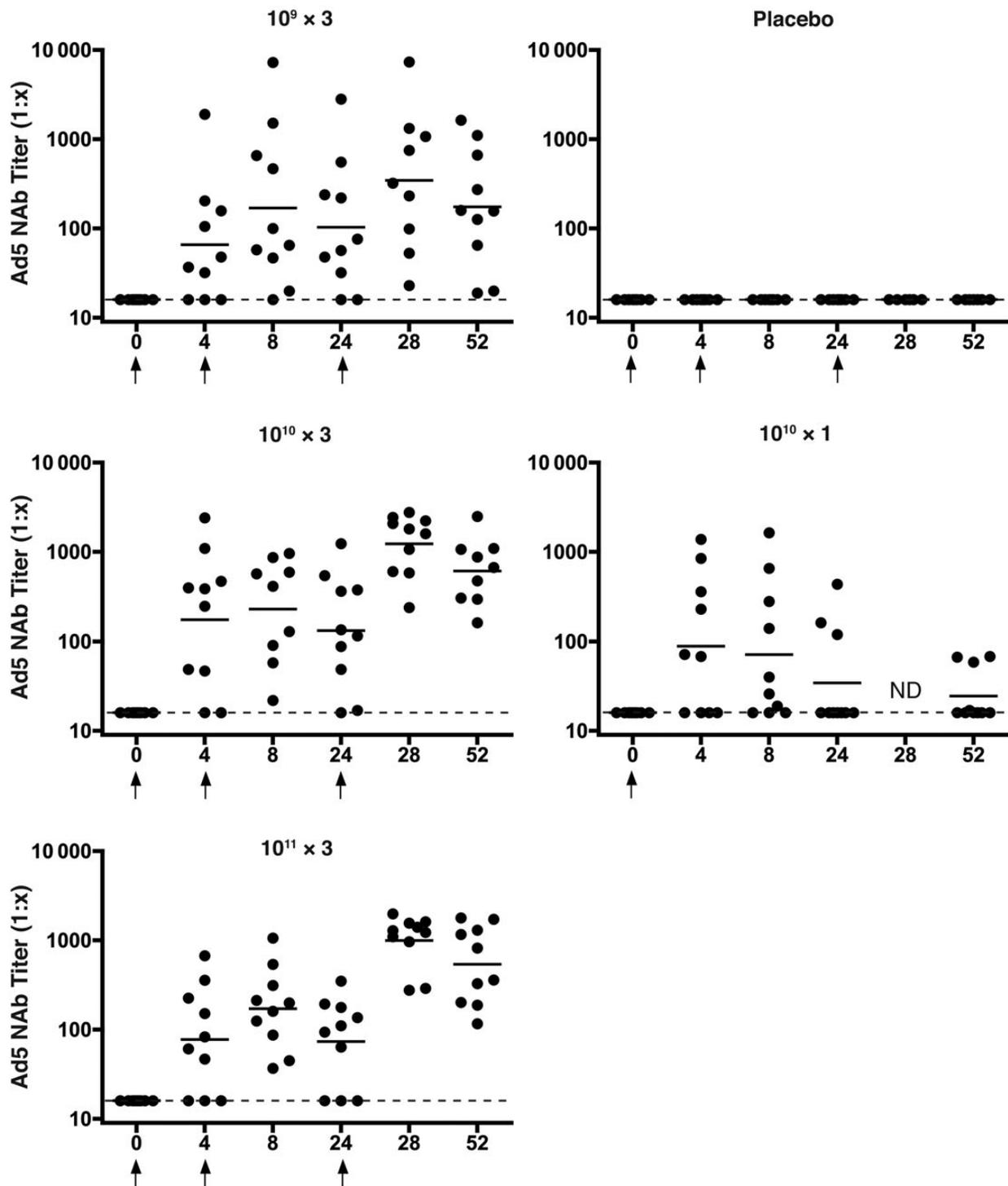


Figure 1. Adenovirus serotype 5 (Ad5) neutralizing antibody (nAb) responses by group. Individual subject responses are shown by week and vaccine group. Dots indicate individual responses at a given time point; horizontal lines, geometric mean titers at a given time point for the group; dashed lines, lower limit of the assay; arrows, times when vaccine or placebo was administered. Abbreviation: ND, not done.

HIV-1 Env-Specific Antibody Responses

All subjects had negative EnvA-specific ELISA binding antibody titers at baseline, and all subjects in the placebo group remained negative throughout the study. Figure 3 shows the

kinetics of the binding antibody responses by dose group. At week 4, after the initial vaccination, 100% (all 40) of the vaccinees had an ELISA response to the homologous EnvA antigen. At week 52 responses remained detectable in all subjects (100%)

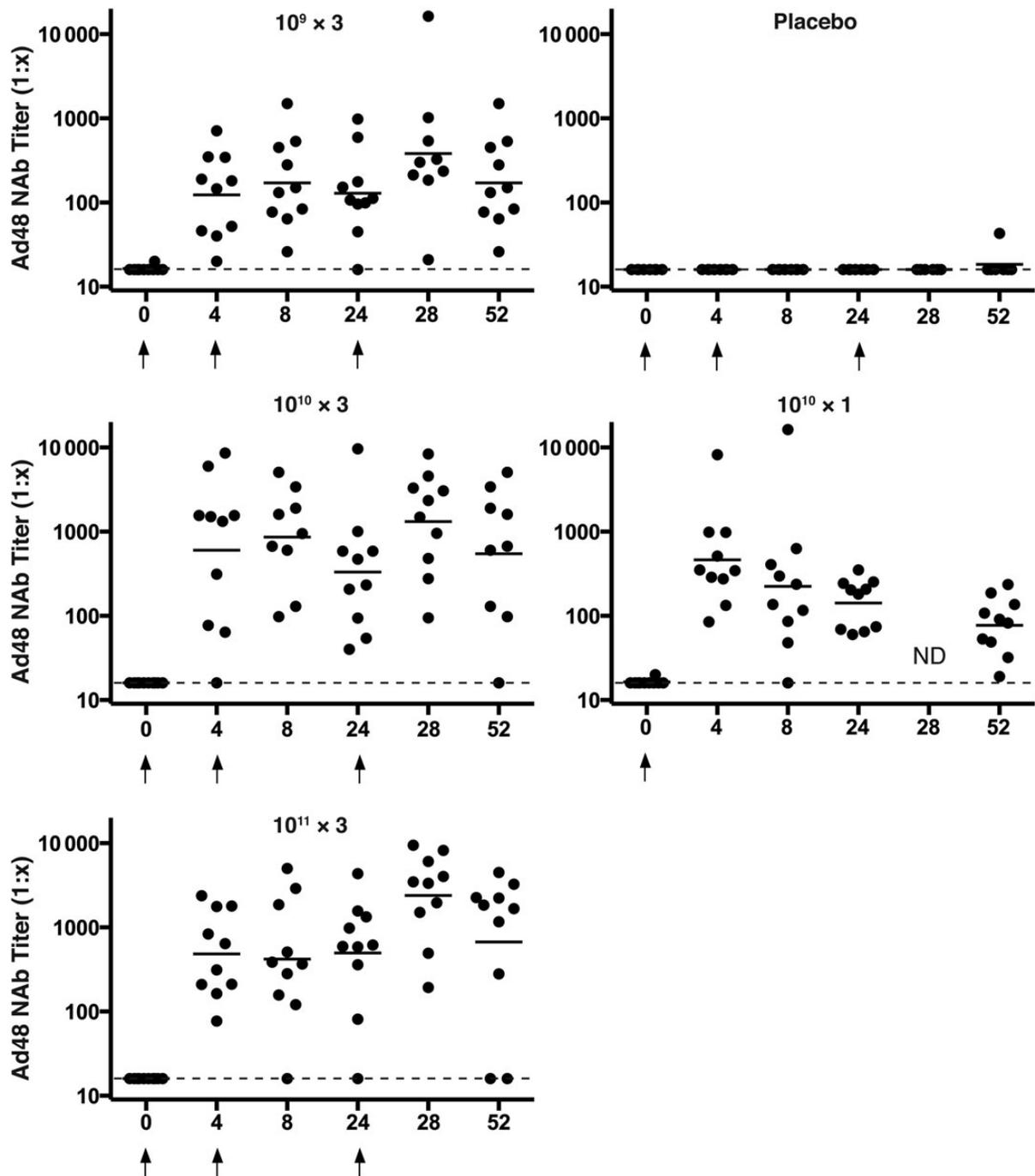


Figure 2. Adenovirus serotype 48 (Ad48) neutralizing antibody (nAb) responses by group. Individual subjects responses are shown by week and vaccine group. Dots indicate individual responses at a given time point; horizontal lines, geometric mean titers at a given time point for the group; dashed lines, lower limit of the assay; arrows, times when vaccine or placebo was administered. Abbreviation: ND, not done.

in the $10^9 \times 3$, $10^{10} \times 3$, and $10^{11} \times 3$ groups and in 80% (8 of 10) in the $10^{10} \times 1$ group. ELISA responses to a heterologous EnvA, UG37, were also detected but somewhat lower than responses to the homologous EnvA; these are presented in the [Supplement](#) and [Supplementary Figure 2](#).

At week 4 a trend with an increase in EnvA ELISA GMT was observed, consistent with a dose response: 1536, 3456, 4805,

and 1081 in the $10^9 \times 3$, $10^{10} \times 3$, $10^{11} \times 3$, and $10^{10} \times 1$ groups, respectively ($P = .05$). These titers were not significantly increased after the second vaccination and decreased by about 74% by week 24 to 243, 1220, and 618 in the $10^9 \times 3$, $10^{10} \times 3$, and $10^{11} \times 3$ groups, respectively. These titers then increased significantly after the third vaccination to 5721, 10 929, and 3420 ($P < .0001$) but declined by week 52 to 440, 2378, 877,

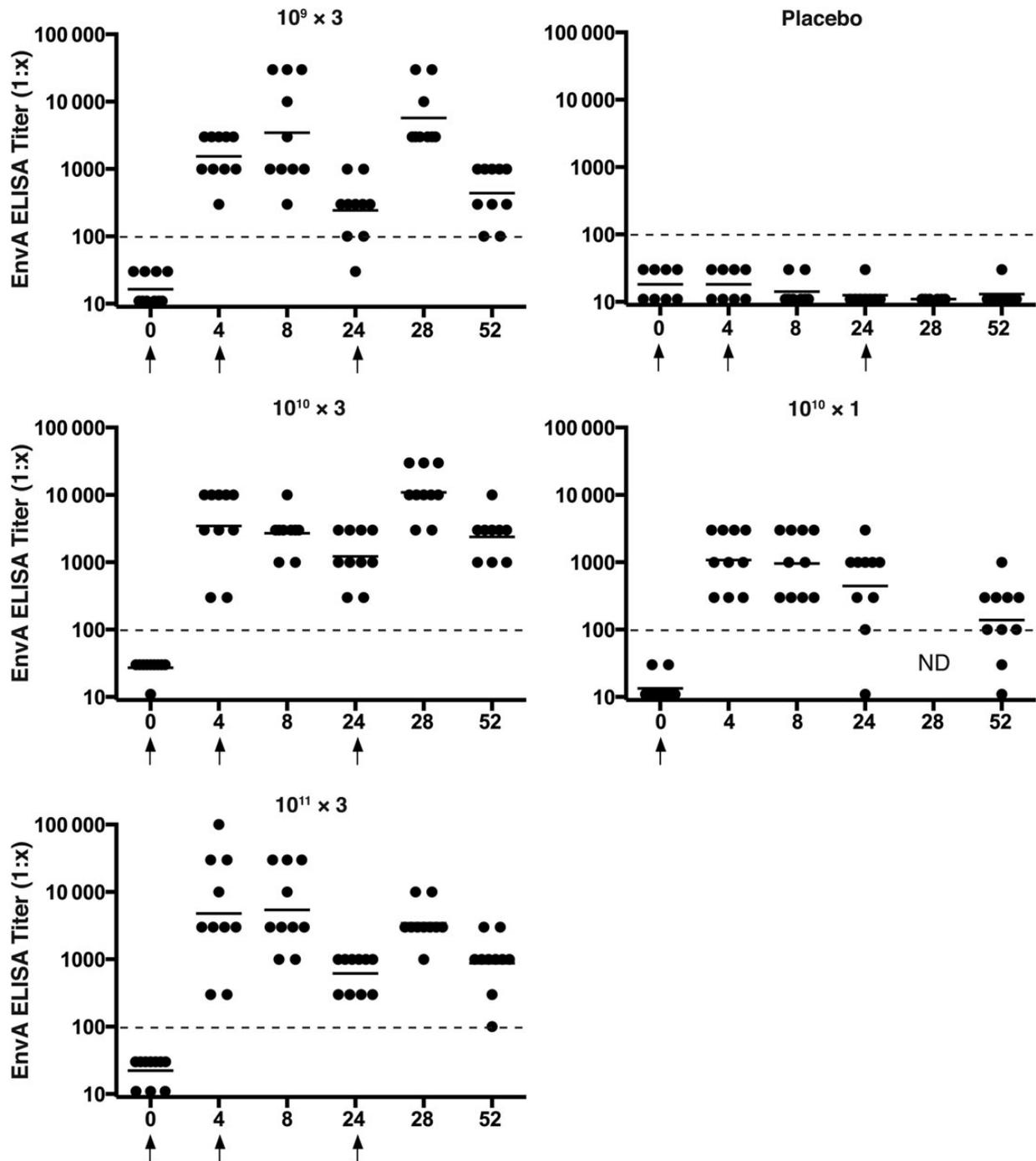


Figure 3. EnvA enzyme-linked immunosorbent assay (ELISA) responses by group. Individual subject responses are shown by week and vaccine group. Dots indicate individual responses at a given time point; horizontal lines, geometric mean titers at a given time point for the group; dashed lines, cutoff for the assay; arrows, times when vaccine or placebo was administered. Abbreviation: ND, not done.

and 139 in the $10^9 \times 3$, $10^{10} \times 3$, $10^{11} \times 3$, and $10^{10} \times 1$ groups, respectively.

The impact of vaccination schedule was assessed by comparing the $10^{10} \times 3$ and $10^{10} \times 1$ groups. As expected, similar ELISA GMTs were observed at week 4 after the first vaccination and were not significantly different at week 8, despite the second

vaccination in the $10^{10} \times 3$ group. A decrease in GMT was observed in both groups by week 24 (1220 for $10^{10} \times 3$ and 444 for $10^{10} \times 1$), followed by an increase to 10 929 in the $10^{10} \times 3$ group after the third vaccination. At week 52, 17-fold higher ELISA responses were observed in the $10^{10} \times 3$ group than in the $10^{10} \times 1$ group (2378 vs 139; $P < .0001$). A similar pattern was

observed with the heterologous UG37 antigen (Supplementary Figure 2).

These data show that Ad5HVR48.ENVA.01 consistently induced EnvA-specific binding antibody responses, and that these responses were substantially augmented by homologous boosting, despite the induction of robust vector-specific nAbs. No significant HIV-specific nAb responses were detected by TZM-bl assays against a panel of tier 1 viruses (DJ283.8, SF162.LS, MW965.26, and MS208.A1; data not shown).

HIV-1 EnvA-Specific Cellular Immune Responses

No EnvA-specific cellular immune responses were detected with interferon γ ELISPOT at baseline, and none of the subjects in the placebo group had EnvA-specific ELISPOT responses. Figure 4 shows the kinetics of the response by dose group. At week 4, 39 of 40 vaccinees (98%) had detectable ELISPOT responses. One subject in the $10^{10} \times 1$ group never had a detectable ELISPOT response despite a modest but transient ELISA response to EnvA. At week 52, persistent responses were detected in 32 of 39 subjects (82%): 8, 8, 10, and 6 subjects, respectively, in the $10^9 \times 3$, $10^{10} \times 3$, $10^{11} \times 3$, and $10^{10} \times 1$ groups.

The median ELISPOT responses at week 4 were 165 ($10^9 \times 3$ group), 459 ($10^{10} \times 3$ group), 568 ($10^{11} \times 3$ group), and 473 SFCs/ 10^6 PBMCs ($10^{10} \times 1$ group; all $P < .0001$ for comparison with placebo). These responses were similar in all groups at weeks 8, 24, and 28 despite the booster doses (at weeks 4 and 24) that the first 3 groups received, although there was a trend toward lower responses in the $10^9 \times 3$ group. At week 52, ELISPOT responses were slightly higher in the groups that had received booster vaccinations (120, 233, and 232 SFCs/ 10^6 PBMCs in the $10^9 \times 3$, $10^{10} \times 3$, and $10^{11} \times 3$ groups, respectively) compared with only a single vaccination ($10^{10} \times 1$: 93). These data show that Ad5HVR48.ENVA.01 consistently induced EnvA-specific cellular immune responses and that these responses could be detected for ≥ 1 year after a single vaccination.

DISCUSSION

The novel recombinant Ad5HVR48.ENVA.01 HIV-1 vaccine candidate was generally safe, well tolerated, and immunogenic in this first-in-human evaluation of this chimeric Ad vector. Responses were induced after a single immunization in nearly all subjects, including those who received the lowest dose. All subjects who received the vaccine had both Ad5 and Ad48 vector-specific and EnvA insert-specific humoral immune responses that generally persisted for 1 year. These findings are consistent with the data in the nonhuman primate model where Ad5HVR48 vectors elicited consistent humoral and cellular immune responses and provided partial protection against SIV challenges [22, 23, 27]. Because Ad5HVR48 has many biologic properties that differ from those of Ad5, including a distinct

innate immune cytokine profile [28], its potential as a vaccine platform warrants further study.

Interestingly, although our chimeric vector expressed only 104 amino acids (<1% of the Ad proteome) derived from 7 Ad48 hexon hypervariable domains, the anti-Ad48 nAb titers elicited were higher in magnitude and persisted longer than the anti-Ad5 nAb titers elicited by the remainder of the vector. This finding confirms the chimeric nature of the vector capsid and demonstrates that the 7 short hexon hypervariable regions represent a primary determinant of vector-specific nAbs. Although we have reported this in the context of preclinical studies [22], this has not previously been shown in a vaccine trial in humans. Our data also demonstrate that although dominant vector-specific nAbs are directed against the hexon hypervariable regions (as measured by the Ad48-specific nAbs), other nAb targets also exist (as measured by the Ad5-specific nAbs), potentially against other hexon and fiber epitopes [29, 30].

The impact of preexisting anti-Ad5 or anti-Ad48 nAbs elicited by natural infection could not be assessed in our study because our subjects were all screened to be seronegative for both. In 2 models of Ad5-vectored vaccines, preexisting Ad5-specific nAbs were found to have no impact on immune responses elicited by the insert [31, 32].

Env-specific T-cell responses were elicited at all 3 doses, including the lowest dose (10^9 vp). Because lower doses were not studied, the threshold for the induction of T-cell responses in humans with this vector is unknown. T-cell responses were only minimally boosted by dose (over a 100-fold range) or increased number of immunizations (3 vs 1). Although direct comparisons are not possible owing to differences in assay methods, the insert-specific responses induced by this Ad5HVR48 vector seem comparable to those elicited by Ad5, Ad26, and Ad35 vectors at similar doses and intervals [17, 24, 33].

Env-specific binding antibody responses detected with ELISA were elicited in nearly all subjects after the first immunization, including those who received the lowest dose. A dose-response trend was suggested, with higher titers in the 10^{11} vp group than in the other groups after the initial inoculation, but this effect was mitigated by the booster vaccinations. In the 10^{10} vp dose group, a direct comparison of the effect of the number of immunizations can be made. Here the 3-dose regimen elicited higher ELISA titers compared with the 1-dose regimen, and this difference was maintained at 1 year.

Despite the induction of robust vector-specific nAb responses, EnvA insert-specific antibody responses were increased after boosts with the homologous vectors, and we found no evidence that vector-specific nAbs inhibited insert-specific cellular or humoral immune responses. On the contrary, the few significant interactions we observed suggest that there is a modest, but positive, association between induction of antivector neutralization activity and immune responses elicited by the insert.

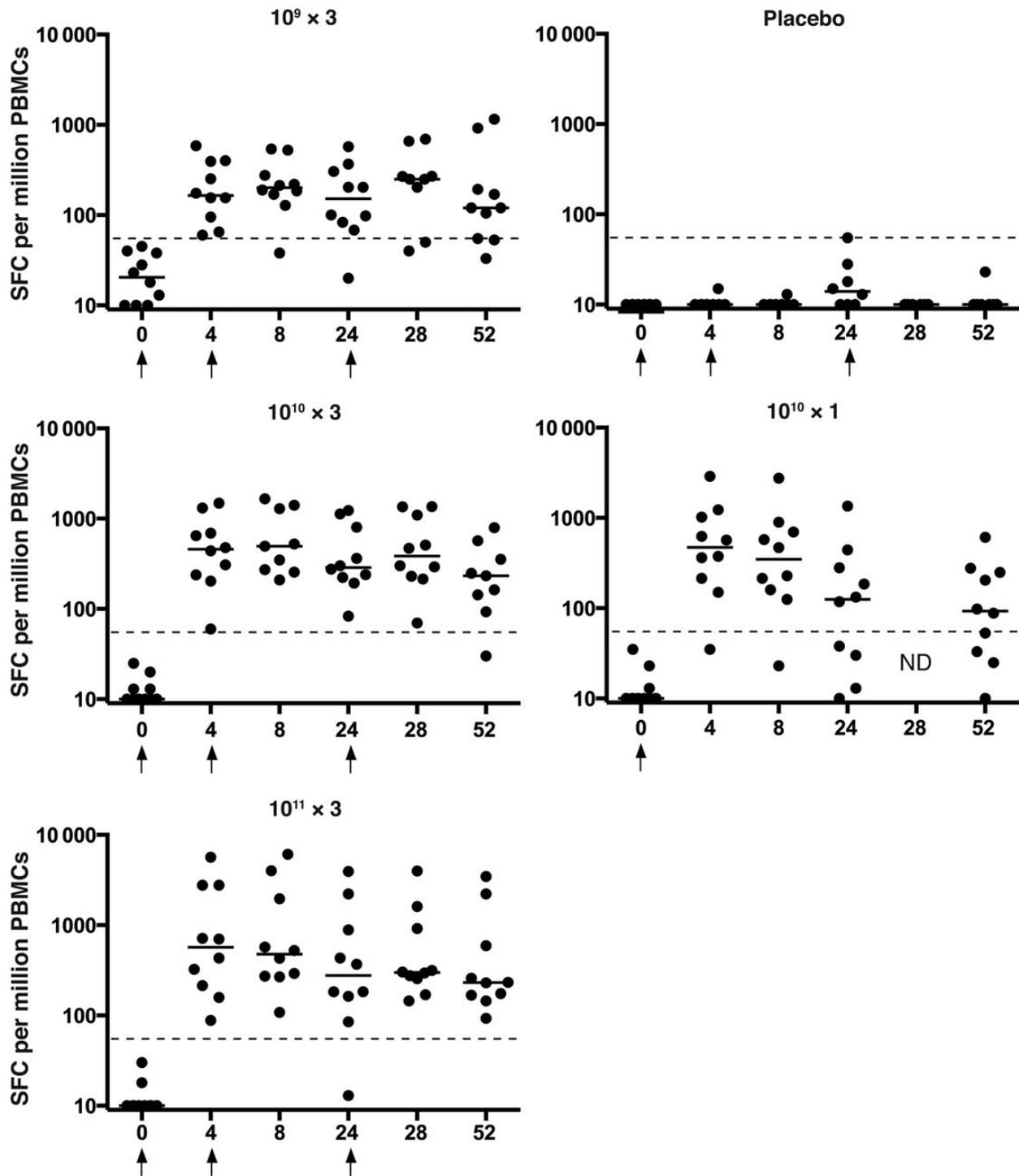


Figure 4. EnvA enzyme-linked immunospot assay responses by group. Individual subject responses are shown by week and vaccine group. Dots indicate individual responses at a given time point; horizontal lines, median values at a given time point for the group; dashed lines, cutoff for the assay; arrows, times when vaccine or placebo was administered. Abbreviations: ND, not done; PBMCs, peripheral blood mononuclear cells; SFCs, spot-forming cells.

A phase IIB study of the Merck Ad5-gag/pol/nef vaccine showed no protective efficacy and possible enhanced HIV-1 acquisition in certain subgroups [1]. Our vaccine prototype is different than this prior vaccine in several important ways. First,

we use chimeric Ad5 with hexon hypervariable regions derived from Ad48 as a vaccine vector, which has been shown in animal models to have major biologic differences, including lack of hepatic tropism and different innate immune profiles [11, 13, 15,

16, 28, 34]. Second, our vector expresses HIV-1 Env as a test antigen, which is potentially relevant because Env-specific antibodies seem to play a role in blocking acquisition of infection in both human [35] and nonhuman primate studies [36–38]. However a DNA-prime/Ad5-boost vaccine study was recently halted for lack of efficacy despite including HIV-1 Env immunogens in the regimen [7].

These data demonstrate the safety and immunogenicity of the novel recombinant Ad5HVR48.ENVA.01 vaccine in humans for the first time. Importantly, Env-specific humoral and cellular immune responses were consistently elicited over a 100-fold dose range with only minimal reactogenicity at the highest dose studied. Moreover, vector-elicited nAb responses were higher for Ad48 than Ad5, confirming that human Ad-specific nAbs are primarily, but not exclusively, directed against the hexon hypervariable regions. Further clinical evaluation is needed to determine whether preexisting Ad5 and/or Ad48 immunity will alter the safety or immunogenicity profile observed. The chimeric Ad5HVR48 vector is a biologically distinct vaccine vector compared with the parental Ad5 vector and therefore warrants additional investigation as a vaccine vector for both HIV and other pathogens.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. M. G. P. and M. W. are employees of Crucell Holland. Patents for the Ad5HVR48.ENVA.01 construct are held in part by Crucell and Beth Israel Deaconess Medical Center, and no licensing agreements, royalties or income are associated with these patents.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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