

Therapeutic Immunization with Human Immunodeficiency Virus Type 1 (HIV-1) Peptide-Loaded Dendritic Cells Is Safe and Induces Immunogenicity in HIV-1-Infected Individuals[∇]

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Treatments for human immunodeficiency virus type 1 (HIV-1)-positive individuals that augment HIV-1 suppression and have potential for achieving long-term control of HIV-1 viremia in the absence of antiretroviral therapy (ART) are urgently needed. We therefore conducted a phase I, clinical safety trial of a dendritic cell (DC)-based vaccination strategy as immunotherapy for HIV-1-positive individuals on ART. We studied 18 HIV-1-positive subjects on ART who underwent leukapheresis to obtain peripheral blood mononuclear cells for DC generation from monocytes cultured with cytokines. Mature DC were pulsed with three HIV-1 HLA*A0201 Gag, Env, and Pol peptides and one influenza A virus matrix protein peptide. The vaccine was administered to donors randomized to receive two vaccinations, either intravenously or subcutaneously. The primary end points were safety and tolerability of two doses of peptide-DC vaccine (3 million versus 10 million). Secondary end points included gamma interferon (IFN- γ) enzyme-linked immunospot assay responses and clinical correlates of an immune response to vaccination. Autologous DC-peptide vaccine was safe, well tolerated, and feasible for use in all participants. Adverse events were rare. Although the trial was not powered to assess an immunologic response, a significantly increased frequency of HIV-1 peptide-specific IFN- γ -positive cells was observed 2 weeks following the second vaccine, with three individuals responding to all four peptides. DC vaccination was safe, was feasible, and showed promise of immunogenicity in ART-treated, HIV-1-positive individuals. Additional studies of DC immunization strategies for HIV-1 infection are warranted.

Administration of potent antiretroviral therapy (ART) results in dramatic declines in the morbidity and mortality due to human immunodeficiency virus type 1 (HIV-1) infection in the majority of treated persons. Initiation of ART is usually accompanied by substantial decreases in HIV-1 viral load and increases in CD4⁺ T-lymphocyte counts (21, 22). Studies with long-term survivors and with subjects treated during acute infection show that vigorous HIV-1-specific cytotoxic T-lymphocyte (CTL) responses and strong HIV-1-specific TH1 responses correlate with long-term control of viral replication in the absence of therapy, resulting in prolonged, symptom-free survival (17, 19, 23, 24, 30). Unfortunately, limited restoration of HIV-1 specific T-helper cell and CTL reactivity in persons with chronic HIV-1 infection on ART (3, 19, 27) mandates lifelong therapy and generally persistent, albeit low-level, HIV-1 replication. While innate and acquired immune responses appear to be responsible for the initial control of viremia in acute HIV-1 infection, naturally occurring immune responses appear to fade over time in the majority of HIV-1-infected individuals, resulting in disease progression (4, 10, 15). HIV-1-infected individuals on ART with suppressed plasma

viral loads progressively lose HIV-1-specific CTLs, suggesting that persistent viremia is required to maintain high frequencies of HIV-specific CTLs. In chronic HIV-1 infection, discontinuation of ART has been uniformly accompanied by a rapid rebound of plasma HIV-1 RNA to pretreatment, steady-state levels, indicating persistence of the HIV reservoir and absence of immune control (8, 20, 25). For these reasons, immunotherapeutic strategies with the potential to suppress viral replication and with the goal of eliciting broad, robust, and durable HIV-1-specific TH1 and CTL responses are needed.

Dendritic cells (DC) are known to play a critical role in the generation of highly specific immune responses against a variety of pathogens. DC acquire antigens in the periphery and, upon appropriate activation, migrate to lymph nodes, where they initiate generation of antigen-specific CD4⁺ and CD8⁺ T-cell responses (16). DC have been used extensively as adjuvants and antigen carriers in vaccination strategies for a variety of disease states, primarily malignancies, to induce antigen-specific T-cell responses with little or no toxicity (29, 32).

We and others have proposed that antigen-expressing DC could be an effective immunotherapy for HIV-1 infection (6). For this test-of-concept, phase I safety study, we used autologous DC loaded with highly conserved, immunodominant, HLA*A0201-restricted CTL peptides, including three different HIV-1 peptides and a single influenza A virus matrix peptide for immunization. Peptide-based vaccines are limited by the requirement for HLA specificity. We therefore chose for this

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study three HIV-1 CTL peptides that represent a selected subset of highly conserved HIV-1 synthetic peptides which were derived from the three major structural proteins of HIV-1 (Env, Gag, and Pol) and exhibit cross-reactive major histocompatibility complex binding to the HLA-A2 supertype family (1). Each of these HIV-1 CTL epitope peptides induces recall CTL responses from HIV-1-infected individuals, indicating that they are naturally processed and presented during the course of HIV-1 infection (1). Influenza A matrix peptide 58–66 represents a dominant epitope recognized by the majority of HLA*A0201-positive individuals. It has been safely and effectively used as an immunogen in numerous vaccination studies. Here we present the results of a phase I clinical trial designed to evaluate the safety and feasibility of autologous DC loaded with synthetic HIV-1 peptides.

MATERIALS AND METHODS

Study participants. Eighteen HIV-1-infected adults on ART with plasma HIV-1 RNA levels of ≤ 400 copies/ml plasma for at least 6 months and < 50 copies/ml at screening were enrolled at a single site between March 2003 and September 2005. All subjects expressed the HLA*A0201 allele and were on stable ART for at least 4 weeks prior to entry. Subjects were free from opportunistic infections or malignancies, had an expected survival of at least 12 months, had Karnofsky scores of greater than 70, and met additional laboratory-based safety criteria. Subjects had not received previous experimental HIV-1 vaccines, nor had they received other immunologic therapies, such as steroids or immunosuppressive agents, within 30 days of study entry. All subjects gave written informed consent, and the study was reviewed and approved by the Institutional Review Board of the University of Pittsburgh.

Study design. Participants were randomized to receive autologous DC–HIV-1 peptide vaccines either intravenously (i.v.) or subcutaneously (s.c.). Each subject received two vaccine doses, 3 weeks apart, by the same route of administration. Two dose levels were studied: low dose, 1 million to 3 million cells ($n = 6$), and high dose, 5 million to 10 million cells ($n = 12$). The low-dose group was enrolled first. The enrollment of the high-dose group began after review of the safety data for the low-dose group by the Data Safety Monitoring Board. Subjects were observed for 30 min following each vaccination and called on the day following vaccination to evaluate safety. Study visits were conducted weekly for 8 weeks and then at weeks 12, 16, 20, 24, 36, and 48. Vaccinations were given at study weeks 1 and 4; peripheral blood specimens for immunologic studies were obtained at weeks 6, 8, and 12. The study was reviewed quarterly by an independent Data Safety Monitoring Board convened by the Office of Clinical Research at the University of Pittsburgh.

Vaccine production. Subjects underwent a single leukapheresis at study entry for 2.5 times blood volume to obtain peripheral blood mononuclear cells (PBMC). Vaccine production has been thoroughly described previously (7). In brief, monocytes were isolated by plastic adherence and cultured in the presence of granulocyte-macrophage colony-stimulating factor and interleukin-4 (IL-4) for 6 days as previously described (13, 26). DC were then matured in the presence of IL-1 β , IL-6, and tumor necrosis factor alpha for 24 h and incubated for 2 to 4 h with 10 $\mu\text{g/ml}$ of each of the HIV-1 peptides (Gag 386 to 394, VLAEMSQV; Env 134 to 142, KLTPLCVTL; and Pol 498 to 506, ILKEPVHGV) and influenza A virus matrix protein peptide (58 to 66, GILG FVFTL). DC were pulsed with each peptide separately. The DC were harvested, combined, washed, and counted; assayed for viability, sterility, purity, and maturity by phenotype; and administered to study subjects. The vaccines were produced and evaluated by the Cellular Products Laboratory, which operates as a Current Good Manufacturing Practice facility at the University of Pittsburgh Cancer Institute.

Peptide synthesis. The 9-amino-acid synthetic HIV-1 Gag, HIV-1 Pol, HIV-1 Env, and influenza A virus matrix peptides were synthesized, purified, and stored as described previously (5, 7). Prior to their use for DC pulsing, the peptides were tested for sterility, mycoplasma, and endotoxin.

Immunologic assays. (i) **IFN- γ ELISPOT.** Direct enzyme-linked immunosorbent (ELISPOT) assays to enumerate gamma interferon (IFN- γ)-producing cells were performed using previously described methods (2, 28) at the Immunologic Monitoring Laboratory operated as a Good Laboratory Practice facility at the University of Pittsburgh Cancer Institute and as described previously (7). Briefly, unseparated PBMC were plated in 96-well antibody-coated plates. Stimulator

cells, i.e., autologous DC pulsed with one of the peptides, were then added. Control wells contained unpulsed DC plus unseparated PBMC. The ratio of unseparated PBMC to stimulator cells was 10:1. When experimental values (unseparated PBMC + stimulator cells) were significantly different from the mean number of spots in control wells (background values) as determined by a permutation test, the background values were subtracted from the experimental values. The coefficient of variation for the assay was determined to be 15% ($n = 50$). For each subject, PBMC obtained before and after vaccination were batched and analyzed in the same assay to avoid interassay variability.

(ii) **IL-12 production assay.** The IL-12 production assays were performed as described elsewhere (7). In brief, mature DC (mDC) and peptide-pulsed mDC were cocultured in the presence of the CD40L-expressing cell line J558 for 24 h at 37°C in wells of a 96-well U-bottom plate. Supernatants were harvested, cryopreserved, and tested for IL-12p70 levels by enzyme-linked immunosorbent assay (R&D Systems) performed on thawed and batched supernatants in the same assay. These assays were performed at the Immunologic Monitoring Laboratory, University of Pittsburgh Cancer Institute.

(iii) **Flow cytometry.** The phenotype and maturity of DC were assessed by flow cytometry following DC staining with monoclonal antibodies specific for DC surface markers and purchased from Coulter Beckman (Miami, FL). Conditions used for staining were previously described (12, 31), and isotype controls were used in all experiments. Three- or four-color flow cytometry analysis was performed as previously described using a Coulter Epics XL cytometer with a single 488-nm argon ion laser (12, 31). The amplification and compensation were set according to the standard procedure, using negative controls (isotype control immunoglobulin G1-fluorescein isothiocyanate or immunoglobulin G1-phycoerythrin antibodies). At least 10,000 cells were acquired for analysis, and the data were analyzed using the Expo-32 software.

(iv) **Statistical analysis.** The primary end point of this prospective phase I study was to define the safety and tolerability of two doses of peptide-pulsed, autologous, cultured DC administered either i.v. or s.c. to HIV-1-infected subjects. Secondly, we planned to (i) determine whether immunization with peptide-pulsed DC increased CD8⁺ T-cell responses to HIV-1 and influenza virus peptides in ELISPOT assay, (ii) compare the immune responses to HIV-1 peptide-pulsed, autologous DC given i.v. or s.c. and at a low versus high dose, and (iii) evaluate the relationship between immunologic responses and clinical parameters.

For analysis of ELISPOT assay results, the nonparametric Wilcoxon signed rank test was used. Mean spot counts from triplicate wells at baseline (prior to vaccination) were compared to mean spot counts from triplicate wells at study weeks 4, 6, 8, and 12. While several baseline results were taken, the difference between these was not statistically significant (data not shown), and the decision was made to use a single baseline for comparison. The nonparametric Wilcoxon rank sum test was used to compare mean spot counts of test wells between high and low doses, between the i.v. versus s.c. route, and between subjects with low nadir (≤ 150 cells/mm³) and high nadir (> 150 cells/mm³) CD4⁺ T cell counts. Individually, a positive response to antigen at baseline as measured in IFN- γ ELISPOT assays was defined as the number of spots (mean from triplicate wells) being greater by at least 2 standard deviations than the negative control (unseparated PBMC plus DC) for that assay. A positive response to vaccination was defined as the number of spots being greater, by at least 2 standard deviations, than the baseline count and exceeding the baseline count by at least 20 spots/10⁶ PBMC at any later time point.

RESULTS

Study participants. Baseline characteristics of the study population are listed in Table 1. The study subjects were mostly male (15/18) and white (16/18), with a median age of 44 years. The median baseline CD4⁺ T-cell count was 645 cells/mm³, and the median CD4⁺ T-cell nadir was 259 cells/mm³ ($n = 17$); six subjects had nadir CD4⁺ T-cell count of ≤ 150 cells/mm³, and one subject had no nadir CD4 value available. All subjects completed at least 24 weeks of follow-up; one subject withdrew consent (after week 24) and a second died due to causes unrelated to the study vaccine (week 40).

Safety. The autologous DC-HIV peptide immunizations were generally safe and well tolerated. Seventeen subjects received both doses of vaccine. One subject (high dose, s.c.) experienced an undocumented grade 3 (104°F) fever on the day following the first vaccination, which was considered pos-

TABLE 1. Clinical characteristics of the study participants

Subject	Age (yr)	Gender ^a	CD4 ⁺ T-cell count (cells/mm ³) ^b		Duration of disease (yr)	Pretherapy viral load (copies/ml)	Vaccine dose	Route of administration
			Baseline	Nadir				
1	25	M	1,195	442	5	67,273	Low	s.c.
2	37	M	819	564	11	503	Low	i.v.
3	45	M	642	311	4	68,100	Low	s.c.
4	48	M	699	350	7	NA ^c	Low	i.v.
5	45	F	809	241	15	41,552	Low	s.c.
6	42	M	739	49	15	NA	Low	i.v.
7	32	M	974	340	4	38,058	High	i.v.
8	65	F	645	64	10	1,067,110	High	s.c.
9	48	F	558	59	11	55,031	High	i.v.
10	47	M	471	468	4	56,759	High	s.c.
11	43	M	744	310	11	79,000	High	s.c.
12	59	M	567	150	13	10,899	High	i.v.
13	34	M	464	236	10	69,171	High	i.v.
14	41	M	1,606	723	6	NA	High	s.c.
15	44	M	349	83	9	2,161,402	High	i.v.
16	47	M	646	NA	19	NA	High	s.c.
17	38	M	457	13	8	200,000	High	i.v.
18	47	M	475	259	5	67,273	High	s.c.

^a M, male; F, female.

^b The baseline count was obtained at the time of screening for the protocol. The nadir count is the lowest recorded value for each patient.

^c NA, not available.

sibly related to the vaccine, and the second vaccine was withheld. No other grade 3 or 4 laboratory or clinical events related to study vaccinations were observed. CD4⁺ T-cell counts remained stable and viral loads remained suppressed to less than 50 copies/ml for the duration of follow-up.

Vaccine production. One subject (low dose, i.v.) was unable to undergo leukapheresis because of anatomical irregularities. For this subject, ample DC were obtained from a 100-ml peripheral blood draw performed 1 week prior to each vaccine dose. For the remaining subjects, substantial DC were generated from a single leukapheresis product to allow preparation of multiple vaccine doses. DC generated from study participants were similar to DC obtained from a cohort of uninfected volunteers with respect to the yield, viability, purity, and phenotype (Table 2) (described in more detail elsewhere [5]). The mean yield was 9.1×10^7 (range, 1.3×10^7 to 2.7×10^8) mature DC, compared with 2.5×10^8 (range, 2.3×10^8 to 3.5×10^8) for an uninfected control cohort. The mean viability and purity were 93% (range, 69 to 99%) and 100% (range, 47% to 100%), respectively, compared with 90% (range, 85% to 95%) and 77% (range, 75% to 89%) for uninfected controls. IL-12p70 production, a measure of DC function (11), was variable but not statistically different from that of normal donors (Table 2). There were no statistically significant differences between the phenotypic characteristics of immature DC

or mDC generated from monocytes of the 18 study participants with chronic HIV-1 infection and those of 15 normal donors, as shown previously (7).

Immune responses. At baseline, 9/18 individuals had responses to one or more HIV-1 peptides, and 12/18 had a response to the influenza A virus matrix protein peptide. Three individuals had significant responses to all four peptides (Fig. 1). Following vaccination, in aggregate, statistically significant increases in the frequency of CD8⁺ T cells responding to HIV-1 Gag ($P = 0.02$) and HIV-1 Pol ($P = 0.04$) at week 6 (Fig. 2) were seen. No significant differences were observed between the i.v. and s.c. routes of administration. A significant difference was observed between the high and low doses at week 4 for HIV-1 Env ($P = 0.04$), and a trend toward a significant response was observed at week 4 for Gag ($P = 0.07$) and at weeks 6 ($P = 0.1$) and 8 ($P = 0.05$) for HIV-1 Pol (Fig. 3). Considerable interindividual variability was noted in the overall increase in CD8⁺ T-cell responses, and the resulting significance was attributable to strong responses seen with cells of a few individuals (Fig. 4). Finally, we investigated the effect of pre-ART CD4 nadir by grouping patients based their nadir CD4 (≤ 150 versus >150 cells/mm³). A slight trend toward more immunogenicity in the cohort with higher nadir CD4⁺

TABLE 2. Comparison of properties of mDC derived from study subjects with those of mDC derived from a cohort of normal donors

Subjects (n)	Mean (range)			
	Yield	Viability (%)	Purity (%)	IL-12 (pg/ml) ^b
Study participants (18)	9.1×10^7 (1.3×10^7 – 2.7×10^8)	93 (69–99)	100 (47 ^a –100)	347.7 (11–1,605) ^c
Uninfected volunteers (5)	2.5×10^8 (2.3×10^8 – 3.5×10^8)	90 (85–95)	77 (75–89)	270.0 (8–999) ^d

^a In one subject, a second plastic adherence was required to increase purity as defined by positivity for CD86.

^b IL-12 production levels in DC supernatants were measured as described in Materials and Methods.

^c n = 15: three subjects had insufficient mature DC at the time of scheduled vaccination to permit IL-12 testing.

^d n = 1.

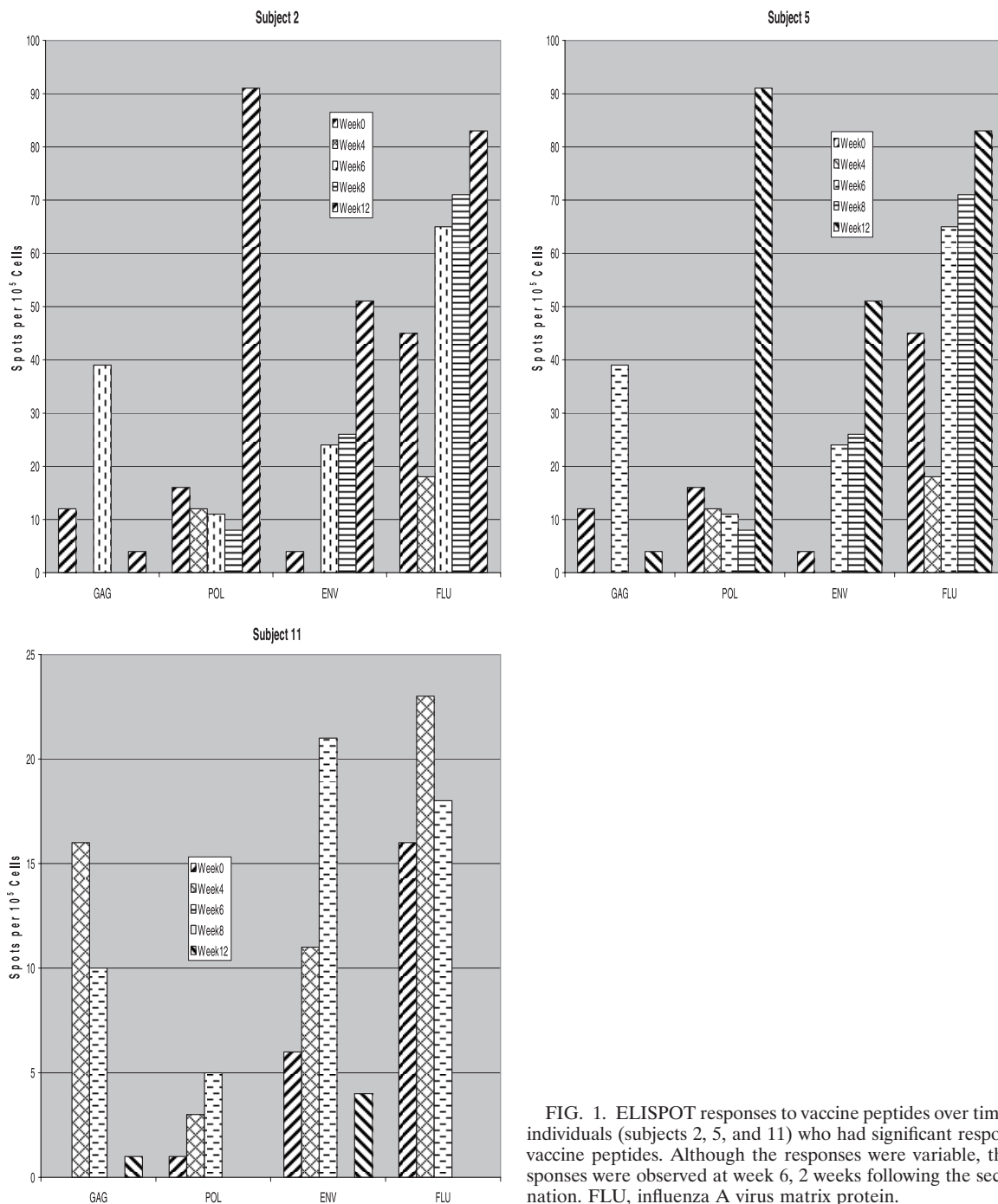


FIG. 1. ELISPOT responses to vaccine peptides over time for three individuals (subjects 2, 5, and 11) who had significant responses to all vaccine peptides. Although the responses were variable, the best responses were observed at week 6, 2 weeks following the second vaccination. FLU, influenza A virus matrix protein.

cell counts was observed, particularly at week 6 for HIV-1 Env ($P = 0.1$), but no significant differences were seen (Fig. 5).

DISCUSSION

In this study, we have demonstrated that vaccination with autologous DC pulsed with HLA-A2-restricted HIV-1 peptides was safe and feasible in chronically HIV-1-infected, ART-treated subjects. Further, although only two vaccinations were given, generation of HIV-1-specific immunologic responses was observed in the setting of chronic HIV-1 infection.

DC-based vaccination represents a potentially promising tool to augment host immune response against HIV-1 infection. This study represents the largest and most completely described trial of autologous DC vaccination in ART-treated individuals and sets a foundation for future trials of increasingly used immunogenic, immune-based therapies. Immune-based therapies in this population have the potential to be a crucial addition to currently available ART as we strive to cure, rather than merely treat, HIV-1 infection. Despite years of research, it remains unknown whether immune manipulation is

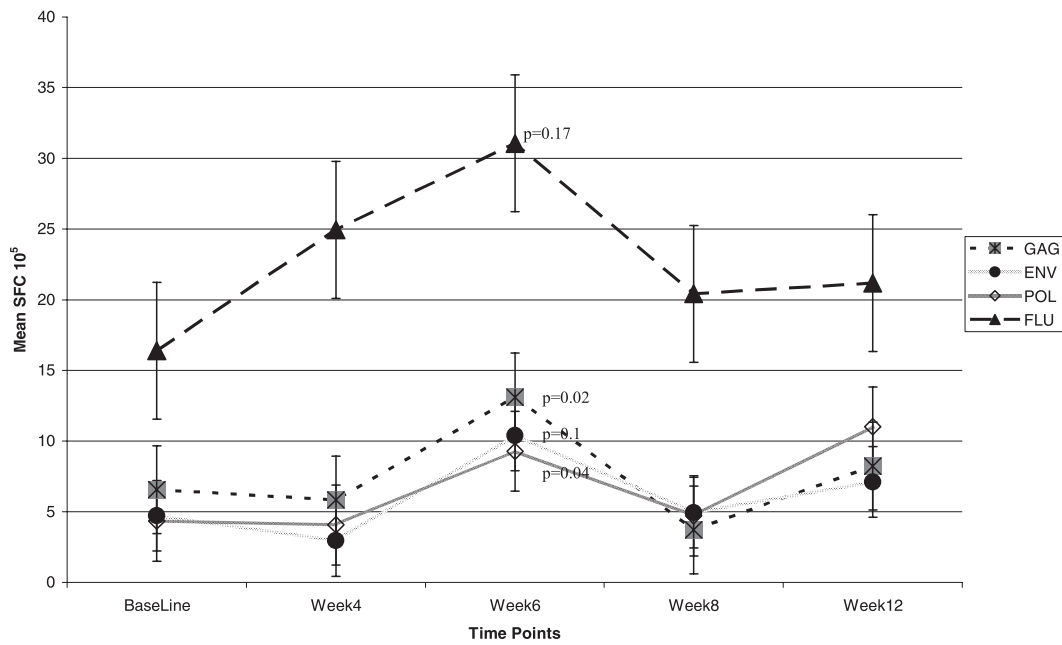


FIG. 2. Actual mean ELISPOT responses per 10⁵ PBMC of all 18 participants. From baseline to week 6, on average, an increase in the frequency of the HIV-1-specific lymphocytes was observed. Responses were highest for the FLU, influenza A virus matrix protein (FLU) peptide, probably as a result of multiple, previous influenza virus vaccinations, but were statistically significant for the Pol and Gag peptides, and there was a trend toward significance for the Env peptide. *P* values represent a statistically significant increase in spot-forming cells (SFC)/10⁵ PBMC above the prevaccination values. Error bars indicate standard deviations.

safe and can decrease viremia and improve immunologic control in chronically HIV-1-infected persons. Our trial examined the safety and efficacy of a therapeutic vaccine in HIV-1-infected subjects on ART.

The results of this study as well as additional characteriza-

tion of DC properties from the study participants at baseline indicated that monocyte-derived DC obtained from leukapheresis of chronically HIV-1-infected subjects with suppressed viral loads were, with few exceptions, phenotypically and functionally comparable to DC from normal donors (7).

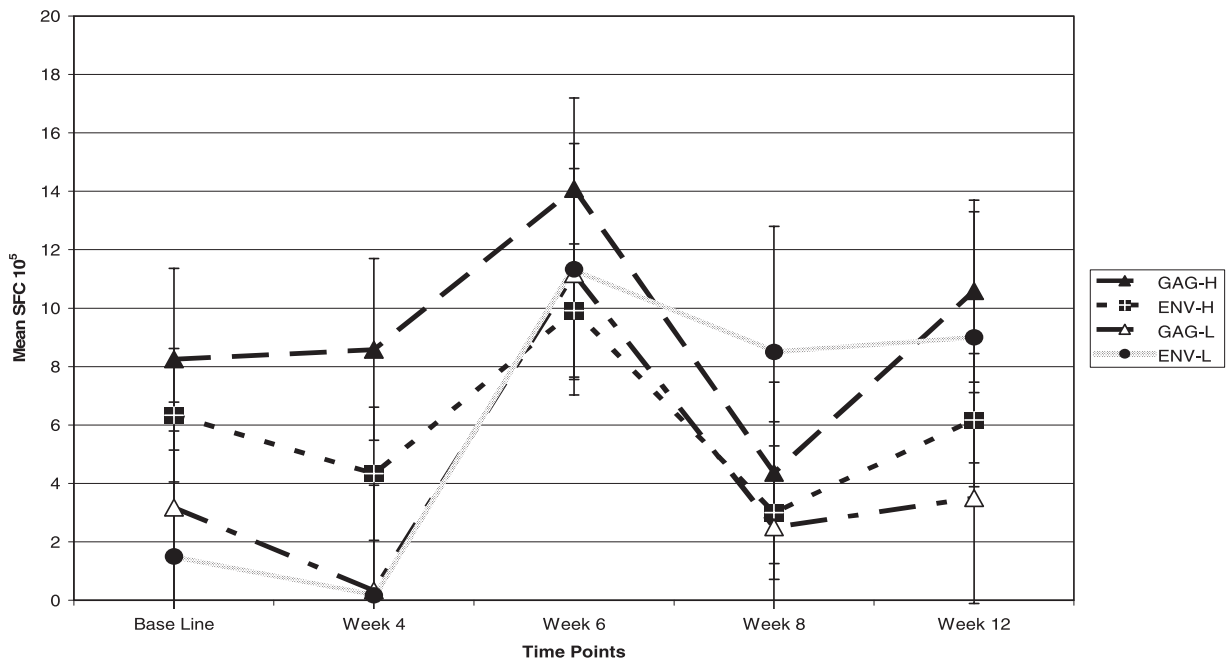


FIG. 3. CD8⁺ T-cell responses to Gag and Env peptides observed from week 0 through week 12 after low- and high-dose vaccination (*P* = 0.07 for Gag and 0.04 for Env by Wilcoxon rank sum test). SFC, spot-forming cells. Error bars indicate standard deviations.

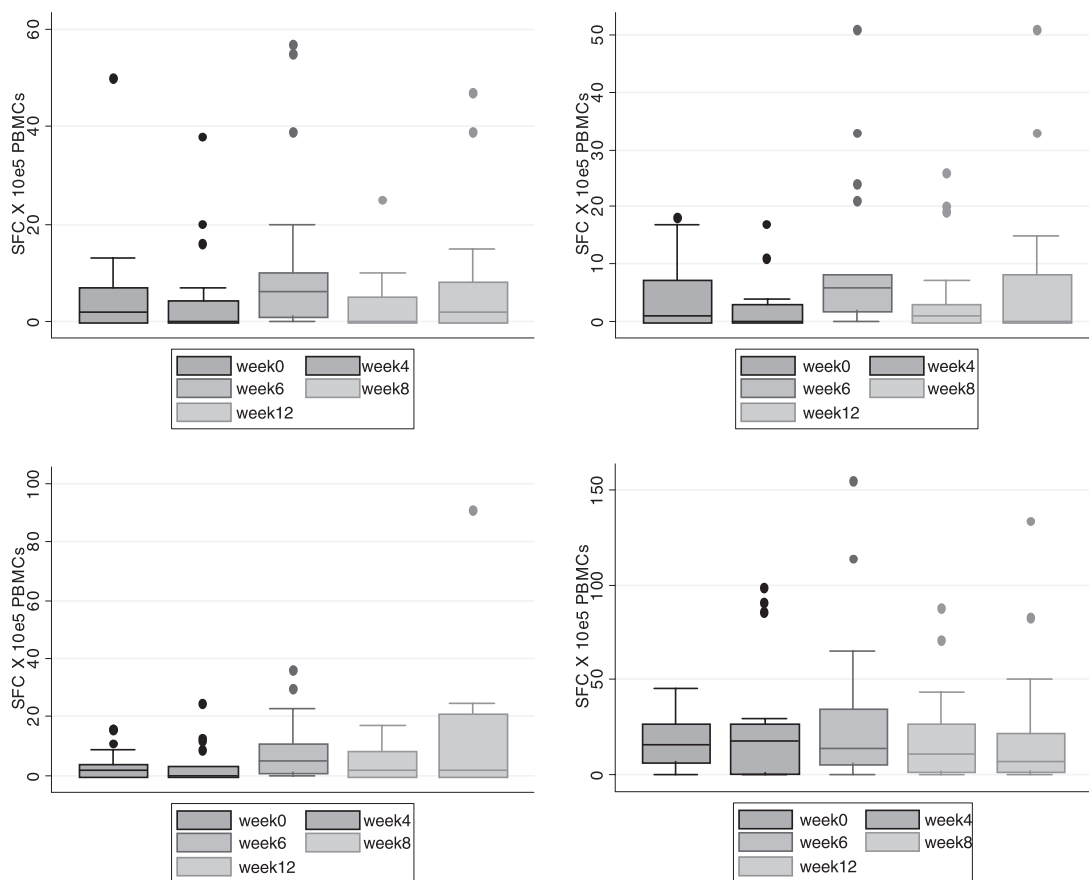


FIG. 4. Box plots for each peptide, showing the medians of the groups as a whole. The results demonstrate that within each group there was considerable variability of response as indicated by the frequency of peptide-specific T cells in the peripheral circulation. FLU, influenza A virus matrix protein. SFC, spot-forming cells. Error bars indicate 95% confidence intervals.

The choices of antigen and adjuvant are of critical importance in all vaccination strategies. Using DC as an adjuvant for vaccination was largely developed in cancer trials, where the use of synthetic peptides as antigens has several advantages: they are relatively easy to produce, they enable monitoring of the peptide-specific cellular responses, they exclude the possibility of infection from the vaccine product, and they minimize the risk of generating immunity to self antigens. For these reasons, HIV-1-specific synthetic peptides were chosen for this phase I safety and feasibility study of DC-based immunization in this ART-treated cohort. It remains unknown and is a subject of much study as to what will emerge as the optimal antigen for HIV-1 vaccination, whether therapeutic or prophylactic. Here we have shown that administration of only two doses of synthetic peptide-pulsed DC, albeit with relatively narrow specificity, represents a feasible and potentially immunogenic strategy.

The goal of immunotherapeutic strategies for HIV-1 infection, i.e., to decrease viral loads and increase CD4⁺ cell counts, is known from years of clinical trials and observations to correlate with decreased morbidity and mortality resulting from HIV-1 infection. This study was neither designed nor powered to detect a clinical or immunologic response. Despite this, we have shown not only that viral loads and CD4 counts remained

unchanged but that certain individuals appeared to increase their HIV-1 peptide-specific CD8⁺ T-cell response.

The results of three other phase I autologous DC-based therapeutic immunization trials have recently been published. Lu et al. (18) used autologous DC pulsed with inactivated, autologous HIV-1 in 18 ART-naïve Brazilian subjects. These DC immunizations appeared to be safe and resulted in an increase in HIV-1-specific CD4⁺ and CD8⁺ T-cell immunity. The observed increase in immune response was associated with a prolonged reduction in plasma HIV-1 RNA in eight of the subjects. Garcia et al. (9) reported that immunotherapy in 12 HIV-1-infected, ART-treated individuals with autologous DC pulsed with inactivated, autologous HIV-1 was safe and resulted in an increase in T-cell lymphoproliferative and HIV-1-specific CTL responses after an analytic treatment interruption. This immunologic effect was associated with a decrease in plasma HIV-1 RNA levels in 4 of the 12 subjects. Finally, Ide et al. (14) administered HIV-1 peptide-pulsed DC to four HIV-1-infected individuals on ART who subsequently underwent analytic treatment interruption. DC vaccination was safe, with two of four subjects demonstrating significant CD8⁺ T-cell IFN-γ responses to some of the HIV-1 peptides (14).

While the methods of DC maturation, antigens, and patient populations of these three studies varied compared to those in

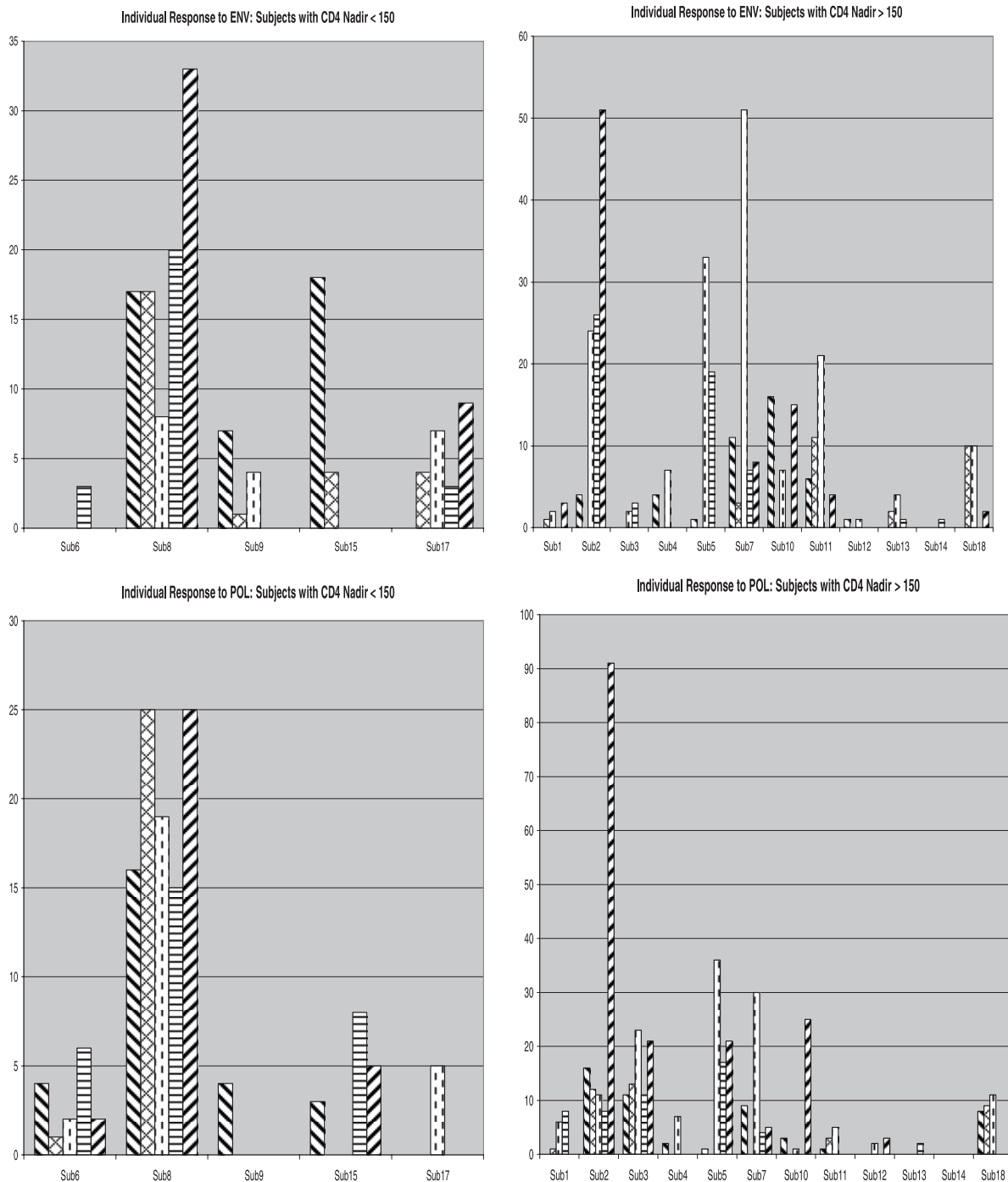


FIG. 5. Actual spot counts (spots/10⁵ cells on the y axis) for responses to Pol (bottom panels) and Env (top panels) by individual subjects (x axis). Hatch patterns represent weeks 0, 4, 6, 8, and 12, respectively. Overall, subjects with higher nadir CD4 cell counts (>150 cells/mm³) (right panels) appeared to respond better to vaccination than subjects with lower nadir CD4 cell counts (≤150 cells/mm³) (left panels).

our clinical trial, there are enough similarities to conclude, based on the safety and limited clinical success of this therapy, that administration of autologous DC vaccines shows substantial promise as an immunotherapeutic strategy for treatment of chronic HIV-1 infection. Our phase I trial demonstrated, for the first time, that vaccination with autologous DC matured and pulsed with HLA-A2-restricted HIV-1 peptides was fea-

sible and safe in a cohort of ART-treated, HIV-1-infected individuals. We have also shown that a significant increase in the frequency of CD8⁺ T cells responsive to HIV-1 peptides was achieved following peptide-pulsed DC vaccine. We have demonstrated that a higher dose (5 million to 10 million DC) appeared to be more effective than a lower dose (1 million to 3 million DC) in increasing the frequencies of HIV-1 peptide-

reactive T cells. Significant interindividual variability in the immunologic response to the vaccine peptides was observed, with a trend toward a better response among those with the higher CD4⁺ T-cell nadir. We observed no differences in immunogenicity between the s.c. and i.v. routes of administration. This study was limited by a relatively small sample size which consisted of predominantly male subjects with a restricted age range. In summary, our study represents a significant advance in showing that under very rigorously controlled conditions, very small doses of a limited antigen can be immunogenic in a subset of individuals, and therefore this shows substantial promise as an immunotherapeutic strategy for chronic HIV-1 infection. Additional studies with virologic end points are urgently needed to evaluate alternative antigen-DC combinations and to further our comprehension of the mechanisms responsible for the interindividual immunologic response variability.

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