Prevalence and Interactions of Patient-Related Risks for Nonadherence to Antiretroviral Therapy Among Perinatally Infected Youth in the United States

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Abstract

Adherence to antiretroviral regimens continues to be a significant problem in HIV-infected individuals facing a lifetime of therapy. Youth who were infected through perinatal transmission enter into adolescence often with a history of multiple medication regimens. Thus, adherence can be a particularly important issue in these young people, as medication options can often be limited. This was a cross-sectional, observational study to determine the prevalence of personal barriers to adherence and to identify associations among the following barriers in subjects 12 to 24 years old: mental health barriers, self-efficacy and outcome expectancy, and structural barriers. Among the 368 study participants, 274 (74.5%) were adherent and 94 (25.5%) were nonadherent to highly active antiretroviral therapy (HAART). No significant differences were found between adherent and nonadherent subjects according to mental health disorders. Adherence was associated with some but not all structural barriers. Both self-efficacy and outcome expectancy were significantly higher in adherent versus nonadherent subjects ($p < 0.0001$). In subjects with low self-efficacy and outcome expectancy, adherence differed according to the presence or absence of either mental health or structural barriers, similar to findings in behaviorally infected adolescents. Interventions that address the breadth and clustering of adherence barriers in adolescents are needed to have the maximum chance for positive effects.

Introduction

COMBINATION ANTIRETROVIRAL THERAPY has improved dramatically over the past decade. Infants and children who were infected through mother to child transmission are now living into adolescence and young adulthood. Pediatric acquired HIV is now seen as a chronic illness, with more effective therapeutics resulting in children living longer with HIV.^{1,2} These children and adolescents face a number of obstacles, which may include cognitive developmental delays, delayed puberty, and psychological distress, including depression and anxiety.^{3–5} Compared to adolescents infected through risk behaviors, perinatally infected adolescents have been treated for many years, often with early less potent and more toxic regimens. Many have experienced a parent under care for HIV or the death of a parent from HIV. It cannot be assumed that barriers to adherence among perinatally infected

adolescents are the same as those of adolescents infected later in life through risk behaviors. There may be unique differences among the populations requiring specific interventions depending upon the age and mode of infection.

Factors influencing adherence can be divided into three major categories: patient-related factors, medication-related factors, and factors related to the system of care.⁶ In a recent article in *AIDS Patient Care and STDs*, we reported on the prevalence and interactions of patient-related risks for nonadherence among U.S. youth infected through risk behaviors.⁷ In that study, we examined patient-related barriers that included the following: self-efficacy, outcome expectancy, mental health, and structural barriers.

Self-efficacy for antiretroviral adherence is one's sense of being able to adhere to the medications prescribed. Outcome expectancy for antiretroviral therapy is one's sense of benefit from taking therapy. Structural barriers are environmental

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factors in everyday life that can interfere with adherence to therapy. The structural barriers that we studied included the following: a place to sleep; medical insurance; transportation to get medications; transportation to the clinic; getting the medications filled; problems related to work or school; and problems related to family or child care, either their own children or someone else's children. Items were selected from both literature review and clinical experience of the investigators. These factors, in addition to mental health issues, have been shown to impact the ability to adhere to antiretroviral therapy.^{6,8-14}

In our study of adolescents and young adults infected through risk behaviors, of the 396 subjects, 148 (37.4%) self-identified as nonadherent. No significant differences were found between adherent and nonadherent subjects for the presence of mental health disorders. Adherence was significantly associated with all but one structural barrier. Both self-efficacy and outcome expectancy were higher among adherent versus nonadherent subjects ($p < 0.0001$). Grouping subjects according to low self-efficacy and outcome expectancy for adherence, adherence differed according to the presence or absence of mental health disorders and structural barriers ($p < 0.0001$).⁷ These data suggested that adolescents have significant problems with nonadherence and that individuals often face multiple personal barriers.

In the current study we investigated the prevalence of and relationships between possible barriers to antiretroviral medication adherence among perinatally infected youth: self-efficacy, outcome expectancy, mental health issues, and structural barriers to adherence. We hypothesized that although perinatally infected subjects may have adequate social support because of long-standing infection with HIV and parental involvement, developmental issues related to adolescence may lead to problems with adherence.

Methods

This was a cross-sectional, observational study designed to assess patient-related factors associated with HIV medication nonadherence and how these factors are associated with one another in adolescents and young adults. The target population for this study consisted of adolescents and young adults, 12 through 24 years of age, infected with HIV through perinatal transmission, who were eligible and offered and/or prescribed HAART based on the US Public Health Service (DHHS) guidelines. The study included individuals who were currently prescribed HAART, subjects who were prescribed HAART in the past, and subjects who had never been on HAART because they refused to initiate therapy although it was recommended to them by their provider. The study was approved by the Institutional Review Boards at each site recruiting subjects.

Procedures

Study procedures have been described in depth previously.⁷ In brief, participants were recruited through either the Adolescent Trials Network for HIV/AIDS Interventions (ATN) or the Pediatric AIDS Clinical Trials Group (PACTG), through sites funded to conduct HIV-related research. A total of 19 sites recruited subjects to this study.

Consent was obtained from either the subject or parent, depending on the requirements of the Institutional Review

Board at the site and the age of the subject. At each site, study questions were asked via face-to-face interviews with the subject by a study coordinator trained in clinical research. Specific variables were considered present only if they were reported as present at the time of either the interview or chart review, which was performed within 14 days of subject enrollment into this study. The interview was performed prior to chart abstraction.

Medication adherence

The Adherence Staging Algorithm, pilot tested and modified based on findings from Phase I of the study, was administered in a face-to-face interview in a private setting. Subjects were classified as adherent or nonadherent on the basis of their responses to questions asking about their experiences in taking these medications. The responses to the adherence questions were dichotomized as "started HAART and currently adherent" versus "other," with the other category including all nonadherent subjects: those prescribed HAART but refused to take them, those prescribed HAART but now stopped taking them completely, those prescribed HAART but taking less than the full regimen, and those prescribed HAART but non-adherent. A subject was considered adherent if they adhered to 85% or greater of doses in their current antiretroviral regimen; for a subject prescribed to take medications twice a day, this corresponds to missing no more than two doses per week, while for a subject on once a day therapy this corresponds to missing no more than one dose per week. This was a global self-assessment of adherence with 85% chosen due to the risk for viral breakthrough and resistance at lower levels of adherence.¹⁵

Chart abstraction

Study coordinators reviewed patient charts and abstracted the following information: diagnoses of mental health disorders, including substance dependence and abuse; most recent CD4⁺ T-cell counts and HIV RNA levels; occurrence of category C AIDS-defining conditions; and current antiretroviral regimen. The presence of mental health disorders was based on clear documentation of a disorder in the medical record and classified into the following categories: mood disorders, schizophrenia, anxiety, attention deficit hyperactivity disorder (ADHD), developmental delay, and "other" mental health disorders. Data on substance use and abuse were poorly and inconsistently documented in the medical record. Thus, data on substance abuse are not considered further.

Interview measures

Self-efficacy for adherence. Ten items adapted from the Adult AIDS Clinical Trials Group (AACTG) adherence instrument were administered.⁶ All items were prefaced with, "How confident are you that you can . . .", and were scored on a scale ranging from 0 (not at all confident) to 10 (completely confident). Items addressed issues related to the treatment schedule (e.g., How confident are you that you can: make taking your medication part of your daily routine?; stick to taking your medications even if you aren't feeling well?). Selected items from this scale have been utilized in research studies with adults and found to have very good internal consistency.¹⁶

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION OF PERINATALLY HIV-INFECTED YOUTH ACCORDING TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY MEDICATION ADHERENCE ($n = 368$)

Demographic characteristics	Overall ($n = 368$)	Adherence		<i>p</i> value ^a
		Adherent ($n = 274$)	Nonadherent ($n = 94$)	
Gender: <i>n</i> (%)				
Female	203 (55.2)	148 (72.9)	55 (27.1)	0.47
Male	165 (44.8)	126 (76.4)	39 (23.6)	
Age:				
Mean (SD)	16.4 (2.7)	16.0 (2.5)	17.6 (2.9)	<0.0001
Median	15.7	15.5	17.3	<0.0001
Race: <i>n</i> (%)				
Asian/Pacific Islander	3 (0.8)	2 (66.7)	1 (33.3)	0.32
Black/African American	221 (60.1)	162 (73.3)	59 (26.7)	
Native American/Alaskan Native	2 (0.5)	1 (50.0)	1 (50.0)	
White	46 (12.5)	39 (84.8)	7 (15.2)	
Other/mixed race	96 (26.1)	70 (72.9)	26 (27.1)	
Hispanic or Latino origin: <i>n</i> (%)				
Yes	107 (29.1)	77 (72.0)	30 (28.0)	0.51
No	261 (70.9)	197 (75.5)	64 (24.5)	
AIDS-defining condition: <i>n</i> (%)				
Yes	232 (63.0)	172 (74.1)	60 (25.9)	0.25
No	133 (36.1)	101 (75.9)	32 (24.1)	
Unknown	3 (0.8)	1 (33.3)	2 (66.7)	
CD4 count (cells/mm ³):				
Mean (SD)	496.7 (339.3)	559.0 (337.8)	316.3 (273.8)	<0.0001
Median	462.5	532.5	271.0	<0.0001
Unknown	2	2	0	
HIV-1 RNA (copies/ml):				
Mean	102,123	63,409	176,851	0.21
SD	500,307	186,128	814,441	
Median	7,784	4,769	16,188	0.0006
Unknown	116	108	8	
Geometric mean ^b	7,036	4,518	16,546	0.0002

^aFisher's exact test was used to assess associations of adherence with categorical measured variables. For continuous variables (age, CD4 count, and HIV-1 RNA) the Student's *t*-test and nonparametric testing was used for assessing associations with adherence.

^bThe geometric mean is the antilog of the mean of log₁₀-transformed HIV-1 RNA values and is interpreted similarly to the simple mean.

Outcome expectancy for adherence. Outcome expectancy for antiretroviral adherence was assessed through seven items on the subject's impression of the impact of taking antiretroviral therapy. Murphy et al.¹⁷ adapted questions from a medication adherence study with adults,¹⁸ and those items with high internal consistency were selected for use in this study. A five-point Likert scale, from strongly disagree to strongly agree, was used. Both positive expectancies (e.g., taking medications as prescribed will help to stay well), and negative expectancies (e.g., taking medication as prescribed will result in troublesome side effects) were assessed.

Both the self-efficacy (SE) for adherence and outcome expectancy (OE) regarding antiretroviral treatment were derived as the sum of responses to each series of questions.

Environment (structural barriers). Seven questions were asked to investigate the environment of the adolescent that may impact medication adherence. Subjects were asked if any of the following made it difficult for them to take their HIV medications: having a place to sleep; problems with medical insurance, transportation to pick up medications or get to the clinic for provider visits; problems getting the medication prescriptions filled; problems related to job or school; and problems related to family or child care, either their children

or someone else's children. Items were selected from both literature review and clinical experience of the investigators. The responses were recorded as either yes or no responses.

Statistical analysis

Simple univariate statistics (mean, standard deviation [SD], median, percentages) were used to describe the characteristics of the study population. The Student's *t* test and Wilcoxon rank sums test were used to assess associations with adherence for continuous characteristics and Fisher's exact test for categorical measures. HIV-1 RNA was log₁₀-transformed for analysis. For scaled measures such as SE and OE, Cronbach α was used to assess how well the variables contributing to each scale measured a single unidimensional latent construct. Based on Cronbach α , SE (0.88) has acceptable reliability but OE (0.52) does not. This suggests that the variables contributing to SE are measuring the same underlying construct, while those for OE may not be measuring the underlying construct they are intended to. The wider range for Cronbach α obtained with sequential deletion of variables from the OE scale supports this possibility. Logistic regression was used to investigate the association of the barriers to medication regimen.

The final analyses were restricted to those subjects with both high SE and OE or low SE and OE, given inherent

ambiguity in interpreting the relationship of SE and OE to adherence that would otherwise arise if discordant categories (high SE/low OE or low SE/high OE) were included.

Analyses were carried out using SAS, version 8 (SAS Institute, Cary, NC), with *p* values of 0.05 or less to define statistical significance.¹⁹ Multiple comparison corrections were not used, and missing values (varying in number among the outcomes) were not imputed.

Results

A total of 368 adolescents and young adults HIV infected through perinatal transmission were enrolled into the study. Overall, 55.2% of the study population was female, 60.1% black/African American, 29.1% self-identified as Hispanic or Latino origin, and 63.0% had an AIDS-defining condition. The median CD4⁺ T cell count was 462.5 cells/mm³, and the median HIV-1 RNA was 7784 copies per milliliter (geometric mean 7036). Among the 368 subjects, 274 (74.5%) were adherent and 94 (25.5%) were nonadherent to HAART. Of those who were nonadherent, 4 subjects were prescribed HAART but never started, 33 had started HAART but had now stopped, 28 were prescribed HAART but were taking less than HAART, and 29 had started HAART but were non-adherent. Adherence was not associated with gender, race, Hispanic/Latino origin or AIDS defining condition (*p* > 0.2; Table 1). The mean and median age of those who were adherent was significantly less than that of those who were nonadherent (*p* < 0.0001). As might be expected, the mean and median CD4 counts were higher among adherent than nonadherent subjects (*p* < 0.0001). Median and geometric mean HIV-1 RNA level were significantly lower in adherent than non-adherent subjects (*p* < 0.001).

The relationship of mental health disorders to adherence is shown in Table 2. Having a formal diagnosis of a major mental health disorder was not associated with adherence overall, nor were any of the individual mental health diagnoses (*p* ≥ 0.3). Structural barriers to adherence are presented in Table 3. Subjects who encountered structural barriers in terms of facing problems with medical insurance, problems related to job or school, and problems dealing with family or taking care of children were less adherent than those not experiencing these barriers (*p* < 0.04). Having a place to sleep at night, experiencing problems with transportation to pick up medicines or get to the clinic for a visit with their provider, and problems getting medication prescriptions filled were not associated with adherence (*p* > 0.1). In terms of the number of barriers experienced, adherence decreased with increasing number of barriers (*p* = 0.0012); 80.4% of those with no barriers were adherent compared to 65.8% among those experiencing one barrier and 59.2% of those experiencing two or more barriers.

Mean [± SE] and median SE differed significantly between adherent (80.3 ± 16.2, 85) and nonadherent (60.7 ± 20.5, 60) participants, as did the mean (29.0 ± 4.3 versus 26.1 ± 5.0, respectively) and median (30 versus 26, respectively) OE (*p* < 0.0001). Although Cronbach α for outcome expectancy is somewhat lower than desired for this type of scale, outcome expectancy regarding antiretroviral treatment was included in the remaining analyses given the exploratory nature of this investigation. Bandura^{20–22} has proposed that behavior is best predicted by considering the combined influence of efficacy beliefs and the types of performance outcomes expected,

TABLE 2. EXAMINATION OF MENTAL HEALTH HISTORY AMONG PERINATALLY HIV-INFECTED SUBJECTS ACCORDING TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY MEDICATION ADHERENCE

Subject carries a formal diagnosis of:	Adherence		<i>p</i> value ^a
	Adherent	Nonadherent	
A major mental health disorder:			
Yes	76 (73.1)	28 (26.9)	0.79
No	187 (74.8)	63 (25.2)	
Unknown	11	3	
Attention deficit hyperactivity disorder (ADHD):			
Yes	18 (85.7)	3 (14.3)	0.30
No	245 (73.6)	88 (26.4)	
Unknown	11	3	
Anxiety:			
Yes	1 (50.0)	1 (50.0)	0.45
No	262 (74.4)	90 (25.6)	
Unknown	11	3	
Developmental delay:			
Yes	3 (75.0)	1 (25.0)	1.00
No	260 (74.3)	90 (25.7)	
Unknown	11	3	
Mood disorder:			
Yes	41 (69.5)	18 (30.5)	0.41
No	222 (75.3)	73 (24.7)	
Unknown	11	3	
Schizophrenia:			
Yes	1 (100.0)	0	1.00
No	262 (74.2)	91 (25.8)	
Unknown	11	3	
Other mental health disorders:			
Yes	12 (70.6)	5 (29.4)	0.78
No	251 (74.5)	86 (25.5)	
Unknown	11	3	

^a*p* value obtained using Fisher's exact test for association of mental health disorders with adherence. The relatively small number of subjects with "unknown" status for formal diagnosis of mental health disorders were excluded from this testing.

particularly when the performance of a behavior does not guarantee good outcomes. A number of studies have found that consideration of the influence of both self efficacy and outcome expectancy beliefs are required to determine their impact and interactions on a range of behaviors.

To better understand the relationship between SE, OE, and adherence, subjects were grouped into quartiles from low to high for SE and OE. Based on logistic regression modeling, SE and OE, categorized in quartiles, were significantly and independently associated with adherence (*p* value of < 0.0001 and 0.0017, respectively).

A 9 *df* test of the interaction of SE with OE did not support the hypothesis that SE modifies the relationship of OE to adherence or, equivalently, that OE modifies the relation of SE to adherence (*p* = 0.37).

To understand the typology of adherence, the association of the eight-level composite variable created to capture the combinations of the three personal barriers to medication

TABLE 3. EXAMINATION OF STRUCTURAL BARRIERS (CURRENTLY AND/OR IN THE PAST SIX MONTHS) AMONG PERINATALLY HIV-INFECTED SUBJECTS ACCORDING TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY MEDICATION ADHERENCE

<i>Do you face any of the following problems that make it difficult for you to take your HIV medications?</i>	<i>Adherence</i>		<i>p value^a</i>
	<i>Adherent</i>	<i>Nonadherent</i>	
Do you always have some place to sleep at night?			
Yes	11 (64.7)	6 (35.3)	0.39
No	263 (74.9)	88 (25.1)	
Problems with medical insurance?			
Yes	11 (52.4)	10 (47.6)	0.035
No	263 (75.8)	84 (24.2)	
Problems with transportation to pick up your medicines?			
Yes	12 (80.0)	3 (20.0)	0.77
No	262 (74.2)	91 (25.8)	
Problems with transportation to get to the clinic for your visit with your provider?			
Yes	21 (65.6)	11 (34.4)	0.29
No	253 (75.3)	83 (24.7)	
Problems getting your medication prescriptions filled?			
Yes	24 (63.2)	14 (36.8)	0.11
No	250 (75.8)	80 (24.2)	
Problems related to your job or school?			
Yes	24 (60.0)	16 (40.0)	0.034
No	250 (76.2)	78 (23.8)	
Problems dealing with your family or taking care of your children, either your own or someone else's children?			
Yes	16 (45.7)	19 (54.3)	0.0001
No	258 (77.5)	75 (22.5)	
Number of structural barriers:			
None	193 (80.4)	47 (19.6)	0.0012
One barrier	52 (65.8)	27 (34.2)	
Two or more barriers	29 (59.2)	20 (40.8)	

^a*p* values were obtained from Fisher's exact test examining the association of structural barriers with adherence.

adherence was examined (Fig. 1). Percent adherence ranged from 33.3% to 95.5%, with adherence consistently above 80% for high SE/high OE and typically lower for low SE/low OE; a generalized Fisher's exact test indicated that adherence differed according to the presence or absence of personal barriers to adherence ($p < 0.0001$). Logistic regression modeling indicated that SE/OE ($p < 0.0001$) and structural barriers ($p = 0.027$) were significantly and independently associated with medication adherence, but that the presence of a mental health disorder was not ($p = 0.2$) after adjusting for the other two barriers; additional modeling indicated that there were no significant interactions among the barriers in their effect on medication adherence. Thus, clustering of adherence barriers appears to occur in subjects with poor adherence.

Discussion

In our current study, SE and OE were significantly related to adherence, regardless of other barriers. Of those subjects with low SE and low OE, who also had a documented mental health disorder and reported experiencing a structural barrier, over half were nonadherent. The finding that these different barriers coexist in some participants leading to higher rates of nonadherence calls for the development of interventions that address multiple barriers to adherence. These findings demonstrate that adolescents infected with HIV, regardless of mode of infection, can often face multiple barriers to adherence and simple, unimodality interventions may be insufficient in addressing the complexities of nonadherence in this population.

Both self-efficacy and outcome expectancy have been shown to impact adherence.^{6,11,12,14,23–26} Although Cronbach α for OE was low, it was independently associated with adherence and thus was included in the analysis. There was no significant interaction of OE with SE, with each being independently associated with adherence. Self-efficacy and outcome expectancy interventions will be integral components to comprehensive adherence interventions given their strong associations with adherence. The development of scales that are validated for these specific populations will be essential first steps toward successful interventions targeting these barriers. Interventions targeting these barriers will need to be tested in ways that would allow their application in clinical settings if they are shown to be effective.

Depression has been commonly associated with poor adherence in HIV-infected persons.^{27–29} In this study, we found no association of mental health barriers with adherence. This finding was similar to our finding in behaviorally infected subjects. It is possible that those with a documented mental health disorder may have been more likely to be under treatment, and if such treatment were successful, it would lead to these problems having less of an impact on adherence. However, because we used chart abstraction to collect these data, it is possible that we may have underestimated the true number of subjects with mental health disorders as they may not have been adequately recorded in the chart. In addition, those with depressive symptoms that do not meet criteria for major depression may also be missed through chart review. This was true also in our study with behaviorally infected

FIG. 1. Distribution of adherence for subjects according to personal barriers to adherence.

adolescents. Further data are needed on mental health disorders and their impact on adherence in this population, especially through direct measures that would help identify both symptoms and true disorders.

Compared to adolescents infected through risk behaviors, subjects in this study were less likely to have structural barriers associated with poor adherence: seven of eight structural barriers were significantly associated with nonadherence in the behavioral group compared to four out of eight in this study. This was an unexpected finding. As these subjects tended to be younger than subjects infected through risk behaviors, one could hypothesize that these youth were more likely to have family support compared to adolescents infected through risk behaviors and therefore, less likely to experience structural barriers to adherence (having no place to sleep; having no transportation). It does raise the important issue that all adolescents may not experience the same issues as barriers, depending on other factors, such as age and route of infection. Such differences would be crucial when developing interventions for a population.

Our study had some significant limitations. First, this was a cross-sectional study. Clearly, barriers could change over time

and an understanding of these changes would be crucial to implementing effective interventions. Second, as noted, we did not measure mental health disorders or substance abuse directly and therefore were limited in interpreting data related to these variables. Third, our measure of outcome expectancy had a low Cronbach α and thus refinement of this scale would be essential for any future studies looking at this variable.

Congruent with our previous study in behaviorally infected adolescents, adolescents often face multiple barriers to adherence. Notably, adherence decreased with increasing number of barriers. These findings make it essential that we understand these barriers and develop interventions that can address multiple barriers in order to have the greatest impact on nonadherence in HIV-infected adolescents prescribed HAART. Future research with interventions that target multiple barriers is greatly needed.

Acknowledgments

The Adolescent Trials Network for HIV/AIDS Interventions (ATN) is funded by grant No. U01 HD040533 and U01

HD040474 from the National Institutes of Health through the National Institute of Child Health and Human Development (B. Kapogiannis, L. Serchuck), with supplemental funding from the National Institutes on Drug Abuse (N. Borek) and Mental Health (P. Brouwers, S. Allison). Additional support was provided by The Pediatric AIDS Clinical Trials Group funded by grant No. U01- A141089.

The study was scientifically reviewed by the ATN's Behavioral Leadership Group. Network, scientific and logistical support was provided by the ATN Coordinating Center (C. Wilson, C. Partlow) at The University of Alabama at Birmingham. Network operations and analytic support was provided by the ATN Data and Operations Center at Westat, Inc. (J. Korelitz, B. Driver).

The following ATN sites participated in this study: University of South Florida (Emmanuel, Lujan-Zilberman, and Callejas), Children's Hospital of Los Angeles (Belzer, Salata, Tucker), Children's Hospital National Medical Center (D'Angelo, Trexler, and Crane), Children's Hospital of Philadelphia (Rudy, Tanney, DiBenedetto), John H. Stroger Jr. Hospital and the CORE Center (Martinez, Bojan, and Jackson), University of Puerto Rico (Febo, Blasini, and Rivera), Montefiore Medical Center (Futerman, Catallozzi, Enriquez-Bruce), Mount Sinai Medical Center (Levin-Carmine, Geiger, Lee), University of California-San Francisco (Moscicki, Auerswald), Tulane University Health Sciences Center (Abdalian, Kozina, Jeanjacques), University of Maryland (Peralta, Colocho, Flores), University of Miami School of Medicine (Friedman, Maturo, Major- Wilson), Children's Diagnostic and Treatment Center (Puga, Leonard, Inman), Children's Hospital Boston (Samples, Cooper, and Mahoney-West), and University of California-San Diego (Spector, Viani, Stangl). The following PACTG sites participated in the study: St Jude Children's Research Hospital (Flynn, Dillard, DiScenza), Children's Hospital of Boston (Samples, Burchett), Boston Medical Center (Cooper, Pelton), University of Florida College of Medicine/Jacksonville (Rathore, Mirza, Thoma).

Author Disclosure Statement

No competing financial interests exist.

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