Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

Hepatic, Renal, Hematologic, and Inflammatory Markers in HIV-Infected Children on Long-term Suppressive Antiretroviral Therapy

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Background. Data on long-term toxicity of antiretroviral therapy (ART) in HIV-infected children are sparse. PENPACT-1 was an open-label trial in which HIV-infected children were assigned randomly to receive protease inhibitor (PI)- or nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based ART.

Methods. We examined changes in clinical, immunologic, and inflammatory markers from baseline to year 4 in the subset of children in the PENPACT-1 study who experienced viral suppression between week 24 and year 4 of ART. Liver enzyme, creatinine, and cholesterol levels and hematologic parameters were assessed during the trial. Cystatin C, high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), D-dimer, and soluble CD14 (sCD14) were assayed from cryopreserved specimens.

Results. Ninety-nine children (52 on PI-based and 47 on NNRTI-based ART) met inclusion criteria. The median age at initiation of ART was 6.5 years (interquartile range [IQR], 3.7–13.4 years), and 22% were aged <3 years at ART initiation; 56% of the PI-treated children received lopinavir/ritonavir, and 70% of NNRTI-treated children received efavirenz initially. We found no evidence of significant clinical toxicity in either group; growth, liver, kidney, and hematologic parameters either remained unchanged or improved between baseline and year 4. Total cholesterol levels increased modestly, but no difference between the groups was found. IL-6 and hs-CRP levels decreased more after 4 years in the NNRTI-based ART group. The median change in IL-6 level was –0.35 pg/ml in the PI-based ART group and –1.0 in the NNRTI-based ART group ($P = .05$), and the median change in hs-CRP level was 0.25 μg/ml in the PI-based ART group and –0.95 μg/ml in the NNRTI-based ART group ($P = .005$).

Conclusion. These results support the safety of prolonged ART use in HIV-infected children and suggest that suppressive NNRTI-based regimens can be associated with lower levels of systemic inflammation.

Keywords. antiretroviral therapy; children; HIV; toxicity.

Combination antiretroviral (ARV) therapy (ART) has improved the outcome of children with HIV disease significantly. Although protease inhibitor (PI)-based therapy has been shown to improve virologic outcome in children younger than 3 years [1], no ARV class has shown consistent superiority in regard to virologic suppression in older children. Thus, clinicians select ARV regimens largely on the basis of availability and short-term toxicity, because data on the long-term toxicity of different ART regimens in HIV-infected children are sparse. Despite improved immune function and long-term viral suppression, chronic HIV infection in adults is associated with increased morbidity and death caused by non–acquired immunodeficiency syndrome (AIDS)-related conditions, including cardiovascular, renal, hepatic, and neurologic disease [2, 3]. Although the reasons are multifactorial, long-term morbidity of those who are treated for HIV infection is thought to be caused partly by chronic inflammation that is not ameliorated completely by ART [3–5]. Although non–AIDS-related clinical morbidities in children are less well demonstrated because of their overall lower risk for these conditions, the cumulative effect of a prolonged inflammatory state is likely to be significant given the duration of HIV infection and need for lifelong ART, starting in infancy. Studies have found increased risk in HIV-infected adolescents for future cardiovascular, bone, and renal disease [6–9]. Therefore, even small differences in ART toxicities and inflammatory markers might be clinically significant over time in ART-treated children.

PENPACT-1 was an international long-term open-label 2 × 2 factorial design trial in which HIV-infected children were assigned randomly to PI-based or nonnucleoside

Received 1 December 2016; editorial decision 17 May 2017; accepted 3 June 2017.

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Journal of the Pediatric Infectious Diseases Society 2017;6(3):e109–e15

DOI: 10.1093/jpids/pix050

reverse-transcriptase inhibitor (NNRTI)-based ART and to switch to second-line therapy at a higher versus low viral load [10]. In the primary analysis, no difference between treatment or switch criteria in virologic outcome and serious adverse events was found. The long-term nature of this trial provides the opportunity to further explore ART toxicity and markers of inflammation in ART-treated children.

METHODS

Population

At the start of the study, children participating in the PENPACT-1 study were either ART naive or had received ARVs for less than 56 days as part of mother-to-child transmission prevention. Children were assigned randomly to start 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus either a PI or an NNRTI and to switch from first-line to second-line ART at a viral load threshold of 1000 copies/ml or 30 000 copies/ml; none of the children in our analysis switched to second-line therapy during the trial. The specific ART was chosen by the treating clinician according to the randomized group. Drug substitutions within the same class were allowed for nonvirologic reasons such as toxicity or a change in availability. Children participating in the PENPACT-1 study who had no confirmed viral load of >400 copies/ml between week 24 and year 4 after ART initiation and had samples available for testing from baseline and after year 3 were included in this analysis. Post–year 3 samples were selected as close to year 4 as possible.

Clinical Assessments

Children underwent assessments including growth measurement, measurement of liver enzyme and creatinine levels, a complete blood count, and measurement of quantitative HIV RNA viral load at screening, baseline, weeks 2, 4, 8, 12, 16, and 24, and then every 12 weeks until the last randomly assigned child reached 4 years of follow-up. Nonfasting triglyceride and cholesterol levels were measured at baseline and every 24 weeks throughout the trial. Laboratory assessments were performed at the local study site according to standard procedures.

Cystatin C, high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), D-dimer, and soluble CD14 (sCD14) levels were measured from stored cryopreserved specimens from either screening or baseline and the available sample taken closest to year 4 by the Laboratory for Clinical Biochemistry Research at the University of Vermont. hs-CRP and cystatin C levels were measured using the BNII nephelometer (Siemens Healthcare Diagnostics, Deerfield, IL). IL-6 levels were measured by using a ultrasensitive chemiluminescent enzyme-linked immunosorbent assay (ELISA) (QuantiGlo HSHuman IL-6 immunoassay [R&D Systems, Minneapolis]). sCD14 levels were measured with an enzyme-linked immunosorbent assay (Quantikine sCD14 immunoassay [R&D Systems]). D-Dimer levels were measured by using immunoturbidometric methods on the Sta-R analyzer, Liatest D-DI (Diagnostica Stago, Parsippany, NJ).

Statistical Analysis

Participant baseline characteristics in the treatment arms were compared by using the Fisher exact, χ^2, or Wilcoxon rank-sum test as appropriate. Medians and interquartile ranges (IQRs) were calculated for clinical measures at baseline and at year 4. Changes in clinical measures were calculated as the value at 4 years minus that at baseline. The medians, their distribution-free 95% confidence intervals [11], and IQRs were calculated for the changes in clinical measures from baseline to year 4. Changes in clinical measures between the 2 treatment arms were compared using the Wilcoxon rank-sum test. The analyses presented here were exploratory; 2-sided P values of ≤.05 were identified as statistically significant with no adjustment for multiple tests. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). All analyses were as-treated. Height, weight, and BMI z scores were calculated on the basis of British 1990 growth centiles [12].

RESULTS

Population

Ninety-nine children (52 on PI-based and 47 on NNRTI-based combination ART) from a country in Europe or the Americas maintained viral suppression on their initial ART regimen and had stored samples available from either screening or baseline and close to year 4 (Table 1). Samples from screening or baseline were drawn initially between September 2002 and January 2005, and the year 4 samples were drawn between June 2005 and April 2009 (median year 4 study week, 192; range, weeks 141–216). Two participants originally randomly assigned to the NNRTI arm substituted a PI within the first 2 weeks of treatment as a result of adverse events and were included in the PI group for these analyses. The median age at initiation of ART was 6.5 years (IQR, 3.7–13.4 years), 22% were aged <3 years at ART initiation, and 53% were male. The median baseline viral load was 5.1 log copies/mL (IQR, 4.6–5.6 log copies/mL), and the median CD4% was 15.5% (IQR, 6.5%–22.0%). Fifty-six percent of the PI-treated children received lopinavir/ritonavir, and 70% of the NNRTI-treated children received efavirenz in their initial regimen. We found no statistically significant differences in baseline demographic or clinical characteristics between the treatment arms.

Growth, Immunology, and Clinical Parameters

Table 2 shows baseline and 4-year values for all parameters and changes from baseline to 4 years for the entire group. The 95% confidence intervals for these changes exclude 0 for everything except CD8% and CD4/CD8 ratio. Table 3 compares changes

Table 1. Baseline Characteristics

Characteristic	Treatment Class		
	PI (n = 52)	NNRTI (n = 47)	Total (N = 99)
Sex (n [%])			
Male	26 (50)	26 (55)	52 (53)
Female	26 (50)	21 (45)	47 (47)
Age (median [IQR]) (y)	5.7 (3.3–13.5)	6.6 (4.2–13.4)	6.5 (3.7–13.4)
<3 y (n [%])	12 (23)	10 (21)	22 (22)
≥3 y (n [%])	40 (77)	37 (79)	77 (78)
Race (n [%])			
White	21 (40)	16 (34)	37 (37)
Black	20 (39)	23 (49)	43 (43)
Other	11 (21)	8 (17)	19 (19)
Country (n [%])			
Argentina	2 (4)	4 (9)	6 (6)
Austria	1 (2)	1 (2)	2 (2)
France	6 (12)	4 (9)	10 (10)
Germany	4 (8)	4 (9)	8 (8)
Italy	4 (8)	5 (11)	9 (9)
Romania	12 (23)	8 (17)	20 (20)
Spain	1 (2)	0 (0)	1 (1)
UK/Ireland	9 (17)	7 (15)	16 (16)
US/PACTG sites	13 (25)	14 (30)	27 (27)
HIV RNA viral load (median [IQR]) (log_{10} copies/mL)	4.9 (4.6–5.7)	5.4 (4.5–5.6)	5.1 (4.6–5.6)
Baseline CD4% (median [IQR])	16.0 (7.0–26.5)	14.0 (6.0–17.5)	15.5 (6.5–23.0)
NRTIs (backbone) (n [%])			
LMV ABC	15 (29)	17 (36)	32 (32)
LMV ZDV	18 (35)	20 (43)	38 (38)
LMV STV	18 (35)	8 (17)	26 (26)
Other	1 (2)	2 (4)	3 (3)
PIs (n [%])			
LPV/r	29 (56)	0 (0)	29 (29)
NFV	21 (40)	0 (0)	21 (21)
None	2 (4)	47 (100)	49 (49)
NNRTIs (n [%])			
EFV[a]	2 (4)	33 (70)	35 (35)
NVP	0 (0)	14 (30)	14 (14)
None	50 (96)	0 (0)	50 (51)

Abbreviations: ABC, abacavir; EFV, efavirenz; HIV, human immunodeficiency virus; IQR, interquartile range; LMV, lamivudine; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PACTG, pediatric AIDS clinical trials group; PI, protease inhibitor; STV, stavudine; ZDV, zidovudine.

[a]Two participants randomly assigned to the NNRTI arm and initially started on EFV were reassigned to receive LPV/r within the first 2 weeks and were included in the PI group for analysis.

over 4 years between the study arms. Overall, at 4 years, no evidence of significant liver, kidney, or hematologic dysfunction was found in either treated group. Growth, liver, kidney, and hematologic parameters either did not show significant changes or improved between baseline and year 4. Median alanine aminotransferase and aspartate transferase levels and the aspartate transferase platelet ratio index were lower at year 4, and no difference between the PI-treated and NNRTI-treated children was found. Hematologic parameters were stable, and we found no evidence of significant neutropenia at year 4. Hemoglobin levels rose slightly over the 4 years, and a slightly greater increase was noted in the NNRTI-treated group than in the PI-treated group. Cholesterol levels were higher at year 4 in the PI-treated group than in the NNRTI-treated group, but the difference was not significant. Triglyceride levels decreased in both groups over the 4 years, but because not all the samples were drawn with the child having fasted, triglyceride levels were not included in our analysis. The CD4% increased from a median of 16% (IQR, 7%–22%) to 33% (IQR, 25%–39%) at 4 years, and we found an improvement in the CD4/CD8 ratio with no difference according to treatment group. Height and weight z scores improved in both groups, and no difference between treatment arms was found.

Inflammatory Markers

We found a decrease in each of the inflammatory markers over the 4 years of the study; the 95% confidence intervals for the decreases in IL-6 and D-dimer levels did not include 0. Both IL-6 and hs-CRP decreased more after 4 years in the NNRTI-based ART group than in the PI-based ART group; these differences were statistically significant. The median change in IL-6 levels was –0.35 pg/ml in the PI-treated group and –1.01 pg/ml in the NNRTI-treated group ($P = .05$), and the median change in hs-CRP levels was 0.25 μg/ml in the PI-treated group and –0.95 μg/ml in the NNRTI-treated group ($P = .005$) (Table 3).

Sensitivity Analysis

Because nelfinavir is no longer a preferred PI, a sensitivity analysis was conducted excluding the 21 participants who were taking nelfinavir initially. The results were similar to those discussed here, and all differences were in the same direction.

DISCUSSION

Our data support the long-term safety of ART in children. Although the importance of early ART for infants and symptomatic children is unquestioned [13], the data for the benefit of starting ART for older asymptomatic children are less robust [14]. All current international [15, 16] and most national [17] guidelines recommend starting all children with HIV on ART regardless of their age or CD4 cell count; however, concerns remain about the potential long-term toxicity of ART in children who might be stable immunologically for years before therapy is initiated [18, 19]. Our data suggest that children who are virologically suppressed on therapy show little evidence of long-term renal, hepatic, or hematologic toxicity. In contrast, apart from total cholesterol levels, all parameters that we examined improved or were stable over the 4 years of this study.

The toxicities of individual ARVs are well characterized [17]. Most of these adverse effects improve with time on ART, and the rate of ART discontinuation or switch is generally low [20–22]. In addition, many of the newer ARVs are better tolerated and

Table 2. Change in Clinical Parameters From Baseline to Year 4 in HIV-Infected Children on Suppressive ART

Parameter	N	Baseline (Median [IQR])	Year 4 (Median [IQR])	Change Over 4 y (Median [95% CI])	*P*[a]
ALT (mU/mL)	95	30 (20 to 58)	21 (15 to 30)	–7 (–14 to –4)	<.001
AST (mU/mL)	67	44 (36 to 56)	28 (25 to 34)	–15 (–19 to –8)	<.001
APRI	65	0.40 (0.28 to 0.59)	0.22 (0.17 to 0.30)	–0.14 (–0.22 to –0.09)	<.001
Creatinine (mg/dL)	94	0.50 (0.40 to 0.61)	0.58 (0.45 to 0.70)	0.04 (0.00 to 0.10)	.002
Cystatin C (mg/L)	99	0.77 (0.66 to 0.87)	0.63 (0.57 to 0.69)	–0.11 (–0.15 to –0.07)	<.001
Cholesterol (mg/dL)	81	136 (119 to 154)	179 (154 to 205)	43 (34 to 57)	<.001
Hemoglobin (g/dL)	98	11.10 (10.50 to 11.90)	12.95 (12.30 to 13.90)	1.80 (1.50 to 2.10)	<.001
Neutrophils (1000/mm^3)	89	2.29 (1.49 to 3.18)	2.83 (1.95 to 3.73)	0.50 (0.00 to 0.98)	<.001
Platelets (1000/mm^3)	99	267 (202 to 326)	299 (252 to 347)	27 (4 to 44)	<.001
CD4%	99	16 (7 to 22)	33 (25 to 39)	15 (12 to 19)	<.001
CD8%	83	51.00 (40 to 60)	33 (26 to 42)	–14 (–19 to –12)	.12
CD4/CD8 ratio	74	0.27 (0.11 to 0.51)	1.00 (0.71 to 1.35)	0.63 (0.54 to 0.77)	.42
hs-CRP (µg/mL)	59	1.44 (0.53 to 5.17)	1.35 (0.58 to 4.24)	–0.18 (–0.75 to 0.25)	<.001
IL-6 (pg/mL)	77	1.79 (1.12 to 3.44)	0.94 (0.70 to 1.69)	–0.68 (–1.09 to –0.33)	.04
D-Dimer (µg/mL)	82	0.44 (0.26 to 1.10)	0.17 (0.09 to 0.28)	–0.27 (–0.35 to –0.19)	<.001
sCD14 (ng/mL)	88	1834 (1476 to 2126)	1705 (1373 to 2190)	–101 (–249 to 19)	<.001
Height z score	93	–0.98 (–1.46 to –0.29)	–0.40 (–1.04 to 0.40)	0.43 (0.35 to 0.86)	<.001
Weight z score	96	–0.80 (–1.67 to 0.14)	–0.15 (–0.85 to 0.60)	0.68 (0.29 to 0.89)	<.001
BMI z score	93	–0.10 (–1.20 to 0.57)	0.07 (–0.67 to 0.97)	0.25 (–0.05 to 0.42)	<.001

Abbreviations: ALT, alanine aminotransferase; APRI, AST platelet ratio; ART, antiretroviral therapy; AST, aspartame aminotransferase; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; IQR, interquartile range; sCD14, soluble CD14.
[a]Signed rank test.

provide additional options for treatment should modifying ART as a result of intolerance become necessary. Most studies of ART-associated toxicity in children have reported only grade 3 or higher adverse events or are limited to short-term follow-up [22–24] and include children on ART but with elevated HIV RNA levels. It can be difficult to sort the medication effects from the effects of active viral replication, which itself can lead to elevations in liver enzyme levels [25], neutropenia, thrombocytopenia, and anemia [26, 27]. By selecting the subpopulation of PENPACT-1 participants who remained virologically suppressed throughout the study, the effect of HIV replication on the laboratory parameters studied was minimized.

Table 3. Change in Clinical Parameters Over 4 Years in HIV-Infected Children Initiating PI- Versus NNRTI-Based ART

Parameter	Changes With NNRTI (Median [95% CI])	Changes With PI (Median [95% CI])	Wilcoxon Rank-Sum *P*
ALT (mU/mL)	–5 (–10 to 1)	–11 (–20 to –4)	.08
AST (mU/mL)	–10 (–19 to –4)	–18 (–20 to –8)	.20
APRI	–0.11 (–0.20 to 0.03)	–0.16 (–0.35 to –0.09)	.07
Creatinine (mg/dL)	0.06 (0.00 to 0.10)	0.04 (0.00 to 0.10)	.32
Cystatin C (mg/L)	–0.14 (–0.18 to –0.07)	–0.10 (–0.17 to –0.04)	.44
Cholesterol (mg/dL)	37 (16 to 48)	54 (36 to 65)	.08
Hemoglobin (g/dL)	1.85 (1.60 to 2.50)	1.40 (1.00 to 2.00)	.08
Neutrophils (1000/mm^3)	0.50 (0.00 to 1.00)	0.51 (–0.27 to 1.33)	.84
Platelets (1000/mm^3)	18 (–8 to 42)	36 (0 to 62)	.61
CD4%	17 (13 to 21)	14 (10 to 20)	.13
CD8%	–15 (–21 to –11)	–14 (–23 to –10)	.91
CD4/CD8 ratio	0.69 (0.55 to 0.81)	0.62 (0.38 to 0.78)	.20
hs-CRP (µg/mL)	–0.95 (–2.73 to –0.18)	0.25 (–0.44 to 2.41)	.005
IL-6 (pg/mL)	–1.01 (–2.07 to –0.52)	–0.35 (–1.00 to 0.08)	.05
D-Dimer (µg/mL)	–0.29 (–0.48 to –0.19)	–0.25 (–0.48 to –0.14)	.59
sCD14 (ng/mL)	–38 (–273 to 126)	–135 (–291 to 114)	.57
Height z score	0.42 (0.23 to 1.06)	0.43 (0.23 to 1.14)	.86
Weight z score	0.55 (0.11 to 0.95)	0.75 (0.20 to 1.11)	.71
BMI z score	0.27 (–0.08 to 0.62)	0.19 (–0.15 to 0.62)	.95

Abbreviations: ALT, alanine aminotransferase; APRI, AST platelet ratio; ART, antiretroviral therapy; AST, aspartame aminotransferase; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; sCD14, soluble CD14.

In the primary analysis of the PENPACT-1 study, no differences in virologic outcome or serious adverse events were found between the children randomly assigned to PI-based therapy and those randomly assigned to NNRTI-based treatment [10]. Similarly, in the subset of participants with suppressed viral replication represented in this analysis, we found no significant differences in markers of hepatic, renal, or hematologic function over the 4 years in the groups treated with PI- or NNRTI-based ART. The only measured difference over the 4 years between the 2 groups was in the markers of inflammation; we found a greater decrease in median hs-CRP and IL-6 levels in the children on suppressive NNRTI-based treatment. The clinical significance of this finding is unclear. Our selected PENPACT-1 data provide valuable evidence in this regard for clinicians who wish to evaluate abnormal laboratory results from children on treatment.

HIV infection has been associated with an increase in risk factors associated with the development of cardiovascular disease in adults and children [6, 7, 28–30]. The relative contributions of traditional cardiovascular disease risk factors, uncontrolled viral replication, immune activation, and ARV medications continue to be investigated [31, 32]. The mortality

rate in HIV-infected adults treated episodically with ARVs was higher than that of those who received continuous ARVs in the Strategies for Management of Anti-retroviral Therapy Study (SMART) [33], and the majority of deaths were a result of non-HIV–related causes. Further investigation in the SMART trial revealed death [34, 35] and the risk of development of cardiovascular disease [36] to be associated with plasma levels of IL-6, D-dimer, hs-CRP, and sCD14; however, only D-dimer levels were found to decrease significantly after 6 months of continuous ART in a subgroup of the SMART participants [37]. Although many studies have confirmed higher levels of inflammatory markers in HIV-infected adults [38, 39] and children [40], treatment with ARVs has not been shown consistently to decrease inflammation. D-Dimer and/or IL-6 levels have been found to decrease after starting ARVs in some studies but not in others [37, 41–43]. However, ARV treatment did not result in decreased hs-CRP or sCD14 levels in most studies [37, 43–46]. The populations in most of these studies included people with detectable HIV RNA, which could make interpretation difficult, because an elevated viral load has been shown to be associated, although inconsistently, with higher D-dimer and hs-CRP levels [40, 42, 44, 47–49]. In our population of children with suppressed viral replication for 4 years, D-dimer, IL-6, hs-CRP, and sCD14 levels were stable or decreased on therapy, and the greatest decrease was in levels of IL-6 and D-dimer. Our results are consistent with those from a study that investigated inflammatory markers in HIV-infected adolescents with prolonged virologic control. In this cross-sectional study, sCD14 levels were higher than those in uninfected controls after a median of 4 to 11 years of viral suppression, whereas IL-6 levels were similar to those of the uninfected controls, which suggests an effect of suppressive ART on IL-6 but not sCD14 levels [46].

In our cohort, we found a greater decrease in IL-6 and hs-CRP levels in the NNRTI-treated children. Several studies have investigated the effects of PIs versus those of NNRTIs on inflammatory markers, and their results have conflicted. IL-6 levels were lower in adults treated with nevirapine and efavirenz than in those treated with PI [50], but no effect of PI or NNRTI treatment was found on IL-6 levels in adolescents changing therapy [41]. However, these 2 studies were observational, and the participants were not randomly assigned to their ART regimen. In a substudy of A5202 [32], in which ART-naive HIV-infected adults were assigned randomly to tenofovir/emtricitabine or abacavir/lamivudine and to efavirenz or atazanavir/ritonavir, no difference in the decline of IL-6 levels after 96 weeks was found in participants randomly assigned to receive efavirenz and those assigned to receive atazanavir/ritonavir, and hs-CRP levels were unchanged between baseline and 96 weeks in both groups. To our knowledge, ours is the only study to have investigated inflammatory markers in children randomly assigned to initial ART.

It is a strength of this analysis that all the participants were suppressed throughout follow-up, which makes it more likely that the results are related to the ART rather than the effects of HIV viral replication. However, our study had several limitations, including a relatively small sample size. The analysis was based on single measurements at 2 time points, and we did not require children to be free of minor illnesses at the time of their study visits, which might have affected CRP and IL-6 levels in particular. The study was primarily exploratory; some variables were not available for all individuals, and the analyses were not adjusted for multiple comparisons. The children were on various different regimens that did not allow a determination of the influence of specific NRTIs, NNRTIs, or PIs. In addition, we used no control group; therefore, we do not know if similar changes would have been seen in healthy children or HIV-infected children who were on neither a PI-based nor NNRTI-based ART regimen.

CONCLUSION

In this cohort of HIV-infected children with prolonged viral suppression after being randomly assigned to either a PI-based or NNRTI-based ART regimen, we found no significant differences in routine laboratory measures between the 2 randomized groups. All parameters were stable or improved over the 4 years of treatment with the exception of total cholesterol levels, which were higher at 4 years in both treatment groups. However, an indication of greater decreases in inflammation biomarkers was found in the NNRTI-treated group, which might have implications for the choice of ART for the long-term health of children on ART.

These results support the safety of prolonged ART use in HIV-infected children and suggest that suppressive NNRTI-based regimens might confer some advantage in terms of decreased levels of systemic inflammation.

Notes

Disclaimer. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Financial support. PENTA was supported by the European Commission/European Union Seventh Framework Programme (FP7/2007–2013) under Eurocoord grant agreement 260694, the Sixth Framework contract LSHP-CT-2006-018865, the Fifth Framework Programme contract QLK2-CT-2000-00150, and the PENTA Foundation. UK clinical sites were supported by a grant from the Medical Research Council; sites in France were supported by the Agence Nationale de Recherche sur le Sida et les hépatitis (ANRS); and sites in Italy were supported by a grant from the Instituto Superiore di Sanita-Progetto Terapia Antivirale (2004 and 2005). GlaxoSmithKline and Bristol-Myers Squibb provided drugs in Romania.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under award numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC), and UM1AI106716 (IMPAACT LC), with cofunding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of

Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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