Title: Hepatic, renal, hematologic and inflammatory markers in HIV-infected children on long-term suppressive antiretroviral therapy.

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Abstract:

Background: Data are sparse on long-term toxicity of antiretroviral therapy (ART) in HIV-infected children. PENPACT-1 was an open-label trial randomizing HIV-infected children to protease inhibitor (PI)- vs non-nucleoside 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 PENPACT-1 children who had viral suppression between week 24 and year 4 of ART. Liver enzymes, creatinine, cholesterol and hematologic parameters were assessed during the trial. Cystatin C, hs-CRP, IL-6, d-dimer and sCD14 were assayed from cryopreserved specimens.

Results: Ninety-nine children (52 on PI- and 47 on NNRTI-based ART) met inclusion criteria. Median age at initiation of ART was 6.5 years (IQR 3.7 – 13.4), with 22% age < 3 years at ART initiation; 56% of PI-treated children received lopinavir/ritonavir and 70% of NNRTI-treated children received efavirenz initially. There was no evidence of significant clinical toxicities in either group, with growth, liver, kidney or hematologic parameters either unchanged or improved between baseline and year 4. Total cholesterol levels increased modestly, with no difference between groups. IL-6 and hs-CRP showed greater decrease after 4 years in the NNRTI based ART group. The change in IL-6 was -0.35 pg/ml in the PI group vs -1.0 in the NNRTI group (p=0.05) and the change in hs-CRP was 0.25 μg/ml PI vs -0.95 NNRTI (p=0.005).

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

Introduction

Combination antiretroviral therapy (ART) has significantly improved the outcome of HIV disease in children. While protease inhibitor (PI)-based therapy has been shown to have improved virologic outcome in children less than 3 years of age[1], no antiretroviral (ARV) class has shown consistent superiority in regards to virologic suppression in older children. Thus clinicians select ARV regimens largely on availability and short term toxicity as data are sparse on the long-term toxicity profiles of differing ART regimens in HIV-infected children. In spite of improved immune function and long term viral suppression, chronic HIV infection in adults is associated with increased morbidity and mortality from non-AIDS related conditions including cardiovascular, renal, hepatic and neurologic disease[2,3]. While the reasons for this are multifactorial, long-term morbidity of treated HIV infection is thought to be due in part to chronic inflammation which is not completely ameliorated by ART[3-5]. Although non-AIDS related clinical morbidity in children is 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 life-long ART starting from infancy. Studies in HIV-infected adolescents have demonstrated increased risk for future cardiovascular, bone and renal disease[6-9]. Therefore even small differences in ART toxicity and inflammatory markers may be clinically significant over time in ART treated children.

PENPACT-1 was a long-term international open label 2x2 factorial design trial randomizing HIV-infected children to PI-based vs non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART and to switch to second line therapy at high vs low viral load[10]. In the primary analysis, there was no difference between treatment or switch criteria in virologic outcome and serious adverse events. 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 PENPACT-1 were either ART-naïve or had received ARVs for less than 56 days as part of prevention of mother-to-child transmission. Children were randomized to start two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a PI or 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 the current analysis switched to second line therapy during the trial. The specific ARTs were chosen by the treating clinician according to the randomized group. Drug substitutions within the same class were allowed for non-virologic reasons such as toxicity or change in availability. Children participating in PENPACT-1 who had no confirmed viral load >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 had assessments including growth, liver enzymes, creatinine, complete blood count and quantitative HIV RNA at screening, baseline, weeks 2, 4, 8, 12, 16, 24 and then every 12 weeks until the last randomized child reached 4 years of follow-up. Non-fasting triglycerides and cholesterol 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 (sCD14) were measured from stored cryopreserved specimens from either screening or baseline and the closest available sample to year 4 by the Laboratory for Clinical Biochemistry Research at the University of Vermont. HsCRP and cystatin C were measured using the BNII nephelometer (Siemens Healthcare Diagnostics, Deerfield, IL). IL-6 was measured by ultrasensitive chemiluminescent enzyme-linked

immunosorbent assay (ELISA) (Quantiglo HSHuman IL-6 Immunoassay; R&D Systems). Soluble CD14 was measured with an enzyme-linked immunosorbent assay (QuantikinesCD14 Immunoassay, R&D Systems). D-dimer levels with immunoturbidometric methods on the Sta-R analyzer, Liatest D-DI (Diagnostica Stago, Parsippany, NJ).

Statistical analysis: Participant baseline characteristics were compared between treatment arms using Fisher's exact test, chi-square tests, or Wilcoxon rank-sum tests as appropriate. Medians and interquartile ranges (IQR) were calculated for clinical measures at baseline and year 4. Changes in clinical measures were calculated as the value at 4 years minus baseline. The medians, their distribution-free 95% confidence intervals[11] and interquartile ranges were calculated for the changes in clinical measures from baseline to year 4. Changes in clinical measures were compared between the two treatment arms using Wilcoxon rank-sum tests. The analyses presented were exploratory; two-sided p-values ≤0.05 were identified as statistically significant with no adjustment for multiple tests. Statistical analyses were conducted using SAS v. 9.4 (SAS Institute, Cary, NC). All analyses were as-treated. Height, weight and BMI z-scores were calculated based on British 1990 growth centiles[12].

Results

Population: Ninety-nine children (52 on PI- and 47 on NNRTI-based cART) from countries in Europe and 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 (**Error! Reference source not found.**Table 1). Samples from screening or baseline were initially drawn between 9/2002 and 1/2005 and the year 4 samples between 6/2005 and 4/2009 (median year 4 study week was 192; range weeks 141-216). Two participants originally randomized to the NNRTI arm substituted a PI within the first 2 weeks of treatment due to adverse events and were included in the PI group for these analyses. Median age at initiation of ART was 6.5 years (IQR 3.7 – 13.4), with 22% age < 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) and 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 regimens. There were no statistically significant differences in baseline demographic or clinical characteristics between 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 zero for everything except CD8% and CD4/CD8 ratio. Table 3 compares changes over four years between study arms. Overall at 4 years there was no evidence of significant liver, kidney or hematologic dysfunction 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 amino-transferase (ALT) and aspartate transferase (AST) levels and the AST platelet ratio index (APRI) were lower at year 4, with no difference between the PI vs NNRTI-treated children. Hematologic parameters were stable with no evidence for significant neutropenia at year 4. Hemoglobin levels rose slightly over the 4 years with a slightly greater increase noted in the NNRTI-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 as not all the samples were drawn in a fasted state, triglyceride levels were not included in the analysis. CD4 percent increased from a median 16% (IQR 7,22) to 33% (IQR 25,39)at 4 years, with an improvement in CD4/CD8 ratio and no difference by treatment group. Height and weight z-scores improved in both groups with no difference between treatment arms.

Inflammatory markers: All inflammatory markers showed decreases over the 4 years; the 95% confidence intervals for the decreases in IL-6 and D-Dimer did not include 0. Both IL-6 and hsCRP

showed greater decreases after 4 years in the NNRTI-based ART group; these differences were statistically significant. The median change in IL-6 was -0.35 pg/ml in the PI group vs -1.01 pg/ml in the NNRTI group (p=0.05) and the median change in hsCRP was 0.25 μg/ml PI vs -0.95 μg/ml NNRTI (p=0.005). (Table 3).

Sensitivity analysis: As nelfinavir is no longer a preferred PI, a sensitivity analysis was conducted excluding the 21 participants initially taking nelfinavir (supplemental table). The results were similar 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 guidelines[17] recommend starting all children with HIV on ART regardless of their age or CD4 cell count, however, there remain concerns for potential long-term toxicity of ART in children who may be stable immunologically for years before therapy is initiated[18,19]. Our data suggest children who are suppressed on therapy show little evidence of long-term renal, hepatic, or hematologic toxicity. Conversely, apart from total cholesterol, all parameters studied improved or were stable over 4 years.

The toxicities of individual ARVs are well characterized[171717]. 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 provide additional options for treatment should modifying ART due to intolerance become necessary. Most studies of ART-associated toxicity in children report on 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 enzymes[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.

In the primary analysis of PENPACT-1, no differences in virologic outcome or serious adverse events were seen between the children randomized to PI vs NNRTI-based treatment[10]. Similarly, in the subset of participants with suppressed viral replication represented in this analysis, there were no significant differences in markers of hepatic, renal or hematologic function over the 4 years in the groups treated with PI vs NNRTI-based ART. The only measured difference over the 4 years between the two groups was seen in the markers of inflammation, with 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 wishing to evaluate abnormal laboratory results in children on treatment.

HIV infection has been associated with an increase in risk factors associated with 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 antiretroviral medications continue to be investigated[31,32]. There was higher mortality in the HIV-infected adults treated episodically with ARVs compared to those who received continuous ARVs in the Strategies for Management of Anti-Retroviral Therapy Study[33], with the majority of deaths due to non-HIV related causes. Further investigation in the SMART trial revealed mortality[34,35] and risk of development of cardiovascular disease[36] to be associated with plasma levels of Il-6, D-dimer, hs-CRP and sCD14 levels,

however only D-dimer was found to decrease significantly after 6 months of continuous ART in a subgroup of the SMART participants[37]. While many studies have confirmed higher levels of inflammatory markers in HIV-infected adults[38,39] and children[40], treatment with ARVs has not consistently been shown to decrease inflammation. D-dimer and/or IL-6 levels have been found to decrease after starting ARVs in some studies but not others [37,41-43] . However, ARV treatment has not resulted in decreased hs-CRP or sCD14 in most studies[37,43-46]. [MA1]The[GTW2] populations in most of these studies included individuals with detectable HIV RNA, which could make interpretation difficult as elevated viral load has been shown to be associated with higher D-dimer and hs-CRP levels, although inconsistently[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 were stable or decreased on therapy with the greatest decrease seen in levels of IL-6 and D-dimer. Our results are consistent with a recent report investigating inflammatory markers in HIV-infected adolescents with prolonged virologic control. In this cross-sectional study, sdCD14 levels were higher than uninfected controls after a median of 4-11 years of viral suppression, while IL-6 levels were similar to the uninfected controls, suggesting an effect of suppressive ART on IL-6 but not sdCD14 levels [46].

In our cohort, there was a greater decrease in the levels of IL-6 and hs-CRP in the NNRTI-treated children. Several studies have investigated the effects of PIs vs NNRTIs on inflammatory markers with conflicting results. IL-6 levels were lower in adults treated with nevirapine and efavirenz compared to PI-[50], but no effect of PI vs NNRTI treatment was found on IL-6 levels in adolescents changing therapy[41]. However, both of these studies were observational and the participants were not randomized to their ART regimens. In a substudy of A5202[32] which randomized ART-naïve HIV-infected adults to tenofovir/emtricitabine or abacavir/lamivudine and to efavirenz or atazanavir/ritonavir, there was no difference in the decline of IL-6 levels after 96 weeks in participants randomized to efavirenz vs

atazanavir/rit and hs-CRP levels were unchanged from baseline in both groups. Our cohort is the only study investigating inflammatory markers in children randomized to initial ART.

It is a strength of this analysis that all the participants were suppressed throughout follow-up; this makes it more likely that the results are related to the ARTs rather than effects of HIV viral replication. However, our study has several limitations, including a relatively small sample size. The analysis was based on single measurements at two time-points and there was no requirement that children be free of minor illnesses at the time of study visits which may have impacted CRP and IL-6 in particular. The study is primarily exploratory, with some variables not available for all individuals, and analyses were not adjusted for multiple comparisons. The children were on various different regimens which did not allow a determination of the influence of specific NRTIs, NNRTIs or PIs. In addition, there was no control group. Because of this we do not know if similar changes would have been seen in healthy children or HIV-infected children who were on neither PI- or NNRTI-based ART regimens.

Conclusion

In this cohort of HIV-infected children with prolonged viral suppression after randomization to either a PI or an NNRTI-based ART regimen, we found that there were no significant differences in routine laboratory measures between the two randomized groups. All parameters were stable or improved over the 4 years of treatment with the exception of total cholesterol which was higher at 4 years in both treatment groups. There was however, indication of a greater decrease in biomarkers of inflammation in the NNRTI-treated group. This may have implications for the choice of ART for long-term health of ART treated children.

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

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