

# Immunologic Function and Virologic Suppression Among Children With Perinatally Acquired HIV Infection on Highly Active Antiretroviral Therapy

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**Background:** The goal of highly active antiretroviral therapy (HAART) has been to stabilize and reconstitute immune function and suppress viral replication to the greatest degree possible. Suppression of HIV viral replication has been associated with improved long-term and short-term prognosis. Limited data are available on the level of virologic suppression and immune function of pediatric patients followed in clinical settings in the HAART era.

**Objective:** The objective of this study was to assess the level of virologic suppression and immune function in a cohort of children with perinatally acquired HIV infection followed at dedicated HIV specialty care sites.

**Research Design:** This study comprised a cohort study of HIV-infected children and adolescents.

**Subjects:** Study subjects consisted of 263 HIV-positive children ( $\leq 17$  years old), on HAART, with at least one outpatient visit and CD4 test recorded in 2001 seen at 4 U.S. HIV primary pediatrics and specialty care sites (2 eastern, 1 southern, and 1 western).

**Measures:** Measures consisted of all plasma HIV-1 RNA levels  $\leq 400$  during calendar year 2001.

**Results:** Two hundred sixty-three patients received HIV-related treatment during 2001, with a mean age of 8.5 years. Sixty-eight percent were black, 54% were females, and the majority (85%) was insured by Medicaid. A total of 28.6% had a class C AIDS diagnosis. A total of 23.5% and 34% of patients maintained viral suppression at  $< 50$  copies per milliliter (cpm), or  $< 400$  cpm, respectively, for the calendar year; 32.5% and 38.8%, respectively, fulfilled the criteria if one "blip" to  $< 5000$  cpm was allowed. Forty-eight percent maintained all viral loads  $< 5000$  cpm, and 74.9% overall had HIV-1 RNAs  $\leq 15,000$  cpm. Eighty-seven percent of patients had CD4%  $> 25$ ; only 4.2% had CD4  $< 15\%$ . Overall, 12.5% of patients had either CD4%  $< 15$  or severely decreased absolute CD4 counts (adjusted for age). A total of 4.6% of patients had HIV-1 RNAs  $> 100,000$  cpm and severe immunosuppression. Patients who were less likely to achieve virologic suppression to  $< 400$  cpm included those with CD4 count  $< 200$  cells/mm<sup>3</sup> (odds ratio [OR], 0.06; 95% confidence interval [CI], 0.007–0.46), those with AIDS (OR, 0.5; 95% CI, 0.28–0.94), and those with moderate (OR, 0.42; 95% CI, 0.22–0.79), or severe immunologic suppression (OR, 0.14; 95% CI, 0.046–0.43) based on CD4%.

**Conclusion:** In this multisite, pediatric cohort, the rate of near-complete virologic suppression ( $< 50$  or  $< 400$  cpm) was low. However, the majority of patients have near-normal CD4 counts and viral loads  $< 15,000$  cpm. Follow up will be critical to assess the implications of ongoing low-level viral replication with near-normal CD4 values.

**Key Words:** pediatric HIV infection, virologic suppression, antiretroviral therapy

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The availability of combination antiretroviral therapy, most often involving agents targeted against multiple viral processes (termed highly active antiretroviral therapy [HAART]), has led to a marked decrease in morbidity and mortality among HIV-infected children and adults.<sup>1–6</sup> One measure of treatment efficacy has been the suppression of HIV replica-

tion, as measured by plasma HIV-1 RNA levels (termed viral load [VL]). The optimal outcome of treatment would be long-term suppression of viral replication below the limit of assay quantification, generally set at <400 or 50 copies per milliliter (cpm).

In children, the clinical course of HIV infection may differ from that in adult HIV infection, including, historically, a more rapid progression.<sup>7,8</sup> Perinatally infected infants have much higher baseline viral loads than found in untreated, recently, or chronically infected adults. Historically, children on HAART are less likely to achieve viral suppression than adults on HAART.<sup>9</sup> This may reflect immunologic differences between children and adults, as well as the fact that many antiretroviral agents approved for adult use are difficult to take or poorly tolerated among children, with resultant greater challenges to adherence in the pediatric population. Most reports of HIV-infected children's virologic response to HAART have come from treatment studies, which can be influenced by selection bias in terms of who may be approached for studies and who may be interested or willing to participate in research protocols.

Several studies of HIV-infected children, either untreated, or on mono- or dual therapy, have noted the independent association of short-term risk of mortality with HIV RNA level and CD4 count. Those infants with very high plasma RNA levels in the first 2 months of life (>750,000 cpm) appeared at high risk for rapid progression of their illness.<sup>10</sup> For older infants and children, RNA levels greater than 100,000 cpm and CD4 counts <15% are associated with increased risk of mortality.<sup>11,12</sup> These data illustrate the importance of achieving virologic suppression among children with HIV.

Studies of adults have shown that patients followed in observational cohort studies differ in clinical disease progression and virologic suppression compared with patients followed in clinical trials.<sup>13</sup> In 2 studies of unselected adult patients, 37% to 50% of outpatient urban clinic populations maintained HIV-1 RNA <500 cpm 7 to 14 months after initiating protease inhibitor therapy.<sup>13,14</sup> This is in contrast to the results of clinical trials, in which the initiation of protease inhibitor therapy resulted in up to 80% of patients maintaining plasma viral RNA <400 cpm at 12 to 24 months.<sup>15-17</sup>

There is little available data on the immunologic and VL status of children and adolescents with perinatally acquired HIV infection followed at clinical sites and not enrolled in research trials. In this study, we describe the immunologic and virologic profile of a large multisite observational pediatric cohort, on HAART, followed during 2001.

## METHODS

### Site Selection

HIV Research Network (HIVRN) sites were selected from members of the HIV Quality Care Network of the Infectious Diseases Society of America. The HIVRN is a

consortium of 17 sites that provide primary and subspecialty care to patients with HIV. To be included, a site had to have a minimum dataset available in electronic format or through paper abstraction. The minimum data required were the patients' age, sex, race, HIV transmission risk factor, AIDS-defining illnesses, absolute CD4 count, CD4%, HIV-1 RNA, and use of antiretroviral medication. Data from 4 sites specializing in the care of pediatric HIV-infected patients were included in this analysis. Geographically, 2 sites are located in the eastern United States, one in the southern United States, and one in the western United States. All of these sites have academic affiliations. The median sample size per site was 52 patients (range, 47-118 patients). This analysis was limited to vertically infected children ( $\leq 17$  years old) on HAART who were in longitudinal HIV primary care, as defined by at least one visit to a primary care provider at one of these sites and one recorded CD4 test result within a calendar year. The project was approved by each site's Institutional Review Board (IRB) as well as the IRB of the Data Coordinating Center at Johns Hopkins University.

### Data Collection

The data elements described here were abstracted from electronic or paper records at each site. Abstracted data were sent in electronic format to a data coordinating center after personal identifying information was removed. For this analysis, data collection encompassed the time period of January 1, 2001, through December 31, 2001. Electronic data received by the coordinating center were assessed to ensure that each data element was correctly formatted and that all elements were captured. Data elements with incorrect formatting, with unknown or incomplete information, or other inaccuracies were reviewed with the site and corrected. After this verification process, the data were combined across sites to achieve a uniformly constructed multisite database. A variable identifying the site was included in this database.

### Definition of Variables

Insurance was categorized into private, Medicaid, and self-pay/Ryan White. Patients classified as self-pay/Ryan White were considered to be uninsured. HAART was defined as: 1) 3 or more nucleosides; 2) any use of one or more protease inhibitors (PI) or a nonnucleoside reverse transcription inhibitor (NNRTI) in combination with 2 or more nucleoside RTIs; or 3) a PI, nonnucleoside RTI, or nucleoside RTI combination (NRTI). Patients were considered to be on HAART if they were prescribed any of these combinations during the calendar year. Levels of plasma RNA were assigned a value of 50 if the lower limit of detection (LLD) was 50 cpm, and 400 if the lower limit of detection was 400 cpm. Age was categorized into <2, 2-9, or >9 years. These categories were selected because children under 2 years are often unable to take pills, which limits antiretroviral choices,

and children over the age of 9 have had exposure to pre-HAART drug combinations. AIDS was defined per the Centers for Disease Control and Prevention (CDC) classifications (class C disease is any opportunistic illness, HIV-wasting, progressive encephalopathy, or an HIV-associated malignancy); lymphocytic interstitial pneumonitis (LIP), a class B AIDS-defining illness, was not included in the definition of AIDS used for this analysis. AIDS diagnosis criteria using CD4 percentage and counts, as used in adult and adolescent categorizations, were not considered as denoting AIDS status.<sup>18</sup>

Because the normal ranges for absolute CD4 counts in children are age-dependent (with normal values of 2500–3000 cells/mm<sup>3</sup> in the first year of life), the CDC has published guidelines categorizing immunologic status based on CD4 count and percentage adjusted for age.<sup>18</sup> We defined immunologic categories following CDC guidelines on age-adjusted CD4 counts and CD4%. CD4% cutoffs were: class 1 (no immune suppression), ≥25%; class 2 (moderate immune suppression), 15% to 24%; and class 3 (severe immune suppression), <15% (Table 1). We assigned immunologic category based on the first CD4 values recorded in 2001.

HIV-1 RNA suppression was defined as all HIV-1 RNA test results in 2001 being <400 cpm, allowing for one increase of HIV-1 RNA to <5000 cpm (a “blip”). In addition, sensitivity analyses were performed for alternative outcomes, including all HIV-1 RNAs <50 cpm, HIV-1 RNAs <50 cpm with one blip, all HIV-1 RNA <400 cpm, and all HIV-1 RNAs <5000 cpm.

**Data Analysis**

To examine bivariate associations between individual demographic and clinical variables associated with virologic suppression, we performed logistic regression analyses (STATA 8.0, College Station, TX). Multivariate logistic regression was performed using age, race, gender, immune stage, AIDS diagnosis, and insurance. CD4 count was not included in the multivariate model because it was not age-adjusted. All analyses were adjusted for site to account for differences in demographics or practice variation by geographic region.

**RESULTS**

Of 290 children followed in the HIVRN in 2001, 263 were on HAART and were included in this analysis. The demographic and clinical characteristics of the study sample are shown in Table 2. The sample had a slight female predominance (54%). The majority were black (68%); 19% were Hispanic and 12% were white. Of patients with known insurance status, 85% were covered by Medicaid. The median age was 9 years, with a range of less than 1 to 17 years (mean, 8.5 years; standard deviation, 4 years). Of the patients followed during calendar year 2001, 98% had 3 or more outpatient visits. Thirty percent of patients had class C disease. All 263 patients received at least one NRTI. Only 3% were treated with NRTI-only regimens, 85% received at least one PI, and 61% received at least one NNRTI during the calendar year.

The initial CD4% and absolute CD4 count obtained during the study year were used for analysis. The mean and median initial CD4 counts were 910 and 787 cells/mm<sup>3</sup>, respectively. Overall, 8.3% of patients had CD4 counts less than 200 cells/mm<sup>3</sup>, with 3% <50 cells/mm<sup>3</sup>. Thirteen percent of patients had CD4 values placing them in the severely immune suppressed category (class C) based on CD4% <15 and/or absolute counts adjusted for age. Of the patients with a history of a diagnosis of AIDS, 60% were in immune category 1, and 62% of those without a history of AIDS were in immune category 1. Conversely, 20% of those with a history of AIDS were in immune category 3 compared with 9% of those without a previous diagnosis of AIDS. The median HIV-1 RNA, from the initial contact in the study year, was 1486 cpm, with 43% of patients being virally suppressed at 400 cpm or less; however, nearly 10% had an initial HIV-1 RNA over 100,000 copies/mL.

Figure 1 demonstrates rates of virologic suppression using different criteria of suppression. Through the study year, 39% of patients maintained viral suppression to <400 cpm, allowing for one value >400 but <5000 cpm. Using a more stringent definition of viral control, 34% of patients maintained all values <400 cpm for 12 months. Of the patients from the 3 sites with viral assays of lower limit of

**TABLE 1.** Pediatric Classification System: Immune Categories Based on Age-Specific CD4<sup>+</sup> T Cell Count and Percentage\*

Immune Category	<12 Mo		1–5 Yr		6–12 Yr	
	No./mm <sup>3</sup>	(%)	No./mm <sup>3</sup>	(%)	No./mm <sup>3</sup>	(%)
Category 1: No suppression	≥1500	(≥25%)	≥1000	(≥25%)	≥500	(≥25%)
Category 2: Moderate suppression	750–1499	(15–24%)	500–999	(15–24%)	200–499	(15–24%)
Category 3: Severe suppression	<750	(<15%)	<500	(15%)	<200	(<15%)

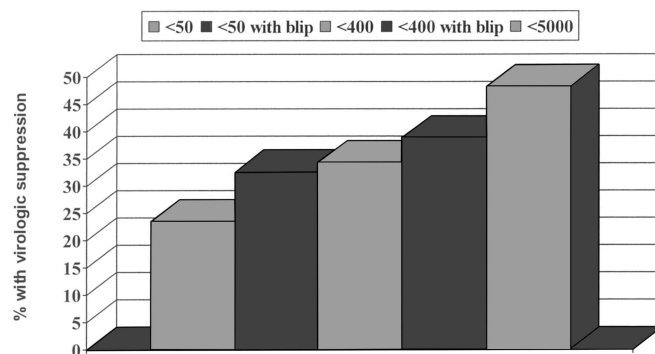
\*Modified from: Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 yr of age. *MMWR Morb Mortal Wkly Rep.* 1994;43:1–10.

**TABLE 2.** Demographic and Clinical Characteristics of 263 HIV-Infected Children on Highly Active Antiretroviral Therapy

Patient Demographics	2001 (n = 263)
Age (years)	
Mean	8.5
Median	9
Range	0–17
Sex	
Male	122 (46.0%)
Female	141 (54.0%)
Race	
White	32 (12.2%)
Black	179 (68.1%)
Hispanic	51 (19.4%)
Other	1 (0.4%)
Initial CD4 (cells/mm <sup>3</sup> )*	
Median	787
≤50	8 (3.0%)
51–200	14 (5.3%)
201–500	55 (20.9%)
>500	186 (70.7%)
Initial CD4%*	
<15	11 (4.2)
15–24	21 (8.0%)
>24	231 (87.8%)
Initial HIV-1 RNA (copies/mL)*	
Median	1486
≤400	113 (42.9)
401–1000	12 (4.6)
1000–100,000	61 (23.2)
10,000–100,000	52 (19.8)
>100,000	25 (9.5)
Immune category*	
1	162 (61.6%)
2	68 (25.9%)
3	33 (12.6%)
AIDS	n = 257
Class C disease	77 (30.0%)
No AIDS	180 (70.0%)
Insurance	n = 212
Private	13 (6.1%)
Medicaid	181 (85.4%)
Ryan White	18 (8.5%)

\*First value reported in calendar year 2001.

detection <50 cpm (n = 200 subjects), 23.5% had HIV-1 RNAs less than 50 cpm for the calendar year; 32.5% were suppressed to <50 cpm, allowing for one transient increase to <5000 cpm. Almost half of the patients, 48.3%, maintained

**FIGURE 1.** HIV-1 RNA suppression in 2001.

viral suppression of <5000 cpm throughout the study year. Of the patients with initial viral load >5000 cpm, the median HIV-1 RNA was 14,500 cpm (mean, 141,126 cpm). Overall, 45% of patients had normal CD4 counts and HIV-1 RNA <5000 cpm, whereas 9.5% of patients had a HIV-1 RNA of >100,000 cpm and 4.6% had both a HIV-1 RNA >100,000 cpm and class 3 immune status (Table 3).

In bivariate analysis, CD4 count <200 cells/mm<sup>3</sup> (odds ratio [OR], 0.06; 95% confidence interval [CI], 0.007–0.46), stage 2 immunologic category (OR, 0.42; 95% CI, 0.22–0.79), stage 3 immunologic category (OR, 0.14; 95% CI, 0.046–0.43), and AIDS status (OR, 0.51; 95% CI, 0.28–0.94) were associated with failure to achieve virologic suppression (all values <400 cpm, allowing for one blip) (Table 4). Age, race, gender, and insurance status were not associated with virologic suppression. In multivariate analysis, immunologic category 2 (adjusted odds ratio [AOR], 0.41; 95% CI, 0.21–0.79) and immunologic category 3 (AOR, 0.16; 95% CI, 0.051–0.49) remained significantly associated with lack of virologic suppression. There was a nonsignificant trend towards significance for AIDS status (AOR, 0.56; *P* = 0.08). Sensitivity analysis was performed using <50 cpm and <400 cpm without a blip, and the results were unchanged.

**TABLE 3.** Immunologic Category versus HIV-1 RNA at Initial Visit in 2001

Immune Status	<5000 copies/mL	5000–100,000 copies/mL	>100,000 copies/mL	Total
1	119 (45.2)	39 (14.8)	4 (1.5)	162 (61.6)
2	33 (12.5)	26 (9.9)	9 (3.4)	68 (25.9)
3	9 (3.4)	12 (4.6)	12 (4.6)	33 (12.6)
Total	161 (61.2)	77 (29.3)	25 (9.5)	263 (100)

Note: Entries are numbers of patients and percentage of total (in parentheses).

**TABLE 4.** Bivariate and Multivariate Analysis of Factors Associated With Virologic Suppression

Characteristic	Bivariate*		Multivariate*	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Age				
<2 yr	1.0	Reference	1.0	Reference
2–9 yr	–1.12 (0.48–3.18)	0.695	1.76 (0.61–5.07)	0.298
>9 yr	1.15 (0.44–2.99)	0.773	1.78 (0.62–5.13)	0.286
Male	0.94 (0.57–1.57)	0.824	1.00 (0.58–1.75)	0.972
Race/ethnicity				
White	1.0	Reference	1.0	Reference
Black	0.54 (0.24–1.19)	0.125	0.62 (0.26–1.45)	0.272
Hispanic	0.84 (0.32–2.20)	0.727	0.96 (0.34–2.66)	0.932
CD4 Count				
<200	0.06 (0.007–0.46)	0.007		
>200	1.0 (Ref)	Reference		
AIDS status				
No AIDS	1.0	Reference	1.0	Reference
AIDS	0.51 (0.28–0.94)	0.029	0.56 (0.29–1.08)	0.08
Immunologic category				
1	1.0 (Ref)	0.007	1.0	Reference
2	0.42 (0.22–0.79)	0.001	0.41 (0.21–0.79)	0.008
3	0.14 (0.046–0.43)		0.16 (0.051–0.49)	0.001
Insurance				
Uninsured	1.0	Reference	1.0	Reference
Private	1.11 (0.26–4.80)	0.884	0.63 (0.13–2.98)	0.558
Medicaid	0.76 (0.29–2.01)	0.582	0.63 (0.28–1.76)	0.382

\*Adjusted for care site.

## DISCUSSION

The widespread use of HAART for HIV-infected adults and children has resulted in a significant decrease in morbidity and mortality.<sup>1,4–6</sup> Suppression of viral replication, as measured by viral load, has been a marker of treatment efficacy and improved short- and long-term prognosis. In the adult population, baseline viral loads have been a factor in the timing of initiation of HAART, and increases in viral load are an indication for consideration of a change in therapy. Recently, information has readjusted this view such that the CD4 count may be a more important marker of when to initiate therapy in adults and of short-term risk of opportunistic infections.<sup>19</sup> Similar data are not yet available for pediatric patients.

HIV-infected infants and children have higher baseline, pretreatment viral loads than adults. Untreated infants followed from birth had plasma RNA levels of 250,000 cpm at 1 and 2 months of life, which declined slowly to median values of 34,000 cpm at 24 months of age.<sup>10</sup>

The data reported from the current, unique observational cohort were collected from 4 geographically diverse sites, providing comprehensive primary and specialty care to

HIV-infected children. Thus, it should not be surprising that we found, in this cohort, low rates of viral suppression and, consistent with the adult literature, lower rates than seen in clinical trials.<sup>13</sup> Our cohort included all patients receiving HAART therapy cared for at the network sites, thereby avoiding selection biases that can arise in clinical trials with limited slots in which participants are selected in part based on interest in participation.

In the pediatric population, rates of virologic suppression, even from research trials, have been lower than that reported in adult cohorts. In one of the most effective treatment regimens, Pediatric AIDS Clinical Trials Group study 382, in which PI and NNRTI-naive children initiated combination therapy for NRTIs, efavirenz, and nelfinavir, Starr et al reported that at 48 weeks of therapy, 76% of patients had maintained HIV-1 RNA <400 cpm and 63%, <50 cpm.<sup>20</sup> In another pediatric study, PI therapy (nelfinavir or indinavir) was initiated in PI-naive but treatment-experienced patients, and 69% and 50% of patients had HIV-1 RNA <500 and <40 cpm, respectively, after 2 years of treatment. Using an intent-to-treat analysis, missing equals failure, 56% had

HIV-1 RNA <500 and 41% <40 cpm.<sup>21</sup> In a study of ritonavir given to PI-naive, but again heavily treated pediatric patients, 7 of 22 patients (32%) maintained HIV-1 RNA <200 cpm after a median follow up of 15 months.<sup>22</sup> Resino et al reported on an observational cohort of 95 children followed after the initiation of HAART.<sup>23</sup> Patients were censored when they switched to a second-line HAART regimen. They reported 61% of patients had HIV-1 RNA <400 cpm at the end of the study (median follow up, 27.5 months).

There are little data available for rates of suppression in a pediatric clinical cohort followed longitudinally since the advent of HAART. The studies reported here reported either on patients entered into clinical treatment trials or followed from the onset of a specific treatment regimen. As such, they would be expected to have results superior to those reported here and found in comparable clinical settings. Our cohort was an older and more treatment-experienced group compared with pre-HAART studies. We report on all patients followed during the study year, not just those initiating or changing therapy. More comparable to our cohort would be the results of patients followed at Ryan White-funded clinical sites between 1996 and 1998.<sup>24</sup> Using a retrospective chart review method, of randomly selected patients, 41.7% of patients had viral loads <4000 cpm. It was not clear if these patients maintained this level of suppression throughout the 3-year observational period.

The clinical significance of low-level intermittent viremia is unclear. Early data suggested that any HIV-1 RNA values above the limit of detection were associated with earlier time to virologic failure.<sup>25,26</sup> In contrast, Havlir et al,<sup>27</sup> using any HIV-1 RNA >50 cpm, found those with intermittent viremia were not more likely to have reached defined virologic failure criteria (HIV-1 RNA >200 cpm on 2 consecutive tests) through a median follow up of 48 weeks. It is unclear if levels of viral replication above 400 cpm but <5,000 cpm predict progression of clinical disease. The clear concern is the possible fostering of virologic resistance if replication is allowed to continue at measurable rates.

An important difference between this pediatric study population and adult cohorts is the nearly universal insurance coverage for children through Medicaid, private insurance, or care provided by Ryan White-funded centers. Nearly 85% of our sample was covered by Medicaid. Insurability, therefore, was not a factor in availability of drug therapy. Also, unlike adults, we did not find any differences in rates of virologic suppression by race, HIV risk factor, or treatment regimen.<sup>28–31</sup> Our sample had a high proportion of blacks and those with elevated CD4 counts. Therefore, our study may have been underpowered to detect a difference as a function of these variables.

Our study has several potential limitations. First, the sample may not generalize to all HIV care sites. Data were obtained from only 4 clinical sites. The sites in the sample do

encompass a broad geographic distribution, and multisite studies afford greater generalizability than single-site studies. In addition, we did not have access to socioeconomic variables such as income and education, which have been shown to be associated with adherence to HAART. Third, although our sample of children with HIV infection is larger than other studies, it is still small. Statistical tests may have low power, especially for subanalyses by immune status. Finally, we relied on sites with experienced HIV providers who have high rates of HAART and opportunistic illness prophylaxis use compared with other studies.<sup>32–35</sup> Previous data suggest that providers with HIV experience have lower patient mortality rates and higher use of antiretroviral therapy.<sup>36</sup>

Although our population failed, as a whole, to suppress viral replication to the lowest levels (<50 or <400 cpm), the majority retained intact CD4 counts and viral replication rates in a relatively low range, with 75% having plasma viral RNA levels of <15,000 cpm. Even among children with a prior AIDS diagnosis, 60% had CD4 counts within immune category 1.

With fewer treatment choices available, and less pharmacokinetic data to guide them, pediatric providers of HIV care may be reluctant to switch regimens for asymptomatic patients with normal CD4 counts and relatively low levels of viral replication. It will be informative to follow this cohort through the next few years and assess if viral replication in the 5000 to 15,000-cpm range predicts the rapid development of resistance and/or clinical deterioration. If so, it might be more therapeutic to either change medication regimens earlier and/or consider some of these patients for therapeutic drug interruptions, restarting medications only when their CD4 counts drift below preset limits (such as the 350 cells/mm<sup>3</sup> guideline suggested in adult treatment guidelines).

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## APPENDIX

### Participating Sites

- Montefiore Medical Group, Bronx, New York (Robert Beil, MD)
- Alameda County Medical Center, Oakland, California (Kathleen Clanon, MD)
- Wayne State University, Detroit, Michigan (Lawrence Crane, MD)
- Community Health Network, Rochester, New York (Steven Fine, MD)
- St. Jude's Children's Hospital, Memphis, Tennessee (Patricia Flynn, MD)
- Johns Hopkins University, Baltimore, Maryland (Kelly Gebo, MD, MPH)
- Montefiore Medical Group, Bronx, New York (Marc Gourevitch, MD)
- Montefiore Medical Center, Bronx, New York (Lawrence Hanau, MD)
- Community Medical Alliance, Boston, Massachusetts (James A. Hellinger, MD)
- Henry Ford Hospital, Detroit, Michigan (John Jovanovich, MD)
- Parkland Health and Hospital System, Dallas, Texas (Philip Keiser, MD)

Oregon Health and Science University, Portland, Oregon (P. Todd Korthuis, MD, MPH)

University of California, San Diego, California (W. Christopher Mathews, MD, MSPH)

Johns Hopkins University, Baltimore, Maryland (Richard D. Moore, MD, MHS)

Tampa General Health Care, Tampa, Florida (Jeffrey Nadler, MD)

Nemechek Health Renewal, Kansas City, Missouri (Patrick Nemechek, DO)

Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Richard Rutstein, MD)

St. Luke's Roosevelt Hospital Center, New York, New York (Victoria Sharp, MD)

Alameda County Medical Center, Oakland, California (Silver Sisneros, MD)

Drexel University, Philadelphia, Pennsylvania (Peter Sklar, MD)

University of San Diego, Owen Clinic, San Diego, California (Stephen Spector, MD)

Drexel University, Philadelphia, Pennsylvania (James Witek, MD)

### **Sponsoring Agencies**

Agency for Healthcare Research and Quality, Rockville, Maryland (Fred Hellinger, PhD, John Fleishman, PhD, Irene Fraser, PhD)

Health Resources and Services Administration, Rockville, Maryland (Richard Conviser, PhD)

Substance Abuse and Mental Health Services Administration, Rockville, Maryland (Joan Dilonardo, PhD)

Substance Abuse and Mental Health Services Administration, Rockville, Maryland (Laura House, PhD)

Office of AIDS Research, NIH, Bethesda, Maryland (Paul Gaist, PhD)

### **Data Coordinating Center**

Johns Hopkins University (Richard Moore, MD, Principal Investigator, Jeanne Keruly, CRNP, Kelly Gebo, MD, Erin Reilly, MPH, Liming Zhou)