Safety of 2 Recombinant Human Immunodeficiency Virus Type 1 (HIV-1) Envelope Vaccines in Neonates Born to HIV-1–Infected Women


To determine the safety of 2 candidate vaccines against human immunodeficiency virus type 1 (HIV-1), a randomized, placebo-controlled, multicenter trial compared low, medium, and high doses of the vaccines or an adjuvant among infants born to HIV-infected women. No local or systemic reactions of grade 2 or greater were reported 48 h after the subjects underwent immunization. Grade 3 or 4 chemistry toxicities occurred in 5 (3%) and grade 3 or 4 hematologic toxicities in 17 (11%) of 154 vaccinated subjects (not significantly different from 29 adjuvant recipients). CD4+ cell percentages of \(<20\)% occurred at least once in 9 vaccinated subjects and 1 control subject. Sustained CD4+ cell percentages of \(\leq20\)% occurred in 4 HIV-infected children. Fourteen infants (8%) were confirmed to be HIV-infected; median CD4+ cell counts among these children were 2074, 1674, 1584, and 821 cells/mm^3 at birth and weeks 24, 52, and 104, respectively. Thus, both vaccines were safe and well tolerated in neonates, and there was no evidence of accelerated immunologic decline in HIV-infected infants.
be safe and immunogenic at all ages, even for newborn infants. Initiation of protection during infancy would allow for protection during the period of breast-feeding. In addition, the immunization could be administered concurrently with other routine childhood immunizations, which would lessen the overall cost of introducing a new vaccine.

The present study was designed to determine the safety and immunogenicity of 2 candidate envelope-based vaccine products in newborn infants. The immunogenicity data have been reported [8]. We describe the safety profile of these vaccine products.

METHODS

Study design. Pediatric AIDS Clinical Trials Group (PACTG) protocol 230 was a multicenter, phase I, randomized, placebo-controlled study of recombinant glycoprotein (rgg) 120-MN/ aluminum hydroxide (alum; VaxGen; VG) and rgp120-SF2/MF59 (Chiron; Ch), given at low (VG, 30 μg; Ch, 5 μg), medium (VG, 100 μg; Ch, 15 μg), or high (VG, 300 μg; Ch, 50 μg) doses, compared with adjuvant alone. The initial cohorts (A and B for VG and Ch, respectively) were given escalating doses and received immunizations on a schedule of birth (<72 h of age) and at weeks 4, 12, and 20. Two additional cohorts were added (C and D for VG and Ch, respectively) to increase the sample size for selected analyses. An optimum dose of each product was selected on the basis of safety and immunogenicity results from cohorts A-D, and a final group of infants received this dose on an accelerated schedule of birth and at weeks 2, 8, and 20. Table 1 provides details regarding the study design and patient enrollment.

Vaccines. VG is produced in cultured Chinese hamster ovary cells and absorbed into alum with thimerosal. The corresponding placebo is alum with thimerosal in Tris-buffered saline. Both were supplied by VaxGen.

Ch is produced in genetically engineered Chinese hamster ovary cells. The MF59 adjuvant is 0.5% polysorbate 80, 0.5% sorbitan trioleate, and 0.5% squalene. Both the vaccine and the adjuvant were in a citrate buffer, and both were supplied by Chiron Vaccines. The antigen and the corresponding adjuvant were mixed to give appropriate antigen doses in a final volume of 0.5 mL, which is administered im into the thigh.

Study population. Infants born to women infected with HIV-1 and enrolled for vaccination before they were 72 h of age were eligible. Infants were excluded if any of the following occurred: birth at <37 weeks of gestation, receipt of investigational medications, significant medical illness, significant laboratory abnormalities, or breast-feeding. Other exclusion criteria included receipt of HIV-specific immunotherapy or current maternal hepatitis B virus infection. Because the trial began enrollment before the results of PACTG 076 [9] were known, infants were initially excluded from the study if they had received zidovudine at the time of study entry. Immediately upon the release of results of PACTG 076, zidovudine therapy was encouraged for all study infants [10].

Toxicity evaluation. Toxicity evaluation included clinical monitoring before and 1 h and 48 h after immunization, with additional follow-up evaluations done throughout the 104-week study period. Laboratory evaluation included complete blood count and platelet count; measurement of levels of blood urea nitrogen, creatinine, aspartate aminotransferase, and alanine aminotransferase; urinalysis; and determination of CD4+ cell percentage and absolute number. These laboratory evaluations were performed at regular intervals throughout the study period. Local or systemic reactions that occurred during the first 48 h after any immunization are described. Other adverse events were included if they occurred at any time over the 2-year follow-up period.

Statistical analysis. Adverse events were categorized as grade 1 or 2 (mild), grade 3 (moderate to severe), and grade 4 (severe or life-threatening), by use of criteria established by the PACTG 230 protocol team, to promote uniformity in reporting across study sites. The study-specific grading was established by the team before the development of the present grading system in the PACTG. All grade 3 and 4 toxicities were reviewed by the protocol team, which was blinded to subject treatment assignment (vaccine or adjuvant control). Toxicities were judged to be treatment related if, in the opinion of the protocol team or the site investigator, there was no identified alternative cause for the event. Because of low frequency of adverse events, the data are summarized descriptively, with statistical tests restricted to those specified below.

Kruskal-Wallis tests were done to assess the statistical significance of comparisons across racial/ethnic groups (white, black, and Hispanic) for absolute neutrophil counts (ANCs), to examine whether the relatively frequent occurrence of ANC toxicity in the study could be explained on the basis of race/ethnicity. For the binary data, either Fisher’s exact or χ² tests were used to test associations, depending on the cell frequencies. Fisher’s exact test was used to assess the difference in infection rates between the pooled vaccinated group and the placebo group and to examine the association between infection and the use of zidovudine during the first week of life. The χ² test was used to test the difference in the use of zidovudine between placebo recipients and vaccinated subjects.

RESULTS

One hundred eighty-eight subjects were randomized, but 5 did not receive vaccine and were removed from the study. We describe only the 183 subjects who received at least 1 vaccination. Twenty-six PACTG sites participated in the study, and each site
enrolled 1–26 subjects. Of the study subjects, 51% were female. The race/ethnicity of the enrolled infants was reported as follows: black, 82 (45%); Hispanic, 52 (28%); white, 43 (24%); Asian, 1 (1%); and other, 5 (3%). Baseline CD4+ and CD8+ cell counts (absolute numbers and percentages) were not different between the treatment groups.

The entire 4-vaccination series was received by 156 subjects (85%). Vaccination was started but discontinued early for 27 subjects (15%). Sixteen subjects (9%) discontinued treatment after 1–3 doses because of noncompliance, loss to follow-up, or parental request. Eleven subjects (6%) discontinued after 2 or 3 immunizations for reasons related to toxicity (whether attributed to treatment or not), HIV progression, or death. Premature discontinuation of vaccination occurred for 17 (21%) of 80, 7 (10%) of 74, and 3 (10%) of 29 VG, Ch, and adjuvant control recipients, respectively.

Local and systemic reactions to vaccination were infrequent and, when they did occur, mild. The worst overall reaction within 48 h of vaccination was a grade 2 reaction, which 5 infants experienced; 46 infants had a grade 1 reaction and 132 within 48 h of vaccination was a grade 2 reaction, which 5 and, when they did occur, mild. The worst overall reaction (21%) of 80, 7 (10%) of 74, and 3 (10%) of 29 VG, Ch, and adjuvant control recipients, respectively.

Local and systemic reactions to vaccination were infrequent and, when they did occur, mild. The worst overall reaction within 48 h of vaccination was a grade 2 reaction, which 5 infants experienced; 46 infants had a grade 1 reaction and 132 infants had no reactions. There were no grade 3 or 4 reactions. The 5 grade 2 reactions included induration (5 mm × 5 mm), vomiting, fussiness, cutaneous reaction not at the site of injection, and fussiness with a temperature of 38.8°C (n = 1 each). The grade 2 reactions were evenly distributed in the Ch and VG arms (2 each), with 1 in the MF59 placebo arm.

Chemistry toxicities were also uncommon. Grade 3 or 4 chemistry toxicities occurred in 1 (3%) of 29 placebo recipients and 5 (3%) of 154 vaccine recipients. All 6 subjects with grade 3 or 4 chemistry events had elevated levels of aspartate aminotransferase, and 3 subjects also had grade 4 elevations in levels of alanine aminotransferase. Four of the 6 children with grade 3 or 4 chemistry toxicities were HIV-infected. The 2 subjects with grade 3 or 4 elevations in aspartate aminotransferase levels who were not HIV-infected were judged by the team to have causes for their abnormal chemistry value that were not related to treatment. One of these subjects had an abnormal liver enzyme value only at week 0, before receipt of vaccine; the other had a grade 3 elevation in the level of aspartate aminotransferase once only, 4 weeks after receipt of the final immunization. The latter child was in the alum adjuvant control arm. All grade 3 and 4 toxicities are summarized in table 2.

The most frequent toxicity to occur in children in this study was hematologic. Grade 3 and 4 events occurred in 7 (24%) of 29 placebo recipients, compared with 17 (11%) of 154 vaccinated subjects. The most common hematologic event was low ANC, which occurred in 23 (13%) of 183 subjects. The protocol team judged that the low ANC was not related to treatment for 18 (78%) of the 23 subjects who had ANC values of grade 3 or 4. Low ANC was most often attributed to the concomitant use of trimethoprim-sulfamethoxazole or zidovudine. Further evaluation demonstrated that ANC toxicity of grade 3 or higher was more prevalent among the adjuvant control recipients than among vaccine recipients and that no treatment arm accounted for a disproportionate percentage of the grade 3 or 4 ANC events.

To examine the high rate of low ANC observed in the overall PACTG 230 study population, the mean and median ANC were broken down according to racial/ethnic groups. The data were restricted to the vaccinated, HIV-uninfected subjects to make the sample more homogenous. Figure 1 shows the median ANC according to age for infants of each race/ethnic group. The ANC value at birth tended to be lower among black infants than among African and Hispanic infants, but the difference was not statistically significant (P = .28). However, there were significant ANC differences among ethnic/racial groups at weeks 24, 76, and 104 (P = 004, 003, and .02, respectively), with black infants consistently exhibiting the lowest ANC scores. ANC toxicity of grade 3 or higher occurred in 2 (5%) of 43 white subjects, 15 (18%) of 82 black subjects, and 4 (8%) of 52 Hispanic subjects.

Signs and symptoms, regardless of whether they were temporally associated with vaccine use, were evaluated during each protocol evaluation during the study period. No adjuvant control recipient reported grade 3 or 4 signs or symptoms, whereas 5 (3%) of 154 vaccinated subjects reported such events. None of the events were judged by the protocol team to be related to treatment. The events included diarrhea at week 52 (>6 months after last vaccination), signs of increased intracranial pressure secondary to head trauma, diarrhea and weight loss secondary to Salmonella infection, and rash in 2 infants, one of whom also had neonatal jaundice.

Four subjects died during the course of the study, 2 of whom were HIV-infected, and both of whom died secondary to HIV disease progression. The 2 deaths in children who were not HIV-infected were clearly not attributable to study vaccine: 1 was due to trauma and the other to a methadone overdose.

Fourteen (8%) of the 183 subjects were determined to be HIV-1–infected. Eleven of these subjects were in cohorts A and B, the cohorts that enrolled subjects the earliest (table 1). All 14 of the infected subjects received vaccine. Three infants were culture-positive for HIV-1 at birth, and the remainder had initially negative culture results that were followed by positive culture results. The difference in infection rates between those who received vaccine (14 of 154) and those who received placebo (0 of 29) was not statistically significant (P = .08; Fisher’s exact test).

The use of treatment with antiretroviral agents for infants after delivery changed during the study enrollment (table 1). In the lowest-dose arms of cohorts A and B, none of the vaccinated infants received zidovudine during the first week of life, whereas, in the medium- and high-dose arms, zidovudine was administered in the first week of life for 18 (38%) of 31 and...
Table 1. Enrollment cohorts, immunization schedules, and distribution of infants enrolled in the study of envelope vaccines.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Vaccine, adjuvant</th>
<th>Schedule</th>
<th>Dose, µg</th>
<th>Receiving vaccine</th>
<th>Receiving adjuvant</th>
<th>HIV-infected</th>
<th>Dates of enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>VaxGen, alum</td>
<td>Birth, weeks 4, 8, 20</td>
<td>30</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td>August 1993-February 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>15</td>
<td>4</td>
<td>2</td>
<td>February 1994-April 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300</td>
<td>14</td>
<td>4</td>
<td>2</td>
<td>May 1994-October 1994</td>
</tr>
<tr>
<td>B</td>
<td>Chiron, MF59</td>
<td>Birth, weeks 4, 8, 20</td>
<td>5</td>
<td>14</td>
<td>4</td>
<td>1</td>
<td>August 1993-February 1994</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>15</td>
<td>16</td>
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<td>1</td>
<td>February 1994-April 1994</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td>May 1994-October 1994</td>
</tr>
<tr>
<td>C</td>
<td>VaxGen, alum</td>
<td>Birth, weeks 4, 8, 20</td>
<td>30</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>February 1995-April 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>6</td>
<td>0</td>
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<td>February 1995-April 1996</td>
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<tr>
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<td></td>
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<td>300</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>February 1995-April 1996</td>
</tr>
<tr>
<td>D</td>
<td>Chiron, MF59</td>
<td>Birth, weeks 4, 8, 20</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>February 1995-April 1996</td>
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<tr>
<td></td>
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<td>15</td>
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<td>50</td>
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<td>0</td>
<td>0</td>
<td>February 1995-April 1996</td>
</tr>
<tr>
<td>Optimum dose</td>
<td>VaxGen, alum</td>
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<td>100</td>
<td>15</td>
<td>4</td>
<td>0</td>
<td>May 1996-November 1996</td>
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<tr>
<td></td>
<td>Chiron, MF59</td>
<td>Birth, weeks 2, 8, 20</td>
<td>5</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>May 1996-November 1996</td>
</tr>
</tbody>
</table>

NOTE. In cohorts A and B, 49% of infants received therapy with zidovudine in first week of life; in other cohorts, 100% of infants received zidovudine.

All HIV-infected infants were in the group of vaccinated subjects; there were no infected infants among 29 adjuvant control recipients.

Table 2. All grade 3 and 4 toxicities observed during period of study, including both those attributed to vaccine and those not.

<table>
<thead>
<tr>
<th>Timing of event, type of toxicity</th>
<th>Vaccine (n = 154)</th>
<th>Adjuvant control (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 48 h of immunization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local or systemic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any time during study period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td>5 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>17 (11)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td>5 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>
they had received the last dose of vaccine. For HIV-uninfected subjects, the changes in CD4⁺ cell percentages and absolute counts over time were not different between vaccine and adjuvant control recipients (figure 2).

**DISCUSSION**

This is the first study to evaluate the safety of an HIV-specific vaccine product in a population of infants born to HIV-1–infected women. The 2 envelope-based vaccines that were tested in this study were found to be safe and well tolerated in this population. This is consistent with the findings of a smaller study of older HIV-infected children who received either 1 of these vaccines or another envelope-based vaccine [9]. The safety of these products has also been established in a study of HIV-negative adult volunteers [11].

In addition, this is the first report of the use of the adjuvant MF59 in neonates. All infants in the Ch arm, including those in the adjuvant control group for that arm, received the MF59 adjuvant. The toxicities in the Ch group were not more severe than those seen in the VG group, who received alum as the adjuvant. This suggests that MF59 is safe for use in infants. Premature discontinuation of vaccination occurred more frequently in the VG group than it did in the Ch and adjuvant control recipients (percentage of patients who discontinued treatment, 21%, 10%, 10%, respectively), but the difference was not statistically significant \( P = .09; \chi^2 \) test). In addition, the reasons for treatment discontinuation were reviewed and we determined that they were not related to the vaccine products. Causes for discontinuation included loss to follow-up, relocation of subject to another city, or placement of subject into foster care.

Laboratory and clinical toxicities occurred frequently in this patient population, but for each of the laboratory parameters...
that were studied, the abnormalities occurred in the vaccinated group at the same or a lower frequency compared with that in the adjuvant control group. The one clinical parameter that occurred more frequently among vaccine recipients than among placebo recipients was the occurrence of grade 3 and 4 signs and symptoms. However, all of these events were judged by the study team to be unrelated to treatment; that is, in each case there were clearly identified alternative explanations for the event.

The frequent occurrence of hematologic toxicity in the study appears to have been related to lower ANC values for black infants. This event is clearly not related to use of study vaccines, because it occurred more commonly in placebo recipients than it did in vaccines. Leukopenia that results in low ANC values has been described in healthy American black persons [12]. In addition, the frequent occurrence of low ANCs in children born to HIV-infected women was previously reported in a study of zidovudine-treated and -untreated children who were enrolled in PACTG 076 [13]. This finding highlights the need to develop grading tables for laboratory toxicities that are based on the distribution of these parameters in the racial/ethnic population that will be enrolled in the study.

Theoretical safety issues that have been raised with regard to HIV envelope-based vaccines have included concerns that they could enhance the likelihood of HIV transmission or accelerate immunologic decline when HIV infection does occur. In our study, the HIV-1 infection rates between the vaccine and control groups were not significantly different. Ten percent of the vaccinated subjects were infected with HIV, a transmission rate consistent with that seen in other populations in which peripartum zidovudine prophylaxis was administered [1, 10, 14]. Therefore, the perinatal HIV-1 transmission rate seen in PACTG 230 did not suggest an increase in transmission from these vaccine products compared with those seen among comparable patient populations outside of the present study. However, the study was not designed to detect a difference in infection rates between vaccinated and adjuvant control recipients or between groups that received the 2 different vaccine products. Furthermore, this trial was not designed to determine vaccine efficacy. Efficacy of these and other candidate vaccines in neonates would require study of cohorts in which transmission via breast feeding continues to be a significant problem.

Concern has been raised, on the basis of rapid HIV disease progression in 1 HIV-infected adult vaccine recipient, that the prior receipt of an envelope vaccine may accelerate the immune decline in a person who subsequently becomes HIV-infected. Further study of larger numbers of adults after they have experienced vaccine failure has shown that disease progression does not proceed in an accelerated fashion [15]. In our study, 3 of the HIV-infected children had culture results that were positive for HIV at birth, and we presume that they had established HIV infection before receipt of the vaccine. Eleven of the study subjects had culture results that were negative for HIV at the time that they received their first vaccine, and they became HIV-positive subsequent to the vaccination. Rates of decline in CD4+ cell percentages and absolute numbers in HIV-infected infants who were enrolled in PACTG 076 were similar to the rates of decline seen in the vaccinated subjects in the current study. Therefore, the HIV-infected children had no evidence of an accelerated decrease in CD4+ cells that is different from what would be expected in a similarly treated group of nonvaccinated infants. In addition, the HIV-uninfected vaccinated subjects had CD4+ cell percentages and absolute counts identical to those of the adjuvant control recipients, and both groups showed the same normal, age-related decrease in CD4+ cell count that would be expected in uninfected children [16]. These findings indicate that the vaccine, in the absence of HIV infection in the child, has no impact on the CD4+ cell percentage.

Previous trials of HIV-negative adults who had received envelope-based vaccines and subsequently became HIV-infected have established that HIV infection can occur after receipt of vaccine [15]. HIV-1 infections occurred among vaccinated infants in the present study. This study was not designed to determine vaccine efficacy; however, it is apparent that these envelope products, given in the present manner to infants after they are exposed to HIV, do not eliminate mother-to-infant transmission of HIV.

In summary, the recombinant gp120 products that we studied were safe and well tolerated in neonates born to HIV-infected women. Local and systemic toxicities did occur, but they were generally of similar frequencies among vaccine and adjuvant control recipients.

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References


