Clinical and virologic response to combination treatment with indinavir, zidovudine, and lamivudine in children with human immunodeficiency virus-1 infection: A multicenter study in The Netherlands

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Objective: To evaluate the clinical, immunologic, and virologic response to indinavir, zidovudine, and lamivudine in children with human immunodeficiency virus-1 (HIV-1) infection.

Study design: Twenty-eight HIV-1–infected children (3 months to 16 years of age) with or without prior treatment with reverse-transcriptase inhibitors and a HIV-1 RNA >5000 copies/mL and/or a CD4 cell count less than the lower limit of the age-specific reference value were treated with indinavir, zidovudine, and lamivudine. Pharmacokinetics of indinavir were determined in each child.

Results: The combination treatment was well tolerated in the majority of patients. Clinical improvement was seen in all patients. After 6 months of therapy, 70% of the patients had an HIV-1 RNA load below 500 copies/mL, whereas 48% of the children had a viral load below 40 copies/mL. Relative CD4 cell counts in relation to the lower limit of the age-specific reference value increased significantly from a median value of 79% at baseline to 106% after 6 months of therapy. The doses of indinavir necessary to achieve area under the curve values comparable to adult values varied from 1250 mg/m^2/d to 2450 mg/m^2/d.

Conclusions: Highly active antiretroviral therapy consisting of indinavir, zidovudine, and lamivudine in children reduced HIV-1 RNA to less than 500 copies/mL in 70% of the children within 6 months. Improved CD4 cell counts were observed in most patients, as was a better clinical condition (no invasive or opportunistic infections, increased weight gain). Side effects of the triple therapy were mild. Highly active antiretroviral therapy can be used as successfully in children as in adults. (J Pediatr 2000;136:780-8)

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Since its introduction in 1996, combination therapies that include 2 reverse-transcriptase inhibitors and a protease inhibitor have rapidly become standard therapy for adults with human immunodeficiency virus-1 infection.[1] However, data on efficacy of these combinations in children with HIV-1 infection are limited and are derived from studies with small numbers of children. The relative immaturity of the immune system, differences in pharmacokinetics and pharmacodynamics of antiviral drugs, and specific

issues concerning adherence to therapy complicate the extrapolation from therapeutic results in adults to those in children.

Recent studies in children with HIV infection treated with a combination of 2 reverse-transcriptase inhibitors showed superior results as compared with monotherapy.[2-12]

Alternatively, monotherapy with the protease inhibitor indinavir resulted in marked, but only temporary, reductions of viral load in antiretroviral therapy naive and experienced adult patients, as well as in children.[13,14]

Several small observational and retrospective studies reported that triple therapy including a protease inhibitor may be as effective in pre-treated HIV-1–infected children as in adults, as shown by a decrease of viral load and an increase of CD4 cell count similar to those in adults who had previously received antiretroviral therapy.[4,15-20] The measurement of these 2 surrogate markers has largely become the basis for the prediction of clinical and virologic response in adults.[21] Plasma HIV-1 RNA levels and CD4 lymphocyte counts are also independent predictors of the clinical course in HIV-infected infants and children.[6]

Here we report the results of the initial 6 months in a prospective, open, uncontrolled, Dutch multicenter study, which evaluates the clinical, immunologic, and virologic response to combination therapy with indinavir, zidovudine, and lamivudine in children with HIV-1 infection.

METHODS

Inclusion and Exclusion Criteria

Children between the ages of 3 months and 18 years were eligible for enrollment. Children were included when the plasma HIV-1 RNA test result was positive on 2 subsequent occasions (children <18 months old) or when the HIV serology was positive (children >18 months old) in the presence of one of the following abnormal test results: a mean HIV-1 viral load of >5000 copies/mL (mean of 2 measurements with <4 weeks in between) and/or CD4 cell counts <1750/mm^3 for those below 1 year of age, <1000/mm^3 for those 1 to 2 years of age, <750/mm^3 for those 3 to 6 years of age, and <500/mm^3 for those more than 6 years of age.[22] Patients were excluded if they had been treated with antiviral agents other than zidovudine and/or didanosine or zalcitabine. There were no restrictions with regard to sex, ethnicity, or route of acquisition of HIV-1 infection.

Protocol

The study protocol was approved by the medical ethical committees of all the participating centers. Written informed consent was obtained from parents or legal guardians. Blood samples were taken twice before triple therapy was started (4-2 weeks and 2-0 weeks before initiation of the study) for hematologic tests (hemoglobin, hematocrit, white blood cell count, differential blood cell count, platelet count), serum biochemical tests (sodium, potassium, calcium, albumin, hepatic enzymes, creatinine, urea, amylase, total bilirubin), serum immunoglobulin analysis (IgA, IgG, and IgM concentrations), and virologic and immunologic tests. The same tests were performed at days 7, 14, and 28 after initiation of triple therapy and after 2, 3, and 6 months. Urine was collected for analysis at all time points. At each visit, a physical examination was performed, weight and length were measured, and parents were asked about the presence of adverse events. Length-for-age scores and weight-for-length scores were determined by using the Dutch reference curves for age and sex.[23] These scores were also available for 21 children during their lives before highly active antiretroviral therapy (HAART) was started (hospital medical records and/or records from the school doctor or health center). We defined response of growth to treatment as catch-up growth to the original percentile or an end to the ongoing deviation in children with impaired growth (deviation from the original percentile of length-for-age score and/or weight-for-length score) at baseline. Lymphocyte subsets were analyzed with the FACSCount System (Becton Dickinson Immunocytometry Systems, San Jose, Calif).[24] Plasma HIV-1 RNA quantification was analyzed by an in vitro (polymerase chain reaction) test (most samples: Amplicor HIV-1 monitor test version 1.5 [Roche Diagnostic Systems] and a few samples: NASBA assay, nuclisen-sHIV-1 RNA [Organon Teknika, Boxtel, The Netherlands]) with a lower limit of detection of 500 and 400 copies/mL. If plasma HIV-1 RNA was below this lower limit, plasma samples were subsequently tested with a modified, ultrasensitive procedure that increases the analytical sensitivity of the Amplicor HIV-1 monitor test to a detection limit of 40 copies/mL.[25]

Medication and Pharmacokinetics

Medication was given in the following doses: indinavir, 400 mg/m^2 every 8 hours; zidovudine, 120 mg/m^2 every 8 hours; and lamivudine, 4 mg/kg every 12 hours. Indinavir was administered as standard capsules of 200 mg and 400 mg or as capsules of 150 mg and 300 mg, which were prepared at the pharmacy. When patients were too young to swallow capsules, indinavir capsules had to be opened by the caregivers and dissolved in 5 to 10 mL of water. In children in whom problems were encountered with the ingestion of indinavir, the drug was changed to nelfinavir (30 mg/kg every 8 hours). Zidovudine was administered either as syrup (10 mg/mL) or as capsules of 100 mg and 250 mg, depending on the child's age. Lamivudine was administered as syrup (10 mg/mL) or as tablets of 150 mg. The importance of taking the indinavir 1 hour before or 2 hours after meals was repeatedly emphasized. Parents received a list of low-fat food and drinks

Table I. Baseline characteristics of the study patients

Median age in years (range)	6.0 (0.3-16.6)
Sex (male/female)	14/13
Race/ethnicity	
Non-white	23
White	4
Route of acquisition	
Vertical	21
Blood products	4
Unknown	2
Clinical stage (CDC classification)*	
N1	2
N2	3
A1	3
A2	4
A3	4
B2	5
B3	1
C2	1
C3	4
No prior treatment	14
Prior treatment with	
Zidovudine	11
Zidovudine/zalcitabine	2
Median copies of HIV RNA/mL plasma (range)	127,500 (725-761,500)
Naive to antiretroviral therapy	210,000 (23,900-761,500)
Experience with antiretroviral therapy	23,250 (725-718,000)

*Clinical and immunologic categories as defined by the US Centers for Disease Control and Prevention (CDC).[32]

that they could give to their children in this period before and after the medication was given. A day-to-day medication scheme including the times when no fat-containing food or drinks were allowed was also given.

At day 28, patients were admitted to the day-care unit to determine the steady-state pharmacokinetics of indinavir. When a dosage adjustment of indinavir was necessary to normalize the area under the curve concentration (AUC) curve to adult values (20 mg/L/h, range 10-30 mg/L/h), this procedure was repeated.

Adherence

Drug adherence was assessed by interviews of the parents, by measurement of indinavir plasma levels, and by medication diaries, which were made for each child individually. When possible, children who were old enough were asked to apply stickers in their diaries every time they took their medication. These diaries were checked at every visit. When there were problems with adherence, coaching of parents and children was intensified.

In the analyses, poor adherence was defined in patients for whom interviews of the parents, medication diaries, and/or plasma levels of indinavir showed that serious problems (ie, more than one time) existed. Good adherence was defined in patients for whom interviews, medication diaries, and plasma levels of indinavir showed no problems.

Adverse Events

Adverse events were defined as any clinical sign or symptom, or meaningful abnormality in laboratory test, excluding disorders associated with HIV-1 infection. All adverse events were rated according to severity and relation to study drug.

Statistical Analyses

The primary measures of antiretroviral drug activity were the magnitude and duration of changes in plasma HIV-1 RNA and CD4 cell counts over a period of 6 months. One child dropped out of the study within 1 week and was lost to follow-up; the remaining 27 patients were included in the intention-to-treat analyses. In the determinations of the median change from baseline, viral loads of patients below the detection limit were considered to be 40 copies/mL. For occasional missing data in this intention-to-treat analysis, the last observation carried forward method was used to obtain viral loads. In 5.4% of the patients, one or more values at key time points (median, 1; range, 1-4) were missing. CD4 cell counts in relation to the lower limit of the age-specific reference value[22] were calculated by dividing the individual value at the different time points by the lower limit of the reference value. Changes in CD4 cell counts and viral load results were evaluated by using the Wilcoxon signed-rank test. The relations between the plasma HIV-1 RNA levels at month 6 and various characteristics (baseline viral load, prior treatment, adherence) were investigated by using multiple linear regression analysis for normally distributed data. In this analysis, both viral load results were logarithmically transformed, and allowed for the fact that various children at month 6 had an HIV-1 RNA load that was lower than the detection limit (ie, left-censored data).[26] All P values are 2-tailed.

RESULTS

Twenty-eight HIV-1–infected children were enrolled at 5 centers between April 1997 and July 1998. The

evaluation of the first 24 weeks is presented in this report. Baseline characteristics of the 27 children for whom follow-up data are available are presented in Table I. The median age of the children was 6.0 years (range, 3 months–16.6 years); 12 patients were not previously treated, and 15 had received prior treatment with nucleoside reverse-transcriptase inhibitors, mostly with zidovudine monotherapy for an average of 34 months (range, 8-118 months). The median HIV-1 RNA level was 127,500 copies/mL (range, 725-761,500 copies/mL). Eight children were too young to swallow capsules and received indinavir dissolved in water. Despite its bitter taste, 6 of these young children had no problems with adherence. Two other infants had problems with the administration of indinavir, necessitating a change to nelfinavir within 2 weeks after start of the therapy.

In 19 of 27 patients (70%), the dose of the indinavir had to be increased according to the pharmacokinetics to achieve AUC values between 10 and 30 mg/L/h. In 9 patients the dose had to be increased to 1500 mg/m^2/d, in 6 patients to 1800 mg/m^2/d, in 1 patient to 2000 mg/m^2/d, and in 2 patients to 2450 mg/m^2/d. In 7 patients 1250 mg/m^2/d was adequate. Because 2 patients were administered nelfinavir at day 28, no steady-state pharmacokinetics of indinavir were determined in these patients.

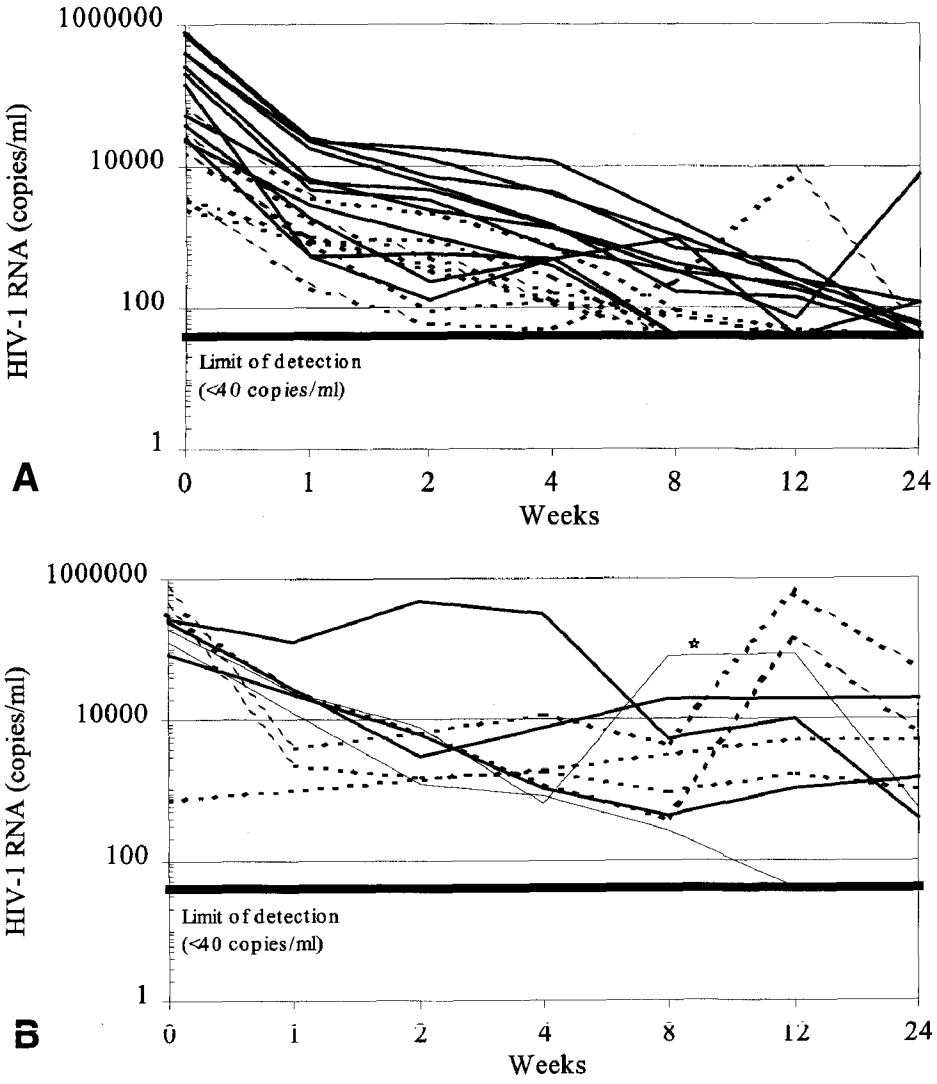

Fig 1. **A,** Levels of HIV-1 RNA in 18 patients who completed therapy without documented poor adherence. Note non-linearity of horizontal axis. Patients who had previously received antiretroviral treatment are represented by *dotted curves*. **B,** Levels of HIV-1 RNA of 7 patients with poor adherence and the 2 patients *(thin solid lines)* who switched to a different medication scheme within 2 weeks after start of therapy. One of the latter was also non-adherent (indicated by *star*). Patients who had previously received antiretroviral treatment are represented by *dotted curves*.

Clinical Findings

All patients improved in their overall condition as shown by increased activity, appetite, and well-being as reported by their caregivers. No serious invasive or opportunistic infections were seen. In 81% (17/21) of the children, deviation of the original percentile in the length-for-age and/or weight-for-length reference curve (5 children, deviation in the length-for-age curve; 2 children, deviation in the weight-for-length curve; and 10 children, deviation in both curves) was observed at baseline. A response (catch-up growth or the end of ongoing deviation) was seen in 76% (13/17) of these patients. None of the patients showed progression of their Centers for Disease Control and Prevention classification stage, and no acquired immunodeficiency syndrome (AIDS)–defining events occurred. Two patients were admitted to the hospital for a short period (10 days): one because of hematuria and vomiting and the other because of hematuria and hypertension.

HIV-1 Virologic Responses

Levels of HIV-1 RNA after start of HAART are demonstrated in Fig 1 according to adherence or change of medications. Table II shows the median changes of the viral load from baseline and the proportion of patients whose viral load levels decreased to <500 and <40 copies/mL in an intention-to-treat analysis.

Fig 2 shows scatter plots of the changes in viral load from baseline to month 6 of therapy according to adherence to therapy in all patients (panel *A*), therapy-naive children who had never had antiretroviral therapy (panel *B*), and previously treated children (panel *C*). Children with poor adher-

Table II. Virologic results

Weeks after start of treatment	Median change in viral load from baseline (range)*	Viral load <500 copies/mL	Viral load <40 copies/mL	Viral load <500 copies/mL in case of good adherence	Viral load <40 copies/mL in case of good adherence
1	Tot: −1.26 (−2.45 to +0.70) Na: −1.29 (−2.45 to +0.70) Exp: −1.24 (−2.25 to 0.00)	0%	0%	0%	0%
2	Tot: −1.69 (−3.05 to +0.26) Na: −1.76 (−3.05 to +0.26) Exp: −1.59 (−2.86 to 0.00)	0%	0%	0%	0%
4	Tot: −1.91 (−2.50 to +0.43) Na: −1.98 (−2.50 to +0.08) Exp: −1.90 (−2.44 to +0.43)	Tot: 33% (9/27) Na: 20% (3/15) Exp: 50% (6/12)	0%	Tot: 47% (9/19) Na: 25% (3/12) Exp: 86% (6/7)	0%
12	Tot: −2.63 (−3.56 to +0.85) Na: −2.96 (−3.56 to −0.35) Exp: −1.94 (−3.13 to +0.85)	Tot: 67% (18/27) Na: 80% (12/15) Exp: 50% (6/12)	Tot: 37% (10/27) Na: 33% (5/15) Exp: 42% (5/12)	Tot: 95% (18/19) Na: 100% (12/12) Exp: 86% (6/7)	Tot: 53% (10/19) Na: 42% (5/12) Exp: 71% (5/7)
24	Tot: −2.78 (−4.09 to +0.85) Na: −2.96 (−4.09 to −1.10) Exp: −1.94 (−3.24 to +0.85)	Tot: 70% (19/27) Na: 80% (12/15) Exp: 58% (7/12)	Tot: 48% (13/27) Na: 47% (7/15) Exp: 50% (6/12)	Tot: 95% (18/19) Na: 92% (11/12) Exp: 100% (7/7)	Tot: 68% (13/19) Na: 58% (7/12) Exp: 86% (6/7)

Tot, Total of the patients; *Na*, naive to antiretroviral therapy at baseline; *Exp*, experience with antiretroviral therapy at baseline.
*All *P* values < .001.

ence to therapy have less change in HIV-1 RNA load compared with those with good adherence. Throughout the range of baseline HIV-1 RNA loads, almost all patients with good adherence had an optimal response. In all pretreated patients with good adherence an optimal response was seen, and in all pretreated patients with poor adherence a suboptimal response was seen. However, 3 of the 5 patients with prior treatment and poor adherence had a high baseline viral load (median, 260,000 copies/mL; range, 725-718,000 copies/mL), whereas all pretreated patients with good adherence had a relatively low viral load (median, 43,985 copies/mL; range, 2,680-761,500 copies/mL). According to multiple regression analysis, the plasma HIV-1 RNA at month 6 did not significantly correlate with baseline viral load and prior treatment. In case of poor adherence to therapy, the median HIV-1 RNA load at month 6 was found to be 158-fold higher ($P < .001$) compared with patients with adequate adherence.

Although baseline HIV-1 RNA and the initial response until 2 months after the start of the therapy did not differ between children whose initial dose appeared adequate and those whose AUC values required an increase in dose, statistically significant differences ($P = .026$ and $P = .014$) were found 3 and 6 months after the start of the therapy.

CD4 Cell Counts

Fig 3, *A*, shows relative CD4 cell counts in relation to the lower limit of the age-specific reference value. In the whole group of 27 patients, the median relative CD4 cell count was 79% (range, 2%-250%) at the start of therapy and 69% (range, 2%-208%) after 1 month of therapy. After 3 months, there was an increase to a median of 82% (range, 4%-278%), and after 6 months, a significant ($P = .007$) increase to a median of 106% (range, 2%-266%) was seen. Fig 3, *B*, shows the absolute CD4 cell counts in 3 different age groups (<2 years, 2-5 years, and >5 years). The median absolute CD4 cell count of all patients was 0.61 (range, 0.01-4.99) at baseline, 0.52 (range, 0.01-3.19) after 1 month, 0.66 (range, 0.02-3.56) after 3 months, and 0.71 (range, 0.01-4.38) after 6 months of treatment ($P = .04$).

If patients with documented poor adherence were excluded, increases of CD4 cell counts were also not significant at time points before 6 months of therapy; after 1 month, the median relative CD4 cell count decreased from 74% (range, 2%-250%) before start of the therapy to 68% (range, 2%-208%). After 3 months, relative CD4 cell counts were 76% (range, 14%-278%) and after 6 months 106% (range, 40%-266%) ($P = .009$). Fig 3, *C*, shows the absolute CD4 cell counts in 3 different age groups (<2 years, 2-5 years, and >5 years). The median absolute CD4 cell count in these patients was 0.61 (range, 0.01-4.99) at baseline, 0.51 (range, 0.01-3.19) after 1 month, 0.64 (range, 0.07-3.56) after 3 months, and 0.78 (range, 0.2-4.38) after 6 months

of treatment (P = 0.05). In patients with documented poor adherence, no significant changes in CD4 cell counts were seen.

Adverse Events

Combination therapy was well tolerated by almost all children. In 2 children, medication had to be switched to another combination within 2 weeks after starting treatment with indinavir. This was done because of vomiting in one child and because of extreme dislike of the medication in another infant who could not swallow capsules. Five other patients had vomiting, 3 had nausea, 2 had diarrhea, and 4 patients had a skin rash. Three patients had loss of appetite, 3 patients loss of weight, and 3 patients hematuria, which resolved after discontinuing medication for 2 days and re-emphasizing the importance of adequate fluid intake. In total, 11 (41%) of the 27 patients studied had adverse events.

DISCUSSION

In this study the 24-week results of treatment of HIV-1–infected children with HAART consisting of indinavir, zidovudine, and lamivudine are reported. A good clinical response was seen in all children. No serious invasive or opportunistic infections occurred since the initiation of triple therapy. Impaired growth was seen in 81% of the children at baseline and responded to therapy in 76%. Abnormal growth seems to be one of the most sensitive indicators of disease progression in children; weight gain may be another indicator of efficacy of antiretroviral therapy.[27-30]

Our results show that HAART can be used as successfully in children as in adults, despite specific problems encountered in treatment of HIV-1–infected children (ie, possible differences in pharmacokinetics and pharmacodynamics between adults and children), the relative immaturity of the immune system in young children, and specific pediatric issues concerning adherence to therapy. Because we have observed substantial interindividual differences in the pharmacokinetics of indinavir in children (unpublished data), we propose to measure indinavir pharmacokinetics (and possibly also pharmacoki-

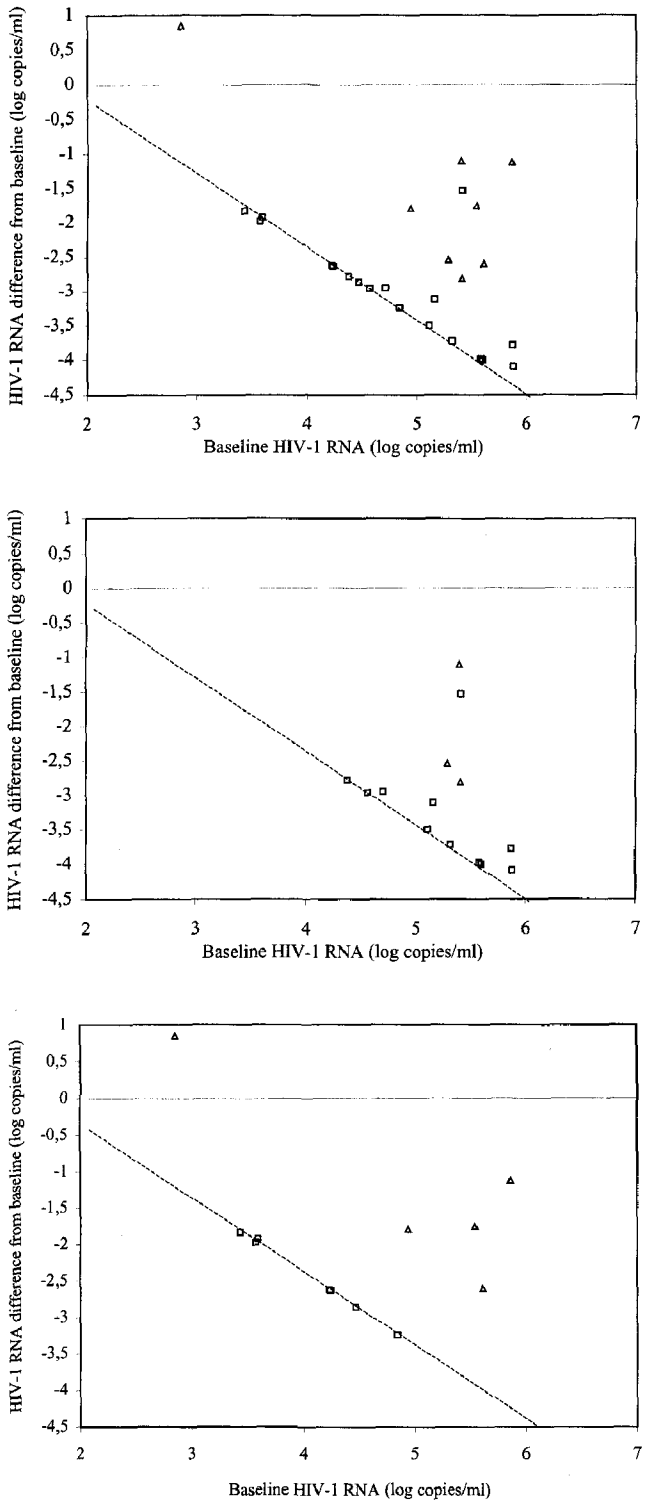

Fig 2. Change in HIV-1 RNA from baseline to month 6 versus baseline HIV-1 RNA in all patients **(A)**, naive patients **(B)**, and pretreated patients **(C)** according to poor adherence *(triangles)* and good adherence *(squares)* to therapeutic regimen. *Diagonal dashed line* represents maximal virologic response [y = log (40) − x].

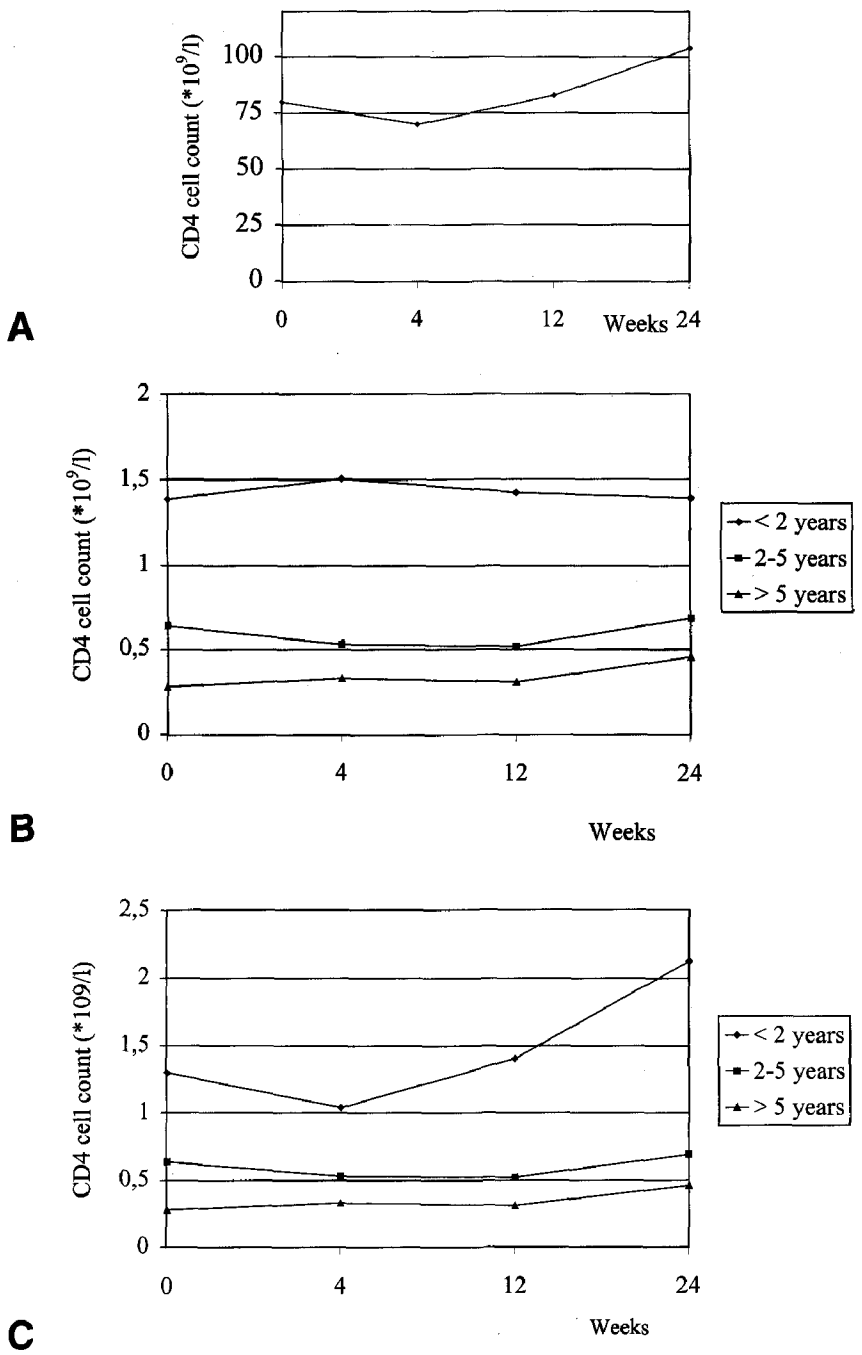

Fig 3. **A,** Median relative CD4 cell counts of all patients in relation to lower limit of age-specific reference value. **B,** Median absolute CD4 cell counts of all patients. Patients are divided into 3 groups in accordance with age-related differences in reference values. **C,** Median absolute CD4 cell counts of 19 patients who completed therapy without documented poor adherence. Patients are divided into 3 groups in accordance with age-related differences in reference values.

netics of other protease inhibitor drugs) to determine the individual dosage to result in an AUC that is comparable to adult values. Combination therapy reduced the plasma HIV-1 RNA load to <500 copies/mL in 70% of the children and to <40 copies/mL in 48% of the children within 6 months of therapy. After exclusion of patients with poor adherence, viral load reductions were observed to be reduced to <500 copies/mL in 95% of the patients at month 6 and to <40 copies/mL in 68% of the children at month 6. These results are comparable to results obtained in adults. Gulick et al[1] reported a decline of the viral load to <500 copies/mL in 90% of the patients at week 24 with the same HAART regimen. Our results are particularly reassuring considering the fact that no preselection of patients was made on the basis of expected problems with adherence. The virologic response rate in this study is better than that observed with a combination of zidovudine and lamivudine in children, that is, reduction of viral load to <500 copies/mL in only 46% of the patients after 6 months.[2] Indinavir alone produced less pronounced reductions in viral load than indinavir in combination with zidovudine and lamivudine, with a maximum decrease of 1.35 $\log_{10}$ after 24 weeks with a dosage of 1500 mg/m^2/d. These reductions could not be sustained, because after 8 weeks of indinavir monotherapy, viral load increased to approximately 0.5 $\log_{10}$ copies/mL below baseline.[14] Data from other studies with HAART consisting of a combination of a protease inhibitor and 2 reverse-transcriptase inhibitors in children are limited. With median declines of the viral load varying from 0.6 $\log_{10}$ to 2.3 $\log_{10}$ after 24 weeks of therapy, none of these studies describes a decline of the viral load comparable to the median decline of this study (2.8 $\log_{10}$).[4,16-20]

In addition to the marked reductions of plasma RNA load, a significant increase of CD4 cell count was seen with a median relative increase from 79% of the lower limit of the reference value to 106% after 6 months of therapy. Plasma HIV-1 RNA and CD4 cell count are both surrogate markers of response, but recent studies in children showed that plasma HIV-1 RNA levels and CD4 lymphocyte counts are independent predictors of clinical course. As in adults, a linear, age-independent relationship exists between $\log_{10}$ plasma RNA and relative risk of disease progression, which strongly supports therapeutic efforts to achieve plasma virus levels as low as possible.[6]

The combination of indinavir, zidovudine, and lamivudine was general-

ly well tolerated. In 59% of the patients no adverse events were seen. Adverse events were mild and mainly gastrointestinal symptoms. Hematuria, which resolved under adequate hydration and a short discontinuation of the indinavir, was seen in only 3 patients. In contrast to reports in adults in which in 12% of the patients had clinical nephrolithiasis, no nephrolithiasis was seen.[1]

In children, special attention is needed to achieve ingestion of antiretroviral drugs. Even under study conditions, 8 of 27 patients (29%) had problems with the strict regimen, which resulted in less reduction in viral load. In order to facilitate adherence, a pediatric formulation of indinavir is urgently needed.

Because a low plasma concentration of indinavir is a major and independent risk factor for virologic treatment failure,[31] calibration of the pharmacokinetics of indinavir (data not shown) to adequate adult values makes this study unique and may be partially responsible for the good results. Although our results have not been obtained by a controlled trial, reported efficacy in previous studies with indinavir monotherapy and therapy with 2 reverse-transcriptase inhibitors makes it highly unlikely that these therapies would have comparable results.

Taken together, our data show that combination therapy consisting of a protease inhibitor and 2 reverse-transcriptase inhibitor drugs is as efficacious and generally well tolerated in children as in adults.

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