Evaluation of HIV-1 Immunogen, an Immunologic Modifier, Administered to Patients Infected With HIV Having 300 to $549 \times 10^6/L$ CD4 Cell Counts
A Randomized Controlled Trial

James O. Kahn, MD
Deborah Weng Cherng, MS
Kenneth Mayer, MD
Henry Murray, MD
Stephen Lagakos, PhD
for the 806 Investigator Team

STANDARD ANTIRETROVIRAL therapies (ARTs) inhibit critical viral enzymes and lead to lower levels of human immunodeficiency virus (HIV) RNA.\textsuperscript{1-3} Improved function of the immune system, including increases in CD4 cell counts, coincides with the reduction in HIV RNA and with longer survival.\textsuperscript{4-8} The decrease in viral load and the increase in CD4 cell counts are accepted surrogates for reduction in disease progression with ART.\textsuperscript{9-11} A complementary strategy to reduce disease progression involves identifying agents that may directly improve the immune system’s function. An improved immune system may lead to reduced viral replication.\textsuperscript{12}

One strategy to boost the immune system’s ability to reduce disease progression includes administering small amounts of viral antigens to enhance the immune system’s control over viral replication.\textsuperscript{13-15} Referred to as therapeutic vaccination or immunization, this strategy was considered a low-cost, well-tolerated, practical solution to supply the immune system with targeted antigens necessary to boost immune responses that may have waned to reassert control over viral replication. However, this strategy is controversial.\textsuperscript{16,17} Studies of therapeutic immunizations report only modest changes in surrogate markers.\textsuperscript{18-22} Thus, for therapeutic vaccination, surrogate markers would not substitute for clear evidence of reduced clinical disease progression.

Context

Despite enormous improvements achieved through the use of antiretroviral therapies (ARTs), the risk for eventual human immunodeficiency virus (HIV) disease progression remains high. Agents that enhance the immunologic mechanism for viral recognition might reduce disease progression.

Objective

To determine whether the addition of HIV-1 Immunogen would confer added clinical efficacy to that achievable by ARTs.

Design and Setting

Multicenter, double-blind, placebo-controlled, randomized trial beginning March 1996 and ending May 1999 conducted at 77 centers in the United States providing primary care or referral care for persons infected with HIV.

Patients

Adults infected with HIV who have baseline CD4 cell counts between $300 \times 10^6/L$ and $549 \times 10^6/L$ without prior acquired immunodeficiency syndrome–defining conditions receiving stable ART (or no therapy) were screened and 2527 were randomized.

Interventions

Ten units of HIV-1 Immunogen, derived from a Zairian HIV isolate, inactivated and formulated with incomplete Freund adjuvant, was administered intramuscularly every 12 weeks. The placebo was incomplete Freund adjuvant. Changes in ARTs were allowed.

Main Outcome Measures

HIV progression-free survival; secondary end points included overall survival, changes in HIV RNA, CD4 cell counts, CD4 percentage, body weight, and immunogenicity.

Results

The overall event rate was 1.8 per 100 person-years of follow-up. Fifty-three subjects developed clinical progression in each treatment group (relative risk [RR], 0.97; 95% confidence interval [CI], 0.66-1.42; \( P = .89 \)). There were 19 and 23 deaths in the placebo and HIV-1 Immunogen groups, respectively (RR, 0.81; 95% CI, 0.44-1.48; \( P = .49 \)). There were no statistically significant differences between the groups with respect to changes in HIV RNA (\( P = .59 \)), CD4 percentage (\( P = .63 \)), or body weight (\( P = .89 \)). Subjects in the HIV-1 Immunogen group had an increase in average CD4 cell count of approximately $10 \times 10^6/L$ greater than the placebo group (\( P = .02 \)).

Conclusion

HIV-1 Immunogen with unrestricted ART failed to demonstrate an increase in HIV progression-free survival.

©2000 American Medical Association. All rights reserved.

(Reprinted) JAMA, November 1, 2000—Vol 284, No. 17 2193
gression and a study with clinical end points to demonstrate activity for this treatment strategy.

In early human studies, HIV-1 Immunogen (a whole inactivated HIV isolate stripped of envelope proteins and conjugated with incomplete Freund adjuvant [IFA]) increased immune responses, but the surrogate marker data were inconsistent and plasma HIV reduction was not observed. Treatment with HIV-1 Immunogen was an unlikely replacement for ARTs, but it was hypothesized that it would contribute to overall control of HIV replication and to enhance immune mechanisms so that disease progression would be reduced. It was further hypothesized that HIV-1 Immunogen might be most effective among persons with a more intact immune system resulting from ART. To assess the clinical efficacy of HIV-1 Immunogen, we conducted a large clinical study of whether HIV-1 Immunogen, when administered with ART, could reduce disease progression among persons infected with HIV relative to that achievable by ART alone.

**METHODS**

**Study Design**

Study 806 was a multicenter, double-blind, placebo-controlled, randomized clinical trial comparing HIV-1 Immunogen to placebo among persons infected with HIV who had CD4 cell counts between 300 and 549 × 10^6/L or a mean CD4 cell count between 300 and 549 × 10^6/L from 2 CD4 cell measurements taken no more than 1 month apart and performed within 30 days prior to study randomization; a hemoglobin level greater than 90 g/L (women) or 100 g/L (men) within 30 days prior to study; platelets at least 75 × 10^9/L; absolute neutrophil cell count greater than 7.5 × 10^9/L; serum alanine level 5 times greater than the normal upper limit, and a creatinine level less than 2 times the normal upper limit; and taking approved or investigational agents for at least 30 days and not receiving any investigational vaccine or immune-based therapy for 3 months prior to study entry.

**Interventions**

**HIV-1 Immunogen and Placebo.** The HIV-1 Immunogen was derived from a Zairian HIV isolate (HZ321) subtype M and HUT-78 cell line. The HIV-1 Immunogen was chemically and physically inactivated as previously described. Western blot analyses indicate that all HIV proteins and glycoproteins are present, although gp160 and gp120 are in trace amounts only. The host cell membrane proteins are also present. The HIV-1 Immunogen is formulated with IFA. Ten units of the HIV-1 Immunogen were administered as an intramuscular injection every 12 weeks. The placebo consisted of IFA without HIV proteins. The HIV-1 Immunogen (Remune; Immune Response Corp [IRC], Carlsbad, Calif) and placebo were manufactured and provided by the study sponsor as single-dose prefilled syringes.

**ART and Comitant Medications.** All approved or investigational ARTs were allowed. Use of any experimental antiviral drugs and disease-modifying concomitant medications, specifically any experimental drug directed primarily or secondarily as treatment for HIV was also allowed. Immunomodulators and experimental vaccines were not allowed. Prophylaxis for patients with Pneumocystis carinii pneumonia and CD4 cell counts of less than 200 × 10^6/L; prophylaxis for Mycobacterium avium-intracellulare when the CD4 cell counts are less than 75 × 10^6/L; oral ganciclovir for cytomegalovirus prevention when CD4 cell counts are below 50 × 10^6/L; and anti-fungal therapy for prophylaxis or treatment were all allowed. Other medications as deemed medically necessary by the clinician were also allowed.

**Enrollment and Study Measurements.** After consent was obtained and within 30 days prior to receiving the first injection, each subject’s medical history was reviewed, a physical examination was performed, and laboratory studies were performed to assess study eligibility. Subjects meeting all the inclusion criteria were randomized in equal proportions to either the HIV-1 Immunogen or placebo group. The randomization was stratified by CD4 cell count (<400 × 10^6/L vs >399 × 10^6/L), baseline ART (no current or previous ART, no current but previous ART, zidovudine monotherapy, zidovudine in combination with other ARTs, mono-therapy or combination ART involving didanosine, zalcitabine, stavudine, or lamivudine but not zidovudine, other), and disease stage (asymptomatic vs symptomatic) using permuted blocks, with dynamic balancing by site.

Injections were administered intramuscularly at day 1 and then at approximately every 12 weeks for a total of 13 planned vaccinations. At each visit, subjects were monitored with a physical examination. Assessment of HIV disease was performed and a diary card to assess reactogenicity of the injection was provided. The CD4 cell count, plasma for HIV RNA determination, and safety laboratory evaluations were to be performed every 24 weeks and at the time of suspected clinical progression. In addition, at the time of randomization, a randomly selected 10% subset of subjects was iden-
tified to have blood samples drawn for immunologic and virologic assays at 12-week intervals instead of the usual 24-week intervals for helping to evaluate whether immunologic or virologic markers fulfilled the criteria of surrogate markers. Apart from the more frequent collection of blood samples, this group was seen and evaluated according to the same procedures as all other subjects. It was not clear at the outset what viral load assay was to be used or how many stored blood samples were to be assayed for viral load. Ultimately, the sponsor performed post-baseline HIV RNA determinations on approximately 88% of all randomized subjects. The HIV RNA determinations were performed using the Roche ultrasensitive assay. Lymphocyte proliferation assays were performed as previously documented on 224 participants at baseline, but only 141 patients had results at baseline, week 24, and week 48 to compare groups for immunogenicity.25

### Efficacy End Points

The primary efficacy end point for this study was initially defined to be AIDS-free survival; ie, time to the development of AIDS-defining opportunistic infections or death, whichever occurs first. For reasons described below, the definition of the primary end point—hereafter referred to as HIV progression-free survival—was expanded to include aspergillosis infection; disseminated *Bartonella henselae* infection; blastomyocosis; invasive candidiasis; cytomegalovirus encephalitis; cytomegalovirus syndromes; cryptococcal meningitis; mucocutaneous herpes simplex; Kaposis sarcoma; microsporidiosis (non-AIDS); mucormycosis; HIV-associated myopathy (non-AIDS); pulmonary, brain, or disseminated nocardiosis (non-AIDS); extrapulmonary pneumocystosis; non–central nervous system toxoplasmosis; disseminated herpes zoster; recurrent oropharyngeal candidiasis; and recurrent localized varicella zoster.

The clinical end point committee (J.K., K.M., and H.M. were voting members) evaluated all clinical events in a blinded fashion and end points were determined by unanimous decision. Subjects continued to receive blinded treatment and study procedures until clinical end point confirmation was received from the clinical end point committee. If a subject permanently discontinued treatment and study procedures, research staff attempted telephone or letter contact every 3 months. All study subjects who discontinued treatment were followed up to ascertain disease progression and vital status.

Secondary efficacy end points available for analysis in this report include overall survival, changes in HIV-RNA, CD4 cell count, CD4 percentage, p24 antibody titers, body weight, and immunogenicity. Additionally, during the conduct of the study and prior to any examination of results, a virologic substudy was defined to assess whether HIV-1 Immunogen would prolong time to virologic failure in the subset of patients who were virologically suppressed at the time of enrollment. The substudy consisted of those patients who, at the time of randomization, were receiving at least 3 antiretroviral medications, including 1 protease inhibitor (PI), and having an HIV RNA level of less than 400 copies/mL. Virologic failure was defined as either the addition of 2 new antiretroviral agents or an increase in viral load to more than 500 copies/mL (baseline HIV RNA <50 copies/mL) or to more than 2000 copies/mL (baseline HIV RNA between 50 and 400 copies/mL). Three secondary analyses were also prospectively defined for the virologic substudy for patients receiving at least 2 ARTs at baseline or patients with fewer than 50 viral copies/mL, or both.

### Roles of the Sponsor, Clinical Research Organization, and Study Team Leadership

The IRC contracted with the study chair (J.K.), study statistician (S.L.), and co-chairs (K.M. and H.M.) to independently conduct and analyze this study. The study team consisted of the study chair, study statistician, study co-chairs, a protocol statistician (D.W.), and a representative of the sponsor. The IRC assembled the data safety monitoring board (DSMB) with approval from the study team leadership (J.K. and S.L.). The final interpretation of the study results and responsibility for preparing the results for publication was determined to be the responsibility of the study team leadership.

The IRC provided all financial support for the study and coordinated the medical monitoring of sites. The IRC contracted with Quintiles Inc (Durham, NC), a clinical research organization responsible for data management and laboratory data. When a patient was deemed to be eligible for the trial and had provided consent, Quintiles contacted an independent organization to confirm eligibility and obtain a (blinded) treatment assignment. No information is available on the total number of patients who were screened but not enrolled into the study. For patients who were randomized, information collected at study visits was captured by site monitors and centrally reviewed and processed by Quintiles, who provided a copy of the database to the study team prior to each DSMB meeting. When a patient was found to have a suspected clinical end point, IRC and Quintiles arranged for a description of the circumstances of the event. The end point was sent to the clinical end point committee for evaluation. The IRC performed all viral load and lymphocyte proliferation assays, were blinded to treatment assignment, and provided these data to the study team in advance of each DSMB meeting. A final batch of viral load results was processed by the sponsor following the recommended termination of the study by the DSMB (and after the study was unblinded) and provided to the study team in September 1999.

### Statistical Analysis

The study was designed to detect a 50% greater risk of clinical progression in the control group compared with the HIV-1 Immunogen group with 90% power, based on a 2-sided test at the .05 significance level and a 6% annual rate of
clinical progression in the control group. This required 1098 subjects per group, followed up for an average of 2.5 years. Increasing this sample size by 14% to account for the attenuating effects of dropouts and for the multiplicity of 3 planned interim analyses gave a sample size of 1250 subject per arm, or a total of 2500 subjects.

The Wilcoxon test and Fisher exact test were used to compare treatment groups with respect to baseline characteristics. With respect to the primary efficacy outcome, the prespecified primary analysis compared the treatment groups’ HIV progression-free survival using the stratified log-rank test, with stratification by disease stage (symptomatic vs asymptomatic) and CD4 cell count (<400 × 10^6/L vs >399 × 10^6/L) at the time of randomization. Kaplan-Meier curves were used to display the distribution of HIV progression-free survival by treatment group. Subjects who had not yet developed a primary end point or were lost to follow-up by the time of the last diagnosed primary end point (July 3, 1999) were censored at this time point. The estimated placebo to HIV-1 Immunogen relative risks (RRs) and associated 95% confidence intervals (CIs) were obtained from fitting Cox stratified proportional hazards model. Secondary analyses of the primary efficacy end point include unstratified log-rank tests and comparisons adjusting for baseline covariates using Cox proportional hazards regression model. Time until death, duration of treatment, time until loss to follow-up, time to virologic failure, and time until changing ART were analyzed using the Kaplan-Meier estimator and log-rank test.

The protocol-specified comparisons of the HIV-1 Immunogen and control groups with respect to changes in CD4 cell counts, percentage of CD4-bearing lymphocytes, and plasma-associated HIV RNA were based on the summary statistic approach,\textsuperscript{27} in which a slope was estimated from each subject’s log-transformed values. Analysis of body weight changes was also based on the summary statistic approach, but without log-transformed values and using the normalized area-under-the-curve metric instead of the slope. The resulting sets of values for the 2 groups were then compared using a nonparametric test such as the Wilcoxon or van der Waerden test.\textsuperscript{27,28}

The protocol did not specify which of these tests would be used, so we focus on the Wilcoxon test because it was the more common; however, similar results were obtained using the van der Waerden test. Additional analyses of these secondary end points were based on using the slope metric for body weight and the area-under-the-curve metric for HIV RNA, CD4 cell count, and CD4 percentage. Time to the first grade 3 or worse laboratory and clinical abnormality were assessed using the log-rank test by censoring information at the visit following last blinded inoculation. All efficacy analyses used the intent-to-treat approach and all reported P values were 2-sided. Because of the conservative spending function used to assess the primary end point during the interim analysis, no adjustment was made of the P value for the comparison of groups with respect to the primary end point in this final analysis. All reported P values for the secondary end points were unadjusted for multiplicity of tests.

**Interim Monitoring**

Three interim efficacy/safety analyses were scheduled for presentation to the DSMB when approximately 25%, 50%, and 75% of the total expected number of primary end points occurred in the placebo group. The Lan-DeMets procedure, using an O’Brien-Fleming spending function, was used to provide guidelines for terminating the trial due to differences between the HIV-1 Immunogen and control group with respect to HIV progression.\textsuperscript{29}

In addition, a preplanned initial DSMB meeting was held in March 1997 to assess accrual rates, adverse events, and the logistics of the study, but not efficacy. At this initial DSMB meeting, the DSMB noted that the increased use of PIs could lead to lower clinical progression or death rates than were anticipated when the protocol was designed. Following the meeting, the study team, the DSMB, and the sponsor discussed this issue in detail and decided to expand the list of diagnoses that would qualify as a primary end point. This expanded definition was proposed and approved by the DSMB prior to unblinded examination of the efficacy data. The first DSMB meeting comparing disease progression in the HIV-1 Immunogen and control groups took place in June 1998, and the DSMB recommended that the study be continued. In March 1999, the DSMB approved the virologic substudy proposed by the study team and sponsor, with the intent that it be presented at the second DSMB meeting.

In May 1999, following the second DSMB meeting to evaluate efficacy, the DSMB recommended that the trial be terminated. The study chair and sponsor were presented the study results and notified of their recommendation on May 15, 1999. The basis for the recommendation was the lack of evidence of a difference between the HIV-1 Immunogen group and the control group with respect to clinical progression and that continuation of the study was unlikely to lead to a demonstrable difference between the groups. The lack of a clinical difference was consistent with the lack of any prespecified meaningful effects on CD4 cell count, CD4 percentage, and HIV RNA.

Once it was decided to stop the study, the final study database was to be made available to the study team in December 1999, based on an update that included the final patient visits in the summer of 1999. However, we could not obtain a complete and final data set from the sponsor. Consequently, the results in this article are based on all information available to the study leadership, consisting of the database used to prepare the analyses for the May 1999 DSMB meeting, plus updated information on clinical end points (confirmed by July 3, 1999) and HIV RNA (all data processed by September 1999). We estimate that we have 95% of the confirmed clinical progressions that would...
have been available in the final database. In addition, while we have some CD4 and body weight information on virtually all randomized subjects, we estimate that these represent 75% to 80% of the measurements that would have been available in the final database, with most of the missing values occurring more than 2 years following randomization. Similarly, we estimate that the final database would have included approximately 25% additional follow-up time of subjects for clinical adverse events and laboratory toxic effects.

**RESULTS**

A total of 2527 subjects from 77 sites in the United States were randomized between March 1996 and May 1997, of whom 1262 were randomized to receive HIV-1 Immunogen and 1265 to receive IFA placebo. The treatment groups were well balanced with respect to baseline information (TABLE 1). At the time of randomization, 27% of the subjects were not receiving ART, 5% were receiving monotherapy, and 57% were receiving combination ART (31% of the total population were receiving combination ART during the study). The categories of ART involving saquinavir, indinavir, or ritonavir but not saquinavir were combination therapy of at least 2 reverse transcriptase inhibitors, including zidovudine, didanosine, nevirapine, stavudine, and lamivudine.

The prevalence of ARTs used is similar in the 2 treatment groups, as is the distribution of time to changing or adding a HIV PI (Figure 3B). Approximately 40% of the subjects either added or discontinued a PI within 48 weeks. The average number of ARTs added was 3.2 (3.1 for those randomized to HIV-1 Immunogen and 3.2 for placebo). In each treatment group, the number of new ART added ranged from 1 to 11.

A total of 106 participants experienced the primary end point of HIV progression-free survival, of which 35 were deaths occurring prior to clinical progression and 71 were opportunistic infections or malignancies; the overall event rate was 1.8 per 100 person-years of follow-up (TABLE 2). The distribution of clinical disease progression by specific diagnosis is shown in TABLE 3. The greatest number of cases was observed among persons with recurrent oropharyngeal candidiasis (n = 13), probably an early marker of immune dysfunction.

There was no evidence of a treatment difference with respect to the primary efficacy end point (Table 3, FIGURE 4). Of the 106 participants experiencing a primary end point, 53 were in the HIV-1 Immunogen group and 53 were in the control group (RR, 0.97; 95% CI, 0.66-1.42). Unstratified analyses and regression analyses adjusting for baseline characteristics gave similar results. Of the 53 progressions in the HIV-1 Immunogen group, 20 were deaths prior to an opportunistic infection or malignancy and 33 were an opportunistic infection or malignancy. For the 53 progressions in the placebo group, 18 were deaths, 8 were nonfatal opportunistic infections or malignancies, and 27 were a combination of events.

©2000 American Medical Association. All rights reserved.
**Figure 2.** Prevalence of Antiretroviral Therapy by Treatment Group

![Graph showing prevalence of antiretroviral therapy by treatment group.]

**Figure 3.** Time to Change Antiretroviral Therapy (ART) and Protease Inhibitor (PI)

![Graph showing time to change ART and PI by treatment group.]

HIV indicates human immunodeficiency virus.
group, the corresponding numbers were 15 and 38. There was no significant difference between the HIV-1 Immunogen and control groups with respect to overall mortality (Table 3). A total of 42 subjects died, of whom 23 were in the HIV-1 Immunogen group and 19 were in the control group (RR, 0.81, 95% CI, 0.44-1.48; P = .49).

Some postrandomization HIV RNA results were available for 2226 subjects. There was no significant difference between the HIV-1 Immunogen and control group with respect to changes in viral load (P = .59). Similar results were obtained when using the van der Waerden test instead of the Wilcoxon test and also when using the area-under-the-curve summary statistic instead of the slope. Using the slope metric, the estimated mean change in viral load at 1 year was a 0.30 log10 decline for the HIV-1 Immunogen group and a 0.31 log10 decline for the control group.

Subjects in the HIV-1 Immunogen group had a significantly greater increase in CD4 cell count than those in the control group (P = .02). The mean number of CD4 cells in both treatment groups increased between baseline and week 48 values (Figure 5B), with the increase in HIV-1 Immunogen group being approximately 10 cells greater than that in the control group. There were no statistically significant differences between the HIV-1 Immunogen and control groups with respect to CD4 percentage (Figure 5C, P = .63) or body weight (Figure 5D; P = .89). Comparisons of the 2 treatment groups using the area-under-the-curve metric (or the slope metric for body weight) or using the van der Waerden test instead of the Wilcoxon test gave similar results.

The HIV-1 Immunogen elicited significant immunogenicity. At least a 5-fold increase in the lymphocyte proliferation assay to HIV and p24 antigen at week 24 and 48 was observed in 45% and 34% of patients randomized to HIV-1 Immunogen, respectively, (95% CI, 31%-56%) compared with 1% and 1% in the control group (95% CI, 21%-44%) (P < .001 for both comparisons). The substudy of 250 patients with plasma samples obtained every 12 weeks instead of every 24 weeks was also analyzed. In this group, the unadjusted (for multiple tests) treatment comparisons resulted in no significant differences between the HIV-1 Immunogen and placebo groups with respect to viral load (P = .14), CD4 cell count (P = .71), CD4 percentage (P = .74), and body weight (P = .64).

A total of 133 subjects experienced laboratory toxic effects of grade 3, of which 71 were in the HIV-1 Immunogen group and 62 were in the control group. The secondary analyses of the substudy gave similar results.

Table 2. Clinical Progression and Death by Treatment Group*

<table>
<thead>
<tr>
<th>Clinical progression</th>
<th>HIV-1 Immunogen (n = 1262)</th>
<th>IFA Placebo (n = 1265)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of adults who experienced progression</td>
<td>53</td>
<td>53</td>
<td>0.97 (0.66-1.42)</td>
<td>.89</td>
</tr>
<tr>
<td>Opportunistic infection or malignancy</td>
<td>33</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths prior to infection or malignancy</td>
<td>20</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per 100 person-years</td>
<td>1.8</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>23</td>
<td>19</td>
<td>0.81 (0.44-1.48)</td>
<td>.49</td>
</tr>
<tr>
<td>Rate per 100 person-years</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus; IFA, incomplete Freund adjuvant; RR, relative risk; and CI, confidence interval.
†All deaths, whether preceding or following opportunistic infection or malignancy.

Table 3. Patients With Clinical Disease Progression*

<table>
<thead>
<tr>
<th>HIV-1 Immunogen (n = 1262)</th>
<th>IFA Placebo (n = 1265)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent oropharyngeal candidiasis</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Recurrent herpes simplex</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Kaposis sarcoma</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Recurrent pneumonia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Disseminated herpes zoster</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mycobacterium other than Mycobacterium tuberculosis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent varicella zoster</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>M tuberculosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus; IFA, incomplete Freund adjuvant.
COMMENT

This was the first large-scale clinical trial to determine if an immunologic modifier, added into a background of ART (including no ART), would reduce the risk of clinical disease progression or death. The results of this trial failed to demonstrate that the addition of HIV-1 Immunogen to ART conferred any effect on HIV progression-free survival relative to that achievable by ART alone.

The number of participants who experienced a primary end point (n=106), though smaller than anticipated when the study was designed, is still considerable and, with the lack of any evidence for a clinical improvement in the HIV-1 Immunogen group, are adequate to exclude a beneficial effect of HIV-1 Immunogen of the magnitude targeted when the study was designed.

With respect to secondary efficacy end points in this study, subjects randomized to HIV-1 Immunogen demonstrated no significant improvement compared with those randomized to placebo with respect to mortality, HIV RNA, CD4 percentage, and body weight. Subjects in the HIV-1 Immunogen group exhibited a statistically significant improvement in CD4 cell count relative to the control group (P=.02). However, the magnitude of the benefit to CD4 cell counts conferred by HIV-1 Immunogen (average of approximately 10×10^6/L during the period of follow-up) might not be large enough to be clinically significant. Because of the number of secondary end points analyzed, without adjustment of P values for multiple comparisons, it is also possible that this difference was spurious.

The lack of evidence of a beneficial effect from HIV-1 Immunogen among the 435 subjects in the virologic substudy, when baseline viral replication was at its lowest levels, was particularly discouraging, and further (posthoc) evaluation of these patients revealed no significant differences with respect to any of the following secondary efficacy measures: CD4 cell count (P=.39), CD4 percentage (P=.99), viral load (P=.35), and body weight (P=.34).

This study provided the first information regarding disease progression among a large group of well-treated patients with CD4 cell counts between 300 and 549×10^6/L that was collected in the controlled setting of a randomized trial. The progression rate of 1.8 per 100 person-years of observation was one third of what had been reported in the literature prior to the widespread introduction of PIs. This provides additional evidence of the long-term benefits of highly active ARTs and has important implications for several ongoing studies that attempt to determine the effect of single agents (mostly immune-based therapies) when used with widespread effective ART.

The clinical events that were detected demonstrated that oral candidiasis was the most common manifestation of disease progression. Lymphoma was the second most common clinical progression event. The number of lymphomas surprised us and may suggest that with suppression of opportunistic infections, the relative incidence of lymphoma and Kaposi sarcoma may increase and account for a greater number of new index AIDS diagnoses. Despite the availability of prophylaxis for opportunistic infections, recurrent oropharyngeal candidiasis and Pneumocystis carinii pneumonia were the most common opportunistic infections.

This study also provides key information regarding the common clinical dilemma of identifying, implementing, and maintaining patients receiving an active and effective ART regimen. This study was the largest randomized trial of persons infected with HIV.
in the past decade, occurred during a time of increased use of highly active ARTs, and imposed no restrictions on the use of these agents. Patients in this study switched medications often and added an average of 3 new medications during the first study year. Switching of ARTs was not restricted to patients with high viral loads, but was also seen among those patients with undetectable viral load, with approximately 50% adding a new ART within a year following randomization.

The design of this study was aimed at assessing whether HIV-1 Immunogen could provide additional efficacy compared with that achievable by unrestricted use of ARTs. An alternative design would have been to select patients based on ART use and restrict patients from changing ARTs during follow-up. While such an approach would have provided a more homogeneous background to assess an immunologic agent, it is questionable whether such a design would have been practically feasible or appropriate. A restricted entry criterion might not be relevant and limiting choices would likely increase the loss to follow-up and further reduce any relevance of the study to the care of patients infected with HIV. Furthermore, ARTs have been clearly shown to provide important benefit to patients with HIV/AIDS. The most common clinical practice for patients involves changing ARTs to maximize viral suppression and immune benefit. We remain convinced that the design we chose, which did not limit access to ARTs for this study with clinical end points, is the most clinically relevant.

One limitation of the study, however, was the infrequent assessment of immunologic and virologic markers. A more frequent assessment of these markers, for example, would have given greater power to detect a transient ef-

Figure 5. Mean Changes From Baseline for Log_{10} RNA, CD4 Cell Count, CD4 Percentage, and Body Weight

HIV indicates human immunodeficiency virus; IFA, incomplete Freund adjuvant. Error bars indicate 95% confidence intervals.

©2000 American Medical Association. All rights reserved.
EVALUATION OF HIV-1 IMMUNOGEN WITH ANTIRETROVIRAL THERAPY

fect of HIV-1 Immunogen. However, the large sample size of this study provides persuasive evidence against a sustained effect of HIV-1 Immunogen on these markers. Another limitation of the study was the incomplete database. It seems unlikely that the additional data would have qualitatively changed any of the efficacy results because the number of additional clinical end points that would have been obtained is small and much of the additional viral load and CD4 data that would have been obtained is for visits occurring more than 2 years following randomization. Thus, a late-emerging effect of HIV-1 Immunogen could have been missed due to the lack of this marker information, however, the likelihood of this seems low.

A disagreement developed between the study team and the sponsor that ultimately led us to analyze a final but incomplete data set. In addition, we could not obtain from the sponsor a list of the site coinvestigators who participated in this trial so that the manuscript could be shared with them and they could be acknowledged for their efforts. We decided to publish the available data that were presented to the DSMB and that led to their recommendation to terminate the study. This was done to complete our task of informing our research colleagues, to fulfill our responsibility to inform patients of the outcome of this study, and to contribute to their understanding of HIV-1 Immunogen if it was to be studied in another clinical trial.

Funding/Support: Support for this project included The Immune Response Corp and grant P30 MH59037 from the University of California, San Francisco, Center for AIDS Research (Dr Kahn).

Acknowledgment: We thank the data safety monitoring board for their valuable guidance: Richard Polard, MD (co-chair), University of Texas, Galveston; Clifford Lane, MD, National Institutes of Health, Bethesda, Md; David De Mets, PhD (co-chair), University of Wisconsin, Madison; and John Fahey, MD, University of California, Los Angeles. The fifth member refused acknowledgment. We also thank Heather Gorski for her programming assistance. We are especially grateful to the site investigators and participants, whose efforts made this study possible.

REFERENCES

26. Choi DJ, Dube S, Spicer TP, Slade HB, Jensen FC, Poiesz B. HIV type 1 isolate 2312, the strain used to make a therapeutic HIV type 1 immunogen, is a subtype recombinant. AIDS Res Hum Retroviruses. 1997;4:357-361.
3.9%]; \( P = .46 \) vs controls). A significantly greater rate of decrease was seen in fatigued patients (4.0% per repeat [2.1%-10.7%]; \( P < .005 \) vs nonfatigued patients, \( P < .005 \) vs controls). A significant correlation was seen between fatigue severity and rate of decrease in muscle grip strength (\( r = 0.69, P < .001 \) in patients; Figure). No association was found between muscle fatigability and liver disease severity (data not shown).

Comment. Patients with PBC who complained of fatigue showed a markedly accelerated decrease in muscle function on repeat activity compared with both control subjects and nonfatigued patients. Moreover, there was a strong correlation between the rate at which grip strength is lost and the severity of the fatigue experienced by the patient, suggesting that peripheral muscle fatigability may contribute to the symptom complex experienced by some patients. The etiology of this abnormality in repeat muscle function remains unclear and there appears to be no simple relationship with liver disease severity. We could not exclude a volitional component to the decrease in repeat muscle function, although the finding of normal initial grip strength in the fatigued patients would argue against this. Further studies of peripheral muscle and neuromuscular junction function in PBC-related fatigue are warranted. If a significant peripheral motor system contribution to fatigue in PBC is confirmed, this may suggest new modalities of treatment for this troubling symptom.

Jennifer Goldblatt, B Med Sci
Oliver F. W. James, MD
David E. J. Jones, MD, PhD
Centre for Liver Research
University of Newcastle
Newcastle-upon-Tyne, England


CORRECTION

Incorrect Text: In the Original Contribution entitled “Evaluation of HIV-1 Immunogen, an Immunologic Modifier, Administered to Patients Infected With HIV Having 300 to 549 \( 10^6 \) CD4 Cell Counts: A Randomized Controlled Trial” published in the November 1, 2000, issue of THE JOURNAL (2000;284:2193-2202), errors occurred on pages 2195, 2197, and 2202. On page 2195, column 3, the second to last sentence in the full paragraph should be: “The IRC performed all lymphocyte proliferation assays and contracted with an independent laboratory to perform viral load assays.” In the first paragraph of the “Results” section on page 2197, the following sentence has been corrected because of an incorrect percentage: “At the time of randomization, 27% of the subjects were not receiving ART, 5% were receiving monotherapy, and 68% were receiving combination ART (31% of the total population were receiving a PI).” On page 2202, the second sentence in the second column should be: “In addition, we could not obtain an updated list of the site coinvestigators who participated in the trial so that the manuscript could be shared with them and they could be acknowledged for their efforts.”