

# Sleep Disturbances in Children With Human Immunodeficiency Virus Infection

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**ABSTRACT.** *Objective.* To describe the sleep patterns and level of fatigue in children and adolescents (6–18 years of age) with HIV infection, compared with ethnic-, gender-, and age-matched healthy children in the home setting.

*Design.* Descriptive, comparative.

*Setting.* Conducted in each child's home environment.

*Study Participants.* Eighteen HIV-infected and 15 noninfected children completed the study. The Centers for Disease Control and Prevention HIV classifications for the 18 HIV-infected children were: A ( $n = 7$ ), B ( $n = 6$ ), and C ( $n = 5$ ).

*Methods.* A symptom diary was developed using a previously validated fatigue assessment scale, modified for use with children. Content validity of the diary was established with a panel of 5 experts in child development and pediatric HIV disease. Children were asked to complete the diary each morning and evening for 3 days. Each child wore a wrist actigraph during the same period.

*Results.* The HIV-infected children had significantly more wake time after sleep onset, compared with noninfected children (13.55% vs 7.47%). The HIV-infected children had more awakenings (25.33 vs 16.71) and were awake for longer periods (3.01 vs 1.01 minutes), compared with noninfected children. By parent report, 7 HIV-infected children napped and 2 noninfected children napped, indicating greater daytime fatigue in the HIV-infected children. HIV-infected children also reported a greater level of evening tiredness (2.47 vs 1.8).

*Conclusions.* The findings from this study suggest that sleep disturbances occur in HIV-infected children, similar to findings previously described in HIV-infected adults. Additional research is necessary to characterize the nature and patterns of sleep disturbance and fatigue related to pediatric HIV-infection, to assess the impact these may have on daily activities, and to develop strategies to improve sleep for these children. *Pediatrics* 1999; 104(5). URL: <http://www.pediatrics.org/cgi/content/full/104/5/e62>; *human immunodeficiency virus infection, sleep, fatigue, actigraphy.*

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ABBREVIATION. HIV, human immunodeficiency virus.

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Sleep is a primary function of life, and both quantity and quality of sleep are affected by a person's health status. Sleep disturbances, daytime drowsiness, and fatigue are significant problems for human immunodeficiency virus- (HIV-) infected men<sup>1-5</sup> and women<sup>4-6</sup> that affect daily functioning and well being. Sleep disturbances, particularly increased awakening after sleep onset and daytime fatigue, increase with advancing disease.<sup>3,4,7</sup> Sleep may be influenced by other factors, such as medication and diet. However, there are conflicting data on the effects of antiretroviral agents on sleep in HIV-positive adults. Richman et al<sup>8</sup> found that significantly more patients had sleep disturbances when treated with zidovudine. Other investigators found no effect of zidovudine on sleep<sup>4</sup> or daytime fatigue.<sup>6</sup>

The prevalence, severity, and effects on daily activity of sleep disturbances and fatigue have not been described in HIV-infected children. The incidence, frequency, or severity of symptoms also has not been examined, with respect to the stage of disease and the treatment of children. The impact of these symptoms on a child's ability to perform daily activities, such as school and play, also is unknown.

Sleep patterns of healthy<sup>9,10</sup> and ill children in the home setting have been described using parent and child reports. Shapiro et al<sup>11</sup> characterized the pain and fatigue in 18 children with sickle cell disease over a 10-month period by having the children complete daily diaries. Pain was correlated with decreased sleep and increased school absenteeism. Using questionnaires and home diaries, Vir et al<sup>12</sup> found that 28 of 30 (93%) adolescents with asthma experienced more frequent sleep disturbances and slept for shorter periods than did healthy adolescents. Sleep diaries and parental reports of child sleep habits revealed that children with Attention Deficit Hyperactivity Disorder had delayed sleep onset and sleep disturbances.<sup>13</sup>

A more objective measure of sleep, the wrist actigraph, provides quantitative movement data that are analyzed using an algorithm previously validated by sleep electroencephalogram to calculate sleep onset, duration, sleep efficiency (ie, total time spent asleep divided by total time spent in bed), and mean activity level.<sup>14</sup> An actigraph algorithm has been developed and validated in children<sup>12</sup> to study sleep disturbances of various etiologies.<sup>14-16</sup> Multiple mea-

asures of sleep quality, such as parent and child reports and wrist actigraphy, may provide more precise and complete information regarding disturbed sleep and daytime sequelae, including fatigue. These measures have not been used to evaluate the sleep and fatigue of HIV-infected children.

The Pediatric Acquired Immunodeficiency Syndrome Clinical Trails Group Supportive Care Quality of Life Committee has encouraged the development of protocols to study methods to improve supportive care of HIV-infected children.<sup>17</sup> However, these protocols cannot be developed until there is sufficient description of the phenomenon of symptoms experienced by children. In this article, we report our findings that HIV-infected children exhibited sleep and fatigue problems, compared with noninfected children as part of a larger study in which the overall symptom experience of HIV-infected children in the home setting was described.

## METHODS

### Setting and Patient Selection

Children (6–18 years of age) with documented HIV infection from the Ryan White HIV Clinic and the Pediatric Clinical Research Center at the University of California, San Francisco and from the Pediatric Clinical Research Center at the Children's Hospital, Oakland were invited to participate in the study. Children with unknown HIV status were excluded from the study. Noninfected siblings or friends also were invited to participate, if referred by the HIV-infected child's parent. Additional noninfected children, matched for age, gender, and ethnicity with the HIV-infected children, were recruited from the local community. Children with chronic medical conditions or who used medication regularly were excluded from the control group. All children were able to read and write English.

Informed consent was obtained from the parent or legal guardian before enrollment in the study. Assent also was obtained from children who were  $\geq 8$  years of age. The institutional review board of each site approved the study.

Children initially were asked to complete the diary each morning and evening for 7 days. However, after  $\sim 20\%$  of the subjects had been enrolled, the children were asked to complete the diary for only 3 days, because some of the wrist straps on the actigraph broke or the actigraphs were removed for sport activities.

### Instruments

#### *Symptom Diary*

A symptom diary was developed using previously validated pediatric pain assessment scales,<sup>18,19</sup> a fatigue assessment scale<sup>20</sup> that was modified for use with children, and appetite and gastrointestinal distress assessment scales that were developed for this study. The content validity of the diary was established with a panel of 5 experts in child development and pediatric HIV disease. A pilot study was conducted with 7 children to determine the ease of use and compliance with use of the diary. Following the pilot study, two versions of the diary were prepared with age appropriate graphics and language; the school age version was used for children 6 to 11 years of age and the adolescent version was used for children 12 to 18 years of age.

#### *Parent Interviews*

Before the children began the study, parents were interviewed about their child's sleep habits. Parents and children also were interviewed at the end of the study and were asked questions regarding how representative the study period was of the child's usual sleep. Parents and children were asked about other physical or emotional factors that might have influenced the children's sleep during the study period. Children were asked to complete the diary each morning and evening for the study.

### *Wrist Actigraphy*

A wrist actigraph (Mini Motionlogger AAM-32; Ambulatory Monitoring Inc, Ardsley, NY) was worn by each child during the same period that the diary was kept. The actigraph movement-sampling interval was 30 seconds. Children were asked to press the actigraph event marker at bedtime when the lights were turned out, in the morning when they awoke, and at the beginning and end of naps. Sleep onset, number of awakenings, total sleep minutes, length of awakenings, sleep efficiency, and wake after sleep onset were calculated using the automatic scoring program in Action 3 (Ambulatory Monitoring Inc) analyzing activity data in 2-minute intervals.

### Statistical Analysis

Sample characteristics were analyzed using descriptive statistics. The mean values for the actigraph sleep parameters and fatigue scale were calculated for the total number of days completed by each child. The first night actigraph data were not used in the analysis to control for the possible first night effects of the child adapting to wearing the wrist device. Mean values for the study period for each child were used in the analyses. Comparisons between the HIV-infected and noninfected groups were analyzed using  $\chi^2$  analysis and the Student's *t* test. Associations between the actigraph and diary data were analyzed using  $\chi^2$  analysis and the Spearman rank correlation.

## RESULTS

### Sample Population

A convenience sample of 18 racially diverse children with HIV infection participated in the study, with a mean of 10.61 years of age (range: 6–18; see Table 1). One child acquired HIV from a blood transfusion during the first 3 years of life. All other children were infected by perinatal transmission. The diagnosis of HIV was established in all cases, and disease stage was classified according to criteria for pediatric HIV disease from the Centers for Disease Control and Prevention.<sup>21</sup> Table 2 shows the clinical and immunologic status of the 18 HIV-infected children. Of the children, 5 had nonsymptomatic disease, 6 had mild symptoms, and 4 had moderate symptoms. The mean percent CD4 count was  $0.22 \pm 0.18$  standard deviation. The virus was undetectable in 6 children ( $<500$  copies/mL), 500–100 000 in 3 children, 100 000–500 000 in 6 children, and  $>500$  000 in 3 children. All the children were receiving nucleoside reverse transcriptase inhibitors, with 1 (6%) child receiving monotherapy, 15 (83%) children receiving 2-drug combination therapy, and 2 (11%) children receiving 3-drug combination therapy (see Table 2).

Fifteen noninfected children of similar ethnicity and age also completed the study. The noninfected

TABLE 1. Characteristics of Sample

	HIV-Infected	Noninfected
<i>n</i>	18	15
Age (y; mean $\pm$ SD)	10.61 $\pm$ 3.50	10.87 $\pm$ 3.27
Study period (d; mean $\pm$ SD)	3.50 $\pm$ 2.15	2.73 $\pm$ 2.22
Gender		
Female	7	6
Male	11	9
Ethnicity		
White	7	8
Black	5	5
Hispanic	3	0
Asian	2	2
American Indian	1	0

**TABLE 2.** Characteristics of HIV-Infected Children (*n* = 18)

Case	HIV Classification	CD4%	Viral Load	Treatments			
				IVIG	NRTI	NNRTI	PI
1	N3	11	366	x	2 drug	-	x
2	N2	24	146	x	2 drug	-	-
3	A2	14	472	-	3 drug	x	-
4	N3	8	552	x	2 drug	-	-
5	B3	1	109	x	2 drug	-	-
6	N3	2	750	-	3 drug	x	-
7	N3	28	750	-	2 drug	x	-
8	B1	43	<0.5	x	2 drug	-	-
9	A3	28	<0.5	x	2 drug	-	x
10	A1	24	107	x	2 drug	-	x
11	A2	19	<0.5	-	2 drug	-	x
12	A3	33	1.4	x	2 drug	-	-
13	B2	9	<0.5	-	2 drug	-	x
14	B3	80	<0.5	x	2 drug	-	x
15	N2	25	6.6	x	2 drug	-	-
16	A3	15	<0.5	-	1 drug	-	-
17	N1	20	306	-	2 drug	-	-
18	N1	18	1.1	-	2 drug	-	x

HIV classification indicates CDC pediatric HIV classification; CD4%, % lymphocytes; viral load, kcopies per mL; IVIG, monthly intravenous immunoglobulin therapy; NRTI, nucleoside reverse transcriptase inhibitor therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor therapy; and PI, protease inhibitor therapy.

children had no chronic illnesses and were not taking any prescribed medications during the study period. The ages of the noninfected children ranged from 6 to 17 years of age, with a mean age of 10.87 (see Table 1).

The study primarily took place on weekdays (72.4%). There were no differences in any of the actigraph sleep measures based on age, gender, weekend or weekday study period, or length of study period among the HIV-infected and noninfected children. There was moderate to high stability in sleep efficiency across the study period ( $r = .61-.90$ ).

#### Parent Report

Based on parental report, the HIV-infected children slept ~1 hour less per night and had signifi-

cantly more problems sleeping, with nightmares and frequent waking, than did the uninfected children. More HIV-infected children were reported to nap than noninfected children (see Table 3).

#### Child Diary

There were no differences in problems falling asleep, problems sleeping, waking during the night, and degree of tiredness in the morning, reported by HIV-infected and noninfected children. More HIV-infected children reported taking naps and a greater degree of tiredness in the evening than did noninfected children (see Table 3), but the differences were not statistically significant.

#### Actigraphy

The HIV-infected children tended to be in bed longer than did the noninfected children during the study period (see Table 3). There was no significant difference in the latency to sleep onset between the two groups, however, HIV-infected children had significantly poorer sleep efficiency than did noninfected children (81.10% vs 88.41%;  $P = .008$ ). The poor sleep efficiency occurred because HIV-infected children awoke more frequently and stayed awake for longer periods during each waking episode than did noninfected children, and wake time after sleep onset was significantly higher in HIV-infected children, compared with noninfected children (13.55% vs 7.47%;  $P = .02$ ). There were no relationships between actigraph sleep measures and stage of HIV disease, CD4 count, or viral load.

#### Relationship Between Sleep and Napping

Eight (44%) of the HIV-infected children and 5 (33%) of the noninfected children napped during the study period. Children who napped tended to spend less time in bed at night and were awake for longer periods during the night than were children who did not nap. The mean age of children who napped was 11.23 ( $\pm 3.32$  standard deviation). There was no dif-

**TABLE 3.** Differences in Sleep Characteristics in HIV-Infected and -Noninfected Children\*

	HIV-Infected ( <i>n</i> = 18)	Noninfected ( <i>n</i> = 15)	<i>P</i> Value
Parent report			
Total sleep (hours)	8.18 $\pm$ 0.46	9.44 $\pm$ 0.19	.01
Problems sleeping	6 (33%)	1 (6%)	.05
Wakes up during night	8 (44%)	1 (6%)	.006
Nightmares	5 (27%)	0 (0)	.02
Naps	7 (39%)	2 (13%)	.07
Child diary			
Napped during study period	8 (44%)	5 (33%)	.43
Problems falling asleep	10 (56%)	6 (40%)	.29
Problems sleeping	5 (27%)	1 (6%)	.10
Awoke during night	15 (83%)	8 (53%)	.60
Morning tiredness (0-4)	1.71 $\pm$ 0.24	1.53 $\pm$ 0.22	.60
Evening tiredness (0-4)	2.47 $\pm$ 0.27	1.80 $\pm$ 0.24	.08
Actigraph (mean $\pm$ SD)			
Total sleep (h)	9.21 $\pm$ 0.32	8.28 $\pm$ 0.40	.08
Sleep onset (min)	23.68 $\pm$ 3.99	19.31 $\pm$ 3.63	.42
Number of awakenings	25.33 $\pm$ 2.29	16.71 $\pm$ 2.18	.01
Length of time awake (min)	3.01 $\pm$ 0.37	2.05 $\pm$ 0.22	.03
Sleep efficiency (%)	81.10 $\pm$ 1.85	88.41 $\pm$ 1.72	.008
Wake after sleep onset (%)	13.55 $\pm$ 1.80	7.47 $\pm$ 1.61	.02

\*Values reported as mean  $\pm$  standard error of the mean or frequency (%).

ferences in age between the children who napped and those who did not ( $t = -.73$ ;  $P = .47$ ). Two-way analysis of variance indicated differences between the two groups, based on HIV status for sleep efficiency ( $F = 5.19$ ;  $P = .03$ ) with no primary effect or interaction attributable to naps ( $F = 3.38$ ;  $P = .08$ ). Two-way analysis of variance revealed no primary effect or interaction caused by naps for the other actigraph sleep measures.

#### *Relationship Among Parent Report, Child Diary, and Actigraphy*

There was moderate agreement between parent report of nightmares or child waking at night and child report of problems falling asleep or problems sleeping ( $\kappa = 0.41$ – $0.49$ ;  $P < .02$ ). Parent and child reports of night awakening were associated with longer periods of awake during the night, as measured by wrist actigraph (Spearman correlation =  $0.68$ ;  $P = .0001$  and  $.51$ ,  $P = .01$ , respectively). Parent report of night awakening was associated with child report of morning tiredness (Spearman correlation  $.42$ ;  $P = .04$ ).

### DISCUSSION

The results of this study demonstrate that parent report, child diary, and wrist actigraphy can be used to provide important information about the quantity and quality of sleep in school age and adolescent children with HIV infection in the home setting. These findings suggest that children infected with HIV may experience significant sleep disturbances that are consistent with the findings of sleep disturbances previously described in HIV-infected adults.<sup>1–7</sup>

The mechanisms underlying HIV-associated sleep disturbance are unclear. Animal studies suggest that the HIV gp120 protein specifically affects cytokine concentrations in the central nervous system and alters sleep architecture.<sup>22</sup> Sleep disturbances have been found to occur early in the course of HIV infection in adults, before the onset of acquired immunodeficiency syndrome, and may be one of the first symptoms of HIV infection.<sup>1,3,4</sup> It has been hypothesized that these early sleep disturbances occur as a result of brain macrophage production of somnogenic lymphokines (eg, interleukin-1) in response to HIV-infection.<sup>23</sup> We did not find a relationship between sleep disturbance and disease progression in our sample, and additional research is needed to determine whether sleep disturbance is associated with disease progression in HIV-infected children.

Conversely, sleep disturbances and fatigue may precipitate changes in immune system function. Kruger and colleagues<sup>24</sup> suggested that impaired sleep may compromise immune function and increase risk of infection. Moldofsky et al<sup>25</sup> demonstrated increased pokeweed mitogen response and decreased natural killer cell activity after a 40-hour wakeful period in 10 healthy men. Although the impact of sleep disturbances on immune function in HIV-infected individuals has not been studied specifically, interventions to promote sleep in HIV-

infected individuals may prevent additional compromise of immune function.

Sleep disturbances result in daytime fatigue and affect functional status and quality of life in adults with HIV infection.<sup>2,3,7,26</sup> Parents of HIV-infected children reported that their children napped more frequently, but there was no difference in self-report of daytime napping between the HIV-infected and non-infected children in this study. Other measures of child daytime functioning, such as school participation, play, or activity level recorded objectively by actigraphy, may reveal relationships among sleep disturbances, functional status, and quality of life in children with HIV infection.

The effects of diet (ie, caffeine intake) and medication on sleep were not assessed in this study, nor were we able to determine the effects of family sleep practices on the quality of the children's sleep. Additional research using larger samples is needed to address these issues and to describe the time course of sleep disturbance in children as HIV disease progresses. The results of the present investigation indicate that studies of interventions to improve sleep and, specifically, the decrease the frequency and length of night waking are important areas for future research.

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