Perinatal Transmission of Human Immunodeficiency Virus Type 1 by Pregnant Women with RNA Virus Loads <1000 Copies/mL

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In a collaboration of 7 European and United States prospective studies, 44 cases of vertical human immunodeficiency virus type 1 (HIV-1) transmission were identified among 1202 women with RNA virus loads <1000 copies/mL at delivery or at the measurement closest to delivery. For mothers receiving antiretroviral treatment during pregnancy or at the time of delivery (or both), there was a 1.0% transmission rate (8 of 834; 95% confidence interval [CI], 0.4%–1.9%), compared with 9.8% (36 of 368; 95% CI, 7.0%–13.4%) for untreated mothers (risk ratio, 0.10; 95% CI, 0.05–0.21). In multivariate analysis adjusting for study, transmission was lower with antiretroviral treatment (odds ratio [OR], 0.10; $P < .001$), cesarean section (OR, 0.30; $P = .022$), greater birth weight ($P = .003$), and higher CD4 cell count ($P = .039$). In 12 of 44 cases, multiple RNA measurements were obtained during pregnancy or at the time of delivery or within 4 months after giving birth; in 10 of the 12 cases, the geometric mean virus load was >500 copies/mL. Perinatal HIV-1 transmission occurs in only 1% of treated women with RNA virus loads <1000 copies/mL and may be almost eliminated with antiretroviral prophylaxis accompanied by suppression of maternal viremia.

Results from several studies [1–16] show that the maternal level of human immunodeficiency virus type 1 (HIV-1) RNA in the plasma or serum (virus load) is a strong predictor of perinatal HIV-1 transmission. Nevertheless, it is widely accepted that there is no maternal RNA threshold below which perinatal transmission of HIV-1 does not occur. Sporadic cases have been described, in which perinatal transmission occurred, despite maternal HIV-1 RNA levels being <1000 copies/mL at the time of delivery or during the third trimester [1–7]. Since the aim of current antiretroviral therapy is to maintain viral suppression to HIV-1 RNA levels <1000 copies/mL, preferably below the levels of detection of current assays, it would be important to gain insight on the profile of cases in which perinatal transmission occurred, despite low levels of HIV-1 replication in the mother [17–19]. This information might offer helpful hints on how to further reduce HIV-1 transmission, especially in developed countries where many infected pregnant women will have a low virus load secondary to treatment with highly active antiretroviral therapy.

However, no single study of perinatal HIV-1 transmission can evaluate this question, because, even in studies following large cohorts of HIV-1–infected pregnant women, the proportion of women with HIV-1 RNA levels <1000 copies/mL is small, and the transmission rate among such women has been

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very low. Therefore, we established a collaborative registry that included 7 large European and US prospective study teams that have enrolled such patients. Each team provided detailed standardized information on each mother-infant pair with an infected child, including data on possible risk factors of perinatal transmission and virus load measurements. Additional information was collected on important potential confounders from nontransmitting cases with similarly low maternal HIV-1 RNA levels. The final analysis gained strength from the combination of data from several investigators.

Methods

Eligibility Criteria

There were 3 eligibility criteria for the transmission registry. First, infection of the infant had to be documented by standard criteria, including isolation of HIV-1 by culture of peripheral blood mononuclear cells (PBMC) or detection by DNA polymerase chain reaction (PCR) in PBMC on 2 occasions (typically after 3 months of age) and/or persistent positive serology results (ELISA and Western blot) after 15–18 months of age. Second, the mother had to have an HIV-1 RNA level <1000 copies/mL at delivery, as indicated by reverse transcriptase (RT) PCR [20], nucleic acid sequence–based amplification (NASBA) assays [21], or branched-chain DNA assay [22] in plasma (or serum, if plasma was not available). If no value was available at delivery, then the value nearest to delivery during pregnancy should have been <1000 copies/mL. The third criterion was that the study should have been performed in Europe or the United States.

In cohorts in which most "delivery" samples were obtained in the first few days after delivery, we accepted measurements obtained ≤3 days from delivery, since it is unlikely that the postpartum virus load would change rapidly. When HIV-1 RNA levels had been measured by using different methods on the same samples, RT-PCR measurements were preferred over other methods. However, women originating from developing countries were excluded when measurements had been determined by the RT-PCR assay, because the standard RT-PCR assay is unreliable for the detection of several non-B HIV-1 subtypes, which are prevalent in these regions [23]. The analysis included only studies done in developed countries, where antiretroviral regimens are available that may achieve the desired suppression of plasma HIV RNA levels to <1000 copies/mL in the majority of women.

Organization of the International Registry

Study teams working on perinatal HIV-1 transmission in Europe or the United States were invited to contribute data to the registry if they had ≥1 eligible mother-infant pair, as defined above (see Eligibility Criteria). Both cohort studies and randomized trials qualified. Study teams were identified by use of the algorithm described in a previous meta-analysis on perinatal HIV-1 transmission [16] (updated to August 1999) and through extensive communications with field experts, to ensure that all study teams would be included that had presented relevant data as of mid-1999. Seven study teams had eligible cases. This included 2 randomized trials (the Pediatric AIDS Clinical Trials Group [PACTG] protocols 076 and PACTG 185) and 5 cohort studies (the Pediatric AIDS Foundation Ariel project, the Perinatal AIDS Collaborative Transmission Study, the French cohorts [the combined Serogest and Enquete Perinatale Française studies], the Mothers and Infants Cohort Study, and the European Collaborative Study). All studies contributed their pertinent data to the registry. Data on each eligible mother-infant pair were contributed by using prespecified definitions. The data were assessed for completeness and potential logical errors at the coordinating center. Potential questions were clarified through communications with the contributing teams.

Collected Information

The following information was requested on eligible mother-infant pairs with known perinatal transmission: virus load measurements during pregnancy (including the eligibility-determining virus load) and during the first 4 months after delivery, as well as the measuring methods used and the time of the measurements; maternal age and race; year of birth; breast-feeding status; gestational age of infant; multiple gestation; infant birth weight; clinically or histologically documented chorioamnionitis; mode of delivery (cesarean section or vaginal); time from rupture of membranes to delivery; CD4 cell count of the mother at delivery or measurement closest to delivery; presence of clinical AIDS diagnosis in the mother before delivery; cocaine or heroin use by mother after first trimester; heavy alcohol use during pregnancy; any cigarette smoking during pregnancy; antiretroviral therapy during pregnancy (specifying drug[s] and duration/timing of administration); and antiretroviral therapy given to the neonate. Cesarean delivery includes elective (before labor or membrane rupture) and nonelective (after labor or membrane rupture) operative delivery, because these were not clearly separated in many of the databases.

For eligible studies that included both treated and untreated mothers, detailed information on antiretroviral therapy, as well as potential confounders, also was collected from each nontransmitting mother-infant pair, in which maternal HIV-1 RNA levels at delivery or measurement closest to delivery was <1000 copies/mL, and transmission had not occurred. This information included maternal CD4 cell count, gestational age, birth weight, duration of rupture of membranes, and mode of delivery. For studies that included only treated mothers or only untreated mothers, we simply recorded the number of nontransmitting mothers with HIV-1 RNA levels <1000 copies/mL at delivery or at the measurement closest to delivery. Similarly, for 4 additional identified European or US cohort studies with no transmission cases qualifying for the registry, information on the number of women with HIV-1 RNA levels <1000 copies/mL who had or had not received antiretroviral therapy was extracted from published reports [8–11].

Analyses

Unadjusted analyses of the effect of antiretroviral therapy. First, we estimated transmission rates separately for antiretroviral-treated and -untreated mothers with HIV-1 RNA levels <1000 copies/mL. Data were combined across all pertinent studies without any weighting, and heterogeneity of rates among studies was assessed by using Fisher's exact test. Second, unadjusted risk ratios for transmission were estimated for each study, in which both treated and untreated

mothers with HIV RNA <1000 copies/mL had been included; these risk ratios then were combined by the Mantel-Haenszel method. Heterogeneity of the risk ratios was assessed by using the Q statistic [24].

Risk factors in transmitting and nontransmitting cases. For the qualifying transmission cases, descriptive tables were generated with the collected information on maternal, gestational, obstetric, immunologic, and other risk factors. We counted how many cases did not have any identifiable postulated risk factors for vertical transmission. Data on potential predictors of transmission also were summarized per study, comparing transmitting and nontransmitting cases, using the Student's *t* and Mann-Whitney *U* tests, as appropriate. An overall comparison of the 2 groups was also done.

Adjusted analyses. To evaluate the effect of antiretroviral treatment, as well as the effects of other possible predictors of transmission, multivariate logistic regressions were performed, adjusting for study and considering antiretroviral treatment of the mother, maternal CD4 cell count, gestational age, birth weight, duration of rupture of membranes, and mode of delivery as potential predictors. Data were analyzed from the 5 studies that had included both treated and untreated women. A full model with all candidate variables was obtained and then was simplified with backward elimination, according to likelihood ratio criteria. We also evaluated whether neonatal antiretroviral treatment could offer additional information for predicting perinatal transmission.

Subgroup analyses for the effect of antiretroviral treatment. Merging the pertinent data from all studies with both treated and untreated women, we evaluated whether maternal antiretroviral treatment conferred protection from perinatal transmission in low-risk subgroups, including those with maternal CD4 cell counts >500 cells/mm^3, birthweight >2500 g, and cesarean delivery.

Analysis of HIV-1 RNA. We evaluated whether the eligibility HIV-1 RNA measurement was lower than the geometric mean of other measurements in the same patient because of regression to the mean [25]. The percentage of cases in the registry with <1000 copies/mL for all HIV-1 RNA measurements during pregnancy was calculated, as well as 95% confidence intervals (95% CIs). The Wilcoxon test was used for paired comparisons.

For all analyses involving virus load, values below the limit of detection of the assay were imputed as half the limit of detection. Typical cutoffs were 400 or 200 copies/mL for the RT-PCR assays, 500 copies/mL for the branched DNA assay, and 500 or 400 copies/mL for the NASBA and the more sensitive NASBA/NucliSens assays, respectively. The limit of reliable quantification may not be the same as the limit of detection, but all assays give reliable results, at least at the level of 1000 copies/mL.

The SPSS statistical software package (SPSS) was used for analyses. *P* values are 2-tailed.

Results

Unadjusted transmission risk. Forty-four eligible mother-infant pairs (13 black, 2 Hispanic, 28 white, and 1 unknown race) with perinatal transmission were registered in 7 studies from Europe and the United States, with a total of 1202 mothers with maternal HIV-1 RNA virus loads <1000 copies/mL at delivery or at the measurement closest to delivery. The infected children were born between 1987 and 1998. When data from 11 pertinent studies were combined (table 1), the rate of transmission from antiretroviral-treated women with HIV-1 RNA levels <1000 copies/mL at delivery or at the measurement closest to delivery was only 1.0%, with only 8 cases of transmission among 834 treated women with such low levels of viremia. The 95% CIs were 0.4%–1.9%, and there was no significant heterogeneity among studies. Vertical transmission occurred in 36 (9.8%) of 368 women who had similar levels of viremia but had not received antiretroviral therapy during pregnancy or delivery (95% CI, 7.0%–13.4%). Between-study heterogeneity in the transmission rates from untreated women was statistically significant ($P = .01$; table 1). The transmission rate was significantly lower in treated than in untreated women; the risk ratio for transmission was 0.10 (95% CI, 0.05–0.21; $P < .001$) when the total rates in the 2 groups were compared and 0.18 (95% CI, 0.08–0.41; $P < .001$) when study-specific risk ratios were combined with the Mantel-Haenszel method (table 1). There was no significant heterogeneity among the study-specific risk ratios ($P = .13$).

Profile of maternal, immunologic, and obstetric risk factors in transmitting cases. The profile of other postulated risk factors for the 44 eligible cases is shown in table 2. In all, 41 of the 44 cases in the registry had ⩾1 of the following risk factors: CD4 cell count ⩽500 cells/mm^3, gestational age <37 weeks, birthweight ⩽2.500 kg, or rupture of membranes ⩾4 h before delivery.

Other risk factors in transmitting and nontransmitting cases. Other risk factors for transmission were evaluated in the 5 studies that had both treated and untreated women (a subset

Table 1. Perinatal transmission of human immunodeficiency virus type 1 from mothers with virus loads <1000 copies/mL at time of delivery or at the last measurement closest to delivery.

Study team	Mothers receiving ART	Mothers without ART	RR (95% CI)[a]
French[b]	1/346 (0.3)	4/37 (10.8)	0.03 (0.00–0.24)
PACTS	2/154 (1.3)	6/56 (10.7)	0.12 (0.03–0.59)
PACTG 076	1/62 (1.6)	0/47 (0.0)	2.29 (0.10–54.9)
PACTG 185	1/135 (0.8)	—	—
Ariel	3/44 (6.8)	1/14 (7.1)	0.95 (0.11–8.46)
ECS	0/56 (0.0)	24/141 (17.0)	0.05 (0.00–0.82)
MICS	—	1/24 (4.2)	—
WITS	0/22 (0.0)	0/35 (0.0)	1.57 (0.03–76.2)
Fang et al. [8]	—	0/1 (0.0)	—
Melvin et al. [11]	0/5 (0.0)	0/2 (0.0)	0.50 (0.01–19.6)
Dickover et al. [9]	0/10 (0.0)	0/11 (0.0)	1.09 (0.02–50.4)
Total	8/834 (1.0)	36/368 (9.8)	0.10 (0.05–0.21)

NOTE. Data are no. of infected infants/no. of total live births (%), unless otherwise indicated. ART, antiretroviral therapy; CI, confidence interval; ECS, European Collaborative Study; MICS, Mothers and Infants Cohort Study; PACTG, Pediatric AIDS Clinical Trials Group; PACTS, Perinatal AIDS Collaborative Transmission Study; RR, risk ratio; WITS, Women Infants Transmission Study.

[a] When there were zeros in any cell in a 2×2 table, 0.5 was added to all cells, to allow for the estimation of the RR.

[b] French data comprise information for the combination of the Serogest and Enquête Périnatale Française cohorts, which have been combined since 1996; mothers of African origin were excluded from these data.

Table 2. Maternal and obstetrical characteristics and treatment in the 44 cases of perinatal transmission.

Characteristic or treatment	Data
Maternal age, in years, mean (±SD)	26.6 (4.8)
Breast-feeding	0/43 (0)
CD4 cell count, cells/mm^3, mean (±SD)	447 (263)
Clinical AIDS in the mother	0/43 (0)
History of illicit drug use	20/40 (50)
Heavy alcohol use	0/14 (0)
Gestational age, in weeks, mean (±SD)	37.2 (3.4)
Twins	0/44 (0)
Weight at birth, in grams, mean (±SD)	2606 (681)
Chorioamnionitis, clinically or histologically documented	2/20 (10)
Vaginal delivery	37/44 (84)
Rupture of membranes, in hours, median (IQR)	4 (2–6)
Antiretroviral therapy in the mother	8/44 (18)[a]
Starting in first trimester	1/44 (2)
Starting in second trimester	3/44 (7)
Starting in third trimester	1/44 (2)
Delivery only	3/44 (7)
Antiretroviral therapy in the neonate	9/44 (20)[b]

NOTE. Data are no. with characteristic/total no. (%), unless otherwise indicated. IQR, interquartile range.

[a] Zidovudine ($n = 7$), combination of nucleoside reverse-transcriptase inhibitors ($n = 1$).

[b] In 2 of the 9 treated neonates, the mother had received no antiretroviral treatment.

of 42 transmitters and 915 nontransmitters; table 3). In most of the 5 studies, transmitting cases tended to have lower maternal CD4 cell counts, gestational ages, and birthweights and longer duration of rupture of membranes. They were also less likely than nontransmitting cases to have a cesarean delivery, but usually the differences were not formally statistically significant for individual studies. Formal significance was reached when data from all studies were combined for each of these variables, with the exception of the duration of rupture of membranes ($P = .13$).

Adjusted analyses. Adjusted analyses also were done in the 5 studies that included both treated and untreated mothers. Of the 957 mother-infant pairs, information was available on the mode of delivery for 953, birthweight for 948, gestational age for 944, CD4 cell count for 890, and duration of rupture of membranes for 746. Because of the heterogeneity in transmission rates among untreated women and missing data for some variables, sensitivity analyses were done, excluding specific studies and excluding CD4 cell count and the duration of rupture of membranes. There was no evident selection bias in the missing data.

When the data were adjusted for study and all potential confounders, maternal antiretroviral therapy markedly reduced the risk of perinatal transmission (odds ratio [OR], 0.12; $P < .001$), whereas birthweight (OR, 0.89 per 100 g; $P = .014$), cesarean delivery (OR, 0.09; $P = .028$), and CD4 cell count (OR, 0.85 per 100 cells/mm^3; $P = .041$) also were independent predictors of transmission. Gestational age (OR, 1.026 per week; $P = .81$) and duration of rupture of membranes (OR, 1.004 per h; $P = .79$) were not significant in this multivariate model. In the final backward elimination model, the risk of perinatal transmission was independently decreased by maternal antiretroviral therapy (OR, 0.10; $P < .001$), cesarean delivery (OR, 0.30; $P = .022$), higher CD4 cell count (OR, 0.86 per 100 cells/mm^3; $P = .039$), and larger birth weight (OR, 0.92 per 100 g; $P = .003$), after adjusting for study.

Sensitivity analyses excluding outliers were done to explore whether the variation among studies affected the overall results; however, the sensitivity analyses yielded similar results. For example, excluding the European Collaborative Study (as the study with the highest vertical transmission rate among untreated women) gave crude transmission rates of 1.0% and 5.3%, a crude OR of 0.19 (95% CI, 0.08–0.46; $P < .001$) and an adjusted OR of 0.12 (95% CI, 0.04–0.26; $P < .001$), thus showing a similar ~85% reduction in vertical transmission risk associated with zidovudine. Analyses not considering CD4 cell count and duration of rupture of membranes yielded similar results (adjusted OR for maternal antiretroviral therapy, 0.12; $P < .001$).

Neonatal antiretroviral prophylaxis had been used largely in association with maternal antiretroviral treatment, but 12 neonates had been treated without treatment given to the mother, whereas the opposite had occurred in 27 cases. Consideration of neonatal prophylaxis in the final logistic model did not change the effect of maternal treatment or the other predictors, whereas the effect of neonatal prophylaxis was not statistically significant (OR for maternal treatment, 0.09 [95% CI, 0.02–0.48]; $P = .004$; OR for neonatal treatment, 0.79 [95% CI, 0.16–4.0]; $P = .78$). An interaction term between neonatal and maternal treatment was also not significant ($P = .39$), but the power to test the interaction between these 2 variables was limited.

Antiretroviral treatment for mothers also conferred a protective effect against perinatal transmission in all of the low-risk subgroups in analyses that included all 5 studies that had both treated and untreated women. Specifically, the OR for transmission among antiretroviral-treated mothers was 0.06 (95% CI, 0.01–0.27) among 511 mothers with a CD4 cell count >500 cells/mm^3 and 0.07 (95% CI, 0.02–0.22) among 778 neonates with a birth weight >2500 g. No perinatal transmission occurred among 270 mothers who received antiretroviral therapy and had cesarean section, compared with 5 (7.6%) of 66 mothers who had cesarean section but had not received antiretroviral therapy ($P < .001$). Of note, in these 5 studies, 7 (1.8%) of 396 treated mothers who gave birth by vaginal delivery transmitted HIV-1.

Virus load measurements. The eligibility HIV-1 RNA measurement had been obtained within <1 month of delivery in 37 of the 44 women. Thirty-four of the 44 eligibility HIV-1 RNA measurements were <500 copies/mL. Twelve of the 44 women had ⩾1 other RNA measurement during pregnancy or during the first 4 months after delivery. Of these 12 women, 11 (92%) had ⩾1 measurement that was >1000 copies/mL, and, for 10 (83%) of those patients, the geometric mean of all available

Table 3. Study-specific comparisons of major confounders between transmitting (T) and nontransmitting (NT) cases with maternal human immunodeficiency virus type 1 RNA level <1000 copies/mL.

	CD4 cell count, cells/mm^3		Gestational age, weeks		Infant birth weight, g		Rupture of membranes, h[a]		Any cesarean section[b]	
Study	NT cases (n = 849)	T cases (n = 41)	NT cases (n = 904)	T cases (n = 40)	NT cases (n = 907)	T cases (n = 41)	NT cases (n = 711)	T cases (n = 33)	NT cases (n = 911)	T cases (n = 42)
PACTG 076	702 (261)	203	38.7 (2.4)	34	3092 (589)	2500	3.4 (0.4–10)	7.0	28/108	0/1
Ariel	642 (303)	506 (161)	38.3 (3.1)	37.0 (3.5)	3169 (615)	2600 (1105)	6.8 (3.0–14)	4.6 (3.3–8.0)	12/54	0/4
PACTS	612 (303)	646 (212)	39.6 (8.8)	37.4 (3.7)	3040 (962)	2693 (629)	1.0 (0–9.0)	6.5 (1.8–13)	61/200	1/8
French	624 (351)	611 (433)	38.7 (1.7)	39.6 (0.9)	3034 (541)	3300 (417)	3.5 (1.6–7.0)	4.5 (3.3–6.6)	165/377	1/5
ECS	480 (295)[c]	332 (200)[c]	37.7 (2.5)	36.5 (3.6)	2850 (551)[c]	2392 (595)[c]	1.7 (0–4.0)	3.0 (1.3–5.3)	65/172[d]	3/24[d]
All 5 studies	609 (324)[c]	441 (267)[c]	38.6 (4.2)[c]	37.1 (3.4)[c]	3008 (633)[c]	2584 (679)[c]	3.0 (0.9–8.0)	4.1 (2.1–6.5)	331/911[d]	5/42[d]

NOTE. Data are mean (±SD), unless otherwise indicated. No SD is shown for PACTG 076 under T cases because there was only 1 such case in this study. Data are shown only for studies that included both treated and untreated mothers. ECS, European Collaborative Study; IQR, interquartile range; PACTG, Pediatric AIDS Clinical Trials Group; PACTS, Perinatal AIDS Collaborative Transmission Study.

[a] Data are median (IQR).

[b] Data are no. of pregnancies where elective or not elective cesarean section was performed/no. of all pregnancies.

[c] Larger mean in NT cases than in T cases ($P < .05$).

[d] Larger percentage in NT cases than in T cases ($P < .05$).

measurements was >500 copies/mL. However, therapy was often stopped after delivery. Excluding all postpartum measurements, there were 11 patients with virus load measurements, in addition to the eligibility measurement. Of these 11 patients, 5 (45.5%; 95% CI, 16.8%–76.6%) had HIV-1 RNA levels <1000 copies/mL at all measurements during pregnancy or at the time of delivery, and only 4 (36.4%; 95% CI, 10.9%–69.2%) had a geometric mean HIV-1 RNA level <500 copies/mL.

For 7 of the 11 women with multiple available measurements, the eligibility measurement was lower than the average of the other pregnancy measurements. The opposite occurred in 1 case, and the eligibility measurement was within 3-fold (expected intrasubject variation) of the other pregnancy measurement in 3 cases ($P = .03$).

Discussion

In this international registry, the rate of perinatal HIV-1 transmission was only ~1% among antiretroviral-treated mothers whose virus load at delivery or measurement closest to delivery was <1000 copies/mL. This rate was significantly lower than the rate of transmission among women who did not receive any antiretroviral drugs but had similar low levels of viral replication. Although the comparison is largely based on nonrandomized data, adjusted analyses that considered an array of potential confounders yielded practically identical results.

In women with higher virus loads, lowering virus load probably plays a critical role in the prevention of transmission. In the Thailand short-term zidovudine trial [26], in which the baseline median antenatal HIV-1 RNA level was ~15,000 copies/mL and only 0.8% of women had undetectable HIV-1 RNA levels, the impact of zidovudine on HIV-1 RNA levels explained the efficacy of the drug for the large majority of cases. However, results of PACTG 076 [27], in which the baseline median HIV-1 RNA level was 5700 copies/mL and 12% of women had undetectable RNA levels, suggested that zidovudine may reduce perinatal transmission by pathways other than those captured by plasma viremia. Our findings are consistent with both studies, which demonstrates that there is a relatively low risk of transmission with low HIV-1 RNA levels at delivery, but that, even among this group, antiretroviral prophylaxis offers additional clinically significant protection. These data suggest that all HIV-1–infected pregnant women should be given antiretroviral therapy, regardless of their level of plasma viremia [18, 19].

Although our data are derived from studies conducted in developed countries, HIV-1 transmission by either heterosexual [28] or vertical [12–15] routes may be exceedingly rare in developing countries as well, in the presence of low levels of HIV-1 RNA. Although the use of antiretroviral drugs to maintain such low levels of viremia throughout pregnancy is not currently feasible for HIV-1–infected pregnant women in developing countries [29], the use of a potent antiretroviral drug(s) during labor coupled with short-term infant prophylaxis may be an effective option [30].

A limitation of our study is that measurements at delivery were not available for all of the registry mothers. Nevertheless, >80% had a measurement in the last month of pregnancy or within 3 days after delivery. Moreover, in several cohorts with longitudinal data, HIV-1 RNA levels have been very stable over the course of pregnancy [4, 6, 10]. Other measurement issues also may need to be considered. Our results indicate that the eligibility measurements may underestimate the true viremia during pregnancy, perhaps due to regression to the mean [25]. In addition, different assays were used for the determination of HIV-1 RNA levels in the various studies, and testing may have been done under slightly different conditions. Although it is unlikely that interassay differences would be very large [31–33], this variability may, in part, explain the heterogeneity that we observed in transmission rates among the various studies, especially for untreated women. Nevertheless, sensitivity analyses, excluding the study with the highest transmission rate

among untreated women, showed that the prophylactic effect of antiretroviral treatment remained the same.

Our findings have implications for the potential of eradicating perinatal HIV-1 transmission. In developed countries, the use of highly active antiretroviral therapy is standard for the treatment of HIV-1–infected individuals, with the aim of suppressing viral replication below the levels of detection of the current assays, traditionally to <200 copies/mL or even lower. Such treatment is being increasingly used for pregnant women, especially in the United States. Our study used information mostly from zidovudine-treated mothers, but it hints that, at such low levels of viral suppression, perinatal HIV-1 transmission would be exceedingly rare. The large reductions in the rate of transmission that have been recently observed in developed countries [34, 35], concomitant with increasing use of combination antiretroviral therapy in pregnancy, offer empirical support for this statement.

The primary obstacles to the elimination of HIV-1 transmission in this setting would derive from the lack of early diagnosis of HIV-1 infection in pregnant women and the lack of compliance with the currently available highly active combination antiretroviral therapeutic regimens [36]. However, it will be critical to establish the short- and long-term safety of combination antiretroviral regimens for pregnant women and their children. Some nucleoside analogue drugs are mutagenic in in vitro or animal studies and can cause mitochondrial dysfunction among infected individuals receiving long-term treatment, and one study has suggested that in utero exposure to these drugs may be associated with mitochondrial dysfunction in some infants [37–39]. Zidovudine prophylaxis appeared to be safe in the short-term for women and infants who were followed for up to 5.6 years [40, 41]. However, long-term data are not yet available, and definitive information about safety will require many years of follow-up.

The large majority of registered cases had ⩾1 postulated immunologic or obstetric risk factor for vertical transmission. Several women were also using illicit drugs, the importance of which needs further assessment in controlled studies. HIV-1 RNA is not the only determinant of transmission; other risk factors may occasionally cause transmission, despite low levels of viremia.

Adjusted analyses that consider the most important obstetrical and immunologic risk factors of perinatal transmission showed that the effect of maternal antiretroviral therapy was not due to confounding from such factors. Moreover, although maternal and neonatal antiretroviral therapy largely coincided in the same mother-infant pairs, the multivariate analysis suggested that maternal treatment may be more important. An additional protection from neonatal treatment in mother-infant pairs with maternal HIV-1 RNA levels <1000 copies/mL cannot be excluded, but it is not possible to discern from the available data. Maternal and neonatal treatment are highly correlated; thus, their regression coefficients may not be fully reliable when they are included in the same model. CD4 cell count and birthweight were also independent predictors of transmission, but the effect of antiretroviral treatment in the mother remained significant, even in women with high CD4 cell counts and in infants with normal birth weight. Last, in adjusted analyses, the mode of delivery remained a predictor of transmission even in this cohort of women with a low virus load, and this effect appeared to be independent of antiretroviral therapy. However, our databases did not clearly separate elective and nonelective cesarean delivery, and only elective cesarean delivery has been shown previously to reduce the risk of transmission. The potential incremental benefit of elective cesarean delivery in reducing transmission in a population of women at low risk of transmission, such as those receiving antiretroviral therapy who have HIV-1 RNA levels <1000 copies/mL, must be weighed against the potential risk of operative delivery to the mother.

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