

Risk Factors for Opportunistic Illnesses in Children With Human Immunodeficiency Virus in the Era of Highly Active Antiretroviral Therapy

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Objective: To examine the relationship between the use of highly active antiretroviral treatment (HAART) and the occurrence of opportunistic illnesses (OIs) among children perinatally infected with human immunodeficiency virus.

Design: Prospective cohort study.

Setting: Pediatric AIDS Clinical Trials Group 219C cohort.

Participants: From September 15, 2000, to August 31, 2003, 1927 children perinatally infected with human immunodeficiency virus and receiving HAART were followed up.

Main Exposures: Age at initiating HAART, duration of HAART use, CD4⁺ T-lymphocyte percentage, and human immunodeficiency virus 1 viral load.

Main Outcome Measures: Incidence rates for Centers for Disease Control and Prevention OI category B and OI category C events were calculated. The association between main exposures and OI occurrence was estimated using proportional hazards regression.

Results: Of 1927 subjects, 226 (12.7%) developed OIs during follow-up. Incidence rates were 4.99 per 100 person-

years (95% confidence interval, 4.30-5.76) for first OI category B events and 1.47 per 100 person-years (95% confidence interval, 1.12-1.91) for first OI category C events. Duration of HAART use was not related to OI risk. Older age (age >10 years) at HAART initiation was associated with increased risk of a first OI (hazard ratio, 2.48; 95% confidence interval, 1.23-5.00) compared with initiating HAART in children younger than 2 years. This increased risk diminished after adjusting for CD4⁺ T-lymphocyte percentage and Centers for Disease Control and Prevention disease category at HAART initiation. More children with OIs than without OIs had a CD4⁺ T-lymphocyte percentage of less than 15% at HAART initiation (49.6% of children with OIs vs 23.7% of children without OIs), at enrollment (41.2% of children with OIs vs 7.7% of children without OIs), and at the end of follow-up (41.2% of children with OIs vs 8.3% of children without OIs).

Conclusions: Opportunistic illnesses are occurring in the pediatric human immunodeficiency virus population in the HAART era, mainly in children with persistently low CD4⁺ T-lymphocyte percentages. Lack of a sustained response to HAART rather than age at or duration of HAART use is predictive of OI risk.

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THE INTRODUCTION OF HIGHLY active antiretroviral treatment (HAART) has resulted in a declining incidence of opportunistic illnesses (OIs) in individuals with human immunodeficiency virus (HIV).¹⁻⁸ However, OIs among some individuals treated with HAART continue to occur,^{3,4} which may suggest a clinical failure of HAART. Generally, HAART causes a progressive improvement in immune function demonstrated by an increase in CD4⁺ T-lymphocyte (CD4) counts and a decrease in HIV-1 viral load.^{9,10} In children, HAART has been associated with a similar recovery in immunologic status,¹¹⁻¹⁴ although vi-

ral suppression is usually less evident in children compared with adults.¹⁵ A combination of CD4 percentage or counts and HIV-1 viral load have proven to be the best predictors of future disease progression and mortality in both adults and children.¹⁶⁻²⁰

Recently, the long-term effects of HAART on changes in the CD4 percentage were evaluated prospectively in the Pediatric AIDS Clinical Trials Group (PACTG) 219 cohort of children and adolescents with HIV in the United States.² The investigators reported a varied response to therapy according to the level of immunosuppression at the time of treatment initiation; children with the most severe im-

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munosuppression experienced the greatest increase in CD4 percentage over time. However, only about one third of these children achieved a CD4 percentage within the normal range (CD4 percentage $\geq 25\%$) after 3 years. Furthermore, 16% of the children who initiated HAART while their CD4 percentages were in the normal range had decreases in their CD4 percentages to less than 25% during follow-up.²

Few studies have examined the occurrence of OIs in relation to HAART use in pediatric HIV infection. Thus, we used data from a large US cohort of children perinatally infected with HIV who initiated HAART at different ages and levels of immunosuppression to examine the relationship between HAART use and other clinical, demographic, and virologic factors and the occurrence of OIs in the pediatric HIV population.

METHODS

The source population for this study was the PACTG 219C cohort, which began enrollment in September 2000 to assess the long-term effects of in utero, perinatal, and childhood exposure to antiretroviral therapy (ART) in children with HIV across the United States. The PACTG 219C protocol is a revised version of PACTG 219, a protocol initiated in 1993 and described in detail elsewhere.²¹ Children eligible for the current study must have been perinatally infected with HIV and must have received HAART (as defined later) prior to or at enrollment in PACTG 219C. Institutional review board approval was obtained at all of the participating clinical centers, and the children's parents or guardians provided written informed consent. There were 2318 subjects perinatally infected with HIV enrolled in PACTG 219C between September 15, 2000, and August 31, 2003, and 1323 (57.1%) of them were previously enrolled in PACTG 219. Of the 2318 subjects, 12 (0.5%) were never treated with ART, 276 (11.9%) never received HAART, 101 (4.4%) initiated HAART after enrollment in PACTG 219C, and 2 (0.1%) had no follow-up after enrollment and thus were excluded. The remaining 1927 subjects (83.1%) met the eligibility criteria and were subsequently followed up for the occurrence of OIs until August 31, 2003.

At enrollment in PACTG 219C and every 3 months thereafter, participants underwent a physical examination and a medical history was obtained, including information on signs, symptoms, or diagnoses of any OIs (defined according to the Centers for Disease Control and Prevention [CDC] disease classification of pediatric HIV infection).^{22,23} Information on treatment (including prophylactic treatment) or hospitalization for any OIs was also recorded. Measures of HIV-1 viral load and CD4 counts and percentages were also collected at each visit.

Detailed information on lifetime ART use, including start and stop dates of each drug, was obtained at enrollment in PACTG 219C. Use of HAART was defined as combination ART with at least 3 drugs, of which at least 1 was either a protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor.⁸⁻¹⁰ Duration of HAART use was defined as time from HAART initiation to enrollment in PACTG 219C and was categorized into 3 groups: 0 to less than 1 year, 1 to less than 4 years, and 4 or more years. These categories were chosen to represent short-term, medium-term, and long-term HAART use. Subjects were further classified according to age at HAART initiation (ages 0 to <2 years, 2 to <10 years, and ≥ 10 years). In addition, treatment experience prior to initiating HAART, excluding zidovudine prophylaxis, was considered. Any change from one ART drug or combination of drugs to another was considered a change

in regimen. Thus, subjects were categorized as treatment naive, receiving 1 to 2 ART regimens, or receiving 3 or more different ART regimens prior to HAART. Subjects were also classified according to the number of different HAART regimens they received from HAART initiation to enrollment in PACTG 219C (1 HAART regimen and treatment naive at HAART initiation, 1-2 different HAART regimens, and ≥ 3 different HAART regimens).

The main outcome was the first occurrence of an OI during follow-up in PACTG 219C (regardless of OI events before enrollment). All of the OI events were classified according to the CDC's criteria for pediatric HIV infection^{22,23} as category B (OI-B) or category C (OI-C) events based on the type of OI and the subject's history of OIs. If a subject had a first OI-B event and a subsequent OI-C event, both the OI-B and OI-C events were considered in the respective incidence and regression analyses. However, if a subject had a first OI-C event and a subsequent OI-B event, only the OI-C event was considered. For pneumonias, only presumed events (with radiological and clinical evidence of pneumonia) or proven events (that were culture confirmed) were considered.

Incidence rates (per 100 person-years) and exact Poisson 95% confidence intervals (CIs) for the first OI (either OI-B or OI-C) event, the first OI-B event, and the first OI-C event were calculated for the period between September 15, 2000, and August 31, 2003. For these analyses, end of follow-up was defined as the date of the first OI event, date of loss to follow-up, or August 31, 2003, whichever came first. In addition, incidence rates (per 100 person-years) and exact Poisson 95% CIs for specific OIs (both OI-B and OI-C events) were calculated for the follow-up period.

The median CD4 percentage and HIV-1 viral load at enrollment and at the end of follow-up in PACTG 219C were determined for all of the study subjects. Subanalyses were performed among 741 study subjects previously enrolled in PACTG 219 for whom we had information on CD4 percentage at the time of HAART initiation. The HIV-1 RNA measurements were not recorded in the PACTG 219 protocol and thus could not be determined at HAART initiation. In addition, the proportion of subjects in different categories of CD4 percentage and HIV-1 viral load were determined by OI occurrence during follow-up.

The relationship between age at HAART initiation, duration of HAART use, and the risk of a first OI (either OI-B or OI-C) event during cohort follow-up was assessed using Cox proportional hazards regression while adjusting for the following potential confounders: age at enrollment, number of ART regimens prior to initiating HAART, number of HAART regimens before enrollment, adherence to HAART at enrollment, sex, and ethnicity. In a subanalysis including the 741 subjects with information on CD4 percentage at HAART initiation, CD4 percentage and CDC disease category at HAART initiation were added to the regression model to adjust for severity of illness at HAART initiation. The validity of the proportional hazards assumptions was assessed by examining residual plots to determine whether the hazards were approximately constant over time.²⁴ Hazard ratios (HRs), 95% CIs, and *P* values were calculated using the likelihood ratio test.²⁴ All of the analyses were performed using SAS version 8.2 software (SAS Institute, Inc, Cary, NC).

RESULTS

The characteristics of the 1927 subjects in the study population by OI occurrence during follow-up are summarized in **Table 1**. The risk of an OI during cohort follow-up was higher in children who were older, were

Table 1. Characteristics of 1927 Children Perinatally Infected With Human Immunodeficiency Virus Enrolled in Pediatric AIDS Clinical Trials Group 219C Categorized by Opportunistic Illness Occurrence During Follow-up

Variable	Children Without OI, No. (%) (n = 1701)	Children With OI, No. (%) (n = 226)	P Value*
Age at enrollment, y			
0 to <2	86 (5.1)	12 (5.3)	.008
2 to <10	877 (51.6)	92 (40.7)	
10-21	738 (43.4)	122 (54.0)	
Sex			
Female	822 (48.3)	118 (52.2)	.27
Male	879 (51.7)	108 (47.8)	
Ethnicity			
Non-Hispanic white	255 (15.0)	19 (8.4)	.02
Non-Hispanic black	982 (57.7)	138 (61.1)	
Hispanic	438 (25.8)	68 (30.1)	
Other	26 (1.5)	1 (0.4)	
CDC disease category at enrollment			
Asymptomatic or A	688 (40.4)	29 (12.8)	<.001
B	558 (32.8)	79 (35.0)	
C	429 (25.2)	115 (50.9)	
Missing	26 (1.5)	3 (1.3)	
CD4 ⁺ T lymphocytes at enrollment, %			
≥25	1231 (72.4)	89 (39.4)	<.001
15 to <25	330 (19.4)	44 (19.5)	
<15	131 (7.7)	93 (41.2)	
Missing	9 (0.5)	0	
HIV-1 viral load at enrollment, copies/mL			
<400	471 (27.7)	29 (12.8)	<.001
400 to <10 000	797 (46.9)	64 (28.3)	
10 000 to <100 000	321 (18.9)	73 (32.3)	
≥100 000	96 (5.6)	60 (26.6)	
Missing	16 (0.9)	0	
Missing	16 (0.9)	0	
Age at HAART initiation, y			
0 to <2	321 (18.9)	26 (11.5)	.001
2 to <10	1091 (64.1)	141 (62.4)	
10-20	289 (17.0)	59 (26.1)	
Duration of HAART use at enrollment, y			
0 to <1	239 (14.1)	29 (12.8)	.59
1 to <4	1178 (69.3)	164 (72.6)	
4-10	284 (16.7)	33 (14.6)	
ART regimens prior to HAART initiation, No.			
0	350 (20.6)	37 (16.4)	<.001
1-2	833 (49.0)	78 (34.5)	
≥3	518 (30.4)	111 (49.1)	
Different HAART regimens, No.			
1†	231 (13.6)	19 (8.4)	<.001
1-2‡	1032 (60.7)	102 (45.1)	
≥3	438 (25.7)	105 (46.5)	
Adherence to HAART regimen, %§			
100	1380 (81.1)	168 (74.3)	.05
1-99	192 (11.3)	39 (17.3)	
0	64 (3.8)	11 (4.9)	
Missing	65 (3.8)	8 (3.5)	
Missing	65 (3.8)	8 (3.5)	

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral treatment; HIV-1, human immunodeficiency virus 1.

*P values are based on a statistical test of difference.

†Children who were treatment naïve at the time of initiating HAART.

‡Antiretroviral therapy-experienced children by the time of initiating HAART.

§Adherence was recorded during a 3-day period at the time of enrollment in Pediatric AIDS Clinical Trials Group 219C.

Hispanic or non-Hispanic black, were in CDC category C, had a CD4 percentage of less than 15%, had a higher HIV-1 viral load at enrollment, initiated HAART at an older age, and were treated with at least 3 different ART regimens before HAART initiation or at least 3 different HAART regimens before enrollment in PACTG 219C.

Median follow-up time was 28 months (range, 6 days to 35 months), and 316 subjects (16.4%) were censored prior to August 31, 2003. Reasons for censoring included site closure (n=227), subjects moving away from the site (n=41), death unrelated to OI (n=7), investigators being unable to contact the subjects (n=15), par-

ents withdrawing consent (n=14), subjects being unable to adhere to the study protocol (n=8), subjects being too ill (n=3), and imprisonment (n=1).

Subjects were treated with a median of 2 (range, 0-12) different ART regimens prior to HAART initiation followed by a median of 1 (range, 1-17) different HAART regimen before PACTG 219C enrollment. Of the 387 subjects who were treatment naïve when initiating HAART, 250 (64.6%) continued to receive the same HAART regimen through enrollment in PACTG 219C. The first HAART regimen consisted of 2 nucleoside reverse transcriptase inhibitors and 1 PI for 1224 subjects (63.5%), 2 nucleoside reverse transcriptase inhibitors and 1 non-nucleoside reverse transcriptase inhibitor for 279 subjects (14.5%), 1 or 2 nucleoside reverse transcriptase inhibitors, 1 PI, and 1 nonnucleoside reverse transcriptase inhibitor for 395 subjects (20.5%), and other nucleoside reverse transcriptase inhibitor, PI, and nonnucleoside reverse transcriptase inhibitor combinations for 29 subjects (1.5%).

The OI incidence rates per 100 person-years of follow-up in PACTG 219C are shown in **Table 2**. In total, 185 first OI-B events and 57 first OI-C events occurred among 226 subjects during follow-up. The incidence rate was 6.21 (95% CI, 5.42-7.07) per 100 person-years for the first OI regardless of category, 4.99 (95% CI, 4.30-5.76) per 100 person-years for the first OI-B event, and 1.47 (95% CI, 1.12-1.91) per 100 person-years for the first OI-C event. The most frequently occurring OI-B event was bacterial pneumonia, and the most frequently occurring OI-C event was esophageal candidiasis. In 7 children, the OI-C event (2 *Pneumocystis jiroveci* pneumonia events, 3 culture-confirmed sepsis events, and 2 HIV encephalopathy events) led to death within a month after diagnosis. Ten additional children died from AIDS-related OIs after having had a prior OI-C event.

During follow-up, 721 (37.4%) of the participants received prophylaxis against *P jiroveci* pneumonia and 166 (8.6%) received prophylaxis against *Mycobacterium avium* complex infection. Children receiving *P jiroveci* pneumonia or *M avium* complex prophylaxis were significantly older at enrollment and HAART initiation and were more likely to be in CDC category C, have a lower CD4 percentage (<15%), and have a higher HIV-1 viral load (>10 000 copies/mL) at enrollment compared with subjects receiving no prophylaxis during follow-up (all $P < .001$).

The median CD4 percentage improved over time, from 22% (95% CI, 21%-23%) just prior to HAART initiation (among 741 subjects previously enrolled in PACTG 219) to 30% (95% CI, 29%-30%) at enrollment in PACTG 219C, and it persisted at 30% (95% CI, 29%-30%) until the end of follow-up. This increase in median CD4 percentage over time was observed across different subgroups, including sex, ethnic origin, age at HAART initiation, and age at enrollment. However, there were differences in median CD4 percentage levels within subgroups; girls had a significantly higher median CD4 percentage than boys when initiating HAART (25% vs 20%, respectively), at enrollment (31% vs 28%, respectively), and at the end of follow-up (31% vs 29%, respectively). Furthermore, subjects who initiated HAART when they were younger than 2 years had significantly higher me-

Table 2. Incidence Rates of Opportunistic Illnesses per 100 Person-Years During Follow-up for 1927 Children Perinatally Infected With Human Immunodeficiency Virus

Opportunistic Illness	Events, No.	Incidence Rate per 100 Person-Years (95% CI)
First opportunistic illness category	185	4.99 (4.30-5.76)
B events		
Specific opportunistic illness category		
B events		
Bacterial pneumonia	139	3.67 (3.09-4.34)
Oral candidiasis	44	1.13 (0.82-1.52)
Sepsis	19	0.48 (0.29-0.76)
Herpes zoster virus	8	0.20 (0.09-0.40)
Herpes simplex virus stomatitis	7	0.18 (0.07-0.37)
Lymphoid interstitial pneumonia	5	0.13 (0.04-0.30)
Bacterial meningitis	2	0.05 (0.01-0.18)
First opportunistic illness category	57	1.47 (1.12-1.91)
C events		
Specific opportunistic illness category		
C events		
Esophageal candidiasis	19	0.48 (0.29-0.76)
Bacterial infection (recurrent, culture confirmed)	11	0.28 (0.14-0.50)
HIV encephalopathy	11	0.28 (0.14-0.50)
HIV wasting syndrome	11	0.28 (0.14-0.50)
<i>Pneumocystis jiroveci</i> pneumonia	9	0.23 (0.10-0.43)
<i>Mycobacterium avium</i> , disseminated	4	0.10 (0.03-0.26)
Non-Hodgkin lymphoma	2	0.05 (0.01-0.18)
Hodgkin lymphoma	2	0.05 (0.01-0.18)
Histoplasmosis, disseminated	1	0.03 (0.001-0.14)
Herpes simplex virus, disseminated	1	0.03 (0.001-0.14)
Cytomegalovirus retinitis	1	0.03 (0.001-0.14)
Cryptosporidiosis, persistent	1	0.03 (0.001-0.14)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

dian CD4 percentages compared with older children (aged >10 years) at HAART initiation (27% vs 17%, respectively), at enrollment (35% vs 23%, respectively), and at the end of follow-up (34% vs 23%, respectively). The HIV-1 viral load for the study population did not change substantially between enrollment (median viral load, 1081 copies/mL; 95% CI, 809-1397 copies/mL) and the end of follow-up (median viral load, 818 copies/mL; 95% CI, 574-1140 copies/mL).

The proportions of subjects in different categories of CD4 percentage at HAART initiation, at enrollment in PACTG 219C, and at the end of follow-up are shown by OI occurrence during follow-up in **Figure, A**. More subjects with OIs than without OIs were in the low CD4 percentage (<15%) category at HAART initiation (49.6% of subjects with OIs vs 23.7% of subjects without OIs), at enrollment (41.2% of subjects with OIs vs 7.7% of subjects without OIs), and at the end of follow-up (41.2% of subjects with OIs vs 8.3% of subjects without OIs). In addition, the proportion of subjects with normal CD4 percentages ($\geq 25\%$) was more pronounced over time among subjects without an OI (from 48% to 71%) compared with those experiencing OIs (from 23% to 38%). The proportion of subjects in different categories of HIV-1 viral load at enrollment in PACTG 219C and at the end of fol-

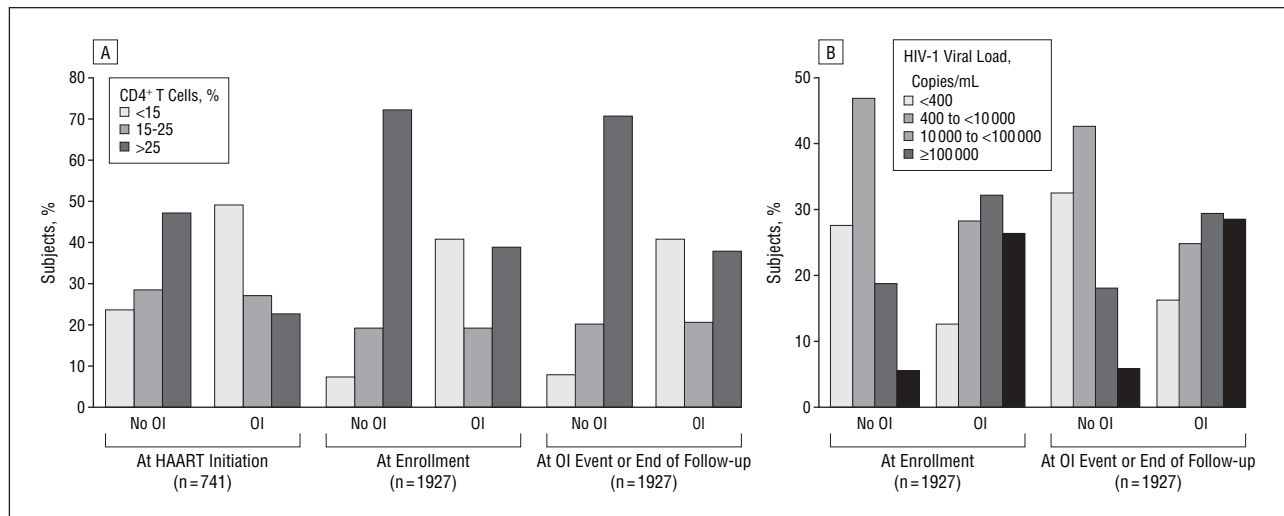


Figure. The proportion of subjects in different categories of CD4+ T-lymphocyte percentage at highly active antiretroviral treatment (HAART) initiation (calculated among the 741 subjects previously enrolled in Pediatric AIDS Clinical Trials Group 219), at enrollment in Pediatric AIDS Clinical Trials Group 219C, and at the end of follow-up in children with and without opportunistic illnesses (OIs) during follow-up (A) and in different categories of human immunodeficiency virus 1 (HIV-1) viral load at enrollment in Pediatric AIDS Clinical Trials Group 219C and at the end of follow-up in children with and without OIs during follow-up (B).

low-up did not change much over time (Figure, B). However, more subjects with OIs than without OIs were in the high viral load categories ($\geq 100,000$ copies/mL) both at enrollment (26.6% vs 5.7%, respectively) and at the end of follow-up (28.8% vs 6.1%, respectively). Also, the proportion of subjects with good viral suppression (< 400 copies/mL) was lower among subjects with OIs compared with those without OIs at enrollment (12.8% vs 28.0%, respectively) and at the end of follow-up (16.4% vs 32.8%, respectively).

The risk of having a first OI (regardless of category) during follow-up in relation to HAART exposure was examined using Cox proportional hazards regression (Table 3). In the multivariate regression model, there was a significantly higher risk of a first OI during follow-up for non-Hispanic black subjects (HR, 2.09; 95% CI, 1.29-3.38) and Hispanic subjects (HR, 1.94; 95% CI, 1.16-3.23) compared with non-Hispanic white subjects. Subjects who enrolled in PACTG 219C when they were aged 10 years or older had a significantly lower risk of a first OI compared with subjects younger than 2 years at enrollment (HR, 0.37; 95% CI, 0.15-0.92). In contrast, subjects who initiated HAART when they were aged 10 years or older had a significantly higher risk of a first OI compared with those initiating HAART when they were younger than 2 years (HR, 2.48; 95% CI, 1.23-5.00). Subjects who switched between 3 or more HAART regimens had a significantly increased risk of a first OI compared with subjects who were treatment naive at HAART initiation and continued to receive the same HAART regimen after HAART initiation (HR, 2.73; 95% CI, 1.40-5.32). There was no relationship between sex, duration of HAART use, number of ART regimens before initiating HAART, or short-term adherence to HAART and the risk of a first OI (Table 3). Regression analysis performed for OI-B and OI-C events separately gave similar results except for boys having a marginally significant lower risk of a first OI-B event during follow-up compared with girls (HR, 0.75; 95% CI, 0.56-1.00).

To control for severity of illness at HAART initiation, we performed separate Cox proportional hazards regression analyses for the 741 subjects previously enrolled in PACTG 219 for whom we had information on CD4 percentage at the time of initiating HAART. Initially, we ran the same multivariate model as shown in Table 3. The results were materially unchanged except for wider CIs, indicating no significant risk of OI according to race or ethnicity, age at HAART initiation, and age at enrollment. Subsequently, CD4 percentage and CDC disease category at HAART initiation were added to the multivariate model as indicators of severity of illness at the time of initiating combination therapy (Table 4). In this adjusted model, only CDC disease category and CD4 percentage at enrollment were related to OI risk during follow-up. Both CDC category B (HR, 3.21; 95% CI, 1.89-5.45) and category C (HR, 3.35; 95% CI, 1.77-6.35) at HAART initiation were associated with a higher risk of a first OI compared with being asymptomatic or in category A. A CD4 percentage of less than 15% at HAART initiation was associated with a 2-fold increased risk of a first OI compared with a normal CD4 percentage ($\geq 25\%$) (HR, 2.04; 95% CI, 1.18-3.53).

COMMENT

Given the fact that there are about 2.1 million children living with HIV or AIDS in the world and that combination therapies have become increasingly available and recommended, it is of greatest importance to define the optimal time to initiate HAART. Our findings that HAART initiation at an older age (age > 10 years) was associated with an increased risk of OIs may have important clinical and policy implications. Despite the obvious risk of fast progression in young children, the question of when HAART should be initiated in children remains controversial. According to the US guidelines,²⁵ treatment intervention as early as possible regardless of the child's

Table 3. Risk of First Opportunistic Illness Among 1927 Children Perinatally Infected With Human Immunodeficiency Virus Enrolled in Pediatric AIDS Clinical Trials Group 219C

Characteristic	Children, No.	Hazard Ratio (95% CI)		P Value†
		Univariate Analysis	Multivariate Analysis*	
Sex				
Female	940	Reference	Reference	.18
Male	987	0.85 (0.66-1.11)	0.84 (0.64-1.09)	
Ethnicity				
Non-Hispanic white	274	Reference	Reference	.005
Non-Hispanic black	1120	1.87 (1.16-3.02)	2.09 (1.29-3.38)	
Hispanic	506	1.88 (1.13-3.12)	1.94 (1.16-3.23)	
Other	27	0.52 (0.07-3.89)	0.58 (0.08-4.34)	
Age at enrollment, y				
0 to <2	98	Reference	Reference	.05
2 to <10	969	0.61 (0.34-1.12)	0.35 (0.16-0.81)	
10-21	860	0.98 (0.54-1.77)	0.37 (0.15-0.92)	
Age at HAART initiation, y				
0 to <2	347	Reference	Reference	.02
2 to <10	1232	1.40 (0.92-2.13)	1.66 (0.92-3.01)	
10-21	348	2.18 (1.37-3.45)	2.48 (1.23-5.00)	
Duration of HAART use at enrollment, y				
0 to <1	268	Reference	Reference	.96
1 to <4	1342	1.02 (0.69-1.51)	0.97 (0.63-1.50)	
≥4	317	1.19 (0.72-1.96)	1.02 (0.58-1.80)	
ART regimens prior to HAART initiation, No.				
0	387	Reference	Reference	<.001
1-2	911	0.80 (0.54-1.18)	0.65 (0.38-1.11)	
≥3	629	1.71 (1.18-2.48)	1.21 (0.70-2.06)	
Different HAART regimens, No.				
1‡	250	Reference	Reference	<.001
1-2§	1134	1.02 (0.63-1.67)	1.20 (0.61-2.37)	
≥3	543	2.45 (1.50-4.00)	2.73 (1.40-5.32)	
Adherence to HAART regimen, %				
100	1548	Reference	Reference	.52
1-99	231	1.58 (1.11-2.23)	1.31 (0.92-1.88)	
0	75	1.31 (0.71-2.42)	1.18 (0.64-2.18)	
Missing	73	1.22 (0.60-2.47)	1.05 (0.51-2.13)	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral treatment.

*Adjusted for all of the variables listed.

†The P values indicate whether there is any significant difference across the categories of each variable in the multivariate model.

‡Children who were treatment naïve at the time of initiating HAART.

§Antiretroviral therapy-experienced children by the time of initiating HAART.

||Adherence was recorded during a 3-day period at the time of enrollment in Pediatric AIDS Clinical Trials Group 219C.

immune function is recommended. In contrast, European²⁶ and World Health Organization²⁷ guidelines recommend postponing treatment in children until the CD4 percentages fall below 15% or 20%.^{25,26} Although some investigators have found that recovery to normal CD4 cell counts is independent of age,²⁸ the recovery of naïve CD4 cells is usually more rapid and effective in young children,^{2,14,29} which may favor early intervention with HAART before severe immunosuppression has occurred.¹⁴ Furthermore, from a long-term perspective, only a small fraction of children who start therapy when their CD4 percentages have fallen below 15% will reach normal CD4 percentages (≥25%). Again, this supports the view that HAART should be initiated as early as possible.²

The CD4 cell count at HAART initiation has previously been demonstrated as a strong predictor for subsequent OI risk.⁴ In accordance, the significant association we found between older age (age >10 years) when initiating HAART and the risk of an OI during fol-

low-up (Table 3) diminished when we controlled for the children's immunologic and clinical status (CD4 percentage and CDC disease category, respectively) at HAART initiation (Table 4). Subjects who already were in CDC category B or C at HAART initiation had a higher risk of additional OIs during follow-up compared with subjects who initiated HAART before development of clinical disease, even after adjustment for their CD4 percentages at HAART initiation (Table 4). In addition, more children with OIs than without OIs had a CD4 percentage of less than 15% at HAART initiation (49.6% of children with OIs vs 23.7% of children without OIs), at enrollment (41.2% of children with OIs vs 7.7% of children without OIs), and at the end of follow-up (41.2% of children with OIs vs 8.3% of children without OIs) (Figure, A). These results suggest that HAART initiation should not be delayed until the CD4 percentage has fallen below 15% or the child has already experienced an AIDS-defining illness.

Table 4. Risk of First Opportunistic Illness Among 741 Children Perinatally Infected With Human Immunodeficiency Virus Enrolled in Pediatric AIDS Clinical Trials Group 219C Controlling for CD4⁺ T-Lymphocyte Percentage and Centers for Disease Control and Prevention Category*

Characteristic	Children, No.	Hazard Ratio (95% CI)		P Value‡
		Univariate Analysis	Multivariate Analysis†	
Sex				
Female	353	Reference	Reference	.06
Male	388	0.77 (0.53-1.11)	0.70 (0.48-1.02)	
Ethnicity				
Non-Hispanic white	92	Reference	Reference	.32
Non-Hispanic black	385	1.40 (0.71-2.75)	1.50 (0.75-3.01)	
Hispanic	258	1.83 (0.92-3.61)	1.84 (0.92-3.67)	
Other	6	1.58 (0.20-12.36)	1.32 (0.16-10.63)	
Age at enrollment, y				
0 to <2	3	3.36 (0.46-24.49)	4.95 (0.41-59.91)	.52
2 to <10	333	Reference	Reference	
10-21	405	1.72 (1.17-2.55)	1.03 (0.63-1.70)	
CDC disease category at HAART initiation				
Asymptomatic or A	354	Reference	Reference	<.001
B	251	4.59 (2.80-7.53)	3.21 (1.89-5.45)	
C	103	4.80 (2.69-8.58)	3.35 (1.77-6.35)	
Missing	33	2.13 (0.73-6.21)	1.82 (0.60-5.53)	
CD4 ⁺ T lymphocytes at HAART initiation, %				
≥25	324	Reference	Reference	.03
15 to <25	212	1.87 (1.11-3.15)	1.35 (0.79-2.33)	
<15	205	3.96 (2.48-6.31)	2.04 (1.18-3.53)	
Age at HAART initiation, y				
0 to <2	29	Reference	Reference	.46
2 to <10	514	1.40 (0.44-4.45)	1.12 (0.26-4.86)	
10-21	198	2.20 (0.68-7.11)	1.52 (0.32-7.24)	
Duration of HAART use at enrollment, y				
0 to <1	87	Reference	Reference	.69
1 to <4	559	1.23 (0.65-2.30)	0.86 (0.44-1.69)	
≥4	95	1.77 (0.83-3.75)	0.70 (0.30-1.65)	
ART regimens prior to HAART initiation, No.				
0	48	Reference	Reference	.04
1-2	386	0.84 (0.36-1.98)	0.56 (0.19-1.63)	
≥3	307	1.82 (0.79-4.19)	0.93 (0.32-2.66)	
Different HAART regimens, No.				
1§	30	Reference	Reference	.001
1-2	504	1.71 (0.42-7.02)	1.25 (0.21-7.32)	
≥3	207	4.58 (1.12-18.79)	2.71 (0.47-15.71)	
Adherence to HAART regimen, %¶				
100	582	Reference	Reference	.44
1-99	97	1.65 (1.03-2.65)	1.50 (0.91-2.47)	
0	29	1.24 (0.50-3.05)	1.12 (0.44-2.87)	
Missing	33	0.72 (0.23-2.29)	0.76 (0.24-2.47)	

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HAART, highly active retroviral treatment.

*Subjects were those who were previously enrolled in Pediatric AIDS Clinical Trials Group 219 for whom information on CD4⁺ T-lymphocyte percentage at the time of HAART initiation was available.

†Adjusted for all of the variables listed.

‡The P values indicate whether there is any significant difference across the categories of each variable in the multivariate model.

§Children who were treatment naive at the time of initiating HAART.

||Antiretroviral therapy-experienced children by the time of initiating HAART.

¶Adherence was recorded during a 3-day period at the time of enrollment in Pediatric AIDS Clinical Trials Group 219C.

Our findings of an increased risk of OIs during follow-up among non-Hispanic black and Hispanic children (Table 3) compared with non-Hispanic white children have been previously observed yet not fully explained in the literature.³⁰ Genetic variation in immunologic status between ethnic groups has been suggested, especially since social disparities (such as access to treatment or adherence) have not been significantly associated with ethnic groups.^{2,31} In accordance, we found lower me-

dian CD4 percentages among both non-Hispanic black and Hispanic subjects at HAART initiation, at enrollment, and at the OI event compared with non-Hispanic white subjects, and race or ethnicity was no longer predictive of risk in the model adjusted for the CD4 percentage at HAART initiation (Table 4). The relationship between sex, immunologic parameters, and clinical outcomes is less clear.^{32,33} We found that girls had higher median CD4 percentages at all of the time points during

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follow-up whereas their viral loads were similar to those of boys. In contrast, the CD4 percentage-adjusted analyses showed that boys had a slightly lower risk of a first OI-B event compared with girls, a finding that has previously been reported for mortality in our pediatric cohort.²¹

This study has a number of potential limitations, including confounding by severity of illness. Previous analyses of this study population indicated that the most severely ill children were the first to start PI-based treatment.²¹ To adjust for severity of illness, we included measures of immunologic (CD4 percentage) and clinical (CDC

disease category) status at HAART initiation. These 2 measures, together with sex and age-adjusted weight, have recently been used in a Pediatric AIDS Severity System score and have proven to be highly predictive of mortality in children with HIV (W.M.D., G.R.S., Kate Buchacz, PhD, Geoffrey A. Weinberg, MD, Kenneth McIntosh, MD, unpublished data, December 31, 1996). Indeed, the increased risk of a first OI associated with an older age at initiating HAART disappeared when we adjusted for CD4 percentage and CDC disease category at the time of HAART initiation (Table 4). Unfortunately, HIV-1 RNA

measurements at HAART initiation were unavailable for our subjects, which precluded adjustment for this variable in our analyses.

Other potential limitations include our measure of duration of HAART use, which was based on lifetime experience at enrollment and may not have represented HAART use at the actual time of OI occurrence. In addition, we did not take into account any interruptions or discontinuation of HAART after enrollment in PACTG 219C but rather used an intention-to-continue-treatment approach. However, previous data from the PACTG 219 cohort indicate that very few children (<5%) discontinue HAART once it has been initiated.²¹ Furthermore, our risk estimates were based on the first OI to occur in PACTG 219C follow-up and may not have been the first OI while receiving HAART. Despite accrual of our study population from institutions across the United States, our results may not be generalizable to the underlying base population of children with HIV, especially since our study was conducted within a self-selective cohort of children who may have participated in previous ART clinical trials in the United States. Nevertheless, our study included 1927 children, thus representing a relatively large sample of children with HIV receiving care in the United States.

We conclude that OIs are still occurring in the pediatric HIV population after the introduction of HAART, but at lower incidence rates than in the pre-HAART era.³⁴ Low CD4 percentage (<15%) and CDC disease category B or C at the time of HAART initiation remained the strongest predictors of OIs in the pediatric HIV population in the era of HAART. A larger proportion of children with OIs than without OIs had a CD4 percentage of less than 15% at both HAART initiation and OI occurrence. Presumably, it is not the duration of HAART use or the age at HAART initiation but rather the sustained response to HAART that predicts the risk of OIs after HAART initiation. The optimal time to initiate HAART in children can only be, and needs to be, assessed in future randomized studies.

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Atkins Diet in 1906?

Diet is alone sufficient to improve the condition; its chief feature is the exclusion of the two elements, starch and sugar, from the food. In one year, on this diet, Mr Banting reduced his weight 46 pounds. Meat Diet, very successful in 42 cases, the diet being confined to rump-steak, hot water and codfish, for 14 days, excluding absolutely everything else.

—From *Materia Medica Pharmacy and Therapeutics*, 1906