Long-term Experience With Combination Antiretroviral Therapy That Contains Nelfinavir for up to 7 Years in a Pediatric Cohort

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ABSTRACT

OBJECTIVE. We sought to provide long-term data on the clinical, immunologic, and virologic response to highly active antiretroviral therapy in infants and children who are naive to protease inhibitors.

METHODS. HIV-1–infected children who were naive to protease inhibitors were treated with a combination of nelfinavir and 2 nucleoside reverse transcriptase inhibitors (stavudine and lamivudine) in an observational, prospective, single-center study. Virologic failure-free survival was assessed by Kaplan-Meier analyses. The increase in CD4⁺ T cells during follow-up was estimated with a generalized linear model incorporating repeated measurements.

RESULTS. Thirty-nine HIV-1–infected children were included and followed for a median period of 227 weeks (interquartile range: 108–275 weeks). The virologic failure-free survival rate was 74%, 66%, 58%, and 54% after 48, 96, 144, and 240 weeks, respectively. Children who experienced virologic failure in 48 weeks (or 96 weeks) were younger at baseline compared with the responders (0.8 vs 5.3 years). Eighteen children remained on the regimen for >5 years. All children, including the nonresponders, showed a sustained immunologic response. Grades 3 to 4 toxicity was observed in 2 patients only. Eleven developed clinically evident lipodystrophy.

CONCLUSION. Combination therapy can be used safely in infants and children over a long period. Young age is strongly associated with virologic failure. Although the virologic response declined, immunologic parameters and clinical improvement were sustained up to 7 years, at the expense of lipodystrophy.
SINCE THE FOOD and Drug Administration approval of nelfinavir, indinavir, and ritonavir for children in 1997, the first trials in a limited number of children showed virologic and immunologic improvement.\textsuperscript{1–3} Mortality, disease progression, and hospital admissions in HIV-infected children have declined substantially since the introduction of highly active antiretroviral therapy (HAART), just as has been seen in adults.\textsuperscript{4–6} In adults, it was shown that most patients had changed their first regimen after 4 years of HAART because of virologic failure and the availability of alternative drug regimens. In adults, a continued increase in CD4\textsuperscript{+} T cell count was seen in patients who experienced sustained virologic suppression.\textsuperscript{7,8} However, one cannot extrapolate results in adults to children because of differences in immunity (e.g., the immaturity of the immune system and larger thymic output); in pharmacokinetics and pharmacodynamics of antiretroviral drugs in infants and children; and, most important, in formulation, availability of drugs, and strict adherence to therapy. Studies have shown that the age-adjusted CD4\textsuperscript{+} T-cell numbers increase in infants and children, especially in the more immunocompromised ones, even when failing in viral suppression.\textsuperscript{9} Despite reasonably good virologic response rates at 48 and 96 weeks of HAART, data from several pediatric studies have shown that the virologic response in children is less prominent compared with adults.\textsuperscript{1,3,9–14}

Infants and children often start antiretroviral therapy at very young ages and have to use their medication lifelong. Hence, there is an urgent need for more long-term data on virologic, immunologic, and clinical response to HAART in children. The rationale for this study was to evaluate the long-term virologic; immunologic; and clinical; especially growth, effectiveness, and safety of a combination antiretroviral therapy that contains nelfinavir, lamivudine, and stavudine in children who were included in the Pediatric Amsterdam Cohort on HIV (PEACH).

METHODS

Patients

The PEACH was established in 1992 when antiretroviral therapy became available for children. Current American and European treatment guidelines for HIV-1 infection in children recommend the use of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor.\textsuperscript{15,16} According to the history of antiretroviral therapy, some children in PEACH had initially been treated with azidothymidine (AZT), followed by AZT combined with dideoxynosine (ddI) or dideoxycytidine (ddC), until the introduction of nelfinavir (NFV) as the first PI available for children. Because of the previous use of certain NRTIs, NFV was combined with stavudine (d4T) plus lamivudine (3TC). Between September 1997 and January 2005, a prospective, observational study was performed. Inclusion took place until January 2002. Until then, of the 48 children in follow-up, 39 children were included in the study using the NFV-containing treatment regimen. HIV-1–infected children were eligible when they were aged 3 months to 18 years and had a plasma viral load (pVL) of >5000 copies per mL (mean of 2 measurements in <4 weeks) and/or CD4\textsuperscript{+} T cell counts <1750/μL for those who were younger than 1 year, <1000/μL for those who were between 1 and 2 years, <750/μL for those who were between 3 and 6 years, and <500/μL for those who were older than 6 years. Previous exposure to AZT, ddC, or ddI was allowed. There were no restrictions with regard to ethnicity, gender, route of HIV acquisition, or disease stage. Nine children were excluded because they did not meet the inclusion criteria. Five were immunologically stable and did not start any antiretroviral therapy. Four children in the cohort started another regimen during the inclusion period. The Medical Ethical Committee of our institute approved the protocol. Parents or caregivers gave written informed consent.

Medication

Patients received d4T (1 mg/kg twice daily as oral solution or capsules) plus 3TC (4 mg/kg twice daily as liquid formulation or tablets) plus NFV (30 mg/kg 3 times daily or 45 mg/kg twice daily as pediatric formulation [50 mg of NFV per gram of powder or as tablets]).\textsuperscript{17} Children who were able to swallow capsules received the NFV tablets, and smaller children were using the NFV powder dissolved in water or milk or crunched tablets in some custard. Dosage adjustments were performed according to the weight of the children and, in case of NFV, consecutive plasma levels. It was recommended that the children take their regimen with food.

Protocol

At each visit, physical examination was performed, including weight, length, and head circumference measurements. The same 2 physicians clinically diagnosed lipodystrophy during the study. Independent scorings were made and were considered clinically evident when both agreed. Blood was drawn before; at 1 and 2 weeks; and 1, 2, and 3 months after initiation of HAART and every 3 to 4 months thereafter. At each visit, NFV levels were analyzed to adjust dosing when necessary.

Lymphocyte subsets were analyzed with the FACScan (Becton Dickinson Immunocytometry Systems, San Jose, CA). Age correction for CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells was done by dividing the counts by the mean of an age-matched healthy control group.\textsuperscript{18} From 1997 to 2000, pVL was measured routinely using NucliSens HIV-1 QT (bioMérieux, Boxtel, Netherlands) with a lower limit of quantification (LLQ) of 400
copies per mL. From 2001 to 2005, pVL was measured using Versant HIV-1 bDNA 3.0 (Bayer, Mijdrecht, Netherlands) with an LLQ of 50 copies per mL (input 1 mL of plasma).

Virologic failure was defined as 2 consecutive pVL >1000 copies per mL after a pVL <400 copies per mL. Patients who never reached a pVL <400 copies per mL were defined as failing at the first measurement that was higher than the previous one after an initial decline in pVL (pVL nadir).

Adverse events were recorded during the study period and defined as any clinical sign or symptom or meaningful laboratory test abnormality that was possibly or probably related to the study medication, excluding HIV-related disorders. The National Institute of Allergy and Infectious Diseases (Division of AIDS) toxicity table was used for grading severity of pediatric adverse events. Parents were asked for the presence of anamnestic adverse events at every visit.

We analyzed the growth of the children by means of the z scores (standard normal deviation) of height and length. These scores were calculated with the use of the Growth Analyser 2.0 software (Dutch Growth Foundation, Rotterdam, Netherlands) using Dutch reference values.

Statistics

The primary outcome measure was virologic failure-free survival, which was assessed using Kaplan-Meier analysis. Censoring was applied when the last patient visit or a switch to a simplified regimen occurred before virologic failure. The secondary outcome measures were factors that were associated with virologic failure, changes in CD4+ and CD8+ T cells over time, changes in growth parameters (weight, height) over time, and reported adverse events. The mean age-adjusted CD4+ and CD8+ T cells (age correction for CD4+ and CD8+ T cells was done by dividing the counts by the mean of an age-matched healthy control group), and height and weight z scores were modeled using a mixed model that incorporated repeated measurements. This model handles missing data adequately by estimating the outcome given a specific covariate structure. The estimates of a specific level of the fixed effects were modeled using the “first order autoregressive” approach. Differences in these estimates between different levels of the variable were tested for significance using t statistics. Success or failure of treatment after 24 weeks was added to all models as a time-dependent variable.

Where subgroups of patients are compared, the differences between groups were evaluated using the Fisher’s exact test for categorical data and the Kruskal Wallis test for continuous data. All statistical analyses were performed using SPSS for Windows version 11.5 (SPSS, Chicago, IL). A 2-sided P < .05 was considered statistically significant.

**RESULTS**

All 39 HIV-1–infected children who started antiretroviral treatment with d4T, 3TC, and NFV between September 1997 and January 2002 were included in the present analyses. Baseline characteristics are shown in Table 1. Sixteen (41%) children had been pretreated with 1 or 2 NRTIs (AZT, ddI, or ddC) for a median of 179 weeks before enrollment (interquartile range [IQR]: 104–310 weeks). The median age of the children at baseline was 4.7 (1.1–8.8) years.

<table>
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<tr>
<th>TABLE 1 Baseline Characteristics of Children Who Started With NFV-Containing Regimen and Comparison Between Pretreated and Antiretroviral-Naive Children</th>
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<td>Total</td>
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<td>CD4+ T cells, median (IQR), abs per μL</td>
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<td>HIV-1 RNA, median (IQR), log copies per mL</td>
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<td>Height for age, median (IQR)</td>
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CDC-C indicates HIV pediatric classification by the Centers for Disease Control and Prevention. MMWR 1994;43:1–19; MTCT, mother-to-child transmission; abs, absolute number.
4.7 years (IQR: 1.1–8.8 years). Thirty-four (87%) children acquired HIV infection perinatally from their HIV-infected mother, 16 (41%) children presented with Centers for Disease Control and Prevention C classified AIDS-defining symptoms. The majority (69%) of the children were black (African/Surinamese), whereas 18% were white, 10% were mixed/Caribbean, and 3% were Asian. The children were on study medication for a median duration of 185 weeks (IQR: 69.5–264.9 weeks).

The study medication had to be discontinued in 26 (69%) children during the follow-up for the following reasons: virologic failure (n = 16), major toxicity (n = 2; diabetes and high cholesterol, both with complete recovery), poor palatability and refusal (n = 1), and switch because of simplification of therapy (n = 4). Although routinely assessed, other grades 3 to 4 toxicity adverse events were not reported. Three were lost to follow-up. One child initially started with the study medication, but nevirapine was added to the regimen because of a very high pVL (>5 x 10^6 copies per mL), but once HIV-RNA reached undetectable levels, NFV was stopped after 20 weeks.

**Virology**

At baseline, the median pVL for the whole group was 4.9 log_{10} copies per mL (IQR: 4.4–5.4 log_{10} copies per mL). There was no significant difference between the naive and pretreated patient groups. The median time to reach undetectable pVL was 7.6 weeks (IQR: 2.2–12.6 weeks).

Of the patients for whom therapy failed or study medication was discontinued at any time during the follow-up of 240 weeks (n = 29), 7 never had a pVL below the LLQ. These were young (median age: 0.7 years; IQR: 0.3–1.0 years). Of the remaining 32 children (median age: 5.3 years; IQR: 3.0–9.4 years) in this observational cohort, 22 showed a rebound of their pVL after having had a period of viral suppression below the LLQ. Eight of 22 patients whose pVL had become undetectable during treatment but were subsequently failing did so in the first year of therapy (Table 2). Children who experienced virologic failure at 48 and 96 weeks on HAART after an initial period of successful virologic suppression were younger at the start of HAART compared with those without virologic failure (median: 0.8 vs 5.3 years at 48 weeks [P = .003] and 1.0 vs 4.8 years at 96 weeks [P = .098]; Fig 1).

Sixteen children with virologic failure continued study medication after failure occurred for a median period of 3.3 years (range: 0.3–6.5 years). Reasons to continue the failing antiretroviral regimen were the presence of stable CD4^+ T cell counts and a stable clinical condition without any deterioration. All patients had stopped trimethoprim-sulfamethoxazole prophylaxis. These children had developed antiretroviral drug resistance mutations, and alternative drugs were not available at that time. Later, appropriate switches to second-line HAART regimens could be made successfully.

**Immunology**

At baseline, the median CD4^+ T cell count for the total study population was 470/μL (IQR: 140–850/μL) and adjusted for age (0.33; IQR: 0.08–0.51). In relative terms, to the total number of lymphocytes, the CD4^+ T cell percentage was 17% (IQR: 11–23%). The baseline CD4^+ T cell percentage was significantly lower in children who were pretreated (15%) compared with children who had not received previous antiretroviral medication (20%). The median CD8^+ T-cell counts for the total study population was 1230/μL (IQR: 750–1980/μL) and adjusted for age (1.2; IQR: 0.8–1.9).

The median age-adjusted CD4^+ T-cell counts demonstrated an increase in the first 48 weeks of treatment (Fig 2A), which was similar for the children who had a virologic failure and those who had not (P = .95; Fig 2A, insert). The age-adjusted absolute CD8^+ T-cell counts and the CD8^+ T-cell percentage demonstrated a slight but nonsignificant decrease in the total study population as well as in the subgroups on the basis of virologic response (Fig 2B).

| TABLE 2 | Number of Patients on HAART, Virologic Response and Failure, Reasons to Stop, and Lipodystrophy |
| Weeks After Start | 0 | 24 | 48 (1 y) | 72 | 96 (2 y) | 144 (3 y) | 192 (4 y) | 240 (5 y) | 288 (6 y) | 336 (7 y) |
| No. of children on NFV-containing HAART | 39 | 38 | 34 | 32 | 30 | 27 | 22 | 18 | 8 | 5 |
| No. with success | 32 | 26 | 22 | 19 | 14 | 11 | 10 | 5 | 2 |
| No. after failure | 6 | 8 | 10 | 11 | 13 | 11 | 8 | 3 | 3 |
| Reason to stop | | | | | | | | | | |
| Virologic failure | 1 | 1 | 1 | 5 | 2 | 5 | 1 |
| Lost to follow-up | | | | | | | | | | 3 |
| Grade 3 or 4 toxicity | 1 | 1 |
| Switch therapy* | 2 | 1 | 1 |
| Intolerance | 1 |
| Lipodystrophy | 1 | 2 | 3 | 5 |

*While undetectable, simplification.
Disease Progression and Toxicity

None of the children developed an AIDS-defining illness or died while on study medication. Clinically evident lipodystrophy was seen in 11 (28%) children after a median of 49 months (range: 10–83 months): 9 with lipoatrophy; of these 9 children, 2 in combination with an adipose trunk (1 of these 2 was pretreated extensively for 305 weeks and developed lipodystrophy within the first year of HAART) and 2 in combination with a buffalo hump; of 2 additional children out of the 11, 1 with a solitary adipose trunk and 1 with a solitary buffalo hump. In 2 of these 11 children the pVL stayed undetectable for 7 years; the others failed due to nonadherence.

Growth and Development

Growth parameters are shown in Fig 3. The median height-for-age z score at baseline for the total study population was −1.08 (IQR: −2.26 to −0.58), and the median weight-for-height z score was −0.28 (IQR: −0.99 to 0.48). There were no statistically significant differences between naive and pretreated children at baseline.

After the first year of HAART, the height-for-age z scores gradually increased to a plateau but never reached the mean of the general mixed Dutch population, which by definition is 0 (Fig 3A). Height for age was significantly higher than baseline from week 96 onward. In the first year of HAART, there was a remarkable increase in weight-for-height z scores. The increase was seen mainly in the first 24 weeks after the start of HAART from median −0.3 to 0.5 (Fig 3B). Comparing virologic responders and nonresponders during follow-up, we did not observe significant differences in height-for-age z score and weight-for-height z scores with regard to baseline results over time (P = .50 and P = .57, respectively).

DISCUSSION

We demonstrated in the present analyses that a NFV-containing regimen for up to 7 years is feasible and effective to some extent. Of the 39 included patients, 18 were on the initial regimen after a follow-up of 240 weeks (≈5 years) and 5 after 336 weeks (≈7 years). The virologic failure-free survival rate at 5 years of follow-up was 54%. All children showed an adequate increase in CD4 cells, regardless of virologic failure. The frequency of reported grades 3 to 4 adverse events was low. After start of HAART, the growth of these children slowly but progressively improved.

The reported virologic response rate did not differ
from other studies in children.9–12,19–22 Studies on NFV in combination with 2 NRTIs have shown viral response rates (intention-to-treat) of 69% at <400 copies per mL and 44% at <50 copies per mL and, when combined with an additional nonnucleoside reverse transcriptase inhibitor, ~80% at <400 copies per mL and 63% at <50 copies per mL after 48 weeks, respectively.10,11,22 Our study population is small (n = 39), but the follow-up of this cohort using NFV-containing HAART is over an extended period of time.

Children with virologic failure at 48 and 96 weeks were younger at the start of HAART. The relation between virologic failure and age at start of HAART was reported earlier by Walker et al.13 One explanation could be that younger children were initially dosed for NFV according to the manufacturer's instructions, which turned out to be too low.17,23,24 However, drug levels in these young children were not very low to absent, and recent data from the 2NN study group (the regimen contains 2 nonnucleoside reverse transcriptase inhibitors) in adults suggest that drug levels in therapy-adherent patients have a poor sensitivity to predict virologic failure.25 This may hold true for pediatric cohorts as well. A recent analysis indeed demonstrated early viral decay rates in HIV-infected children starting with HAART with a median of 2.1 days (IQR: 1.8–3.0 days), similar to adults.26 Importantly, there was no difference in baseline pVL between the treatment-naive and pretreated children. This makes a biological basis for the relation between age and virologic failure unlikely and makes non-

FIGURE 2
A, Age-adjusted CD4+ T-cell count during 240 weeks of follow-up on HAART. Follow-up of all patients during treatment with NFV-containing regimen. Inset, A comparison is shown between children with undetectable pVL and children whose therapy failed. No difference over time was found between the groups. Interaction term (time \( \times \) virologic success), \( P = .9 \). Bars indicate standard errors of the mean (SEM). B, Age-adjusted CD8+ T-cell count during 240 weeks of follow-up on HAART. Follow-up of all patients during treatment with NFV-containing regimen. Inset, A comparison is shown between children with undetectable pVL and children whose therapy failed. No difference over time was found between the groups. Interaction term (time \( \times \) virologic success), \( P = .9 \). Bars indicate SEM.
adherence probable as an explanation for virologic failure at very early age.

Immune reconstitution occurred irrespective of virologic response, indicating that HIV-1–infected children have a greater capacity to sustain lymphocyte numbers compared with adults, even in the presence of virologic failure. Studies in adults have demonstrated that restoration of functional immunity correlated with increases in the number of naive T cells, reflecting a critical role of the thymus. Because of an intact thymus, children have a greater capacity to restore immunity as indicated by their rapid CD4+ T-cell recovery on initiation of HAART.

At baseline, there was no significant difference in growth-related parameters (height for age, weight for age, and weight for height) between naive and pre-
treated children. Whereas Chantry et al^10 demonstrated the short-term beneficial effect of NRTIs on height, weight, and head circumference, in our cohort, the pre-treated children had not profited in this respect from the previous use of antiretroviral therapy. In the first year on HAART, there was a remarkable increase in weight-for-height z score.

With respect to toxicity, only 2 patients had to stop the study medication because of adverse events (diabetes and high cholesterol). However, long-term follow-up demonstrated a high prevalence of lipodystrophy, especially in children with longer use of the study medication, as was recently reported in children by Sanchez Torres et al^11 as well. We already observed clinically evident lipodystrophy in 8 of the 11 children after 4 years of therapy only. Although more objective measures for body composition and lipodystrophy are warranted, the rapid increase in weight-for-height z scores within 24 weeks makes an early development of lipodystrophy unlikely and suggests possible drug-related effects at a different level. Additional studies have to investigate whether an altered metabolism or energy expenditure may explain our finding in pediatric patients, as recently suggested by a study of PIs on protein catabolism.^12,13 HIV infection may interfere with sexual maturation and the onset of puberty.^34 This could influence especially the growth velocity. However, in our cohort, the median age at start of HAART was 4.7 years (IQR: 1.1–8.8 years); leaving out the oldest quartile from the analysis, similar growth parameters were obtained (data not shown). Although the contribution of d4T to the development of lipodystrophy is not yet clearly proved, we have to consider that the combined use of d4T and NFV may have played an important role in the high prevalence of lipodystrophy in our cohort.

HIV itself and endocrinologic and immunologic factors in combination with social environment all may contribute to the growth-related phenomenon. No relevant alteration in endocrinologic parameters was found in previous studies. Protease-containing regimens have demonstrated a more profound effect on growth, especially in children who reached undetectable pVL and in those with advanced disease at baseline. Growth was independent of virologic success in our cohort.

**CONCLUSIONS**

We have demonstrated that an NFV-based HAART regimen can be given safely over a long period of almost 7 years. Although the criteria of when to start HAART have changed over time, the clinical implications of our findings on a strong association between young age and virologic failure are important. In light of our data and recent discussion on clinical practice and regimen switches, when to start with HAART in young children remains unclear and may be reconsidered.

Given the high virologic failure rate at young age observed in our cohort and the high prevalence of lipodystrophy, one should address questions about adherence, long-term exposure to HAART, and adverse effects when considering early initiation of HAART in children. Once treatment has been decided on, it needs to be investigated whether there is a role for directly observed therapy to improve and guarantee both adherence and virologic success.

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