Using CD4 Percentage and Age to Optimize Pediatric Antiretroviral Therapy Initiation

WHAT’S KNOWN ON THIS SUBJECT: In HIV-infected children, decisions to start antiretroviral therapy must weigh immunologic benefits against potential risks. Current guidelines recommend using CD4 percentage and age when deciding to start treatment. Population-level effects of these factors on immunologic recovery are unknown.

WHAT THIS STUDY ADDS: Starting antiretroviral therapy at higher CD4 percentages and younger ages maximizes potential for immunologic recovery. However, not all benefits are sustained, and viral failure may occur. Our results help clinicians better weigh immunologic benefits against viral failure risks.

abstract

BACKGROUND: Quantifying pediatric immunologic recovery by highly active antiretroviral therapy (HAART) initiation at different CD4 percentage (CD4%) and age thresholds may inform decisions about timing of treatment initiation.

METHODS: HIV-1-infected, HAART-naive children in Europe and the Americas were followed from 2002 through 2009 in PENPACT-1. Data from 162 vertically infected children, with at least World Health Organization “mild” immunosuppression and CD4% <10th percentile, were analyzed for improvement to a normal CD4% (≥10th percentile) within 4 years after HAART initiation. Data from 209 vertically infected children, regardless of immune status, were analyzed for CD4% outcomes at 4 years and viral failure within 4 years.

RESULTS: Seventy-two percent of baseline immunosuppressed children recovered to normal within 4 years. Compared with “severe” immunosuppression, more children with “mild” immunosuppression (difference 36%, 95% confidence interval [CI]: 22% to 49%) or “advanced” immunosuppression (difference 20.8%, 95% CI: 5.8% to 35.9%) recovered a normal CD4%. For each 5-year increase in baseline age, the proportion of children achieving a normal CD4% declined by 19% (95% CI: 11% to 27%). Combining baseline CD4% and age effects resulted in >90% recovery when initiating HAART with “mild” immunosuppression at any age or “advanced” immunosuppression at age <3 years. Baseline CD4% effects became greater with increasing age (P = .02). At 4 years, most immunologic benefits were still significant but diminished. Viral failure was highest in infancy (56%) and adolescence (63%).

CONCLUSIONS: Initiating HAART at higher CD4% and younger ages maximizes potential for immunologic recovery. Guidelines should weigh immunologic benefits against long-term risks. Pediatrics 2014;134:e1104–e1116

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KEY WORDS: child, HIV, immunologic, reconstitution, treatment failure

ABBREVIATIONS: CD4%—CD4 percentage; CDC—Centers for Disease Control and Prevention; CI—confidence interval; DHHS—Department of Health and Human Services; HAART—highly active antiretroviral therapy; LTFU—loss to follow-up; RCT—randomized controlled trial; WHO—World Health Organization

(Continued on last page)
Determining optimal timing for initiation of highly active antiretroviral therapy (HAART) in children infected with HIV remains a challenge. Globally in 2012, 3.3 million children were living with HIV, and 210,000 children died due to AIDS. Although HAART has improved long-term survival, only 34% of eligible children currently receive treatment. Treatment guidelines must consider public health implications for not only disease progression, but also long-term complications of drug toxicities, inadequate adherence, resistance mutations, and cost-effectiveness. For HIV-infected infants, immediate HAART initiation is clearly needed, given its strong survival benefit and improved neurodevelopmental outcomes, faster growth recovery, and the population's high mortality. However, for HIV-infected children presenting outside of infancy with minimal HIV-related symptoms, the clinical benefits of early HAART initiation are unclear.

Quantifying immunologic benefits of treatment initiation at different CD4 percentage (CD4%) and age thresholds may inform public health decisions regarding optimal HAART initiation timing. Population-level immunologic effects of HAART initiation at different CD4% and age combinations have been poorly quantified because most previous studies have only assessed associations. HIV-infected children who initiate HAART at lower CD4% reach lower peak CD4 levels, perhaps from persistent effects of chronic immune activation. HAART initiation at younger ages is associated with better immunologic recovery. Some longitudinal studies have quantified long-term CD4 trajectories on HAART based on pretreatment CD4 and age, allowing predictions that are child-specific. However, projected immunologic impacts at population levels have not been established.

Our aim was to quantify population-level impacts of HAART initiation at different CD4% and age thresholds on CD4% recovery. Our primary outcome was the proportion of immunosuppressed children ever achieving a normal CD4% (≥10th percentile for age) within 4 years of HAART initiation. Secondary outcomes were CD4% at 4 years after HAART initiation and the proportion of children with a normal CD4% at 4 years. The proportion of immunosuppressed children ever having a normal CD4% within 4 years of HAART initiation reflects biological capacity for CD4% reconstitution. The CD4% and proportion of children normal at 4 years reflect outcomes inclusive of initial CD4% recovery, potential immunologic failure, and possible immune restoration on a subsequent regimen.

METHODS

Participants

PENPACT-1 (Pediatric AIDS Clinical Trials Group 390/Paediatric European Network for Treatment of AIDS 9) was an international, multicenter, phase 2/3, randomized, open-label, 2-by-2 factorial trial enrolling HIV–infected children (aged >30 days to <18 years) in Europe, North America, and South America between September 25, 2002, and September 7, 2005. Eligible children had not been treated with antiretrovirals or only received antiretrovirals to reduce mother-to-child transmission (excluding single-dose nevirapine) for ≤56 days and met local indications for HAART.

Procedures

At entry, children were randomly assigned (1:1) in 2-by-2 factorial design: (1) to start HAART with 2 nucleoside reverse transcriptase inhibitors plus either a protease inhibitor or nonnucleoside reverse transcriptase inhibitor and (2) to switch from first-line to second-line HAART at viral load thresholds of either 1000 copies/mL or 30,000 copies/mL. CD4% and HIV RNA viral loads were measured at randomization (baseline, week 0); weeks 2, 4, 8, 12, 16, 24; and then every 12 weeks until the last enrollee reached 4 years of follow-up (August 31, 2009). Full study details are described elsewhere.

Because previous PENPACT-1 analyses found no significant differences among randomized arms, we pooled participants across arms. To minimize confounding from unknown duration of infection, analyses were restricted to participants who were infected vertically.

For the primary outcome (CD4% recovery within 4 years), data from vertically infected children with at least “mild” immunosuppression at baseline by World Health Organization (WHO) Immunologic Classification and CD4% <10th percentile for age were analyzed to determine the proportion of children who improved to normal CD4% (≥10th percentile for age) at any time within 4 years of follow-up. For secondary outcomes, data from all vertically infected children, regardless of baseline immune status, were analyzed for outcomes at 4 years after HAART initiation: CD4% and proportion of children with normal CD4% (see definitions in the next section).

Definitions

To account for age-related variability of CD4%, we defined normal CD4% recovery based on data from healthy, urban-dwelling, pediatric patients in the United States. For the primary outcome, recovery to normal was defined as 2 consecutive CD4% measurements ≥10th percentile-for-age. Time of recovery was defined as the first of these CD4% measurements. Participants lost to follow-up without recovery were censored in Kaplan-Meier analyses and counted as failures in regression analyses.

For secondary outcomes, CD4% at 4 years was defined as the mean of CD4% measurements at weeks 192 and 204. At week 192, all participants were ≥3
years old, and CD4% 10th percentile-for-age after 3 years old ranges between 28% to 31% without a consistent age-related trend. Thus, the definition of normal CD4% at 4 years was simplified to be mean CD4% \( \geq 30\% \). Participants missing 4-year CD4% measurements were excluded from secondary outcome analyses.

Baseline CD4% was categorized according to a modified version of the WHO Immunologic Classification for HIV-Associated Immune Deficiency. As this classification switches to CD4 cell counts after age 5 years, we used the following immunodeficiency (CD4%) categories for subjects \( \geq 5 \) years (same as ages 3 to <5 years; see also the Centers for Disease Control and Prevention (CDC) HIV infection classification systems): “none/not significant” >25%, “mild” 20% to 25%, “advanced” 15 to <20%, and “severe” <15%.

**Statistical Analysis**

Bivariate categorical analyses were performed by using Fisher’s exact test. Continuous variables were analyzed by using linear regression. Trend linearity was assessed by using polynomial expansion and restricted quadratic splines with knots between quintiles. Recovery to normal CD4% within 4 years, 162 participants had follow-up CD4% measurements at 4 years. LTFU was only observed in Europe, North America, and South America; 263 were included in the main trial analysis. For analysis of CD4% recovery within 4 years, 162 participants with baseline immunosuppression were included, and 209 qualified for analyses of CD4% status at 4 years (Supplemental Fig 4). The baseline characteristics of all 209 vertically infected participants are shown in Table 1. At baseline, WHO-staged CD4% was associated with age, race, and gender; marginally associated with continent and CDC clinical stage; and not associated with growth parameters (weight-for-age z score, height-for-age z score, and BMI-for-age z score) or baseline viral load. Age at HAART initiation was associated with race, continent, growth parameters, baseline viral load, and baseline CD4% but not associated with gender or CDC clinical stage.

Eighty-seven percent (182 of 209) of participants had follow-up CD4% measurements at 4 years. LTFU was only associated with continent (Europe 5%, North America 27%, South America 10%; \( P < .001 \)). Correcting for LTFU did not meaningfully alter study results (data not shown).

Of 162 children with baseline immunosuppression, the estimated probability of achieving a normal CD4% within 4 years was 72% (95% confidence interval [CI]: 64% to 78%); mean CD4% at 4 years was 30.9 (95% CI: 29.5 to 32.3); 56% of participants (95% CI: 48% to 64%) had normal CD4% at 4 years. Of 209 children with any baseline immune status, mean CD4% at 4 years was 32.8 (95% CI: 31.5 to 34.2), with 84% (95% CI: 57% to 71%) of children having normal CD4% at 4 years.
Baseline CD4%

CD4% recovery within 4 years was significantly associated with WHO-staged baseline CD4% (Kaplan-Meier, $P < .001$; Fig 1). In regression models, baseline CD4% was significantly associated with all three 4-year CD4% outcomes: proportion of immune suppressed children ever recovering a normal CD4% within 4 years (unadjusted $P < .001$, adjusted $P < .001$; Fig 1); CD4% at 4 years (unadjusted $P < .001$, adjusted $P < .001$; Table 2); and proportion of children normal at 4 years (Table 2).

Age at HAART Initiation

CD4% recovery within 4 years was significantly associated with age (Kaplan-Meier, $P < .001$; Fig 2). The association between age and CD4% recovery was approximately linear (by significance testing) for all three 4-year CD4% outcomes (Fig 3A–3C). In multivariable linear regressions adjusting for gender and race, each 5-year increase in age at HAART initiation had an estimated (1) reduction of 19% in proportion of children ever having a normal CD4% within 4 years (95% CI: 11% to 27%; $P < .001$), (2) decrease in CD4% at 4 years of 2.9 percentage points (95% CI: 1.4% to 4.3%; $P < .001$), and (3) reduction in proportion of children with a normal CD4% at 4 years of 7% (95% CI: –1% to 16%; $P = .08$).

Combined Effects of Baseline CD4% and Age

The interaction between baseline CD4% and age on the probability of ever recovering a normal CD4% within 4 years was statistically significant (unadjusted $P = .009$, adjusted $P = .02$; Table 3). This interaction was synergistic with increasing age, baseline CD4% had a stronger effect on the capacity to recover a normal CD4% within 4 years. However, interactions

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**TABLE 1** Characteristics of Children According to WHO Staged CD4% and Age at HAART Initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>WHO Immunologic Classification for HIV-Associated Immunodeficiency at HAART Initiation</th>
<th>Age (y) at HAART Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe</td>
<td>Advanced</td>
</tr>
<tr>
<td>Age, $n$ (%)</td>
<td>91</td>
<td>40</td>
</tr>
<tr>
<td>0–4 y</td>
<td>41 (41)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>5–9 y</td>
<td>27 (39)</td>
<td>18 (26)</td>
</tr>
<tr>
<td>10–17 y</td>
<td>23 (58)</td>
<td>9 (23)</td>
</tr>
</tbody>
</table>

Gender

| Female, $n$ (%) | 35 (34) | 18 (17) | 25 (24) | 25 (24) | 103 | .003 | 5.6 (4.5) | .59 |

Race, $n$ (%)

| Male | 56 (53) | 22 (21) | 9 (8) | 19 (18) | 106 | | 6.0 (4.6) |

Age, $n$ (%)

| 91 | 40 | 34 | 44 | 209 | | | |

Race, $n$ (%)

| 2 | 0.0 (1.4) | 2 | 1.0 (0.8) | 2 | 0.8 (1.2) | -0.7 (1.5) | .81 | $r = 0.32$ | <.001 |

BMI

| -1.0 (1.4) | -1.0 (0.8) | -0.8 (1.1) | -0.8 (1.3) | -0.9 (1.2) | .81 | $r = 0.16$ | .02 |

Baseline viral load log$_{10}$ copies/mL, M (SD)

| 5.2 (0.9) | 5.1 (0.8) | 4.8 (1.0) | 5.0 (0.8) | 5.1 (0.9) | .31 | $r = -0.54$ | <.001 |

Baseline CD4%, M (SD)

| 10.2 (5.7) | 18.5 (3.8) | 25.4 (4.9) | 35.6 (7.1) | 19.6 (11.4) | N/A | $r = -0.44$ | <.001 |

N/A, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

$^*$ Comparisons used Fisher’s exact test for categorical variables and linear regression for continuous variables.

$^a$ $P$ values are not reported because any differences were determined by randomization.

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The interaction between baseline CD4% and age on the probability of ever recovering a normal CD4% within 4 years was statistically significant (unadjusted $P = .009$, adjusted $P = .02$; Table 3). This interaction was synergistic with increasing age, baseline CD4% had a stronger effect on the capacity to recover a normal CD4% within 4 years. However, interactions...
between baseline CD4% and age were not significant for CD4% at 4 years (unadjusted $P = .91$; adjusted $P = .91$) or the proportion of children with normal CD4% at 4 years (unadjusted $P = .50$, adjusted $P = .59$; Table 4).

A model including baseline CD4%, age, gender, race, and a baseline CD4%-by-age interaction predicted >90% probability of CD4% recovery within 4 years when initiating HAART with “mild” immunosuppression at any age or with “advanced” immunosuppression at age <3 years. Adolescents with WHO “severe” immunosuppression had the lowest recovery probabilities, but the small sample size of adolescents made these estimates imprecise (Table 3). Trends were similar for CD4% outcomes at 4 years (Table 4).

**Viral Failure**

Of 209 vertically infected participants, 82 (39%) experienced viral failure within 4 years. Twenty-nine (14%) failed to suppress to ≤400 copies/mL by week 24, and 53 (25%) suppressed but experienced virologic rebound to >400 copies/mL. One participant (0.5%) was LTFU before week 24. Viral failure was not associated (Cox model, unadjusted $P = .36$, adjusted $P = .23$) with baseline immunodeficiency classification (adjusted Kaplan-Meier failure probability: “none” 32%, “mild” 54%, “advanced” 44%, “severe” 40%). Viral failure and age had a bimodal relationship (Cox model, unadjusted $P < .001$, adjusted $P < .001$) with peaks in infancy and adolescence (adjusted Kaplan-Meier failure probability: 0 to <1 year 56%, 1 to <3 years 34%, 3 to <5 years 32%, 5 to <8 years 24%, 8 to <13 years 38%, 13 to <18 years 63%; Fig 3D).

**DISCUSSION**

On the basis of these PENPACT-1 results, initiating HAART at healthier immunologic stages and younger ages may have profound impacts on immunologic recovery. We suggest that HAART initiation when children first have “mild” immunosuppression would result in almost all children experiencing full CD4% recovery. Similarly, HAART at younger ages would yield high probabilities of immune recovery and may blunt negative effects of “severe” immunosuppression. Although not all children maintained immune recovery (demonstrated by more attenuated immunologic benefits at 4 years) most CD4% outcomes at 4 years were still improved in children starting HAART at healthier CD4 levels and younger ages. Our results quantify the magnitude of these effects on immunologic outcomes to help inform public health planning.

The PENPACT-1 data align with US Department of Health and Human Services (DHHS) pediatric HIV treatment guidelines.3-4 The DHHS recommends initiating HAART in all HIV-infected infants and any HIV-infected children with AIDS or most CDC Clinical Category B or C conditions; confirmed plasma HIV RNA levels
## TABLE 2
CD4% Outcomes at 4 Years, Comparing WHO Immunodeficiency Classification None, Mild, Advanced Versus Severe Suppression

<table>
<thead>
<tr>
<th>Baseline WHO Immunodeficiency Classification</th>
<th>Unadjusted</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Unadjusted</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4% Mean (95% CI)</td>
<td>Difference vs Severe&lt;sup&gt;b&lt;/sup&gt; Mean (95% CI)</td>
<td>CD4% Mean (95% CI)</td>
<td>Difference vs Severe&lt;sup&gt;b&lt;/sup&gt; Mean (95% CI)</td>
<td>Proportion Normal % (95% CI)</td>
</tr>
<tr>
<td>None, n = 37</td>
<td>40.0 (37.4 to 42.6)</td>
<td>11.0 (7.8 to 14.1)</td>
<td>35.9 (36.5 to 40.4)</td>
<td>9.4 (6.7 to 12.0)</td>
</tr>
<tr>
<td>Mild, n = 27</td>
<td>35.3 (32.3 to 38.4)</td>
<td>6.3 (2.8 to 9.8)</td>
<td>35.1 (32.8 to 37.3)</td>
<td>5.9 (2.9 to 9.0)</td>
</tr>
<tr>
<td>Advanced, n = 38</td>
<td>32.1 (29.8 to 34.7)</td>
<td>3.1 (0.0 to 6.2)</td>
<td>33.1 (30.8 to 35.5)</td>
<td>3.9 (0.8 to 7.0)</td>
</tr>
<tr>
<td>Severe, n = 80</td>
<td>29.0 (27.3 to 30.6)</td>
<td>Reference</td>
<td>29.1 (27.3 to 31.0)</td>
<td>Reference</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for age, gender, and race. Mean CD4% and proportion normal are estimated at the covariate distribution of secondary outcomes subset (mean age 5.8 y).

<sup>b</sup> Unadjusted P < .001, adjusted P < .001.

<sup>c</sup> Unadjusted P < .001, adjusted P < .001.

Wald upper 95% confidence limits exceeding 100% were rounded to 100%.

Evidence for early treatment in children aged 1 to 12 years old is less compelling. An RCT in Thailand and Cambodia of HIV-infected children aged 1 to 12 years old found that immediate versus delayed ART resulted in similar 144-week AIDS-free survival with CD4% 15% to 24% found that immediate treatment had better overall survival and morbidity in infants, but clinical outcomes are among prepubertal children. 44 Adult cohort studies suggest that initiating treatment at combinations of CD4% and age treatment thresholds higher CD4 levels (WHO CD4 count < 350 cells/mm<sup>3</sup>) may be associated with better CD4 and CD8 recovery, and lower incidence of opportunistic infections. 

From our PENPACT-1 results, we are confident that younger children, particularly those with poor baseline immunologic potential, should be weighed against potential immunologic benefits of earlier treatment. Adherence recommendations are based on adult data. Adolescent recommendations are based on adult data. Further support earlier treatment at CD4 > 500 cells/mm<sup>3</sup> reduces HIV-related disease progression and death. Adolescents may benefit most dramatcially from earlier HAART initiation (complete finding adherence, or therapeutic approaches for improving immunologic potential). 

Adult cohort studies suggest that initiating treatment at combinations of CD4% and age treatment thresholds higher CD4 levels (WHO CD4 count < 350 cells/mm<sup>3</sup>) may be associated with better CD4 and CD8 recovery, and lower incidence of opportunistic infections. 

Consistent with child-specific preclinical observations, we expect relationships between increased age and head circumference for age. Mental development thresholds, we estimate DHHS-recommended CD4% and age treatment thresholds, we estimate DHHS-recommended CD4% and age treatment thresholds, we estimate DHHS-recommended CD4% and age treatment thresholds, we estimate DHHS-recommended CD4% and age treatment thresholds.
In PENPACT-1, viral failure was worse at age extremes, consistent with studies finding poor viral suppression at younger ages and myriad adherence difficulties in adolescents. For some children, immunologic recovery is transient, and starting HAART earlier may eventually lead to fewer treatment options. Fortunately, HAART initiation at higher CD4 counts may mitigate antiretroviral resistance at viral failure. Still, diminishing immunologic benefits over time and viral failure risks highlight the importance of long-term longitudinal studies for understanding implications of different HAART strategies in children.

Our study was limited by including only participants from a clinical trial in predominantly industrialized countries. Results may not generalize to other settings. Low sample sizes in certain CD4% and age strata, particularly adolescents, decreased precision of estimates and precluded more intricate model specification. Finally, analysis of potential sources of bias suggested possible unmeasured confounding from host immunology and HIV virulence, which were untestable in our data.

CONCLUSIONS

Earlier HAART initiation in children with vertically acquired HIV-1 substantially improves immunologic recovery within 4 years. Optimizing treatment timing by CD4% and age may have significant long-term immunologic benefits. Older children and adolescents, in particular, may benefit from earlier treatment. Nevertheless, immunologic benefits diminished over time, and treatment decisions should weigh potential risks, including viral failure. Estimates of this kind allow immunologic benefits of alternative HAART initiation thresholds to be balanced against their clinical, social, and financial costs.

ACKNOWLEDGMENTS

THE PENPACT-1 (PAEDIATRIC EUROPEAN NETWORK FOR TREATMENT OF AIDS [PENTA 9]/ PEDIATRIC AIDS CLINICAL TRIALS GROUP [PACTG 390]) STUDY TEAM

PENPACT-1 Protocol Team

FIGURE 3
Relationship between age at HAART initiation and (A) proportion of children with normal CD4% within 4 years, (B) CD4% at 4 years, (C) proportion of children with normal CD4% at 4 years, (D) proportion of children with viral failure within 4 years. Panels A, B, and C illustrate splines; panel D illustrates a cubic function.


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France: Hôpital d’enfants Armand Trousseau, Paris: C. Dollfus, M.D. Tabone,
TABLE 3 Projected Probabilities of Ever Recovering a Normal CD4% Within 4 Years, by WHO Immunodeficiency Classification and Agea,b

<table>
<thead>
<tr>
<th>Baseline WHO Immune Deficiency Classification</th>
<th>Age at HAART Initiation</th>
<th>Overallc</th>
<th>n (%) CI</th>
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<tbody>
<tr>
<td>Mild, n = 162</td>
<td>0 to 1 &lt; 1 y</td>
<td>n = 14</td>
<td>75 (62% to 87%)</td>
</tr>
<tr>
<td></td>
<td>1 to &lt; 3 y</td>
<td>n = 25</td>
<td>40 (30% to 50%)</td>
</tr>
<tr>
<td></td>
<td>3 to &lt; 5 y</td>
<td>n = 45</td>
<td>30 (20% to 40%)</td>
</tr>
<tr>
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<tr>
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<td>n = 17</td>
<td>10 (0% to 20%)</td>
</tr>
</tbody>
</table>


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TABLE 4 Projected Probabilities of Having a Normal CD4% at 4 Years, by WHO Immunodeficiency Classification and Agea,b

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REFERENCES


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Methodological advice was provided by C. Poole and S.R. Cole, University of North Carolina—Chapel Hill. Manuscript proofreading and suggestions were provided by R.J. McCulloh, Children’s Mercy Hospital and Clinics, University of Missouri—Kansas City.

Participants, Families, Staff

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(Continued from first page)

Dr Yin conceptualized the study aims, designed the analytical plan, conducted all data analyses, interpreted the results, and drafted and revised the manuscript; Ms Warshaw contributed to development of the study aims, guided the analytical plan, conducted all data analyses, interpreted the results, and reviewed and revised the manuscript; Dr Miller guided the analytical plan, conducted all data analyses, interpreted the results, and reviewed and revised the manuscript; Ms Castro, Ms Harper, Dr Klein, and Dr Lewis contributed to interpretation of results and reviewed and revised the manuscript; Dr. Fiscus conducted laboratory analysis of specimens and reviewed and revised the manuscript; Dr Yin conceptualized the study aims, designed the analytical plan, conducted all data analyses, interpreted the results, and drafted and revised the manuscript; Dr McKinney was Pediatric AIDS Clinical Trials Group co-chair of the study, contributed to development of the study goals, acquired data, and reviewed and revised the manuscript; Dr Tudor-Williams was Paediatric European Network for Treatment of AIDS co-chair of the study, contributed to development of study aims, acquired data, and reviewed and revised the manuscript; Dr McKinney was Pediatric AIDS Clinical Trials Group co-chair of the study, contributed to development of study aims and analytic plan, acquired data, guided data analysis, interpreted results, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

Clinical Trial Registration: This trial has been registered with www.isrctn.org (ISRCTN73318385).

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