The Rate of Serious Bacterial Infections Among HIV-Infected Children With Immune Reconstitution Who Have Discontinued Opportunistic Infection Prophylaxis

Sharon Nachman, MD*; Philimon Gona, PhD‡; Wayne Dankner, MD§; Adrianna Weinberg, MD¶; Ram Yogev, MD¶; Anne Gershon, MD®; Mobeen Rathore, MD***; Jennifer S. Read, MD††; Sharon Huang, MS‡‡; Carol Elgie, BSSS; Kim Hudgens, BS¶¶; and Walter Hughes, MD†††

ABSTRACT. Objective. Receipt of highly active antiretroviral therapy is associated with a decrease in the incidence of opportunistic infections (OIs) among HIV-infected adults. The goal of Pediatric AIDS Clinical Trials Group protocol 1008 was to evaluate prospectively the incidence of serious bacterial infections (SBIs) and other OIs after discontinuation of OI and/or PCP prophylaxis among HIV-infected pediatric subjects who experienced immune reconstitution while receiving stable antiretroviral therapy.

Methods. HIV-infected children and adolescents, 2 to 21 years of age, who had received OI and/or PCP prophylaxis for ≥6 months were enrolled if they had sustained responses (>16 weeks before study entry) to antiretroviral therapy, with CD4+ cell percentages of ≥20% for patients >6 years of age or ≥25% for patients 2 to 6 years of age. Prophylaxis was discontinued at entry. To identify whether any correlation existed between functional immune reconstitution and protection from OIs, subjects were immunized with the hepatitis A virus vaccine. The association between the humoral immune response and the likelihood of developing an OI was evaluated.

Results. A total of 235 HIV-infected subjects from 43 participating sites had a median follow-up period of 132 weeks, yielding 547 person-years of observation. Twenty SBIs were observed among 19 subjects, resulting in an incidence rate of 3.66 SBIs per 100 person-years (95% confidence interval: 2.24–5.66 SBIs per 100 person-years). Sixteen of the events were presumed bacterial pneumonia, with 4 proven SBIs. One participant experienced 2 separate pneumonia episodes, of presumed bacterial cause. Ten subjects who developed SBIs had baseline CD4+ cell counts of ≥750 cells per mm³, and 15 had CD4+ cell percentages of ≥25% at the time of their SBIs. Two subjects died as a result of non-SBI-related causes. There were no statistically significant changes in differences over time in CD4+ cell counts or CD4+ cell percentages between subjects who experienced primary end points and those who did not. There was no evidence that baseline protease inhibitor use, gender, race/ethnicity, age, or CD4+ cell count or percentage affected the time to development of a SBI.

Conclusions. OI or PCP prophylaxis can be withdrawn safely for HIV-infected pediatric patients who experience CD4+ cell recovery while receiving stable antiretroviral therapy. More studies are needed to assess the association between antibody responses to neomycin and the development of SBIs. Pediatrics 2005; 115:e488–e494. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1847; pediatric HIV, bacterial infections, immune reconstitution.

ABBREVIATIONS. OI, opportunistic infection; HAART, highly active antiretroviral therapy; PCP, Pneumocystis jiroveci pneumonia; MAC, Mycobacterium avium complex; PACTG, Pediatric AIDS Clinical Trials Group; SBI, serious bacterial infection; CDC, Centers for Disease Control and Prevention. HAV, hepatitis A virus; CI, confidence interval; PI, protease inhibitor.

Because HIV infection progresses and leads to a profound depletion of CD4+ T lymphocytes, quantification of CD4+ cells has become established as the major criterion for the institution of antimicrobial prophylaxis for opportunistic infections (OIs).1 Several studies have demonstrated the efficacy of prophylaxis for such infections, and national guidelines have been established for standards of practice for the treatment of high-risk HIV-infected infants, children, adolescents, and adults.2–5 Despite the benefits of these antimicrobial drugs (as prophylaxis), all are associated with adverse side effects; therefore, unnecessary and prolonged use of such prophylaxis should be avoided.

Guidelines for antimicrobial prophylaxis for HIV-infected children in the United States were established in 1994,4 when few antiretroviral drugs were available and when the possibility of significant improvement of immune function among these children was unlikely. Since the advent of highly active antiretroviral therapy (HAART), HIV-infected patients receiving such therapy have demonstrated de-
creased plasma HIV RNA concentrations, increased numbers of CD4+ T cells, and significant reductions in the incidence of OIs. These data suggest the possibility of discontinuation of prophylaxis for OIs, including prophylaxis for Pneumocystis jiroveci pneumonia (PCP) and Mycobacterium avium complex (MAC) disease, once HIV-infected patients demonstrate improvement in CD4+ cell counts to levels at which such prophylaxis would not be initiated according to current guidelines. Studies among HIV-infected adults with immune reconstitution after receipt of HAART demonstrated extremely low risks of development of OIs after discontinuation of prophylaxis.

Discontinuation of PCP and MAC prophylaxis among HIV-infected pediatric patients was evaluated in Pediatric AIDS Clinical Trials Group (PACTG) protocol P1008. The study’s primary objective was to evaluate the incidence of serious bacterial infections (SBIs) and other OIs (Centers for Disease Control and Prevention [CDC] category C infections) after OI and/or PCP prophylaxis was discontinued for children who achieved immune reconstitution while receiving antiretroviral therapy. Secondary objectives included evaluation of the durability of immune reconstitution, as defined by the relationship of changes in absolute CD4+ cell counts and CD4+ percentages with time, and the incidence of SBIs and other OIs and evaluation of the association between immune function, as assessed with serum hepatitis A virus (HAV) vaccine antibody responses, and the occurrence of OIs.

METHODS

Study Population and Study Design

HIV-infected children were enrolled at clinical sites funded by the National Institutes of Health to participate in clinical trials and other studies related to HIV infection among infants, children, and adolescents. The institutional review board at each participating site approved the protocol. Appropriated informed consent (and assent, if appropriate) was obtained for each patient before enrollment, and clinical research was conducted in accordance with guidelines for human experimentation, as specified by the US Department of Health and Human Services and by the participating institutions.

Eligibility criteria for enrollment were age between 2 and 21 years; HIV infection; receiving stable (unchanged) antiretroviral therapy, although not necessarily HAART, for >4 months before study entry; and receipt of PCP prophylaxis for a minimum of 6 months, without discontinuation of PCP prophylaxis for >3 months before study entry. However, study entry, children 2 to 6 years of age were required to have a CD4+ cell percentage of ≥25%, and children >6 years of age were required to have a CD4+ cell percentage of ≥20%. Children were not enrolled if they had experienced an episode of proven or presumed PCP in the prior 3 months or had an active infection requiring ongoing antimicrobial therapy, were receiving intravenously administered immunoglobulin, or had a history of malignancy.

Contraindications to study entry and study follow-up times included intravenously administered immunoglobulin for >1 therapeutic intervention, PCP treatment (such as trimethoprim/sulfamethoxazole, atovaquone/azithromycin, dapsone, or pentamidine) for >28 days, or any systemic antifungal prophylaxis for >28 days. Patients who received any of the disallowed medications after enrollment were removed from the study. The protocol required reporting within 72 hours of the occurrence to the protocol team if the patient received any prohibited medication or if the patient discontinued antiretroviral therapy.

All children discontinued PCP prophylaxis at study entry. The occurrence of SBIs and of PCP was to be reported to the protocol team within 72 hours after occurrence. After being reported to the protocol team, children who experienced decreases in CD4+ lymphocyte percentages to <15% (reported on 2 separate occasions), new CDC pediatric clinical case C diagnoses, or a second SBI were offered bacterial/PCP prophylaxis and removed from the study. The study started at week 32 and was completed at week 104 after entry, subjects were to be monitored every 8 weeks for at least 104 weeks and until the last subject completed 112 weeks of study observation. At each study visit, subjects were evaluated for clinical end points, and blood samples were obtained for flow cytometric analyses (performed at PACTG-certified flow cytometry laboratories, all participating in the AIDS Clinical Trials Group quality assurance programs).

A SBI was defined as an infection of a sterile body site (blood, lung, or organ) with a bacterial pathogen (such as Streptococcus pneumoniae, Haemophilus influenzae, or Neisseria meningitidis) known to cause invasive disease. Clinical events were defined according to a list of diagnoses developed as part of the AIDS Clinical Trials Group. Diagnoses were recorded on diagnosis forms as proven (definite), probable (presumed), or possible (suspected). Proven diagnoses were included as end points (eg, proven pneumonia, defined as clinical findings and a chest radiograph temporally consistent [within 7 days] with a diagnosis proven by culture or other specific assays of blood, biopsy, tissue, or broncoalveolar lavage samples). Presumed diagnoses were also included as study end points (eg, presumed pneumonia, which was defined as clinical findings and a chest radiograph temporally consistent [within 7 days] with a diagnosis, with specific assays negative or not performed). Sinusitis, whether proven or presumed, was not considered a SBI for this study, and neither were cellulitis or infections of central or peripheral vascular access lines. Possible diagnoses were not considered as end points. Clinical end points were evaluated by the study team and assessed if criteria for a diagnosis, as defined in the protocol (see Table 3 for a complete listing), were met. SBIs considered proven or presumed included arthritis, bacteremia (primary or secondary), endocarditis, epiglottitis, internal organ abscess, mastoiditis, meningitis, myositis/pyomyositis, osteomyelitis, pneumonia, septic thrombophlebitis, and tracheitis.

A standard, 2-dose, HAV immunization regimen was administered to all study participants without a prior history of HAV infection, vaccination, or recent intravenous immunoglobulin administration. The vaccines were administered at baseline and at week 24, and anti-HAV antibodies were measured at baseline and at week 32. A third, booster dose was given at week 104 or greater for consenting participants. The results of this intervention are not part of this analysis and will be reported separately.

Anti-HAV Antibody Assay

Anti-HAV antibodies were measured with a quantitative ELISA. Precocated HAV microtiter plates (Viral Antigens Inc, Memphis, TN) were incubated with serial dilutions of anti-HAV World Health Organization standards and 100 μL of serum samples diluted 1:21 in assay IgG diluent (Viral Antigens Inc). After 1 hour of incubation, plates were washed and bound antibodies were revealed with alkaline phosphatase-conjugated goat anti-human IgG (ICN, Costa Mesa, CA) and p-nitrophenylphosphate chromogenic substrate (Sigma, St Louis, MO). The antibody titer of each sample was calculated by interpolating its corresponding OD reading on the linear regression curve generated with the World Health Organization standards. This assay was validated with 20 sera from HAV-naive patients and 10 sera with previously determined anti-HAV antibody concentrations (courtesy of Dr Paul Willems, GlaxoSmithKline Vaccine Division).

Statistical Methods

The background incidence rate of SBIs for this study, derived from PACTG protocol 254 (a randomized, phase II/III, double-blind, 2-armed study of micronized atovaquone and azithromycin, compared with trimethoprim/sulfamethoxazole, in the prevention of SBIs when used for children aged 3 months to 19 years with HIV infection), was 2.95 events per 100 person-years (W. Dankner, personal communication). This rate was derived from patients who had achieved a CD4+ cell percentage of ≥20% during the PACTG 254 study but were still receiving prophylaxis (for purposes of determining the SBI rate for PACTG 254, SBI events that occurred before the CD4+ cell percentage increased above 20% were censored). Monitoring 200 patients for a median of 2
years was calculated to provide 81% statistical power, at the .05 significance level, to detect a statistically significant difference between the background incidence rate and an alternative hypothesis incidence rate of ≥9 events per 100 person-years. Therefore, if an event rate of ≥9 events per 100 person-years was observed, then withdrawal of OI or PCP prophylaxis in the P1008 study population would be considered to place patients at increased risk of morbidity and potential death from PCP SBIs and other OIs (eg, toxoplasmosis).

Statistical analyses with χ², Fisher’s exact, and log-rank tests and Cox proportional-hazards regression models were used to test univariate associations between patient characteristics and the risk of developing a SBI. Continuous variables were analyzed with 2-sample t tests, Kruskal-Wallis tests, and Wilcoxon tests. A landmark Cox proportional-hazards regression analysis was used to investigate the association of responses to HAV vaccine and the risk of developing a SBI. In the landmark analysis, only uncensored patients who were event-free at week 32 were included. Distribution-free methods were used when necessary. A probability level of \( P < .05 \) was considered statistically significant. P values and confidence intervals (CIs) were 2-sided. Time to event was defined as the number of days between the primary event date or censoring date and the date of enrollment. Event rate CIs were calculated with the Poisson distribution. Repeated-measures generalized estimating equations with an exchangeable working correlation structure between any 2 measurements for a subject were used to compare CD4⁺ cell count and CD4⁺ cell percentage trajectories according to the primary end point over time.²⁰

RESULTS

Study Population

Between September 1999 and June 2000, 235 eligible subjects were enrolled. The final study visit occurred in January 2003. Baseline characteristics of the study population are shown in Table 1. In this study, 47% of enrollees were male, 50% were black, 30% were Hispanic, and 20% were white. The median age at enrollment was 9 years. Eighteen percent of the children were <6 years of age. The median baseline CD4⁺ cell percentage was 31%, with 85% of the children having CD4⁺ cell percentages of >25%. At enrollment, 84% of subjects were receiving a HAART regimen that included a protease inhibitor (PI). The most common PIs used at entry were nelfinavir (46%) and ritonavir (29%). Of the 93 subjects receiving a non-nucleoside reverse transcriptase inhibitor, 49 were receiving nevirapine and 44 were receiving efavirenz. Some of the subjects were receiving both a PI and a non-nucleoside reverse transcriptase inhibitor. Interestingly, 11% of the children were receiving either single- or dual-nucleoside therapy. There were few changes in antiretroviral therapy during the study follow-up period. Of the 235 eligible subjects for whom PCP prophylaxis was discontinued, 172 (73%) had been receiving trimethoprim/sulfamethoxazole. Sixty-three subjects were receiving MAC prophylaxis before study entry.

Of the 235 subjects, 106 had at least 1 diagnosis reported before entry. The most common diagnoses were presumed pneumonia \((n = 40)\), otitis media \((n = 21)\), proven sepsis \((n = 19)\), presumed oral candidiasis \((n = 17)\), HIV encephalopathy \((n = 17)\), proven pneumonia \((n = 17)\), and asthma \((n = 12)\). None of these conditions was acute or active at study entry.

Of the 235 subjects, 208 (89%) completed the protocol, 21 (9%) were lost to follow-up monitoring, and 4 (1.7%) were lost because of site closure, allowing for a follow-up period of 547 person-years. All subjects completed at least 104 weeks of study. The majority (83% of the 235 subjects) had their last scheduled visit in the study after week 104. The median length of follow-up monitoring was 132 weeks (interquartile range: 109-144 weeks).

The study was overenrolled by 35 patients. With 235 patients monitored for a median of 2.5 years, there was added statistical power to detect a difference between the background incidence rate of SBIs of 81% to 90% and an alternative hypothesis incidence rate of ≥9 events.

Incidence of OIs

Overall, 20 SBIs occurred (incidence rate: 3.66 events per 100 person-years; 95% CI: 2.24–5.66 events per 100 person-years). All SBIs were observed among subjects who were between 4 and 9 years of age at entry, with one half being 6 to 8 years of age at entry. Table 2 presents event rates per 100 person-years according to baseline characteristics, including age at diagnosis. There were no statistically significant differences according to gender, race, or PI use. There were no differences in the distribution of CD4⁺ cell percentages and age at entry between those with and without a SBI. There was no tendency toward seasonality in relation to when the SBIs occurred, with only 5 of the 20 SBI events occurring during the winter months (November through March).

Seventeen of these SBIs were pneumonia, 1 proven and the remaining presumed. One subject experienced a second event (presumed pneumonia) 10 weeks after the first event (also presumed pneumonia). There was 1 event of proven epiglottitis \((H\ influenzae)\), and there were 2 events of proven sepsis
No MAC or PCP events were observed during the study. Table 3 provides additional information regarding each of the 20 SBIs, including the week of study when the SBI occurred, the type of SBI, and the subject’s age, CD4^+ cell percentage, CD4^+ cell count, and antiretroviral therapy regimen.

Sixty-one percent of 211 subjects with recorded data were reported to have had a CD4^+ cell percentage of <15% at some point before entry. However, there was no difference in the proportions of subjects with SBIs between those with CD4^+ cell percentages of <15% (12 of 129 subjects, 9.3%) and those who never had a CD4^+ cell percentage of <15% (5 of 82 subjects, 6%).

### SBIs Diagnosed During the Study Period

During the study, 82 subjects had at least 1 new diagnosis. The most common diagnoses were upper respiratory infection (cause unproven) (n = 21), acute otitis media (n = 19), clinically diagnosed pneumonia with either a negative chest radiograph or no chest radiograph performed (n = 17), and presumed acute/subacute sinusitis (sinus radiograph negative or not performed) (n = 16). Of these 82 subjects, 9 also experienced a SBI. There was no

### Table 2. SBI Incidence Rate per 100 Person-Years, According to Subject Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SBI Events,* No. (%)</th>
<th>Incidence Rate, Cases per 100 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rate</td>
</tr>
<tr>
<td>Overall</td>
<td>20</td>
<td>3.66</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (35)</td>
<td>2.76</td>
</tr>
<tr>
<td>Female</td>
<td>13 (63)</td>
<td>4.44</td>
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<tr>
<td>Race/ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>14 (70)</td>
<td>5.11</td>
</tr>
<tr>
<td>Hispanic (regardless of race)</td>
<td>6 (30)</td>
<td>3.59</td>
</tr>
<tr>
<td>Age at enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 to &lt;6 y</td>
<td>3 (15)</td>
<td>2.70</td>
</tr>
<tr>
<td>6 to &lt;12 y</td>
<td>17 (85)</td>
<td>4.97</td>
</tr>
<tr>
<td>12 to 21 y</td>
<td>0 (0)</td>
<td>0.00</td>
</tr>
<tr>
<td>CD4^+ cells</td>
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<td></td>
</tr>
<tr>
<td>&lt;25%</td>
<td>4 (20)</td>
<td>5.13</td>
</tr>
<tr>
<td>25% to &lt;40%</td>
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</tr>
<tr>
<td>40% to 50%</td>
<td>6 (30)</td>
<td>5.93</td>
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<td>PI use at baseline</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (90)</td>
<td>3.97</td>
</tr>
<tr>
<td>No</td>
<td>2 (10)</td>
<td>2.13</td>
</tr>
</tbody>
</table>

* One subject experienced 2 separate episodes of presumed pneumonia.

### Table 3. Details of 20 SBIs Occurring Among 235 Subjects

<table>
<thead>
<tr>
<th>Event No.</th>
<th>SBI Diagnosis Details*</th>
<th>Patient Characteristics at Diagnosis</th>
<th>Antiretroviral Therapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Week</td>
<td>Description</td>
<td>Age, y</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Pneumonia, presumed</td>
<td>8.3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Pneumonia, presumed</td>
<td>8.7</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Pneumonia, presumed</td>
<td>8.6</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>Pneumonia, presumed</td>
<td>7.4</td>
</tr>
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<td>5</td>
<td>12</td>
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<td>8.6</td>
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<tr>
<td>6</td>
<td>15</td>
<td>Pneumonia, presumed</td>
<td>5.3</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
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</tr>
<tr>
<td>9</td>
<td>17</td>
<td>Bacteremia, proven, primary</td>
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<td>10</td>
<td>18</td>
<td>Bacteremia, proven, primary</td>
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<tr>
<td>11</td>
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<td>12</td>
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<td>74</td>
<td>Epiglottitis, proven</td>
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<tr>
<td>20</td>
<td>99</td>
<td>Pneumonia, presumed</td>
<td>12.0</td>
</tr>
</tbody>
</table>

DDI indicates didanosine; ZDV, zidovudine; D4T, stavudine; 3TC, lamivudine; ABC, abacavir; NVP, nevirapine; SQV, saquinavir; EFV, efavirenz; RTV, ritonavir; NFV, nelfinavir; APV, amprenavir.

* Event 15 and event 16 involved the same patient.
significant difference in the incidence of SBIs between those with or without a new diagnosis while in the study.

Deaths
There were 2 deaths during the study follow-up period. One occurred in study week 10 and involved a 3-year-old, non-Hispanic white girl who developed presumed cardiomyopathy (autopsy refused); the second occurred in study week 66 and involved a 21-year-old, non-Hispanic white male patient with hemophilia and hepatitis C virus infection. No pathologic organisms were isolated at autopsy, and the patient died as a result of multiorgan failure, which was presumed to be related to a hepatic-metabolic event.

Reinitiation of OI and/or PCP Prophylaxis
Twenty-two children experienced a total of 26 safety events meeting the criteria for discontinuation of active study participation and possible reinitiation of OI and/or PCP prophylaxis. One subject had 3 study events and 2 patients each had 2 events. Of the 26 safety events, 16 were decreases in CD4+ cell percentages to <15%, 4 were discontinuation of antiretroviral therapy, 3 were uses of disallowed medications, and 1 was a second SBI. Two subjects experienced a new CDC category C diagnosis event, ie, 1 proven Herpes simplex esophagitis and 1 Hodgkin’s lymphoma.

HAV Vaccine Response and Relationship to Risk of SBIs
Patients were evaluated to determine whether baseline and week 32 anti-HAV antibody responses could be used as surrogate markers of risk for development of a SBI. Of the 227 subjects who were vaccinated at baseline and underwent anti-HAV antibody measurements, 221 received 2 doses of vaccine. The majority of patients (74%, 169 of 227 patients) were seronegative (<20 mIU/mL) at entry. There were no grade 3 or 4 adverse events related to HAV vaccination.

Although the SBI incidence rate among week 32, postvaccine, HAV-seronegative patients was high (18.8 events per 100 person-years), the 95% CI was wide (95% CI: 2.21–65.65 events per 100 person-years) and overlapped with that of week 32 HAV responders. There was a marginally significant difference (Fisher’s exact test, $P = .067$) in the proportions of children who developed SBIs according to whether they were low responders (>20 mIU/mL to <250 mIU/mL) or nonresponders to HAV vaccine or had a high-titer response to HAV vaccine. Cox regression analyses showed that baseline anti-HAV antibody status was not statistically significantly associated with the time to development of a SBI. A landmark Cox regression analysis showed no association between the risk of developing a SBI and anti-HAV antibody responses at week 32 (low responders versus high responders).

DISCUSSION
Current pediatric HIV treatment guidelines suggest that patients should receive PCP prophylaxis indefinitely when their CD4+ cell percentage falls below 15%. However, data for adults suggest that immune reconstitution after HAART allows for the discontinuation of OI and/or PCP prophylaxis. The results of this study reveal that OI and/or PCP prophylaxis can be discontinued safely for HIV-infected children who demonstrate immune reconstitution (CD4+ cell percentage of >15%) while receiving stable antiretroviral therapy. There were no associations between developing a SBI and gender, race/ethnicity, age, PI use, or CD4+ cell percentage at study entry or during the follow-up period. Before entry, proven or presumed pneumonia and sepsis accounted for >75% of all SBIs in this cohort. After study entry, these 3 diagnoses accounted for 100% of SBIs noted. There were 20 SBI events observed among 19 subjects, resulting in an incidence rate of 3.66 SBIs per 100 person-years. All of the pathogens isolated during the study follow-up period were typical pediatric pathogens (Table 3).

The background SBI event rates (all proven bacterial infections and presumed bacterial pneumonia) observed for subjects enrolled in PACTG 254 (immunologically similar to the target population for PACTG 1008) were 3.25 events per 100 person-years (95% CI: 1.31–6.71 events per 100 person-years) for children <6 years of age and 2.67 events per 100 person-years (95% CI: 1.07–5.50 events per 100 person-years) for children ≥6 years of age (W. Dankner, personal communication). Although PACTG 254 and PACTG 1008 SBI event rates were similar, PACTG 254 participants were still receiving OI and/or PCP prophylaxis therapy when they developed immune reconstitution thresholds similar to the levels chosen for entry into PACTG 1008. SBI rates among uninfected children range from 3 to 4 pneumonia events per 100 person-years to 72 cases of invasive pneumococcal bacteremia per 100 000 person-years. In 2003, the rates of invasive pneumococcal disease were 15.9 cases per 100 000 person-years for children 2 to 18 years of age.

The demographic features of patients who entered this study were consistent with the demographic features of the pediatric HIV epidemic in the United States. Historical immunologic data for these patients showed that the study sample represented children who had experienced weakened immune function before coming into the study but eventually showed evidence of immune competency (mean CD4+ cell percentage of 32%) at study entry. Although the presumed pneumonias often did not have a pathogen identified, one could make the argument that these pathogens should be similar to those seen for community-acquired pneumonia, with pneumococci being the leading offenders. We did not investigate how many of these patients had been given pneumococcal polysaccharide vaccine, but we do know that few, if any, would have received the pneumococcal conjugate vaccine because of the timing of this study (before licensure).
It is possible that responses to a neoantigen, such as HAV vaccine in this study, could serve as a surrogate marker of functional immune reconstitution and help predict which patients are at higher risk of developing a SBI despite numerical immune reconstitution. In our sample, there was no statistically significant association between responses to HAV vaccine and the development of a SBI. Perhaps if there had been more SBI events, for evaluation of a larger sample given HAV vaccine, or if we had measured antibody responses 4 weeks after the first vaccine dose given at baseline and correlated the risk of subsequent SBI with these results, we might have observed an association with the response to a neoantigen as a marker of risk for SBI after discontinuation of OI and/or PCP prophylaxis. Alternatively, HAV vaccine response might not be a good marker of increased risk of SBIs.

No PCP or MAC events were observed during the study. PCP was considered unlikely by the treating physicians, because no evaluations for PCP or institution of therapy for PCP occurred with any of the presumed pneumonia events.

A few patients were prematurely removed from this study, including 25 subjects who were lost to follow-up monitoring (because of site closure for 4 patients) and 16 subjects whose CD4+ cell percentages fell to <15%. Similar trends were observed in PACTG 219/219C (the pediatric late outcomes protocol), in which only a small proportion (16%) of 255 participants who started PI-based therapy with CD4+ cell percentages of ≥25% exhibited declines within 3 years to <25%.[25] In our study, only 2 patients developed new CDC category C diagnoses, and 2 patients died as a result of non-SBI-related events.

This study has implications for the care of HIV-infected children. Our analyses suggest that discontinuation of OI and/or PCP prophylaxis for children who demonstrate immune reconstitution does not lead to excessive rates of SBIs. The SBIs that occurred were associated with typical pediatric conditions (proven or presumed pneumonia and sepsis) and pathogens (H influenzae, pneumococci, and streptococci). Although the study was not powered to address specifically the risk of discontinuation of OI and/or PCP prophylaxis, the actual PCP rate in this prospective observational study was quite low (no events among all participants; among 129 subjects definitively known to have had an historical CD4+ cell percentage of <15%, 95% CI of 0–1.2 events). These data, combined with adult data, support the very low risk of a PCP event after discontinuation of OI and/or PCP prophylaxis for children who have achieved immune reconstitution.

This study has several limitations. Plasma HIV RNA concentrations are known to influence the risk of OIs independently of CD4+ cell counts and CD4+ cell percentages. Plasma HIV RNA specimens were collected but have not yet been analyzed. A case-control study using these data and cryopreserved specimens collected during the study is planned for the future.

It is possible that there was an overdiagnosis of SBIs on the basis of clinical criteria for presumed pneumonia. In fact, only 4 patients had positive blood cultures. The other 16 subjects with abnormal chest radiographs could have had pneumonias attributable to viral or other nonbacterial pathogens.

However, the basis for determining sample size and whether withdrawal of OI and/or PCP prophylaxis would result in increased morbidity rates for HIV-infected children involved data from PACTG 254. That study, like ours, used the same outcome measures for SBIs, such as presumed pneumonia. Exploration of factors potentially influencing the occurrence of SBIs was limited by the small number of SBIs, which did not allow for multivariate analyses and restricted the power of the study to detect differences other than very large differences. However, the favorable data from prospective adult studies[14–17] and the generally low rates of disseminated MAC among children, compared with adults, support the safety of discontinuing prophylaxis for this OI in pediatric populations.

CONCLUSIONS

This prospective study suggests that OI and/or PCP prophylaxis can be withdrawn safely for HIV-infected children >2 years of age who demonstrate recovery of CD4+ T cells while receiving antiretroviral therapy. The results of this study should be considered during the development of future guidelines regarding the treatment of HIV-infected children with immune reconstitution. Additional work must be performed by using responses to neoantigens as surrogate markers of immune reconstitution for assessment of functional immune reconstitution.

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REFERENCES


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