

EFFECT OF COMBINATION THERAPY INCLUDING PROTEASE INHIBITORS ON MORTALITY AMONG CHILDREN AND ADOLESCENTS INFECTED WITH HIV-1

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ABSTRACT

Background Combination therapy including protease inhibitors has been shown to be effective in treating adults infected with human immunodeficiency virus type 1 (HIV-1), but there are only limited data regarding the treatment of children and adolescents.

Methods A cohort of 1028 HIV-1-infected children and adolescents, from birth through 20 years of age, who were enrolled in research clinics in the United States before 1996 was followed prospectively through 1999. We used proportional-hazards regression models to estimate the effect on mortality of combination therapy including protease inhibitors.

Results Seven percent of the subjects were receiving combination therapy including protease inhibitors in 1996; by 1999, 73 percent were receiving such therapy. In univariate analyses, a higher base-line percentage of lymphocytes that were CD4-positive, a higher weight for age, a higher height for age, black race, Hispanic ethnic background, younger age, and perinatally acquired infection were associated with a longer median time to the initiation of this type of therapy ($P < 0.001$). After adjustment for covariates, the differences among racial and ethnic groups in the time to initiation were not statistically significant. Mortality declined from 5.3 percent in 1996 to 2.1 percent in 1997, 0.9 percent in 1998, and 0.7 percent in 1999 (P for trend < 0.001). There were reductions in mortality in all subgroups defined according to age, sex, percentage of CD4+ lymphocytes, educational level of the parent or guardian, and race or ethnic background. In adjusted analyses, the initiation of combination therapy including protease inhibitors was independently associated with reduced mortality (hazard ratio for death, 0.33; 95 percent confidence interval, 0.19 to 0.58; $P < 0.001$).

Conclusions The use of combination therapy including protease inhibitors has markedly reduced mortality among children and adolescents infected with HIV-1. (N Engl J Med 2001;345:1522-8.)

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THE combination of human immunodeficiency virus (HIV)-specific protease inhibitors with nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, or both has been demonstrated in adults to slow the progression of HIV type 1 (HIV-1) disease dramatically and to lower mortality.^{1,2} Recent studies provide some evidence of the efficacy and safety of these regimens in children and adolescents,³⁻⁶

but there is only limited evidence of reductions in mortality and morbidity.^{7,8} Current guidelines for the treatment of HIV infection in both adults and children recommend combination therapy including protease inhibitors.^{9,10}

We undertook the present study to estimate the effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1 and to identify any differences according to age, sex, socioeconomic status, or ethnic background in the time of initiation of this therapy.

Research involving adults who are infected with HIV-1 has found excess mortality among ethnic and racial minorities, including black and Hispanic populations,^{11,12} as well as evidence of lower rates of use of essential health services¹³ and delayed initiation of antiretroviral therapy.¹⁴ Possible explanations for these associations include differences in the severity of illness, socioeconomic factors,¹⁵ and differences in the practice patterns of physicians and clinics. Patients treated at clinics with more experience in treating HIV disease may have better outcomes¹⁶ because their clinicians may initiate new therapies earlier, and adherence to combination therapies may vary from site to site.^{17,18} Limited access to therapies could also be a consequence of discrimination on the basis of age, sex, socioeconomic status, or ethnic or racial background.

It is probable that the children and adolescents who are the first to begin combination therapy including protease inhibitors are those who are the most severely ill, as is the case with adults.¹⁹ We attempted to control for this type of confounding by indication^{20,21} by using measures of the severity of illness before the initiation of therapy.

METHODS

Subjects and Study Design

The Pediatric AIDS Clinical Trials Group Protocol 219 (PACTG 219) study is a prospective cohort study designed to assess the long-term effects of prenatal and neonatal exposure to antiretroviral drugs in clinical trials²² and the late effects of antiretroviral

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treatment in children infected with HIV-1. All children and adolescents enrolled in PACTG perinatal or treatment trials were eligible for enrollment. The study was approved by the institutional review board at each participating institution. Written informed consent was obtained from the subject or the parent or legal guardian for those below the legal age. The study population for these analyses included 1028 children and adolescents infected with HIV-1 who had been enrolled in PACTG 219 before January 1, 1996, and who had not died or been lost to follow-up before that date.

Clinical and Laboratory Data

The medical history was obtained, a physical examination was performed, the height and weight were measured, and data on lymphocyte subpopulations were collected at base line and every 6 months for children less than 24 months of age and yearly for children 24 months old or older. We defined the base-line CD4+ lymphocyte count as the last measurement obtained on or before December 31, 1995. CD4+ lymphocyte counts had been obtained for study participants beginning in mid-1995. HIV-1 RNA data were not collected and were not part of routine clinical care until after the beginning of the study period.

Growth

Height and weight measurements were converted to age- and sex-adjusted z scores with the use of international growth standards.²³ A z score of 0 corresponds to the 50th percentile, and a z score of -1.0 indicates 1 SD below the mean.

Medication Use

At each study visit, data were collected concerning any antiretroviral medications used since the last visit. (Information on the precise dates of the initiation of medications and any changes in the use of medications was not collected.) This information was supplemented with more precise information concerning the dates of initiation of the medications used in PACTG clinical trials (for 19 percent of the subjects). In instances in which precise dates were not available and we only knew that initiation occurred sometime between two visits, we calculated regressions predicting survival under the conservative assumption that combination therapy including protease inhibitors began at the time of the earlier visit. For 31 children and adolescents in whom combination therapy including protease inhibitors was initiated before 1996, we used January 1, 1996, as the date of initiation; this date approximates the date of the first evaluation of protease inhibitors in children. In predicting the median time to the initiation of combination therapy including protease inhibitors, we used the midpoint between the two visit dates as the dependent variable if a precise date was unavailable.

We created four categories of antiretroviral therapy: nucleoside reverse-transcriptase inhibitors alone; nonnucleoside reverse-transcriptase inhibitors but no protease inhibitors; one or more protease inhibitors with nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, or both; and no antiretroviral therapy.

Outcome Measures

The primary outcome was death during the interval between January 1, 1996, and December 31, 1999. The time from base line to the initiation of combination therapy including protease inhibitors was a secondary end point.

Other Variables

The number of years of schooling completed by a parent or guardian was used as an indicator of socioeconomic status. Race or ethnic background was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other. Because there were few subjects who were classified as other, they were grouped with the non-Hispanic white subjects. Each participating site was classified according to the total number of children and adolescents enrolled in the study cohort, and quartiles were defined.

Statistical Analysis

We analyzed the time to death and the time to the initiation of combination therapy including protease inhibitors. For the first analysis, the data for subjects who were still alive were censored at the date of the last follow-up visit. We estimated the distribution of survival times with use of the Kaplan-Meier method. Comparisons among survival curves were made by means of the log-rank test. Proportional-hazards regression models were used to evaluate the association between the risk of death and other variables.²⁴ All P values are two-tailed.

Combination therapy including protease inhibitors was initiated in most subjects during the study period (1996 through 1999), but there was no random assignment of subjects to the various types of drug therapy. A major threat to the accuracy of estimates of effectiveness is the likely selection of subjects with more severe illness for the early initiation of combination therapy including protease inhibitors. To control for such confounding by indication,^{20,21} we used proportional-hazards regression models to estimate the effect of combination therapy including protease inhibitors on mortality, with simultaneous control for measures of the severity of illness before the initiation of therapy. The use of combination therapy including protease inhibitors was treated as a time-varying covariate. Indicators of the severity of illness include the log CD4+ lymphocyte counts and weight-for-age and height-for-age z scores. We used the log CD4+ lymphocyte counts in regression analyses (in which we controlled for age) because they predicted mortality better than did the percentage of lymphocytes that were CD4+ positive. Descriptive data concerning the percentage of CD4+ lymphocytes (less than 15 percent or at least 15 percent) are provided for purposes of comparison.²⁵ This measure has been shown to vary less with age than does the log CD4+ lymphocyte count.²⁶

In proportional-hazards regression models, indicators of the severity of illness were treated as time-dependent covariates until the visit when combination therapy including protease inhibitors was initiated. At that point, the updated measure of the severity of illness was fixed and remained constant for any subsequent visits. Thus, we did not control for time-varying log CD4+ lymphocyte counts or weight-for-age or height-for-age z scores after the initiation of combination therapy including protease inhibitors; we took this approach in order to avoid the overcontrol that might result, given the hypothesized effects of such combination therapy on subsequent log CD4+ lymphocyte counts and growth. To test for a linear trend in mortality that was independent of the initiation of combination therapy including protease inhibitors and other covariates, we pooled repeated observations.²⁷

Other covariates in the regression models included the ethnic background (with non-Hispanic white as the reference category), perinatal or nonperinatal infection, sex, age at base line, educational level of the parent or guardian (one of three levels, with completion of high school as the reference category), and the number of subjects enrolled in the study at the same site (one of three categories). For the analyses of the time to the initiation of combination therapy including protease inhibitors, we used proportional-hazards regression models in which we controlled for the base-line covariates.

RESULTS

Participation and Follow-up

A total of 1028 children and adolescents (defined in this study as from birth to 20 years of age at the beginning of the study) met the eligibility criteria; 89 percent of these subjects remained in the study through December 31, 1999. We compared the base-line characteristics of the 11 percent who were lost to follow-up with those of the remaining subjects and found no differences in measures of the severity

of illness (percentage of CD4+ lymphocytes, weight for age, or height for age) and no differences in terms of sex, race or ethnic group, or the educational level of the parent or guardian. There was greater loss to follow-up among subjects 13 to 20 years of age than among those younger than 13 ($P=0.003$) and among subjects who were not infected perinatally than among those who were ($P=0.02$). There was also evidence of greater loss to follow-up at the sites with fewer subjects enrolled in the study ($P=0.003$).

Half the subjects were female, 17 percent were non-Hispanic white, 47 percent were non-Hispanic black, and 35 percent were Hispanic (Table 1). At base line, small percentages of the subjects were younger than 2 years old (4 percent) or older than 12 years old (9 percent), and in one third the percentage of CD4+ lymphocytes was lower than 15 percent. Data on baseline medication use indicate that 86 percent of the subjects were receiving only nucleoside reverse-transcriptase inhibitors, 9 percent were receiving nonnucleoside reverse-transcriptase inhibitors, 3 percent were receiving no antiretroviral medications, and none were receiving combination therapy including protease inhibitors.

Initiation of Combination Therapy Including Protease Inhibitors

In 1996 — the year that combination therapy including protease inhibitors first became available — the rate of reported use in this cohort was low (7 percent). The rate increased to 34 percent in 1997 and to 64 percent in 1998. By 1999, among the subjects who had not died or been lost to follow-up, the rate was 73 percent. In 1999, an additional 24 percent were receiving only nucleoside reverse-transcriptase inhibitors, and 3 percent were receiving combination therapy including nonnucleoside reverse-transcriptase inhibitors and nucleoside reverse-transcriptase inhibitors. All the subjects were receiving some kind of antiretroviral medication in 1999.

By the end of the study period, 33 percent of the cohort had never received combination therapy including protease inhibitors, 38 percent had received combination therapy including one protease inhibitor, 17 percent had received two protease inhibitors (not necessarily concurrently), and 11 percent had received three or more protease inhibitors (not necessarily concurrently). Because some subjects died or were lost to follow-up, the interval during which a subject could receive protease inhibitors varied.

Of the 688 subjects for whom the initiation of combination therapy including protease inhibitors was reported, 67 percent reported receiving nelfinavir, 59 percent reported receiving ritonavir, 20 percent reported receiving saquinavir, 18 percent reported receiving indinavir, and 6 percent reported receiving amprenavir. Among those subjects in whom combination therapy including protease inhibitors was ini-

TABLE 1. BASE-LINE CHARACTERISTICS OF 1028 CHILDREN AND ADOLESCENTS IN THE PROSPECTIVE COHORT WHO WERE ENROLLED BEFORE JANUARY 1, 1996.

CHARACTERISTIC	VALUE
	no. of subjects (%)
Age	
0-1 yr	46 (4)
2-5 yr	392 (38)
6-12 yr	494 (48)
13-20 yr	96 (9)
Sex	
Female	512 (50)
Male	516 (50)
Probable time of infection	
Perinatal	901 (88)
Nonperinatal	74 (7)
Unknown or missing	53 (5)
Educational level of parent or guardian	
Less than high school	316 (31)
Completion of high school	310 (30)
More than high school	322 (31)
Other, unknown, or missing	80 (8)
Race or ethnic group	
Non-Hispanic white	176 (17)
Non-Hispanic black	479 (47)
Hispanic	358 (35)
Other	15 (1)
Antiviral medication use at base line	
Nucleoside reverse-transcriptase inhibitors	886 (86)
Combination therapy including nonnucleoside reverse-transcriptase inhibitors	89 (9)
Combination therapy including protease inhibitors	0
No antiretroviral medications	28 (3)
Unknown	25 (2)
Percentage of CD4+ lymphocytes*	
<15	330 (32)
≥15	687 (67)
	median (interquartile range)
CD4+ lymphocyte count (/mm ³)	519 (189 to 900)
Percentage of CD4+ lymphocytes	22 (10 to 31)
Height-for-age z score†	-0.89 (-1.72 to -0.11)
Weight-for-age z score†	-0.46 (-1.23 to -0.33)
No. of study subjects at site	20 (13 to 30)

*Eleven patients were missing CD4+ lymphocyte data on or before December 31, 1995.

†A z score of 0 corresponds to the 50th percentile, and a z score of -1.0 indicates 1 SD below the mean.

tiated, only 4.8 percent had discontinued this therapy by the end of 1999.

We compared the end-of-study characteristics (in 1999, or in 1998 for those who did not have a follow-up visit in 1999) of the subjects who had never received combination therapy including protease inhibitors with the characteristics of the subjects who had received such therapy. The subjects who had never received this type of therapy were younger than those who had received it (mean, 9.6 years vs. 10.2 years; $P=0.04$), were taller (mean height-for-age z score, -0.4 vs. -1.0; $P<0.001$), weighed more (mean

weight-for-age z score, 0.1 vs. -0.4; $P < 0.001$), and had higher percentages of CD4+ lymphocytes (mean, 28 percent vs. 26 percent; $P = 0.005$).

Predictors of the Initiation of Combination Therapy Including Protease Inhibitors

By 1998, combination therapy including protease inhibitors had been initiated in more than half the subjects. We estimated that the median time to the initiation of such therapy was 2.0 years from January 1, 1996. For subjects in whom the percentage of CD4+ lymphocytes was lower than 15, the median time to the initiation of therapy was 1.4 years, as compared with 2.1 years for subjects with 15 percent or more CD4+ lymphocytes ($P < 0.001$ by the log-rank test) (Table 2). Among non-Hispanic black subjects, the median time to initiation was 0.3 year longer than that among non-Hispanic white subjects (2.0 years vs. 1.7 years; $P < 0.001$). Among Hispanic subjects, there was a similar delay (0.3 year; $P = 0.005$ by the log-rank test). Longer median times to initiation were also found for younger subjects (P for trend < 0.001) and for those who had become infected perinatally ($P < 0.001$).

A multivariate proportional-hazards regression model showed that the time to the initiation of combination therapy including protease inhibitors was significantly shorter for subjects with low CD4+ lymphocyte counts and perinatally acquired infection (Table 3). When we controlled for the severity of illness and the number of study subjects at the site, the association of non-Hispanic black race (hazard ratio, 0.82; $P = 0.06$) and Hispanic ethnic background (hazard ratio, 0.85; $P = 0.15$) with a delayed initiation of combination therapy including protease inhibitors was weaker and was no longer statistically significant.

Mortality Rates and Protease-Inhibitor Therapy

There was substantial reduction in mortality over time, from 5.3 percent in 1996 to 2.1 percent in 1997, 0.9 percent in 1998, and 0.7 percent in 1999 (P for trend < 0.001 , by the log-rank test) (Table 4). There is evidence of reductions in mortality in all subgroups defined according to age, sex, percentage of CD4+ lymphocytes, educational level of the parent or guardian, and race or ethnic group.

A multivariate proportional-hazards regression model showed that the initiation of combination therapy including protease inhibitors was independently associated with a substantial reduction in mortality (hazard ratio for death, 0.33; 95 percent confidence interval, 0.19 to 0.58; $P < 0.001$) (Table 5). There was no evidence of differences in this effect according to sex, age, percentage of CD4+ lymphocytes, educational level of the parent or guardian, or race or ethnic group. Other variables that were independently associated with a greater likelihood of survival were higher log CD4+ lymphocyte counts ($P < 0.001$) and male

TABLE 2. MEDIAN TIME TO THE INITIATION OF COMBINATION THERAPY INCLUDING PROTEASE INHIBITORS, ACCORDING TO BASE-LINE CHARACTERISTICS.

CHARACTERISTIC	MEDIAN TIME FROM JANUARY 1, 1996, TO INITIATION years	P VALUE*
Age at base line		<0.001
0 to 1 yr	2.1	
2 to 5 yr	2.2	
6 to 12 yr	1.8	
13 to 20 yr	1.5	
Sex		0.06
Female	2.0	
Male	1.9	
Probable time of infection		<0.001
Perinatal	2.0	
Nonperinatal	1.3	
Unknown or missing	2.0	
Educational level of parent or guardian		0.76
Less than high school	2.0	
Completion of high school	2.0	
More than high school	1.9	
Other, unknown, or missing	2.0	
Race or ethnic group		<0.001
Non-Hispanic white†	1.7	
Non-Hispanic black	2.0	
Hispanic	2.0	
Base-line percentage of CD4+ lymphocytes		<0.001
<15	1.4	
≥15	2.1	
Height-for-age z score‡		<0.001
Less than -1.72	1.5	
-1.72 to -0.89	2.0	
-0.88 to -0.11	2.1	
-0.10 or higher	2.1	
Weight-for-age z score‡		<0.001
Less than -1.23	1.5	
-1.23 to -0.47	2.0	
-0.46 to 0.34	2.1	
0.35 or higher	2.2	
No. of study subjects at site		0.28
1 to 13	1.9	
14 to 19	2.0	
20 to 30	1.9	
>30	2.0	

*P values were determined by the log-rank test.

†This category includes those who indicated they were of "other" races or ethnic groups.

‡A z score of 0 corresponds to the 50th percentile, and a z score of -1.0 indicates 1 SD below the mean.

sex ($P = 0.06$) (Table 5). The survival benefit associated with combination therapy including protease inhibitors also persisted (hazard ratio for death, 0.32; 95 percent confidence interval, 0.18 to 0.55; $P < 0.001$) after we controlled for the declining trend in mortality over time (P for trend = 0.04). In a regression analysis in which only the initiation of combination therapy including protease inhibitors was used as a predictor (and no measures of the severity of illness were included), the unadjusted risk of death was 0.73 ($P = 0.24$; 95 percent confidence interval, 0.44 to

TABLE 3. HAZARD RATIOS FROM MULTIVARIATE PROPORTIONAL-HAZARDS REGRESSION MODEL PREDICTING THE TIME TO THE INITIATION OF COMBINATION THERAPY INCLUDING PROTEASE INHIBITORS.*

CHARACTERISTIC	HAZARD OF INITIATION	P VALUE
	hazard ratio (95% CI)	
Age (per yr)	0.98 (0.96–1.01)	0.18
Female sex	1.00 (0.85–1.16)	0.95
Probable time of infection		
Perinatal	1.00	
Nonperinatal	1.74 (1.26–2.40)	<0.001
Unknown or missing	1.00 (0.71–1.41)	0.99
Educational level of parent or guardian		
Less than high school	0.89 (0.73–1.09)	0.26
Completion of high school	1.00	
More than high school	1.03 (0.85–1.26)	0.74
Other, unknown, or missing	0.97 (0.72–1.31)	0.84
Race or ethnic group		
Non-Hispanic white†	1.00	
Non-Hispanic black	0.82 (0.66–1.01)	0.06
Hispanic	0.85 (0.68–1.06)	0.15
CD4+ lymphocyte count (per log increment)	0.54 (0.48–0.61)	<0.001
Height-for-age z score (per 1 SD increment)	0.96 (0.87–1.04)	0.31
Weight-for-age z score (per 1 SD increment)	0.94 (0.85–1.03)	0.18
No. of study subjects at site		
1 to 13	1.21 (0.97–1.51)	0.10
14 to 19	1.00 (0.81–1.25)	0.98
20 to 30	1.30 (1.05–1.60)	0.02
>30	1.00	

*CI denotes confidence interval, and SD refers to the SD from the mean in a normal or reference population.

†This category includes those who indicated they were of “other” races or ethnic groups.

1.23). This attenuation of the benefit of the therapy is a consequence of the lack of control for the severity of illness — in other words, of confounding by indication. In sicker children, combination therapy including protease inhibitors was more likely to be initiated earlier.

DISCUSSION

Among children and adolescents, the initiation of combination therapy including protease inhibitors is associated with an estimated reduction of 67 percent in the risk of death, after adjustment for potentially confounding variables. The reduction in risk was similar among all subjects regardless of age, sex, percentage of CD4+ lymphocytes, educational level of the parent or guardian, and race or ethnic group. A similar reduction (71 percent) was found in an Italian study,⁷ although more than 20 percent of the subjects in that study received no antiretroviral therapy, as compared with only 0.1 percent in our study.

TABLE 4. ANNUAL MORTALITY ACCORDING TO BASE-LINE CHARACTERISTICS.

CHARACTERISTIC	ANNUAL MORTALITY				P VALUE*
	1996	1997	1998	1999	
	percent				
All subjects	5.3	2.1	0.9	0.7	<0.001
Age as of Jan. 1, 1996					
0 to 1 yr	4.4	0.0	0.0	0.0	0.08
2 to 5 yr	4.4	1.7	0.9	0.0	<0.001
6 to 12 yr	5.8	2.5	1.0	1.2	<0.001
13 to 20 yr	6.4	2.4	1.5	1.8	0.13
Sex					
Female	6.1	2.0	0.7	0.0	<0.001
Male	4.4	2.2	1.2	1.4	0.004
Probable time of infection					
Perinatal	5.2	1.9	0.9	0.6	<0.001
Nonperinatal	5.7	4.9	0.0	2.4	0.29
Unknown	5.7	2.1	2.3	0.0	0.21
Educational level of parent or guardian					
Less than high school	3.9	2.1	1.9	0.4	0.02
Completion of high school	6.6	2.6	0.4	1.1	<0.001
More than high school	5.4	2.1	0.8	0.8	<0.001
Other, unknown, or missing	5.2	0.0	0.0	0.0	0.01
Race or ethnic group					
Non-Hispanic white†	7.5	2.7	2.2	0.8	0.006
Non-Hispanic black	3.8	2.5	1.2	0.9	0.004
Hispanic	6.0	1.3	0.0	0.4	<0.001
Percentage of CD4+ lymphocytes					
<15	14.6	5.7	3.5	2.6	<0.001
≥15	0.9	0.6	0.0	0.0	0.005
Height-for-age z score‡					
Less than -1.72	11.2	2.8	1.5	1.1	<0.001
-1.72 to -0.89	3.6	2.2	1.4	1.3	0.10
-0.88 to -0.11	4.1	1.8	0.9	0.5	0.01
-0.10 or higher	2.4	1.7	0.0	0.0	0.008
Weight-for-age z score‡					
Less than -1.23	12.0	3.8	1.6	0.6	<0.001
-1.23 to -0.47	3.2	1.3	1.9	1.3	0.34
-0.46 to 0.34	2.8	1.3	0.0	0.9	0.06
0.35 or higher	3.2	2.1	0.4	0.0	0.005
No. of study subjects at site					
1 to 13	7.2	3.5	0.5	0.0	<0.001
14 to 19	5.3	1.3	2.0	0.7	0.01
20 to 30	4.7	1.7	0.4	0.5	0.001
>30	4.1	2.0	0.8	1.5	0.05

*P values were determined by the log-rank test for trend.

†This category includes those who indicated they were of “other” races or ethnic groups.

‡A z score of 0 corresponds to the 50th percentile, and a z score of -1.0 indicates 1 SD below the mean.

Although randomized, controlled clinical trials provide the most valid evidence of efficacy, they can lack generalizability and may provide a limited view of the effect of therapies on outcomes in the population at large. Prospective cohort studies, in contrast, allow the therapeutic effect to be assessed under usual clinical conditions, although inadequate control can bias the results.²⁸

Our study has several possible limitations: inade-

TABLE 5. MULTIVARIATE PROPORTIONAL-HAZARDS REGRESSION MODEL PREDICTING TIME TO DEATH.*

CHARACTERISTIC	HAZARD OF DEATH	P VALUE
	hazard ratio (95% CI)	
Combination therapy including protease inhibitors	0.33 (0.19–0.58)	<0.001
Age (per yr)	0.95 (0.89–1.02)	0.16
Female sex	1.55 (0.98–2.45)	0.06
Probable time of infection		
Perinatal	1.00	
Nonperinatal	1.09 (0.42–2.81)	0.86
Unknown	0.61 (0.23–1.63)	0.33
Educational level of parent or guardian		
Less than high school	0.71 (0.39–1.28)	0.25
Completion of high school	1.00	
More than high school	0.98 (0.57–1.68)	0.94
Other, unknown, or missing	0.65 (0.22–1.89)	0.43
Race or ethnic group		
Non-Hispanic white†	1.00	
Non-Hispanic black	0.72 (0.40–1.28)	0.26
Hispanic	0.74 (0.39–1.39)	0.35
CD4+ lymphocyte count (per log increment)	0.25 (0.20–0.31)	<0.001
Height-for-age z score (per 1 SD increment)	0.97 (0.78–1.21)	0.80
Weight-for-age z score (per 1 SD increment)	0.82 (0.61–1.10)	0.17
No. of study subjects at site		
1 to 13	1.18 (0.63–2.19)	0.61
14 to 19	1.06 (0.56–1.99)	0.86
20 to 30	1.12 (0.57–2.21)	0.74
>30	1.00	

*CI denotes confidence interval, and SD refers to the SD from the mean in a normal or reference population.

†This category includes those who indicated they were of “other” races or ethnic groups.

quate control for confounding by indication, uncertainty about the timing of the initiation of therapy, and limited generalizability of the PACTG 219 sample. We controlled for confounding by indication by means of proportional-hazards regression models in which we controlled for the known indicators of the severity of illness. One potentially important variable for which we did not control is the HIV-1 RNA level.^{29,30} Although measurements of HIV-1 RNA are currently used to help clinicians make decisions about medication, CD4+ lymphocyte counts and percentages were used more commonly when we began our study. Recent data indicate that CD4+ lymphocyte data for patients receiving combination therapies have continuing prognostic value.³¹ Our lack of control for the viral load before the initiation of therapy could have led to an underestimation of the therapeutic effect, however.

Our finding, in unadjusted analyses, of differences according to race or ethnic group in the time to the

initiation of combination therapy including protease inhibitors could be troubling because it might reflect the presence of barriers to access. When we controlled for differences in the severity of illness and other covariates, however, the differences among racial and ethnic groups became statistically insignificant. Although this result is reassuring, continued vigilance is needed to ensure equitable access to treatment for HIV.

The limited number of children and adolescents in our study and the substantial number of different combinations of medications whose use was reported restrict our ability to address hypotheses concerning specific combinations of nucleoside analogues and protease inhibitors. Patients may be switched from one drug regimen to another because of toxic effects or other side effects, because of a lack of response, or because of difficulties with adherence. Newer data collected in PACTG 219 will provide more detail concerning medications and their side effects, as well as about the severity of illness.

The benefits of combination therapy including protease inhibitors in children and adolescents with HIV include a decreased risk of death, improved growth,³² better immune function,³⁻⁶ and a marked decrease in the incidence of infectious complications (unpublished data). However, the risks of long-term therapy in such patients necessitate increased vigilance and consideration of the risk-benefit ratio of aggressive antiretroviral intervention. In adults, the use of combination therapies including protease inhibitors has been associated with hyperglycemia, hyperlipidemia, lipodystrophy,³³ and bone mineral loss including osteonecrosis. Related complications have recently been documented in children.^{34,35} Because of the effects of current therapies on glucose and lipid metabolism, body composition, mitochondrial function, and cardiovascular function, we must ensure that improved survival is not adversely affected as children who were infected with HIV perinatally enter their second and third decades of life. As HIV disease in children in industrialized nations is transformed from an almost uniformly fatal illness to a chronic condition, we must also consider issues of sexuality and the psychosocial challenges associated with adolescence and young adulthood. In the face of the widespread concern about the toxicity, side effects, and unknown long-term consequences of the available therapies, the data from the ongoing PACTG 219 study should be able to provide important assessments of long-term outcomes.

Combination therapy including protease inhibitors markedly reduces mortality among children and adolescents, just as it has among adults. Our results support the use of combination therapies including protease inhibitors in order to prolong the lives of children and adolescents infected with HIV-1. The continued prospective evaluation of children and adolescents receiving these new therapies is important

in improving our understanding of access to the therapies and their effect on mortality, growth, neuropsychological development, other illnesses, and the quality of life.

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