Efficacy of Zidovudine and Human Immunodeficiency Virus (HIV) Hyperimmune Immunoglobulin for Reducing Perinatal HIV Transmission from HIV-Infected Women with Advanced Disease: Results of Pediatric AIDS Clinical Trials Group Protocol 185

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Pediatric AIDS Clinical Trials Group protocol 185 evaluated whether zidovudine combined with human immunodeficiency virus (HIV) hyperimmune immunoglobulin (HIVIG) infusions administered monthly during pregnancy and to the neonate at birth would significantly lower perinatal HIV transmission compared with treatment with zidovudine and intravenous immunoglobulin (IVIG) without HIV antibody. Subjects had baseline CD4 cell counts ≤500/μL (22% had counts <200/μL) and required zidovudine for maternal health (24% received zidovudine before pregnancy). Transmission was associated with lower maternal baseline CD4 cell count (odds ratio, 1.58 per 100-cell decrement; $P = .005$; 10.0% vs. 3.6% transmission for count <200 vs. ≥200/μL) but not with time of zidovudine initiation (5.6% vs. 4.8% if started before vs. during pregnancy; $P = .75$). The Kaplan-Meier transmission rate for HIVIG recipients was 4.1% (95% confidence interval, 1.5%–6.7%) and for IVIG recipients was 6.0% (2.8%–9.1%) ($P = .36$). The unexpectedly low transmission confirmed that zidovudine prophylaxis is highly effective, even for women with advanced HIV disease and prior zidovudine therapy, although it limited the study's ability to address whether passive immunization diminishes perinatal transmission.

In 1994, Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 demonstrated that zidovudine administered to the mother during pregnancy and labor and to the newborn reduced the risk of perinatal human immunodeficiency virus (HIV) transmission by two-thirds; infection rates were 25.5% in placebo compared with 8.3% in zidovudine recipients [1]. However, enrollment into PACTG 076 was restricted to HIV-infected pregnant women with CD4 lymphocyte counts ≥200/μL not receiving or requiring antiretroviral therapy during the current pregnancy. The trial did not address the efficacy of zidovudine prophylaxis in women with more advanced disease or prior zidovudine therapy.

We sought to determine whether infusions of human HIV hyperimmune immunoglobulin (HIVIG) added to zidovudine prophylaxis would further reduce the rate of transmission from women with these characteristics. PACTG protocol 185 en-

Received 16 July 1998; revised 19 October 1998.

Presented in part: 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 1997 (abstract I-117).

The Pediatric AIDS Clinical Trials Group protocol 185 was reviewed and approved by the institutional review boards at each participating center. Each woman (and the father of the child, when available) gave written informed consent for her participation and that of her child. Human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this research.

Financial support: NIH (contracts HD-33162 [J.B., J.W., J.K., W.A.M., E.J., J.G., A.K., A.S.] and HL-57128 [C.V.S.] and cooperative agreements AI-27565 [Johns Hopkins, J.S.L.], AI-27550 [UCLA, E.R.S.], AI-27551 [Baylor, W.T.S., H.H.], AI-27560 [University of Miami, G.S., M.J.O.]).

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The Journal of Infectious Diseases 1999; 179:567–75

0022-1899/99/7903-0005$02.00

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rolled HIV-infected pregnant women with baseline CD4 cell counts ≤500/μL and HIV-related symptoms requiring antiretroviral therapy, who were receiving zidovudine during the current pregnancy for maternal health indications. At the time the study was designed, we estimated that the perinatal transmission rate in the women enrolled in PACTG 185 might be as high as 15%, despite zidovudine prophylaxis, and that additional interventions would be needed to further decrease HIV transmission. This estimate was based on epidemiologic studies in infected pregnant women not receiving antiretroviral therapy, which demonstrated that clinically symptomatic HIV disease, low CD4 lymphocyte count, and high virus load (at that time measured by p24 antigen levels) were associated with an elevated risk of perinatal HIV transmission [2–6]. Additionally, zidovudine prophylaxis was less effective in women who had received zidovudine before pregnancy in a study in France [7].

Passive immunoprophylaxis with polyclonal and monoclonal virus-specific antibodies successfully prevented transmission of simian, feline, and human immunodeficiency viruses in some animal studies [8–12] but not in others [13–15]. PACTG 185 evaluated whether HIVIG infusions administered to the mother monthly during pregnancy and to the neonate at birth combined with zidovudine prophylaxis would significantly lower perinatal HIV transmission compared with infusions of intravenous immunoglobulin (IVIG) without HIV antibody combined with zidovudine prophylaxis.

Methods

Study design. PACTG 185 was a multicenter, randomized, controlled phase III clinical trial conducted between October 1993 and March 1997 at 53 clinical sites in the mainland United States and Puerto Rico. Results from an initial pharmacokinetic and safety substudy of the first 28 mother-infant pairs have been published [16]. Eligibility criteria included laboratory documentation of maternal HIV infection, current receipt of zidovudine, baseline CD4 cell count ≤500/μL, gestational age between 20 and 30 weeks, hemoglobin level ≥8 g/dL, serum creatinine level ≤1.5 mg/dL, and urine protein grade <2+ by dipstick or level <4 g in 24 h of urine collection.

Exclusion criteria included evidence of preexisting fetal anomalies with high probability that the fetus or infant would not survive the study period (e.g., anencephaly), chorionic villous or percutaneous umbilical blood sampling during the current pregnancy, illnesses associated with extensive protein loss, preexisting conditions that required IVIG treatment, receipt of HIV vaccine or passive immunotherapy during the current pregnancy, and severe preeclampsia.

Receipt of nucleoside analogues other than zidovudine and/or nonnucleoside reverse transcriptase inhibitor antiretroviral drugs during the current pregnancy was permitted with protocol chair approval. Protease inhibitor antiretroviral drugs became available only during the last year of the study; because there were no available safety data on use of these drugs during pregnancy during the time PACTG 185 was conducted (late 1993 through early 1997), women receiving protease inhibitors during the current pregnancy were excluded from the study.

Before randomization, subjects were stratified by baseline maternal antenatal CD4 cell count (<200/μL or ≥200/μL), whether zidovudine therapy was initiated before or during the current pregnancy, and the geographic region where the study center was located.

Detailed description of the preparation and content of HIVIG (manufactured as HIV-IG by North American Biologicals, Boca Raton, FL) have been provided elsewhere [16, 17]. Study treatment consisted of HIVIG, 200 mg/kg by intravenous infusion every 4 weeks beginning at 20–30 weeks of gestation through delivery, or standard polyvalent, HIV antibody–negative IVIG (Gamimune N; Bayer, West Haven, CT) at the same dose and regimen. The newborn infant received an intravenous infusion of HIVIG or IVIG (200 mg/kg) within 12 h of birth; the infant received the same randomized study treatment (HIVIG or IVIG) as the mother. Women continued receiving their physician-prescribed antepartum antiretroviral regimen and received intrapartum zidovudine (intravenous loading dose of 2 mg/kg followed by a continuous infusion of 1.0 mg/kg/h until the umbilical cord was clamped); infants received the standard 6-week course of zidovudine prophylaxis (2 mg/kg zidovudine syrup orally every 6 h) starting within 8–12 h of birth [1].

Women were seen monthly for infusions and monitoring during pregnancy and at 6 weeks and 3, 6, 12, and 18 months postpartum. Women were followed for 18 months postpartum to evaluate whether HIVIG infusions had any long-term positive or negative effect on maternal virus load and/or disease progression. HIV quantitative peripheral blood mononuclear cell (PBMC) culture was done at baseline, just before the third infusion, at delivery, and 6 months postpartum; CD4 lymphocyte percentage and absolute number were assessed at baseline, just before the third infusion, and 6, 12, and 18 months postpartum; and blood specimens were obtained for storage at baseline, just before the third infusion, at delivery, and 3, 6, 12, and 18 months postpartum.

Infants were seen at weeks 1, 2, 6, and 12; every 4 weeks from week 16 through week 24; every 12 weeks from week 36 through week 60; and for a final evaluation at week 78 (18 months). HIV quantitative PBMC culture was done at birth, 6 weeks, 24 weeks, and 48 weeks on study; a second, confirmatory culture was done on all children who had an initial positive culture.

Laboratory assays. HIV quantitative PBMC microculture and lymphocyte phenotyping were done in laboratories certified by the ACTG according to published standard methods [18, 19]. HIV antibody EIA and Western blot were done by use of US Food and Drug Administration–approved, commercially available methods. HIV-1 RNA concentration was measured in stored maternal plasma by use of the nucleic acid sequence–based amplification assay according to the manufacturer's instructions (Organon Teknika, Durham, NC). The lower limit of quantitation was 500 copies/mL. Whenever possible, all specimens for an individual patient were assayed in a batched fashion, and all HIV-1 RNA assays were done by a single laboratory.

Statistical methods. The targeted sample size was 400 women per arm, which provided 80% power to detect a 50% reduction in perinatal HIV transmission with HIVIG, assuming transmission in the IVIG arm was ≥15%; noncompliance and loss to follow-up

were together assumed to be ~10%. Data analysis was undertaken on an intent-to-treat basis.

Three interim efficacy analyses were planned, each occurring after ~200 infants achieved 6 months of follow-up; stopping rules were based on O'Brien-Fleming boundaries [20]. HIV infection status for the purpose of the primary efficacy analyses was assessed on the basis of HIV culture data for all children by 6 months of age. Infants with one or more confirmed HIV culture results were designated as HIV-infected; infants without such positive culture results were designated as uninfected. Results of all virologic assays were reviewed in a blinded fashion by a subgroup of the study team. Pregnancies that yielded multiple births were assessed as a single HIV transmission event if any of the infants were HIV-infected and as a single nonoccurrence of transmission if none were HIV-infected.

The transmission rate was estimated by the Kaplan-Meier method [21, 22], with the end point of time to first positive HIV culture. Infants with indeterminate infection status were treated as censored in the efficacy analysis, with their follow-up times set to the latest negative culture. Variances were calculated by Greenwood's formula, with significance tests based on the normal distribution. Alternative analyses based on the restricted subset of infants with definitive HIV status were also done. Prognostic factors for the risk of transmission were evaluated with logistic regression and χ^2 analysis. Stratified analysis of risk factors used the Mantel-Haenszel method.

Results

Enrollment. Enrollment into the initial pharmacokinetic substudy in PACTG 185 began in October 1993. The first efficacy analysis by the independent Data and Safety Monitoring Board was 21 March 1997 and used data entered through 23 December 1996. The current report includes data from all births through the termination of study enrollment on 25 March 1997.

As of 25 March 1997, 501 women had enrolled and 459 had given birth to a total of 467 live-born infants and 1 stillborn infant; there were 9 sets of twins and 449 singleton births (table 1). Three women (<1%) were lost to follow-up and 39 (8%) were still pregnant at the time of the efficacy analysis. There were no significant differences between patients by study arm in terms of these parameters.

Characteristics of women and infants. There were no significant differences between study groups in characteristics of women or infants (table 2). Median maternal age was 26 years, and 87% of women were of minority race/ethnicity; median length of gestation at baseline was 26 weeks. Median baseline CD4 cell count was 306/μL; 22% of women had a baseline CD4 cell count <200/μL and 76% had a baseline CD4 cell count between 200 and 500/μL (5 women were granted exemptions to enter with counts slightly higher than 500/μL). Median baseline HIV-1 RNA level was 9150 copies/mL (range, <500–740,000); 19% of women had >50,000 RNA copies/mL.

Twenty-four percent of women had initiated zidovudine therapy before the current pregnancy. Only a minority of women (54/459, 12%; 27 in the HIVIG arm and 27 in the IVIG arm) received antenatal antiretroviral therapy with drugs other than zidovudine monotherapy during the current pregnancy. Of these, 1 received lamivudine, 2 received zalcitabine, and 3 received didanosine alone; 44 received combination therapy with lamivudine plus zidovudine (28), zalcitabine plus zidovudine (10), stavudine plus zidovudine (3), didanosine plus zidovudine (1), lamivudine plus stavudine (1), or delaviridine plus didanosine (1); and 4 received more than one dual nucleoside analogue combination regimen during the study. Eighty-eight percent of women who delivered had received three or more study drug infusions; the median number of infusions received during pregnancy was four.

Table 1. Status of women and infants in study of HIV hyperimmune immunoglobulin (HIVIG) as of 25 March 1997.

Patient status	HIVIG	IVIG	Total
Women enrolled	254	247	501
Still pregnant	22	17	39
Lost to follow-up	1	2	3
Eligible women who gave birth	231	228[a]	459[a]
Women who died during postpartum period[b]	4	2	6
Live-born infants			
Total	237	230	467
Singletons	225	224	449
Twins	12	6	18
Eligible mother-infant pairs[c]	231	227[a]	458[a]
HIV culture data unavailable	1	3	4
Included in Kaplan-Meier analysis	230	224	454

NOTE. IVIG, intravenous immunoglobulin. Data are no. of patients.
[a] 1 women delivered stillborn infant.
[b] Infants born to these women are included in efficacy analysis.
[c] Twins are counted as single pregnancy outcome.

Elective cesarean delivery was done for 8% and nonelective cesarean delivery was done for 19% of patients (table 2). The median gestational age of delivered infants was 38 weeks. Eighteen percent of infants were born preterm (gestational age <37 weeks), although only 4% were very preterm (<32 weeks). Median birth weight was 3143 g; 15% of infants were of low birth weight (<2500 g). There were no differences between study arms in these parameters.

Safety and toxicities. The few reported toxicities related to study drug infusions were side effects commonly associated with receipt of IVIG infusions, such as chills, headache, and back pain. Seven women experienced 12 episodes of moderate (grade 2) toxicity, and 2 women experienced 5 episodes of serious (grade 3) toxicity related to study drug infusions. No moderate or serious (grade 2 or higher) toxicities related to study drug infusions were reported in infants; 2 infants experienced 3 episodes of mild (grade 1) toxicity. Only 6 women (1%) required discontinuation of study drug infusions, 4 in the HIVIG and 2 in the IVIG arm; no infant required discontinuation of study drug infusions.

Intrapartum and newborn zidovudine were provided as part of the trial. Serious (grade 3 or higher) zidovudine-related he-

Table 2. Characteristics of women and infants in study of HIV hyperimmune globulin (HIVIG) versus intravenus immunoglobulin (IVIG).

Population, characteristic	HIVIG	IVIG	Total
Women			
Age at baseline (years), median ± SD	27 ± 6.0	26 ± 5.8	26 ± 5.9
Race/ethnicity, no. (%)			
Black, not Hispanic	123 (53)	112 (49)	235 (51)
Hispanic	81 (35)	80 (35)	161 (35)
White, not Hispanic	25 (11)	35 (15)	60 (13)
Other	2 (1)	1 (1)	3 (1)
Hard drug use[a]	26 (11)	36 (16)	62 (14)
Maternal gestation length at baseline (weeks), median ± SD	25 ± 3.5	26 ± 3.2	26 ± 3.4
Baseline CD4 cell count/μL, no. (%)			
<200	54 (23)	49 (21)	103 (22)
200–500	174 (75)	177 (78)	351 (76)
>500	3 (1)	2 (1)	5 (1)
Baseline CD4 cell count/μL, median ± SD	298 ± 120.9	321 ± 127.3	306 ± 124.1
Baseline HIV-1 RNA (copies/mL)[b]			
Median ± SD	9,750 ± 84,576	7,450 ± 90,153	9,150 ± 87,301
Range	<500–720,000	<500–740,000	<500–740,000
No. (%) with >50,000	46 (20)	40 (18)	86 (19)
Zidovudine initiation, no. (%)			
Before pregnancy	55 (24)	57 (25)	112 (24)
During pregnancy	176 (76)	171 (75)	347 (76)
Number of maternal study drug infusions, median ± SD	4 ± 1.1	4 ± 1.1	4 ± 1.1
Type of delivery, no. (%)			
Vaginal	167 (72)	170 (75)	337 (73)
Non-elective cesarean	44 (19)	43 (19)	87 (19)
Elective cesarean	20 (9)	15 (7)	35 (8)
Duration of membrane rupture (h), median ± SD	1 ± 13.1	2 ± 8.4	2 ± 11.0
No. (%) with premature rupture (≥24 h)	15 (6)	9 (4)	24 (5)
No. (%) with abruptio placentae	1 (1)	1 (1)	2 (1)
Infants			
Gestational age at delivery (weeks), median ± SD	38 ± 2.6	38 ± 2.8	38 ± 2.7
Preterm (<37 weeks), no. (%)	44 (19)	38 (16)	82 (18)
Very preterm (<32 weeks), no. (%)	9 (4)	10 (4)	19 (4)
Birth weight (g) median ± SD	3150 ± 648	3133 ± 638	3143 ± 643
Birth weight <2500 g, no. (%)	37 (16)	32 (14)	69 (15)

NOTE. Maternal baseline characteristics refer to all women enrolled and delivered by 25 March 1997; infant baseline characteristics refer to all delivered infants.

[a] Use of cocaine, heroin, and/or injection drugs.

[b] HIV-1 RNA copy number was available for 458 women (230 HIVIG and 228 IVIG recipients).

matologic toxicities included anemia in 7 infants (1.5%) and leukopenia in 48 infants (10.3%).

There were 6 maternal deaths in the postpartum period, 4 in the HIVIG and 2 in the IVIG study arm. Deaths were due to HIV encephalopathy with aspiration pneumonia, *Pneumocystis carinii* pneumonia, end-stage renal disease with complicating pneumonia, drug addiction and asthma, sepsis, and unspecified HIV disease progression; none were treatment-related.

There were 7 infant deaths during the study, 3 in the HIVIG and 4 in the IVIG study arm. Deaths in the HIVIG study arm were due to perinatal asphyxia with severe hypoxic ischemia, pneumonia, and renal dysgenesis with multiorgan failure. Deaths in the IVIG study arm were due to sudden infant death syndrome, prematurity, necrotizing enterocolitis and prematurity, and a single stillbirth (maternal diabetes mellitus). None of the deaths were treatment-related, and in 2 of the deaths, no study HIVIG/IVIG or zidovudine had been administered to the infant.

Analysis of transmission and treatment efficacy. Four hundred fifty-nine women gave birth to 468 infants, 1 of whom was stillborn, resulting in 467 live-born infants and 458 mother-infant pairs (9 women gave birth to twins) eligible for analysis (table 1). Four infants did not have an HIV culture available, leaving 454 mother-infant pairs with at least one viral culture result available (table 3). Twenty-two infants were determined to be HIV-infected. The overall Kaplan-Meier transmission rate was 5.0% (95% confidence interval [CI], 3.0%–7.1%). Thirteen infants (6 in HIVIG, 7 in IVIG) were unable to have infection status classified definitively because of loss to follow-up after an HIV culture was obtained but before definitive infection status could be determined at age 6 months. Restricting analysis to the 441 mother-infant pairs with definitive infant infection status determined, the overall transmission rate was similar: 5.1% (95% CI, 3.0%–7.2%).

Maternal baseline CD4 cell count was significantly associated with transmission risk (logistic regression analysis; $P = .005$).

Table 3. Perinatal HIV transmission in study of HIV hyperimmune globulin (HIVIG) versus intravenous immunoglobulin (IVIG).

Characteristic	HIVIG	IVIG	Total
Total no. of infants	230	224	454
No. of infected infants	9	13	22
Positive HIV culture at birth	0	5	5
Negative HIV culture at birth	9	8	17
Kaplan-Meier transmission rate[a] (95% confidence interval)	4.1% (1.5%–6.7%)	6.0% (2.8%–9.1%)	5.0% (3.0%–7.1%)

[a] P for HIVIG treatment effect = .36; required cutoff for significance for first efficacy analysis was $P < .005$.

The Kaplan-Meier estimated transmission rate for women with baseline CD4 cell count <200/μL was 10.0% (95% CI, 4.1%–15.8%) compared with 3.6% (95% CI, 1.6%–5.6%) for women with baseline CD4 cell count ⩾200/μL. In contrast, the Kaplan-Meier estimated transmission rates were similar regardless of time of initiation of zidovudine: 5.6% (95% CI, 1.2%–10.0%) for women who started zidovudine before pregnancy compared with 4.8% (95% CI, 2.5%–7.1%) for those who first initiated zidovudine during the current pregnancy ($P = .75$).

The estimated transmission rate by Kaplan-Meier analysis by treatment arm was 4.1% (95% CI, 1.5%–6.7%) in HIVIG and 6.0% (95% CI, 2.8%–9.1%) in IVIG recipients ($P = .36$) (table 3). In an alternative analysis restricted to infants who had definitive infection status, transmission rates were 4.1% (95% CI, 1.5%–6.8%) in HIVIG recipients and 6.1% (95% CI, 2.9%–9.3%) in IVIG recipients ($P = .35$).

There was a difference between treatment arms in the distribution of infants who had a positive HIV culture at birth (none in HIVIG vs. 5 in IVIG recipients; $P = .05$). HIV DNA polymerase chain reaction (PCR) testing was done on stored cell pellet specimens, and HIV RNA testing (nucleic acid sequence–based amplification; Organon Teknika) was done on stored plasma specimens obtained at birth, for all infected infants with negative birth cultures who had an available stored specimen. Seven of the 9 infected infants in the HIVIG group had a stored birth cell pellet available, 6 of whom also had a stored birth plasma specimen. All infants except 1 were negative by DNA PCR, and all infants, including the DNA PCR–positive infant, had RNA levels that were below the level of assay quantification. Six of the 8 infected infants in the IVIG group with a negative HIV birth culture had a stored birth cell pellet specimen; none of these were positive on DNA PCR testing, and the 2 with available plasma specimens also had HIV RNA levels below quantification limits of the assay.

Most infected infants were identified by 6 weeks of age, and all infected infants except 1 were identified by 6 months of age. One child in the IVIG arm had negative HIV cultures during the study but a persistently positive HIV Western blot antibody assay at age 18 months; at 92 weeks of age, the child was HIV culture–negative but positive by a CD8-depleted DNA PCR and an HIV RNA assay (at a very low number of copies per milliliter). The association between birth culture positivity and gestational age at baseline, mother's HIV culture titer at baseline and delivery, mother's CD4 cell count at baseline, and number of days of antiretroviral use before entry were evaluated. None of these covariates showed significant associations with culture positivity at birth (data not shown).

Table 4 provides transmission rates stratified by risk factors for HIV transmission. No statistically significant association between treatment arms and transmission was observed in these analyses. However, there was a trend toward lower transmission among women receiving HIVIG who started zidovudine before pregnancy (transmission, 1.9% in HIVIG vs. 9.2% in IVIG recipients; $P = .09$) or who had baseline CD4 cell count <200 μL (transmission, 5.6% in HIVIG vs. 14.9% in IVIG recipients; $P = .12$). Among the 182 women who had either baseline CD4 cell count <200/μL or started zidovudine before pregnancy, the transmission rate in HIVIG recipients was 3.2% (95% CI, 0%–6.8%) and in IVIG recipients was 10.3% (95% CI, 3.9%–16.6%) ($P = .06$). In contrast, for women with baseline CD4 cell count ⩾200/μL or who started zidovudine during pregnancy, transmission was 4.7% in HIVIG compared with 3.1% in IVIG recipients ($P = .53$).

Discussion

The overall transmission rate (5.0%) in this study was well below the figure on which the initial power and sample size calculations were based. Given the unexpectedly low overall transmission rate, a conditional power analysis indicated that the ability to detect a 50% treatment effect with 400 women per arm was only 29%. The increased sample size required to address the original hypothesis was deemed too large to enroll in a timely fashion, and on the basis of the first efficacy analysis, the estimated treatment effect appeared to be much less than 50%. On the basis of these considerations, the PACTG 185 Data and Safety Monitoring Board recommended discontinuing enrollment into PACTG 185, unblinding the study participants, and discontinuing HIVIG and IVIG study infusions for all currently enrolled women and infants.

Although PACTG 185 does not answer whether passive immunization can diminish perinatal HIV transmission, the study confirms the efficacy of zidovudine prophylaxis originally demonstrated in PACTG 076 and extends this observation to women with more-advanced disease and prior zidovudine use. The overall low rate of perinatal transmission (5.0%) cannot

Table 4. Transmission rates stratified by potential risk factors in study of HIV hyperimmune globulin (HIVIG) versus intravenous immunoglobulin (IVIG).

Risk factor, stratum	HIVIG		IVIG		Comparison P[a]	Stratified P[b]
	No.	% infected	No.	% infected		
Baseline maternal CD4 cell count/μL						
<200	54	5.6	47	14.9	.12	.29
⩾200	176	3.6	177	3.6	.99	
Maternal zidovudine use						
Begun before pregnancy	54	1.9	55	9.2	.09	.34
Begun during pregnancy	176	4.7	169	4.9	.95	
Duration of membrane rupture[c]						
<4 h	135	3.2	129	5.7	.33	.26
⩾4 h	81	5.0	84	7.2	.56	
Mode of delivery						
Vaginal	167	4.4	167	6.8	.36	ND[d]
Nonelective cesarean	44	4.7	42	5.1	.93	
Elective cesarean	19	—	15	—	ND[d]	
Gestational age at birth						
<37 weeks	41	5.0	35	9.1	.50	.33
⩾37 weeks	189	3.9	189	5.4	.48	
No. of maternal infusions received						
⩽3	110	3.9	103	5.1	.69	.35
4	71	2.8	73	7.0	.25	
⩾5	49	6.4	48	6.3	.99	
Birthweight[e]						
<2500 g	35	6.4	29	14.2	.33	.31
⩾2500 g	195	3.7	195	4.8	.59	
Hard drug use[f] during pregnancy						
Yes	26	—	34	12.2	.03	.36
No	204	4.6	190	4.9	.89	

[a] Comparison P tests for differences between treatment arms at each level of given risk factor; tests are based on Kaplan-Meier method. All pregnancy outcomes with culture data are included.

[b] Stratified P tests for association between treatment arm and HIV transmission, controlling for given risk factor; tests are based on Mantel-Haenszel method. This analysis is restricted to 441 infants with definitive infection status.

[c] Data are missing for membrane rupture duration for 25 women.

[d] Not calculated because of zero transmission events for elective cesarean delivery.

[e] For twin births, minimum weight was used.

[f] Defined as use of cocaine, heroin, and/or injection drugs.

be attributed to use of combination antiretroviral therapy during the study, since only 10% of women had received combination antiretroviral therapy. A transmission rate this low was not anticipated in women with advanced HIV disease receiving zidovudine prophylaxis, although it is within the 95% confidence interval (4.3%–12.3%) for the zidovudine arm in PACTG 076 [1].

We expected that the IVIG control group transmission rate in this study would be higher than observed in the zidovudine-treated women in PACTG 076, because the women enrolled in PACTG 185 had more-advanced HIV disease. However, the relatively low overall transmission rate observed in PACTG 185 is in accordance with epidemiologic data from other recent studies, in which significant effectiveness of zidovudine was observed in women with advanced disease [7, 23]. For example, in a study in Connecticut, 4% of 23 women with CD4 cell counts <200/μL who received zidovudine during pregnancy transmitted HIV to their infants, compared with 39% of 23 infected women with similar CD4 cell counts who did not receive antenatal zidovudine therapy [23].

Consistent with other studies [6, 24–26], a low maternal CD4 cell count was associated with increased risk of transmission in PACTG 185. However, in contrast to data reported from France [7], use of zidovudine before pregnancy did not increase the risk of perinatal transmission in PACTG 185. Additionally, transmission was unrelated to length of zidovudine use during pregnancy. In-depth evaluation of risk factors associated with perinatal HIV transmission in PACTG 185, particularly the relationship between virus load and transmission, will be reported elsewhere.

Could the low rate of perinatal transmission observed in PACTG 185 be due to a nonspecific effect of immunoglobulin on HIV transmission? Several investigators have hypothesized that in utero perinatal HIV transmission might result from transport of virus-antibody complexes across the placental barrier via Fc receptors found on trophoblastic cells [27–29]. Thus, IgG administration could nonspecifically block placental Fc receptors, thereby lowering transplacental transmission. Alternatively, exogenous immunoglobulin could modulate cytokine production by the mother. Inflammatory cytokines, such as interleukin-1β, interleukin-6, and tumor necrosis factor-α, are synthesized in larger quantities in placental cells of HIV-infected

than uninfected women and may play a role in transmission [30]. IVIG down-regulates proinflammatory cytokine production, particularly interleukin-6, and this could be associated with a decrease in transplacental transmission [31]. However, these potential mechanisms would only affect in utero transmission, and most transmission occurs near or during delivery [32].

Additionally, the use of zidovudine prophylaxis during pregnancy in women not receiving IVIG has resulted in low transmission rates consistent with those observed in this study. The French Perinatal HIV Cohort Study evaluated perinatal transmission rates during 1994 and 1995; transmission decreased from 14% in women who did not receive zidovudine to 5% with zidovudine prophylaxis ($P < .01$) [7]. In North Carolina, transmission has declined over time from 21% in 1993 (before use of zidovudine prophylaxis) to 6.2% in early 1996; in women who received all three components of the PACTG 076 zidovudine regimen, transmission was only 3.2% [33]. Data from surveillance between August 1995 and January 1997 in New York State indicates a similarly low 6.1% rate of transmission in women and infants receiving the full three-part zidovudine regimen [34].

The intriguing finding that none of the 9 infected infants in the HIVIG group had a positive HIV culture at birth, whereas 5 (38%) of 13 infected infants in the IVIG group did, suggests that, if HIVIG had a biologic effect, it was primarily on reducing in utero but not intrapartum perinatal transmission. However, the majority of perinatal transmission occurs near or during the intrapartum period [32], and the number of infected infants was small. A passive immunoprophylaxis perinatal trial underway in Uganda, in which HIVIG (from Ugandan donors) is given once in late pregnancy to the mother and at birth to her infant, may provide more information regarding HIVIG efficacy in the future. One infected infant in the HIVIG group was HIV DNA PCR–positive at birth but had undetectable virus by culture and HIV RNA assay. Although in utero HIV transmission may not have been prevented in this patient, it is possible that HIVIG might have significantly decreased replicating virus. High-dose simian immunodeficiency virus hyperimmune globulin administered at days 1 and 14 to macaques after inoculation with simian immunodeficiency virus did not protect against infection but was associated with lower virus loads and slower disease progression in infected animals [35]. Evaluation of disease progression in the infected infants in PACTG 185 will be needed to determine whether there is prognostic significance related to the timing of initial HIV culture positivity in HIVIG-treated infants.

The unexpectedly low overall transmission rate limited the power of PACTG 185 to detect a treatment effect, and the clinical trial was not able to determine whether passive immunization with HIVIG lowers perinatal transmission. However, although not statistically significant, there was an intriguing trend toward lower transmission with HIVIG among women who would be expected to have more-advanced HIV disease and theoretically higher viral load and higher baseline risk of transmission—those with baseline CD4 cell count<200/μL or who started zidovudine before pregnancy. Thus, it should not be concluded that PACTG 185 demonstrated that passive immunization is an ineffective intervention for reducing perinatal transmission. Further study is warranted; the perinatal HIVIG trial in Uganda will provide more-definitive data on the efficacy of HIVIG to reduce transmission.

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