

ANTIRETROVIRAL THERAPY DURING PREGNANCY AND THE RISK OF AN ADVERSE OUTCOME

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ABSTRACT

Background Some studies suggest that combination antiretroviral therapy in pregnant women with human immunodeficiency virus type 1 (HIV-1) infection increases the risk of premature birth and other adverse outcomes of pregnancy.

Methods We studied pregnant women with HIV-1 infection who were enrolled in seven clinical studies and delivered their infants from 1990 through 1998. The cohort comprised 2123 women who received antiretroviral therapy during pregnancy (monotherapy in 1590, combination therapy without protease inhibitors in 396, and combination therapy with protease inhibitors in 137) and 1143 women who did not receive antiretroviral therapy.

Results After standardization for the CD4+ cell count and use or nonuse of tobacco, alcohol, and illicit drugs, the rate of premature delivery (<37 weeks of gestation) was similar among the women who received antiretroviral therapy and those who did not (16 percent and 17 percent, respectively); the rate of low birth weight (<2500 g) was 16 percent among the infants born to both groups; and the rate of very low birth weight (<1500 g) was 2 percent for the group that received antiretroviral therapy and 1 percent for the group that did not. The rates of low Apgar scores (<7) and stillbirth were also similar or the same in the two groups. After adjustment for multiple risk factors, combination antiretroviral therapy was not associated with an increased risk of premature delivery as compared with monotherapy (odds ratio, 1.08; 95 percent confidence interval, 0.71 to 1.62) or delivery of an infant with low birth weight (odds ratio, 1.03; 95 percent confidence interval, 0.64 to 1.63). Seven of the women who received combination therapy with protease inhibitors (5 percent) had infants with very low birth weight, as compared with nine women who received combination therapy without protease inhibitors (2 percent) (adjusted odds ratio, 3.56; 95 percent confidence interval, 1.04 to 12.19).

Conclusions As compared with no antiretroviral therapy or monotherapy, combination therapy for HIV-1 infection in pregnant women is not associated with increased rates of premature delivery or with low birth weight, low Apgar scores, or stillbirth in their infants. The association between combination therapy with protease inhibitors and an increased risk of very low birth weight requires confirmation. (N Engl J Med 2002;346:1863-70.)

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ANTIRETROVIRAL therapy is recommended during pregnancy to reduce the risk of perinatal transmission of human immunodeficiency virus type 1 (HIV-1) infection¹ and to improve maternal health.^{2,3} Data on complications of pregnancy associated with monotherapy or combination therapy with antiretroviral agents are limited.

In 1998, a retrospective Swiss study of 30 women with HIV-1 who had received combination antiretroviral therapy during pregnancy (with protease inhibitors in 13 women and without protease inhibitors in 17) showed that such treatment was associated with a 33 percent risk of premature delivery.⁴ Contemporaneously, the Pediatric AIDS Clinical Trials Group (PACTG) observed that in phase I trials of nelfinavir, ritonavir, or indinavir given in combination with zidovudine and lamivudine during pregnancy, 4 of 11 deliveries (36 percent) occurred before 37 weeks of gestation. We analyzed data from seven large studies involving pregnant women with HIV-1 infection, in order to assess the risk of premature delivery and other adverse outcomes of pregnancy associated with the use of antiretroviral agents.

METHODS

Study Population

We included women enrolled in two completed clinical trials (PACTG studies 076⁵ and 185⁶) and five ongoing, prospective,

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observational studies. The observational studies were two multisite studies (the Perinatal AIDS Collaborative Transmission Studies [PACTS]⁷ and the Women and Infants Transmission Study [WITS]⁸) and three single-site studies (at the University of Miami, the University of Southern California, and the University of California at Los Angeles [UCLA]). The enrollment criteria differed among the studies. PACTG studies 076 and 185 restricted enrollment according to the week of gestation (study 076, 14 to 34 weeks; study 185, 20 to 30 weeks) and the CD4 count (study 076, >200 per cubic millimeter; study 185, <500 per cubic millimeter). In PACTG study 076, previous antiretroviral therapy was a criterion for exclusion; in PACTG study 185, zidovudine use during the pregnancy was a criterion for inclusion. The single-site observational studies included all HIV-1-infected women who delivered at the site; the multisite studies included a subgroup of women who delivered at the sites.^{7,8} Written informed consent was obtained from all women except for those at the University of Miami, where data were abstracted from clinical charts and informed consent at the time of the study was not required. The observational studies excluded women who were also enrolled in PACTG clinical trials of antiretroviral therapy.

The inclusion criteria for our study were documentation of the infant's gestational age at birth, delivery at 20 or more weeks of gestation, singleton gestation, documentation of at least one antenatal CD4+ cell count, and documentation of the use or nonuse of antiretroviral agents during pregnancy. We divided the women into two cohorts according to the date of delivery and the use or nonuse of antiretroviral therapy. Women who delivered between January 1, 1990, and February 28, 1994 (before the general use of zidovudine to decrease the risk of vertical HIV-1 transmission),¹ were in the cohort of women who did not receive antiretroviral therapy (referred to as the untreated cohort). The other cohort included women who received antepartum antiretroviral therapy and delivered from March 1, 1994, through 1998 (referred to as the treated cohort). Women who received antiretroviral therapy only during the intrapartum period were excluded. We excluded from the untreated cohort women who had conceived less than 44 weeks before March 1, 1994, and we excluded from the treated cohort women who had conceived more than 20 weeks before this date in order to reduce the chance of overrepresentation or underrepresentation of premature deliveries, respectively. Women enrolled in PACTS, the UCLA study, or WITS were included in both cohorts (untreated, 469, 20, and 446 women, respectively; treated, 487, 87, and 673 women, respectively). Women enrolled in PACTG study 185, the University of Miami study, or the University of Southern California study were included only in the treated cohort (463, 339, and 74 women, respectively), and women enrolled in PACTG study 076 were included only in the untreated cohort (208 women).

Study Variables

Antiretroviral therapy was categorized as monotherapy, combination therapy without protease inhibitors, or combination therapy with protease inhibitors. If more than one regimen was used before delivery, therapy was categorized hierarchically as follows: combination therapy with protease inhibitors took precedence over combination therapy without protease inhibitors, which took precedence over monotherapy. The infant's gestational age at birth was determined on the basis of the last menstrual period, ultrasound data, or both; if these data were not available, it was based on the pediatric assessment at birth. Premature delivery was defined as delivery at less than 37 weeks of gestation, and very premature delivery as delivery at less than 32 weeks of gestation. Low birth weight was defined as less than 2500 g and very low birth weight as less than 1500 g. Apgar scores at one and five minutes were categorized as normal (≥ 7), possibly abnormal (< 7), or definitely abnormal (< 4). We used the lowest recorded antenatal CD4+ cell count (categorized as < 200 , 200 to 499, or ≥ 500 cells per cubic millimeter) for analysis. Because the exact date that antiretroviral therapy was

started was not known for the majority of women, we used the week of gestation at which therapy was initiated, categorized as less than 27 weeks, 27 weeks or more, or unknown. For the group of women who did not receive antiretroviral therapy, the time of enrollment was categorized according to the week of gestation (< 27 weeks or ≥ 27 weeks). Data for individual patients were submitted to the PACTG Statistical and Data Management Center for analysis.

Statistical Analysis

We performed pairwise comparisons to assess the outcome of pregnancy according to the type of antiretroviral therapy: monotherapy versus any combination therapy, monotherapy versus combination therapy with protease inhibitors, monotherapy versus combination therapy without protease inhibitors, and combination therapy without protease inhibitors versus combination therapy with protease inhibitors. We compared characteristics of the patients and the outcomes of pregnancy according to the use or nonuse of antiretroviral agents (controlling for the study), using stratified Cochran–Mantel–Haenszel tests⁹ for categorical variables and analysis of variance for continuous variables (with logarithmic transformation). Data on outcomes in the untreated group were adjusted for differences in characteristics by direct standardization, with the treated group used as the standard population.¹⁰

For each study, we calculated odds ratios and exact 95 percent confidence intervals⁹ for premature delivery and low birth weight in the infant according to the use or nonuse of antiretroviral therapy. Overall odds ratios for the entire cohort were calculated with the use of the Mantel–Haenszel estimator (stratified according to the study), with 95 percent confidence intervals based on the Robins–Breslow–Greenland variance estimator.⁹ The Breslow–Day test was used to determine whether odds ratios differed among studies.⁹ Overall odds ratios, confidence intervals, and P values were also calculated by exact methods⁹ (the conditional-maximum-likelihood method and Zelen test); these results did not differ substantially from the Mantel–Haenszel estimates and the Breslow–Day P values and are therefore not reported. We performed multivariate logistic-regression analyses to adjust odds ratios and calculate 95 percent confidence intervals, using the profile-likelihood method, for the following covariates: the study, the CD4+ cell count, age, race or ethnic group, presence or absence of a history of premature delivery, year of delivery, and use or nonuse of tobacco, alcohol, and illicit drugs. The Hosmer–Lemeshow test was used to assess the adequacy of the model's fit to the data.¹¹

Sensitivity analyses were performed to determine the effect of two potential sources of bias. Since data on prior premature delivery, a risk factor for subsequent premature delivery, were not available from one of the largest studies (PACTS), separate logistic-regression analyses were conducted for the women for whom data on all risk factors, including the presence or absence of prior premature delivery, were available and those for whom data on all risk factors except prior premature delivery were available. Since some women may have started using antiretroviral agents late in pregnancy (after 37 weeks of gestation), multivariate logistic-regression analyses were repeated with adjustment for the time at which antiretroviral therapy was initiated (< 27 weeks, ≥ 27 weeks, or unknown).

Statistical analyses were performed with the use of SAS, version 8 (SAS Institute), Proc-StatXact, version 4 (Cytel Software), and Stata, version 6.0 (Stata) software. All reported P values are based on two-sided tests. A P value of less than 0.05 was considered to indicate statistical significance; no adjustment was made for multiple comparisons.

RESULTS

A total of 2123 women received antiretroviral therapy during pregnancy (1590 received monotherapy, 396 combination therapy without protease inhibitors,

and 137 combination therapy with protease inhibitors), and 1143 women did not receive antiretroviral therapy. Women who received combination therapy with protease inhibitors had delivered more recently, had lower CD4+ cell counts, and had a higher median age than women who received antiretroviral regimens without protease inhibitors (Table 1). The rate of illicit-drug use was higher among women who received monotherapy than among those who received combination therapy. Women who received antiretroviral therapy had lower CD4+ cell counts and lower rates of tobacco, alcohol, and illicit-drug use than women who did not receive antiretroviral therapy (Table 1).

Unadjusted rates of very premature delivery and, among infants, low birth weight, very low birth weight, abnormal Apgar scores, and stillbirth did not differ significantly between the treated and untreated groups; however, unadjusted rates of premature delivery were significantly lower among treated women (Table 2). The rates of each of these outcomes were also similar among the women who received monotherapy and those who received combination therapy.

Overall, the rates of adverse pregnancy outcomes remained similar in the treated and untreated groups after direct standardization to adjust for differences in the CD4+ count and rates of tobacco, alcohol, and illicit-drug use (Table 2).

Rates of premature and very premature delivery did not differ significantly according to whether the antiretroviral regimen included protease inhibitors (Table 2). Odds ratios for premature and very premature delivery in the group of women who received combination therapy without protease inhibitors, as compared with the group of women who received combination therapy with protease inhibitors, did not vary significantly among the studies (see Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>).

The risk of low birth weight was lower among infants born to women who received combination therapy without protease inhibitors than among infants born to women who received monotherapy (unadjusted odds ratio, 0.58; 95 percent confidence interval, 0.41 to 0.84) and was higher among infants born to women who received combination therapy with protease inhibitors than among those born to women who received combination therapy without protease inhibitors (unadjusted odds ratio, 2.03; 95 percent confidence interval, 1.16 to 3.54). The risk of very low birth weight was also higher among infants born to women who received combination therapy with protease inhibitors than among infants born to women who received monotherapy or combination therapy without protease inhibitors, but these results were not statistically significant. Odds ratios for low and very low birth weight did not vary significantly among stud-

ies in the comparison of combination therapy that did not include protease inhibitors with combination therapy that did (see Supplementary Appendix 1).

Data on all assessed risk factors for adverse outcomes were available for 1598 treated women, and data on all risk factors except prior premature delivery were available for 1936 treated women. After adjustment for covariates other than, or including, prior premature delivery, the risk of premature and very premature delivery among women who received combination therapy with protease inhibitors, as compared with those who received combination therapy without protease inhibitors, was not elevated (Table 3). After adjustment for covariates other than prior premature delivery, combination therapy that included protease inhibitors was associated with higher risks of low birth weight and very low birth weight than was combination therapy without protease inhibitors (Table 3). However, when the analysis was also adjusted for prior premature delivery, only the risk of very low birth weight remained significantly elevated (Table 3), with a wide 95 percent confidence interval. These results did not change when the time of the initiation of antiretroviral therapy was added to the logistic-regression analyses (data not shown).

We also compared the rates of adverse outcomes between women who received antiretroviral therapy and those who did not in multivariate analyses that both excluded and included a history of premature delivery (Table 4). None of the antiretroviral regimens were associated with a significantly increased risk of premature or very premature delivery, as compared with no antiretroviral therapy. As compared with the infants of women who received no antiretroviral therapy, there was a lower risk of low birth weight among infants born to women who received combination therapy without protease inhibitors and a higher risk of very low birth weight among infants born to women who received combination therapy with protease inhibitors (Table 4); however, the latter result was not significant after adjustment for prior premature delivery.

DISCUSSION

In a large cohort of HIV-1-infected women who received antiretroviral therapy during pregnancy, we found that the risk of an adverse outcome of pregnancy was not associated with the use of combination antiretroviral regimens overall. Our analysis was adjusted for several recognized risk factors for adverse outcomes of pregnancy.

Unlike the initial Swiss study,⁴ our study showed that the risk of premature delivery was not significantly higher with combination antiretroviral therapy than with monotherapy or no therapy. The upper limit of the 95 percent confidence interval for the adjusted

TABLE 1. CHARACTERISTICS OF THE 3266 STUDY PARTICIPANTS ACCORDING TO THE USE OR NONUSE OF ANTIRETROVIRAL THERAPY DURING PREGNANCY.

CHARACTERISTIC	ANTIRETROVIRAL THERAPY				P VALUE§	No ANTI-RETROVIRAL THERAPY (N=1143)	P VALUE*
	MONO-THERAPY (N=1590)†	ANY COMBINATION (N=533)	COMBINATION WITHOUT PROTEASE INHIBITORS (N=396)	COMBINATION WITH PROTEASE INHIBITORS (N=137)‡			
Year of delivery — no. (%)					<0.001		<0.001
1990–1993	0	0	0	0		0	1130 (99)
1994	212 (13)	5 (1)	5 (1)	0		217 (10)	13 (1)
1995	547 (34)	16 (3)	16 (4)	0		563 (27)	0
1996	536 (34)	93 (17)	83 (21)	10 (7)		629 (30)	0
1997	256 (16)	271 (51)	210 (53)	61 (45)		527 (25)	0
1998	39 (2)	148 (28)	82 (21)	66 (48)		187 (9)	0
CD4+ cell count					<0.001		<0.001
<200/mm ³ — no. (%)	309 (19)	168 (32)	109 (28)	59 (43)		477 (22)	138 (12)
200–499/mm ³ — no. (%)	872 (55)	277 (52)	227 (57)	50 (36)		1149 (54)	510 (45)
≥500/mm ³ — no. (%)	409 (26)	88 (17)	60 (15)	28 (20)		497 (23)	495 (43)
Median — per mm ³	358	286	301	218	<0.001	343	450
Age					0.07		0.19
<18 yr — no. (%)	59 (4)	17 (3)	13 (3)	4 (3)		76 (4)	27 (2)
18–34 yr — no. (%)	1337 (85)	431 (81)	321 (82)	110 (80)		1768 (84)	987 (88)
>34 yr — no. (%)	184 (12)	81 (15)	58 (15)	23 (17)		265 (13)	113 (10)
Unknown — no.	10	4	4	0		14	16
Median — yr	27	28	27	29	0.003	27	27
Race or ethnic group — no. (%)					0.53		0.07
White	149 (9)	59 (11)	41 (11)	18 (13)		208 (10)	136 (12)
Black	925 (59)	296 (56)	227 (58)	69 (50)		1221 (58)	622 (56)
Hispanic	460 (29)	157 (30)	111 (28)	46 (34)		617 (29)	334 (30)
Other	44 (3)	15 (3)	11 (3)	4 (3)		59 (3)	25 (2)
Unknown	12	6	6	0		18	26
Prior premature delivery — no. (%)					0.73		0.05
Yes	102 (9)	39 (9)	31 (10)	8 (7)		141 (9)	36 (5)
No	1092 (91)	394 (91)	294 (90)	100 (93)		1486 (91)	637 (95)
Unknown	396	100	71	29		496	470
Tobacco use during pregnancy — no. (%)					0.53		<0.002
Yes	556 (36)	150 (29)	108 (28)	42 (31)		706 (34)	597 (55)
No	999 (64)	368 (71)	275 (72)	93 (69)		1367 (66)	497 (45)
Unknown	35	15	13	2		50	49
Alcohol use during pregnancy — no. (%)					0.17		<0.001
Yes	371 (25)	88 (18)	60 (17)	28 (22)		459 (23)	421 (41)
No	1105 (75)	401 (82)	302 (83)	99 (78)		1506 (77)	613 (59)
Unknown	114	44	34	10		158	109
Illicit-drug use during pregnancy — no. (%)¶					<0.001		<0.001
Yes	392 (25)	82 (16)	61 (16)	21 (16)		474 (23)	464 (42)
No	1162 (75)	434 (84)	323 (84)	111 (84)		1596 (77)	629 (58)
Unknown	36	17	12	5		53	50
Week of gestation at start of antiretroviral therapy — no. (%)					0.62		<0.001
<27 wk	970 (71)	289 (67)	223 (67)	66 (66)		1259 (70)	577 (50)
≥27 wk	394 (29)	144 (33)	110 (33)	34 (34)		538 (30)	566 (50)
Unknown	226	100	63	37		326	0

*P values are for the comparison of any antiretroviral regimen with no antiretroviral therapy, in an analysis controlled for the study.

†Monotherapy was assumed to be zidovudine therapy, which was the recommended monotherapy for pregnant women at the time of the studies.

‡Nelfinavir was used in 57 women, saquinavir in 26, indinavir in 23, ritonavir in 15, and multiple protease inhibitors in 15; the specific agent was unknown in 1 woman.

§P values are for the comparison of monotherapy with any combination therapy (with or without protease inhibitors) in an analysis controlled for the study.

¶Illicit drugs were defined as heroin or opiates, methadone, cocaine, and injection drugs.

||For women who did not receive antiretroviral therapy, the week of gestation at the time of enrollment in the study was documented.

ANTIRETROVIRAL THERAPY DURING PREGNANCY

TABLE 2. OUTCOMES OF PREGNANCY ACCORDING TO THE USE OR NONUSE OF ANTIRETROVIRAL THERAPY.

OUTCOME	ANTIRETROVIRAL THERAPY						NO ANTIRETROVIRAL THERAPY (N=1143)			
	MONOTHERAPY (N=1590)	ANY COMBINATION (N=533)	P VALUE*	COMBINATION WITHOUT PROTEASE INHIBITORS (N=396)	COMBINATION WITH PROTEASE INHIBITORS (N=137)	P VALUE†	ANY ANTI-RETROVIRAL REGIMEN (N=2123)	UNADJUSTED	P VALUE‡	ADJUSTED %§
Gestational age at delivery										
<37 wk — no. (%)	254 (16)	80 (15)	0.65	55 (14)	25 (18)	0.15	334 (16)	228 (20)	0.02	17
<32 wk — no. (%)	48 (3)	16 (3)	0.80	10 (3)	6 (4)	0.17	64 (3)	36 (3)	0.45	2
Median — wk	39	39	0.13	39	39	0.28	39	39	0.18	
Birth weight										
<2500 g — no. (%)	258 (17)	68 (13)	0.06	41 (11)	27 (20)	0.009	326 (16)	213 (19)	0.17	16
<1500 g — no. (%)	34 (2)	16 (3)	0.40	9 (2)	7 (5)	0.05	50 (2)	25 (2)	0.92	1
Unknown — no.	27	11		8	3		38	42		
Median — g	3100	3146	0.53	3135	3162	0.10	3110	3020	0.11	
Apgar score										
At 1 min										
<7 — no. (%)	170 (11)	62 (12)	0.72	44 (11)	18 (14)	0.83	232 (11)	110 (11)	0.78	10
<4 — no. (%)	45 (3)	13 (3)	0.53	10 (3)	3 (2)	0.54	58 (3)	33 (3)	0.53	3
Unknown — no.	36	17		12	5		53	160		
At 5 min										
<7 — no. (%)	37 (2)	8 (2)	0.32	7 (2)	1 (1)	0.51	45 (2)	30 (3)	0.07	2
<4 — no. (%)	8 (1)	1 (<1)	0.51	1 (<1)	0	0.49	9 (<1)	4 (<1)	0.74	<1
Unknown — no.	42	17		12	5		59	160		
Stillbirth — no. (%)¶	11 (1)	1 (<1)	0.10	1 (<1)	0	0.50	12 (1)	7 (1)	0.92	1

*P values are for the comparison of any combination therapy (with or without protease inhibitors) with monotherapy, in an analysis controlled for the study.

†P values are for the comparison of combination therapy that included protease inhibitors with combination therapy that did not include protease inhibitors, in an analysis controlled for the study.

‡P values are for the comparison of any antiretroviral regimen with no antiretroviral therapy, in an analysis controlled for the study.

§The rates were adjusted by direct standardization of the data to the CD4+ cell count and the rates of tobacco, alcohol, and illicit-drug use in the cohort of women who received antiretroviral therapy.

¶Data on stillbirths at more than 20 weeks of gestation were collected in all studies except the Perinatal AIDS Collaborative Transmission Studies. The total numbers of women for whom data were available were 1210 for monotherapy, 438 for any combination therapy, 328 for combination therapy without protease inhibitors, 110 for combination therapy with protease inhibitors, 1648 for any antiretroviral regimen, and 681 for no antiretroviral therapy.

odds ratio for premature delivery with combination therapy, as compared with monotherapy, was 1.62, indicating that a substantial effect was unlikely.

Before March 1994, limited numbers of women received antiretroviral therapy for advanced HIV disease. Since then, the majority of pregnant women have received antiretroviral therapy as prophylaxis against vertical transmission.¹²⁻¹⁵ In our study, the treated and untreated women gave birth in different years, which makes it difficult to compare these groups directly; however, the similar rates of premature delivery in the two groups argue against a profound effect of antiretroviral therapy on prematurity.

An analysis of combined data from the European Collaborative Study and the Swiss Cohort Study showed a significant association between the risk of premature delivery and combination therapy, without and with protease inhibitors (odds ratio, 1.8 and 2.6, respectively), after adjustment for the maternal CD4+ cell count and the presence or absence of a history of parenteral drug use.¹⁶ The rates of premature

delivery in the European study were similar to those in our study¹⁶ for women who received no therapy or monotherapy but were higher among women who received combination therapy without protease inhibitors and among those who received combination therapy with protease inhibitors (22 and 29 percent, respectively, as compared with 14 and 18 percent, respectively, in our study).

The reason for the differences between our results and those of the European study is unclear. The risk factors for adverse outcomes of pregnancy are similar in HIV-1-infected women and women without HIV-1 infection.^{17,18} We were able to adjust for more of these factors than were the European investigators, including prior premature delivery and use of alcohol or tobacco. Neither we nor the European investigators could control directly for the stage of maternal disease or the HIV-1 viral load — factors that in some studies were associated with premature delivery.¹⁹⁻²² We found that the risk of low birth weight was lower among infants born to women who received combi-

TABLE 3. RISKS OF ADVERSE PREGNANCY OUTCOMES ACCORDING TO THE ANTIRETROVIRAL REGIMEN.*

OUTCOME	ODDS RATIO (95% CI)	
	ADJUSTED FOR ALL RISK FACTORS EXCEPT PRIOR PREMATURE DELIVERY (N=1936)†	ADJUSTED FOR ALL RISK FACTORS, INCLUDING PRIOR PREMATURE DELIVERY (N=1598)‡
Premature delivery (<37 wk)		
Combination vs. monotherapy	0.96 (0.66–1.40)	1.08 (0.71–1.62)
Combination without PI vs. monotherapy	0.87 (0.58–1.30)	0.95 (0.60–1.48)
Combination with PI vs. monotherapy	1.28 (0.74–2.13)	1.45 (0.81–2.50)
Combination with PI vs. without PI	1.58 (0.86–2.87)	1.80 (0.94–3.43)
Very premature delivery (<32 wk)		
Combination vs. monotherapy	0.83 (0.38–1.77)§	1.17 (0.49–2.72)§
Combination without PI vs. monotherapy	0.71 (0.29–1.62)§	0.97 (0.36–2.41)§
Combination with PI vs. monotherapy	1.78 (0.61–4.53)§	1.96 (0.64–5.28)§
Combination with PI vs. without PI	2.22 (0.70–6.58)§¶	2.70 (0.82–8.49)§¶
Low birth weight (<2500 g)		
Combination vs. monotherapy	0.76 (0.50–1.13)	1.03 (0.64–1.63)
Combination without PI vs. monotherapy	0.59 (0.37–0.93)¶	0.86 (0.51–1.42)
Combination with PI vs. monotherapy	1.52 (0.89–2.54)	1.45 (0.79–2.56)
Combination with PI vs. without PI	2.31 (1.21–4.39)**	2.00 (0.98–4.05)
Very low birth weight (<1500 g)		
Combination vs. monotherapy	1.11 (0.47–2.56)	1.64 (0.59–4.35)§
Combination without PI vs. monotherapy	0.82 (0.29–2.11)	1.23 (0.36–3.73)§
Combination with PI vs. monotherapy	2.93 (1.03–7.47)¶	3.03 (0.93–8.83)§
Combination with PI vs. without PI	3.15 (1.04–9.40)¶††	3.56 (1.04–12.19)§¶††

*CI denotes confidence interval, and PI protease inhibitors.

†These odds ratios are for the subgroup of 1936 treated women for whom data were available on all risk factors except prior premature delivery. Unless otherwise noted, these odds ratios were adjusted for the study; the CD4+ cell count (<200, 200 to 499, or ≥500 per cubic millimeter); age (<18, 18 to 34, or >34 years); race or ethnic group; and use or nonuse of tobacco, alcohol, and illicit drugs. The odds ratios for combination therapy as compared with monotherapy and for combination therapy without protease inhibitors as compared with monotherapy were also adjusted for the year of delivery.

‡These odds ratios are for the subgroup of 1598 treated women for whom data were available on all risk factors, including prior premature delivery. Unless otherwise noted, the odds ratios for this subgroup were adjusted for the study; the CD4+ cell count (<200, 200 to 499, or ≥500 per cubic millimeter); age (<18, 18 to 34, or >34 years); race or ethnic group; use or nonuse of tobacco, alcohol, and illicit drugs; and the presence or absence of a history of premature delivery. The odds ratios for combination therapy as compared with monotherapy and for combination therapy without protease inhibitors as compared with monotherapy were also adjusted for the year of delivery.

§The odds ratio was adjusted for age as a two-category variable (≤34 or >34 years) instead of a three-category variable because there were no events in some strata.

¶The odds ratio was not adjusted for the study because there were no events in some strata.

||P=0.03.

**P=0.01.

††P=0.04.

nation therapy without protease inhibitors than among infants born to women who received no therapy, despite lower CD4+ cell counts in the women who received therapy.

The rate of very low birth weight was higher among infants born to women who received combination therapy with protease inhibitors than among infants born to women who received combination therapy without protease inhibitors, although the overall number of infants with very low birth weight was small, the confidence interval was wide, and we did not adjust for multiple comparisons. The difference may reflect an effect of the stage of maternal HIV disease on birth weight. It is likely that women who received combination therapy with protease inhibitors had

more advanced disease than those who received combination therapy without protease inhibitors.

Forty-three percent of the women who received protease inhibitors had a CD4+ cell count of less than 200 per cubic millimeter, as compared with 12 percent of those who received no therapy, 19 percent of those who received monotherapy, and 28 percent of those who received combination therapy without protease inhibitors. We did not have data available to adjust our analyses for the viral load and the stage of disease. Any small increase in the risk of low birth weight is likely to be outweighed by the substantial benefits of treatment with protease inhibitors for both the mother and the infant.

Our study has some limitations. We did not have

TABLE 4. RISKS OF ADVERSE PREGNANCY OUTCOMES AMONG WOMEN WHO RECEIVED ANTIRETROVIRAL THERAPY AS COMPARED WITH UNTREATED WOMEN.*

OUTCOME	ODDS RATIO (95% CI)	
	ADJUSTED FOR ALL RISK FACTORS EXCEPT PRIOR PREMATURE DELIVERY (N=2936)†	ADJUSTED FOR ALL RISK FACTORS, INCLUDING PRIOR PREMATURE DELIVERY (N=2229)‡
Premature delivery (<37 wk)		
Monotherapy	0.93 (0.70–1.22)	0.70 (0.49–1.01)
Combination without PI	0.94 (0.55–1.54)	0.95 (0.51–1.69)
Combination with PI	1.23 (0.62–2.32)	1.50 (0.72–3.01)
Very premature delivery (<32 wk)		
Monotherapy	1.31 (0.71–2.45)§	0.72 (0.32–1.61)§
Combination without PI	0.47 (0.07–1.81)¶	0.43 (0.06–1.78)§
Combination with PI	1.47 (0.30–5.23)§	1.36 (0.27–5.14)§
Low birth weight (<2500 g)		
Monotherapy	1.20 (0.92–1.57)	0.89 (0.62–1.29)
Combination without PI	0.36 (0.17–0.67)¶	0.45 (0.20–0.92)
Combination with PI	1.79 (0.94–3.30)	1.70 (0.80–3.45)
Very low birth weight (<1500 g)		
Monotherapy	1.17 (0.59–2.36)§	0.68 (0.24–1.84)**
Combination without PI	1.70 (0.65–4.24)**††	1.22 (0.43–3.45)**††
Combination with PI	3.17 (1.05–8.84)††‡‡	2.42 (0.67–8.03)§††

*For all odds ratios, the reference group is the group of women who did not receive antiretroviral therapy. CI denotes confidence interval, and PI protease inhibitors.

†These odds ratios are for the subgroup of 2936 treated and untreated women for whom data were available on all risk factors except prior premature delivery. Unless otherwise noted, these odds ratios were adjusted for the study; the CD4+ cell count (<200, 200 to 499, or ≥500 per cubic millimeter); age (<18, 18 to 34, or >34 years); race or ethnic group; and use or nonuse of tobacco, alcohol, and illicit drugs.

‡These odds ratios are for the subgroup of 2229 treated and untreated women for whom data were available on all risk factors, including prior premature delivery. Unless otherwise noted, these odds ratios were adjusted for the study; the CD4+ cell count (<200, 200 to 499, or ≥500 per cubic millimeter); age (<18, 18 to 34, or >34 years); race or ethnic group; use or nonuse of tobacco, alcohol, and illicit drugs; and the presence or absence of a history of premature delivery.

§The odds ratio was adjusted for age as a two-category variable (≤34 or >34 years) instead of a three-category variable because there were no events in some strata.

¶P=0.003.

||P=0.04.

**The odds ratio was adjusted for age as a two-category variable (≤34 or >34 years) and for race or ethnic group as a three-category variable (white, black, or Hispanic) because there were no events in some strata.

††The odds ratio was not adjusted for the study because there were no events in some strata.

‡‡P=0.03.

data on the precise time of the initiation of antiretroviral therapy, because most of the trials lacked these data. We also did not have information on early pregnancy loss, congenital anomalies, or long-term outcomes for the infants. We were unable to assess the effect of the duration of antiretroviral therapy on the outcomes of pregnancy or the effect of the stage of HIV-1 infection on the association between antiretroviral therapy and outcomes. The observed rates of premature delivery among women who received antiretroviral therapy may be lower than the actual rates because of the inclusion of some women who started antiretroviral therapy too late to be at risk for premature delivery. However, the odds ratios for premature and very premature delivery in association with

antiretroviral therapy did not change when the analyses were adjusted for the time of the initiation of antiretroviral therapy.

Both a low maternal viral load and the use of combination antiretroviral therapy during pregnancy are associated with rates of vertical transmission of HIV-1 of 2 percent or less.^{15,23-27} Guidelines issued by the Public Health Service support the use of combination antiretroviral therapy during pregnancy both to safeguard maternal health and to reduce the risk of vertical transmission of HIV-1 infection.¹ Our data provide reassurance that the risks of adverse outcomes of pregnancy that are attributable to antiretroviral therapy are low and are likely to be outweighed by the recognized benefits of such therapy during pregnancy.

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APPENDIX

The following investigators participated in the clinical studies included in this study: *Women and Infants Transmission Study* — C. Diaz, E. Pacheco-Acosta (University of Puerto Rico, San Juan); E. Cooper, D. Mesthene (Boston-Worcester site, Boston); J. Pitt, A. Higgins (Columbia Presbyterian Medical Center, New York); S. Landesman, E. Handelsman, G. Moroso (State University of New York, Brooklyn, N.Y.); K. Rich, D. Turpin (University of Illinois at Chicago); W. Shearer, S. Pacheco, N. Cooper (Baylor College of Medicine, Houston); S. Adeniyi-Jones, E. Matzen (National Institute of Allergy and Infectious Diseases, Rockville, Md.); R. Nugent (National Institute of Child Health and Human Development, Rockville, Md.); V. Smeriglio, K. Davenny (National Institute on Drug Abuse, Rockville, Md.); and B. Thompson (Clinical Trials and Surveys, Baltimore); *Pediatric AIDS Clinical Trials Group (PACTG) Statistical and Data Management Center* — S. St. Laurent, S. Traite; *PACTG 076* — E.M. Connor (University of Medicine and Dentistry of New Jersey, Newark), R.S. Sperling (Mt. Sinai Medical Center, New York); *PACTG 185* — E.R. Stiehm (UCLA Medical Center, Los Angeles); J. Lambert (Institute of Virology, University of Maryland, Baltimore); J. Moye, R. Nugent (National Institute of Child Health and Human Development, Rockville, Md.); J. Korelitz, J. Whitehouse, R. Harris, J. Bethel (Westat, Rockville, Md.); M.G. Fowler (Centers for Disease Control and Prevention, Atlanta); B. Mathieson (Office of AIDS Research, National Institutes of Health, Bethesda, Md.); *UCLA, Los Angeles* — M. Simshin, M. Dillon, J. Deville, K. Nielsen, M. Keller, A. Devekis; *University of Miami, Miami* — A. Gonzalez Garcia; *University of Southern California, Los Angeles* — M. Khoury; A. Kovacs, F. Kramer, J. Homans; *Perinatal AIDS Collaborative Transmission Studies* — S. Bakshi, M. Purswani, E. Stuard (Bronx-Lebanon Hospital Center, Bronx, N.Y.); L. Koenig, A. Bell, J. Wiener, J. Ethier-Ives, R.J. Simonds, M.G. Fowler (Centers for Disease Control and Prevention, Atlanta); S. Nesheim, M. Lindsey, V. Grimes, F. Lee, M. Sawyer, A. Nahmias (Emory University School of Medicine, Atlanta); E. Abrams, S. Champion, J. Floyd, C. Freeland, P. Prince (Harlem Hospital Center, New York); J. Abadi, J. Dobroszycki, A. Harris, G. Lambert (Jacobi Hospital Center, Bronx, N.Y.); M. Bamji, L. Jackson (Metropolitan Hospital Center, New York); R. Carter, T. Alford, M.A. Chiasson, D. Thea, J. Weedon (Medical and Health Research Association of New York City, New York); M. Mayers, M. Naccarato, V. Nedwin, E. Schoenbaum (Montefiore Medical Center, Bronx, N.Y.); P. Palumbo, A. Bardguez, L. Bettica, T. Denny, J. Oleske (University of Medicine and Dentistry of New Jersey, Newark); P. Vink, J. Farley, L. Alger, P. Nair, S. Hines (University of Maryland School of Medicine, Baltimore).

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