MAJOR ARTICLE

Decreased Risk of Congenital Cytomegalovirus Infection in Children Born to HIV-1–Infected Mothers in the Era of Highly Active Antiretroviral Therapy

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Background. We evaluated the prevalence of congenital cytomegalovirus (CMV) infection before and after highly active antiretroviral therapy (HAART) availability among neonates born to human immunodeficiency virus type 1 (HIV-1)–infected mothers. We also identified maternal risk factors associated with in utero CMV transmission.

Method. Routine screening for congenital CMV infection was performed from 1993 through 2004 in children born to HIV-1–infected mothers included in the French Perinatal Cohort (Enquête Périnatale Française). Interpretable tests on urine samples collected within the first 10 days of life were available for 4797 of the 7563 live-born infants. Prevalence was estimated for different time periods. Univariate and multivariate logistic regression analyses were performed to identify factors associated with CMV transmission in the HAART era.

Results. Among live-born children, the overall prevalence of CMV infection was 2.3% (95% confidence interval, 1.9%–2.8%). Prevalence was higher among HIV-1–infected neonates (10.3%; 95% confidence interval, 5.6%–17.0%) than among HIV-1–uninfected neonates (2.2%; 95% confidence interval, 1.8%–2.7%; $P < .01$). Among HIV-1–uninfected neonates, the prevalence of CMV infection decreased over time, from 3.5% in 1997–1998 to 1.2% in 2003–2004. Delivery period, maternal age, time at antiretroviral treatment initiation, and maternal $CD4^+$ cell count <200 cells/mm^3 close to delivery were independently associated with CMV infection in logistic regression analysis. The percentage of symptomatic CMV infections was 23.1% among HIV-1–infected newborns and 6.7% among HIV-1–uninfected neonates.

Conclusions. The prevalence of congenital CMV infection was high and associated with high morbidity rates among HIV-1–infected neonates. Conversely, the prevalence of CMV infection decreased over time among neonates not infected with HIV-1, reaching levels similar to those observed in the general population, following the introduction and increasing use of HAART for prevention of mother-to-child HIV-1 transmission.

Cytomegalovirus (CMV) is the leading cause of congenital infection in developing countries [1]. Congenital infection results from in utero transmission after maternal primary infection, reinfection, or reactivation of latent infection (i.e., recurrent infection). A recent meta-analysis reported a higher rate of transmission for primary maternal infections than for recurrent infections (32% vs. 1.4%) [2]. The overall prevalence of congenital CMV infection at birth was 0.6%, with considerable differences among the populations studied [2–6].

Most neonatal infections are asymptomatic, and this is more frequently the case for recurrent than for pri-

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mary maternal infection [7]. Approximately 13% of infected children (range, 0%–25%) have CMV-specific symptoms at birth, according to a recent review of the literature based on 15 studies that screened a total of 117,986 infants [8]. Neurological and sensory sequelae occur in 40%–58% of neonates with symptoms, although 13.5% (range, 0.0%–23.5%) of children with no symptoms also developed such sequelae [8]. In asymptomatic neonates, the main sequela was sensorineural hearing loss, which was bilateral in up to 50% of cases [7, 9–11].

A high prevalence of congenital CMV infection was reported among neonates born to human immunodeficiency virus type 1 (HIV-1)–infected mothers in the 3 published surveys so far (2.7%, 4.5%, and 6.5%) [12–14]. These 3 studies were conducted before highly active antiretroviral therapy (HAART) became available. In 1 study, the prevalence of congenital CMV infection was higher among children also infected with HIV-1 than among children without HIV-1 infection (21% vs. 3.8%) [14]. CMV coinfection in children with HIV-1 infection was associated with a more severe course of HIV-1 infection, with higher rates of central nervous system complications [13]. HAART has been available for the prevention of mother-to-child transmission of HIV-1 since 1997. Nothing is known about the frequency and associated morbidity of congenital CMV infection in the HAART era.

We investigated changes in the prevalence of congenital CMV infections from 1993 through 2004, in neonates born to HIV-1–infected mothers included in the French Perinatal Cohort (Enquête Périnatale Française; EPF) as part of a national multicenter survey. During the period studied, neonatal CMV testing was recommended as part of the standardized follow-up for all neonates included in the EPF Cohort. We aimed to identify maternal risk factors in this population, especially in the HAART era, and to determine whether changes in strategies for preventing the mother-to-child transmission of HIV-1 were linked to a decrease in the rate of congenital CMV infection.

MATERIALS AND METHODS

Study population. Prospective data have been collected on HIV-1–infected pregnant women and their children at 96 centers throughout France since 1984 for the EPF Cohort (Agence Nationale de Recherche sur le Sida [ANRS] CO1/10/11). Figure 1 presents a flow chart that describes how the population for the study was selected. Informed consent was obtained from all mothers. Data from clinical and biological examinations were collected; examinations were performed every 6 months from birth until the age of 18 years for HIV-1–infected children and every 6 months from birth until the age of 24 months for HIV-1–uninfected children [15]. No specific recommendations for obstetric and HIV-1 infection care were made, but investigators were encouraged to follow current French guidelines for preventing mother-to-child transmission [16–18]. Antiretroviral therapy did not become routinely available until 1994. Standard care involved prophylaxis with zidovudine monotherapy from 1994 through 1996 and involved combination therapy since 1996 [16–18]. The collection of a urine sample for CMV testing within the first 10 days of life was recommended as part of the standard follow-up during 1993–2004. Data on neonatal CMV infection have not been collected in EPF questionnaires since 2005.

All infants were eligible for this analysis if they were born alive to HIV-1–infected mothers from 1993 through 2004. Infants born to of HIV type 2–infected mothers were excluded. Overall, 5019 (66.4%) of the 7563 eligible infants were screened for congenital CMV infection within their first 10 days of life. The cohort study was approved by the Cochin Hospital Institutional Review Board and the French database watchdog commission (Commission Nationale de l'Informatique et des Libertés).

Assays for congenital CMV infection. From 1993 through 2001, French laboratories used rapid viral culture with inoculation of MRC-5 cells for the detection of CMV in urine [19]. Since 2001, French laboratories have used either rapid viral culture [19] or in-house real-time polymerase chain reaction (PCR) assays [20–22]. The type of screening method was not recorded in EPF questionnaires. The result was indeterminate (because of contamination of cell culture or presence of PCR inhibitors) for 222 (4.4%) of the 5019 newborns, and these infants were excluded from the analysis. The reliability of the CMV screening data reported in the standardized questionnaires was evaluated for the subsample of 1022 children whose urine specimens were tested at the Virology Laboratory of Necker Hospital; the sensitivity and specificity of the reported tests were 96.2% and 99.8%, respectively. Congenital CMV status was available for 4797 children in total, corresponding to 4688 pregnancies.

Maternal CMV serological status. Serological tests for maternal CMV status were not performed systematically, and the results have not been recorded on EPF questionnaires since 2001. A mother was considered to be CMV seropositive if at least 1 CMV immunoglobulin G (IgG) test was positive before or during pregnancy or during the first 7 days after delivery. A mother was considered to be CMV seronegative if all CMV IgG tests performed during pregnancy or at least 1 IgG test performed after delivery had negative results. In other situations (i.e., no test carried out during pregnancy and no negative test result obtained after delivery or in the case of discordant results), maternal serological status could not be determined. During 1993–2000, maternal CMV status during pregnancy was documented in 1929 mothers (87.0%), 1773 (91.9%) of whom

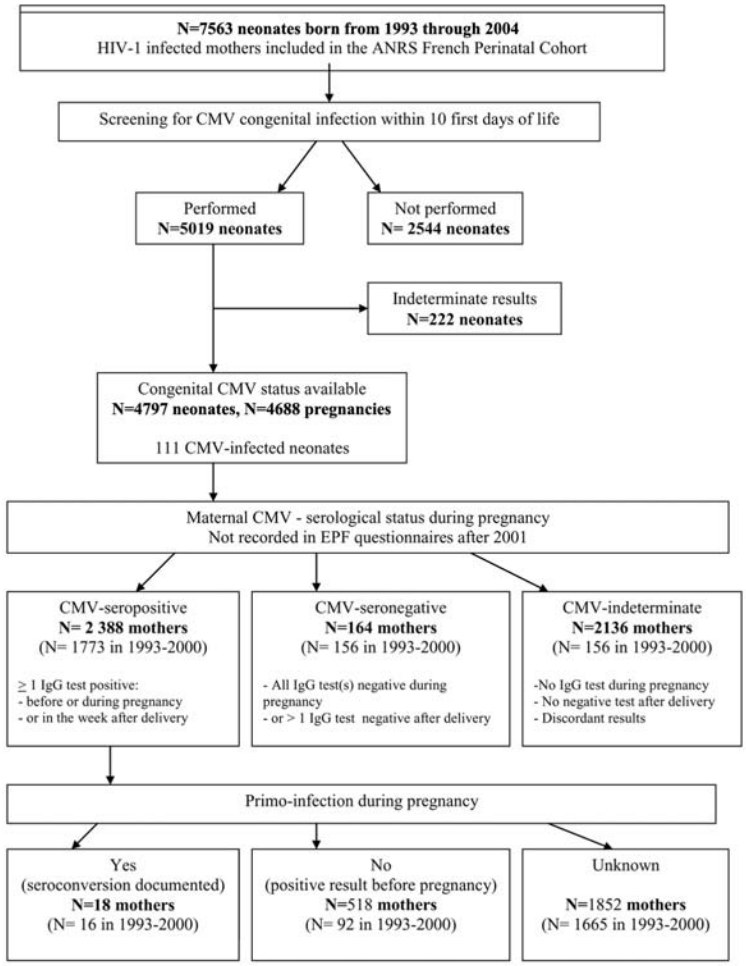

Figure 1. Flow chart of inclusion criteria for the population study. ANRS, Agence Nationale de Recherche sur le Sida; CMV, cytomegalovirus; EPF, French Perinatal Cohort; HIV-1, human immunodeficiency virus type 1.

were CMV seropositive. The precise timing of CMV seroconversion was unknown for 1665 (93.9%) of these women. The occurrence of a primary infection (i.e., seroconversion during pregnancy) was confirmed in 16 mothers.

Neonatal HIV-1 infection. An infant was considered to be infected with HIV-1 if HIV-1 was detected by viral tests performed on 2 separate samples or if anti–HIV-1 antibodies detected by enzyme-linked immunosorbent assay and Western blot persisted after the age of 18 months. An infant was considered to be HIV-1 uninfected if viral test results were negative for 2 separate samples (at least 1 of which was obtained after the end of neonatal prophylactic treatment) or if serological test results were negative after the age of 18 months. For 126 (2.6%) of the 4797 eligible children for whom CMV status was known, HIV-1 infection status remained undetermined because of missing or incomplete virological data.

Variables. We recorded maternal age, geographic origin, obstetric care (parity, gestational age at booking, gestational age at delivery, and mode of delivery), and HIV-1 care (type and time of antiretroviral therapy received during pregnancy, maternal plasma HIV-1 RNA load, and $CD4^+$ cell counts measured closest to the time of delivery). The type of antiretroviral treatment was classified as monotherapy if it involved a single nucleoside reverse-transcriptase inhibitor (NRTI), as bitherapy (or dual-drug treatment) if it involved 2 NRTIs, or as HAART if it involved a combination of $\geqslant 3$ drugs. Birth weight, head circumference, Apgar score, and clinical status at birth (hepatosplenomegaly, seizures, thrombocytopenia, or neurological abnormalities) were recorded systematically. Neonatal symptomatic CMV infection was defined as the presence of $\geqslant 1$ of the following symptoms: hepatosplenomegaly, seizures, thrombocytopenia, and microcephaly (at least >2 standard deviations below the mean) [8]. Chorioretinis and intracranial calcifications were not included in our definition, because data for these conditions were collected through an open question that also concerned other symptoms and diseases.

Statistical analysis. The prevalence of CMV infection at birth was estimated to be the number of CMV-infected infants divided by the total number of live-born children. Prevalence was estimated with exact 95% confidence intervals (CIs), and medians are expressed with interquartile ranges. We used the χ^2 test or 2-tailed Fisher's exact test to compare percentages and the Student's *t* test or Wilcoxon test to compare the means of continuous variables. We estimated the prevalence of CMV infection according to HIV-1 infection status, overall and for 3 periods: 1993–1996 (pre-HAART era), 1997–2000 (first period of the HAART era), and 2001–2004 (later HAART era). We then focused on the HAART era (1997–2004) to identify maternal and obstetric factors associated with congenital CMV infection in children not infected with HIV-1 with use of univariate and multivariate analyses. We performed logistic regression with 2 models; model 2 was more parsimonious. Both models included factors found to be associated in univariate analysis with $P < .20$. Model 1 also adjusted for other factors that have been reported to be associated with CMV infection and viral load at delivery. $P < .05$ was considered to be statistically significant. Statistical analyses were performed using STATA software, version 8.0 (StataCorp).

RESULTS

Characteristics of the neonatal population screened for congenital CMV infection. Overall, 5019 (66.4%) of the 7563 infants born to HIV-1–infected mothers during 1993–2004 were screened for congenital CMV infection within the first 10 days of life. The results obtained could not be interpreted for 222 of these children. The proportion of infants screened at birth increased over time from 56.1% (866 of 1543 children) during 1993–1996 to 64.6% (1632 of 2526 children) during 1997–2000 and 72.2% (2521 of 3494 children) during 2001–2004 ($P < .001$, by χ^2 test for trend). Screening for congenital CMV infection occurred more frequently among infants born to mothers originating from sub-Saharan Africa who were receiving antiretroviral drugs during pregnancy and were serologically tested for CMV infection.

The maternal and obstetric characteristics of the women in the study changed over the study period (table 1); the proportion of multiparous mothers originating from Africa and treated with HAART during pregnancy markedly increased, whereas maternal viral load close to the time of delivery decreased. The proportion of mothers with $CD4^+$ cell counts <200 cells/mm^3 close to the time of delivery tended to decrease between 1993 and 1998 but remained stable thereafter.

Prevalence of congenital CMV infection. Overall, the prevalence of CMV infection was 2300 infections per 100,000 live births (95% CI, 1900–2800 infants per 100,000 live births). One hundred eleven (2.3%) of 4797 infants in the study were infected with CMV. This prevalence decreased significantly over time, from 3.0% of live births (95% CI, 1.9%–4.5%) in 1993–1996 to 1.5% (95% CI, 1.1%–2.1%) in 2001–2004 ($P < .001$). Regardless of period, the prevalence of CMV infection was significantly higher among HIV-1–infected infants (13 [10.3%] of 126 infants; 95% CI, 5.6%–17.0%) than among HIV-1–uninfected infants (94 [2.2%] of 4302 infants; 95% CI, 1.8%–2.7%); $P < .001$) (table 2).

The percentage of neonates with in utero HIV-1 infection (as determined by a positive HIV-1 PCR result within 7 days after birth) tended to be higher among neonates who were coinfected with CMV than among those infected by HIV-1 alone (69.2% vs. 42.2%; $P = .08$).

In the subgroup of mothers for whom such data were available, congenital CMV infection occurred significantly more frequently among the infants of mothers who experienced seroconversion during pregnancy (2 [11.1%] of 18 infants) than among the infants of mothers known to be positive for CMV before pregnancy (10 [1.4%] of 695 infants; $P = .04$).

Factors associated with congenital CMV infection in neonates not infected with HIV-1, during the HAART era. The prevalence of congenital CMV infection decreased significantly from 1997 through 2004 ($P < .004$). The prevalence tended to be higher among children of younger mothers ($P = .06$) and among children of mothers with a $CD4^+$ cell count <200 cells/mm^3 at the time of delivery ($P = .002$). The prevalence of congenital CMV infection was higher for infants with mothers who began receiving antiretroviral therapy during the second trimester of pregnancy, compared with infants of mothers who began receiving treatment before or during the first trimester of pregnancy ($P < .007$). These factors remained independently associated with congenital CMV infection in a logistic regression analysis that also adjusted for geographic origin and sex of the child. Parity, type of antiretroviral therapy (NRTI monotherapy, NRTI bitherapy, or HAART), and maternal viral load near the time of delivery were not associated with congenital CMV infection in univariate or multivariate analyses (table 3).

Symptomatic congenital infection. We found that 23.1% (95% CI, 5.0%–53.8%) of HIV-1–CMV–coinfected neonates experienced CMV-related symptoms. However, only 6.8% (95% CI, 2.5%–13.9%) of infants infected with CMV only experienced CMV-related symptoms ($P = .08$) (table 4).

DISCUSSION

Overall, from 1993 through 2004, the prevalence of congenital CMV infection among children born to HIV-1–infected mothers included in the EPF Cohort was high, with 2300 cases of CMV infection per 100,000 live births (95% CI, 1900–2800 cases per 100,000 live births). The EPF survey included approximately two-thirds of all HIV-1–infected mothers who gave birth in France. During the study period, CMV detection in

Table 1. Changes in maternal and obstetric characteristics of pregnancies in which screening for congenital cytomegalovirus (CMV) infection was performed from 1993 through 2004.

Characteristic	Period							
	All	1993–1994	1995–1996	1997–1998	1999–2000	2001–2002	2003–2004	*P*
Sub-Saharan African origin	2623 (56.4)	126 (41.7)	196 (44.0)	307 (47.9)	467 (52.5)	718 (60.2)	809 (68.5)	<.001
Primiparity	1766 (38.0)	126 (42.3)	176 (39.5)	256 (40.1)	357 (40.2)	454 (38.1)	397 (33.6)	.009
Twin pregnancies	105 (2.3)	6 (2.0)	10 (2.2)	11 (1.7)	24 (2.7)	24 (2.0)	30 (2.5)	.77
Premature delivery	557 (12.0)	25 (8.5)	41 (9.3)	70 (10.8)	118 (13.2)	133 (11.2)	170 (14.4)	.007
Aged <25 years	641 (13.7)	60 (19.9)	74 (16.6)	96 (14.8)	120 (13.4)	157 (13.2)	134 (11.4)	.002
Received ARV at start of pregnancy	1238 (26.8)	19 (6.4)	45 (10.3)	153 (23.8)	321 (36.1)	357 (30.1)	343 (29.3)	<.001
Most recent type of ARV received								
Untreated	311 (6.7)	158 (52.5)	38 (8.6)	19 (2.9)	35 (3.9)	34 (2.9)	27 (2.3)	<.001
Monodrug therapy	1277 (27.5)	142 (47.2)	379 (85.6)	82 (12.7)	300 (33.7)	239 (20.1)	135 (11.5)	
Dual-drug therapy	1148 (24.7)	1 (0.3)	25 (5.6)	483 (74.8)	225 (24.3)	262 (22.1)	152 (12.9)	
HAART	1911 (41.1)	0 (0.0)	1 (0.2)	62 (9.6)	331 (37.2)	653 (55.0)	864 (73.3)	
Duration of pregnancy at ARV initiation								
Treated before pregnancy	977 (21.1)	17 (5.7)	34 (7.8)	105 (16.3)	219 (24.6)	295 (24.9)	375 (26.2)	<.001
4–13 weeks	291 (6.3)	5 (1.7)	45 (10.3)	48 (7.5)	39 (4.4)	61 (5.2)	93 (7.9)	
14–20 weeks	683 (14.8)	25 (8.4)	130 (29.8)	162 (25.2)	118 (13.3)	121 (10.2)	127 (10.9)	
21–27 weeks	971 (21.0)	36 (12.1)	105 (24.1)	129 (20.0)	157 (17.7)	248 (20.9)	296 (25.3)	
28–31 weeks	1070 (23.2)	27 (9.1)	50 (11.5)	139 (21.6)	247 (27.8)	348 (29.4)	259 (22.1)	
⩾32 weeks	319 (6.9)	29 (9.8)	34 (7.8)	42 (6.5)	74 (8.3)	78 (6.6)	62 (5.2)	
Untreated	311 (6.7)	158 (53.2)	38 (8.7)	19 (3.0)	35 (3.9)	34 (2.8)	27 (2.3)	
HAART as first ARV received	1801 (39.0)	0 (0.0)	0 (0.0)	52 (8.1)	302 (34.0)	626 (52.8)	821 (70.1)	<.001
$CD4^+$ cell count closest to time delivery								
<200 cells/mm^3	495 (11.2)	38 (14.7)	70 (17.5)	76 (12.1)	84 (9.7)	113 (9.8)	114 (10.1)	.001
200–350 cells/mm^3	948 (21.4)	49 (18.9)	86 (21.5)	125 (19.9)	202 (23.3)	230 (20.0)	256 (22.6)	
>350 cells/mm^3	2994 (67.5)	172 (66.4)	244 (61.0)	427 (68.0)	581 (67.0)	808 (70.2)	762 (67.3)	
HIV-1 load closest to time of delivery								
<400 copies/mL	2405 (62.7)	…	16 (17.2)	299 (49.6)	458 (53.2)	782 (68.2)	850 (75.2)	<.001
400–1000 copies/mL	326 (8.5)	…	5 (5.4)	77 (12.8)	76 (8.8)	83 (7.2)	85 (7.5)	
⩾1000 copies/mL	1103 (28.8)	…	72 (77.4)	227 (37.7)	327 (38.0)	2827 (24.6)	195 (17.3)	
Maternal CMV IgG tested	1929 (84.2)	252 (83.4)	360 (80.5)	566 (87.4)	751 (84.2)	…	…	.02
Maternal CMV IgG positive	1773 (91.9)	227 (90.1)	327 (90.8)	525 (92.8)	694 (92.4)	…	…	.48
HIV-1 transmission	126 (2.8)	36 (11.8)	31 (6.9)	15 (2.3)	15 (1.7)	21 (1.8)	8 (0.8)	<.001
CMV congenital infection, no. (%) of newborns[a]	111 (2.3)	10 (3.3)	13 (2.9)	25 (3.8)	26 (2.8)	24 (2.0)	13 (1.1)	.002

NOTE. Data are no. (%) of pregnancies, unless otherwise indicated. Data for all characteristics were not available for all pregnancies. Overall, there were 4688 pregnancies during 1993–2004, 302 during 1993–1994, 447 during 1995–1996, 648 during 1997–1998, 893 during 1999–2000, 1194 during 2001–2002, and 1204 during 2003–2004. ARV, antiretroviral therapy; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; Ig, immunoglobulin.

[a] The CMV transmission rate was estimated among the 4797 newborns resulting from the pregnancies.

urine samples was performed for 66% of the neonates born to mothers included in the EPF Cohort.

The prevalence of CMV infection was significantly higher among infants who were also infected with HIV-1 (13 [10.3%] of 126 infants) than among infants who were not HIV-1 infected (94 [2.1%] of 4302 infants; $P < .001$), which was consistent with the findings of a survey carried out before the HAART era [14]. The proportion of HIV-1 infection transmitted in utero tended to be higher among the group of neonates who were coinfected by CMV than among those who were only HIV-1 infected, which may suggest a similar mechanism for coinfection. Nevertheless, this does not exclude the possibility that CMV infection may facilitate HIV-1 infection or vice versa.

Nevertheless, the prevalence of congenital CMV infection remained higher in children not infected with HIV-1 but born to HIV-1–infected mothers than that in the general population of industrialized countries, which varies from 0.2% to 0.9% of live births [4–6]. This may be attributable to the high prevalence of maternal CMV seropositivity; in the EPF Cohort (including both African and non-African women), 92% of mothers were CMV seropositive, whereas CMV seroprevalence is estimated

Table 2. Prevalence of congenital cytomegalovirus (CMV) infection, by period during which delivery occurred and human immunodeficiency virus type 1 (HIV-1) infection status of the newborn (1993–2004).

	Period								
	All (*n* = 4797)		1993–1996 (*n* = 763)		1997–2000 (*n* = 1577)		2001–2004 (*n* = 2457)		
Variable	Proportion of newborns	Percentage of newborns (95% CI)	Proportion of newborns	Percentage of newborns (95% CI)	Proportion of newborns	Percentage of newborns (95% CI)	Proportion of newborns	Percentage of newborns (95% CI)	*P*
Congenital CMV infection									
All	111/4797	2.3 (1.9–2.8)	23/763	3.0 (1.9–4.5)	51/1577	3.2 (2.4–4.2)	38/2457	1.5 (1.1–2.1)	.001
Among CMV-seropositive mothers	NA	NA	18/564	3.2 (1.9–5.0)	48/1248	3.9 (2.8–5.1)	NA	NA	
HIV-1 transmission[a]	126/4428	2.8 (2.4–3.4)	67/754	8.9 (7.0–11.1)	30/1525	2.0 (1.3–2.8)	29/2149	1.4 (0.9–1.9)	<.001
CMV congenital infection according to neonatal HIV-1 status									
HIV-1–infected newborns	13/126	10.3 (5.6–17.0)	4/67	6.0 (1.7–14.6)	3/30	10.0 (2.1–26.5)	6/29	20.7 (8.0–39.7)	.11
HIV-1–uninfected newborns	94/4302	2.2 (1.8–2.7)	19/687	2.8 (1.7–4.3)	46/1495	3.1 (2.3–4.1)	29/2120	1.4 (0.9–2.0)	.001
P		<.001		.15		.033		.001	
In utero HIV-1 infection among HIV-1–infected newborns[b]									
Coinfected with CMV	6/9	66.7	2/4	50.0	3/3	100.0	4/6	66.7	.6
Not coinfected with CMV	43/102	42.2	27/58	46.6	9/24	37.5	7/20	35.0	.6
P		.08		>.99		.08		.34	

NOTE. CI, confidence interval; NA, not available.

[a] For newborns with documented HIV-1 infection status.

[b] Testing for HIV-1 detection during the first 7 days of life was not available for 11 HIV-1–infected neonates.

Table 3. Factors associated with congenital cytomegalovirus infection in human immunodeficiency virus type 1 (HIV-1)–uninfected neonates in the highly active antiretroviral therapy (HAART) era (1997–2004).

				Logistic regression			
	Univariate analysis (n = 3448)			Model 1[a] (n = 3200)		Model 2[b] (n = 3296)	
Variable	Proportion (%) of newborns	OR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
Overall	67/3448 (1.9)	…		…		…	
Period							
2003–2004	11/933 (1.2)	1	.004	1	.010	1	.016
2001–2002	15/1087 (1.4)	1.2 (0.5–2.6)		1.2 (0.5–2.6)		1.1 (0.5–2.5)	
1999–2000	20/824 (2.4)	2.1 (1.0–4.4)		2.1 (1.0–4.6)		2.1 (1.0–4.6)	
1997–1998	21/604 (3.5)	3.0 (1.4–6.3)		2.9 (1.3–6.2)		2.8 (1.3–6.2)	
Geographic origin							
Other than sub-Saharan	22/1437 (1.5)	1	.16	1	.13	1	.16
Sub-Saharan African	44/2000 (2.2)	1.4 (0.9–2.4)		1.6 (0.9–2.8)		1.5 (0.9–2.5)	
Parity							
Primipara	29/1312 (2.2)	1	.46	1	.49	…	
1 or 2 children	27/1643 (1.6)	0.7 (0.4–1.3)		0.8 (0.4–1.4)		…	
3 children	11/479 (2.3)	1.0 (0.5–2.1)		1.1 (0.5–2.5)		…	
Maternal age, median years							
⩾25	53/2992 (1.8)	1	.06	1	.14	1	.057
<25	14/455 (3.1)	1.8 (1.0–3.2)		1.6 (0.8–3.2)		1.8 (1.0–3.3)	
Gestational age, weeks							
⩾37	57/3063 (1.9)	1	.56	1	.60	…	
33–36	8/319 (2.5)	1.4 (0.6–2.9)		1.4 (0.6–2.9)		…	
<33	2/62 (3.2)	1.8 (0.4–7.1)		1.5 (0.4–6.5)		…	
Receiving ARV at the start of pregnancy							
No	49/2382 (2.1)	1	.40	…		…	
Yes	17/1045 (1.6)	0.8 (0.5–1.4)		…		…	
Type of ARV received first during pregnancy							
HAART	33/1546 (2.1)	1	.72	…		…	
2 NRTIs	16/784 (2.0)	1.0 (0.5–1.7)		…		…	
Monodrug therapy	16/1006 (1.6)	0.7 (0.4–1.4)		…		…	
No treatment	1/91 (1.1)	0.5 (0.1–3.8)		…		…	
Time during pregnancy at receipt of first ARV							
First trimester or before pregnancy	14/1037 (1.4)	1	.007	1	.023	1	.026
14–20 weeks	15/468 (3.2)	2.4 (1.2–5.1)		1.7 (0.8–3.7)		1.8 (0.8–3.9)	
21–27 weeks	22/720 (3.1)	2.3 (1.2–4.5)		2.2 (1.1–4.3)		2.3 (1.1–4.5)	
28–32 weeks	10/897 (1.1)	0.8 (0.4–1.9)		0.8 (0.3–1.8)		0.8 (0.3–1.8)	
⩾33 weeks or not treated	5/305 (1.6)	1.2 (0.4–3.4)		0.9 (0.3–2.6)		0.9 (0.3–2.6)	
Maternal $CD4^+$ cell count at delivery, cells/mm^3							
⩾200	52/3005 (1.7)	1	.002	1	.004	1	.003
<200	14/330 (4.2)	2.5 (1.4–4.6)		2.4 (1.3–4.5)		2.5 (1.4–4.7)	
Maternal HIV-1 RNA level at delivery, copies/mL							
<400	36/2112 (1.7)	1	.30	1	.67	…	
400–1000	8/288 (2.8)	1.6 (0.8–3.6)		1.4 (0.7–3.1)		…	
⩾1000	21/897 (2.3)	1.4 (0.8–2.4)		1.0 (0.6–1.7)		…	
Sex of child							
Female	25/1644 (1.5)	1	.079	1	.074	1	.08
Male	42/1787 (2.4)	1.6 (0.9–2.6)		1.6 (1.0–2.7)		1.6 (0.9–2.7)	

NOTE. Data for children born as twins or other multiple were excluded from these analyses. aOR, adjusted odds ratio; ARV, antiretroviral therapy; NRTI, nucleoside reverse-transcriptase inhibitor; OR, odds ratio.

[a] Model 1 was adjusted for all potential noncollinear risk factors, regardless of the P value determined in univariate analysis. Receiving ARV at the start of pregnancy collinear with time in pregnancy at receipt of first ARV and type of HAART (P value near 1) collinear with period were not included in model 1.

[b] Model 2 was adjusted for factors associated with cytomegalovirus infection with a P value <.20 determined in the univariate analysis.

Table 4. Signs and symptoms observed at birth, by human immunodeficiency virus type 1 (HIV-1) and cytomegalovirus (CMV) infection status.

Symptom	HIV-1 uninfected, proportion (%) of newborns			HIV-1 infected, proportion (%) of newborns		
	CMV uninfected (n = 4 208)	CMV infected (n = 94)	P[a]	CMV uninfected (n = 113)	CMV infected (n = 13)	P[a]
Acute fetal distress	209/4128 (5.1)	10/92 (10.9)	.01	8/108 (7.4)	2/13 (15.4)	.3
Apgar score <10	278/4148 (6.7)	12/93 (12.9)	.02	11/112 (9.8)	2/13 (15.4)	.6
Birth weight >2 SDs below mean	195/4158 (4.7)	5/92 (5.4)	.7	5/111 (4.5)	3/13 (23.1)	.03
Lymph enlargement	31/4188 (0.7)	0/93 (0.0)	.4	4/112 (3.6)	1/13 (7.7)	.4
Hepatosplenomegaly	33/4188 (0.8)	4/93 (4.3)	<.001	5/112 (4.5)	1/13 (7.7)	.5
Seizures	7/4187 (0.2)	0/92 (0.0)	>.99	0/112 (0.0)	0/13 (0.0)	
Microcephaly >2 SDs below mean	121/4081 (3.0)	0/92 (0.0)	.11	1/110 (0.9)	2/13 (15.4)	.03
Thrombocytopenia	28/4017 (0.7)	3/93 (3.2)	.03	4/109 (3.7)	0/12 (0.0)	>.99
Neurological signs	143/2360 (6.1)	6/66 (9.1)	.3	2/112 (1.8)	1/13 (7.7)	.3
CMV-related symptoms[b]	184/4071 (4.5)	6/90 (6.7)	.3	9/110 (8.2)	3/13 (23.1)	.11

NOTE. SD, standard deviation.

[a] P values determined by χ^2 test or Fisher's exact test, as appropriate.

[b] CMV-related symptoms include at least 1 of the following symptoms: hepatosplenomegaly, seizures, microcephaly, and thrombocytopenia.

to only be 50% among pregnant women in France in general [23]. A recent meta-analysis demonstrated that the prevalence of CMV congenital infection was related to the level of maternal seroprevalence; a prevalence of CMV congenital infection of 1.0%–1.5% was associated with a maternal seroprevalence of >90% [2]. However, this expected prevalence of CMV infection at birth (1.5%) is nonetheless lower than that observed for neonates without HIV-1 infection in the EPF Cohort (2.3%). Maternal immunosuppression may also have contributed to the higher risk of in utero transmission in this population, because of the higher frequency of CMV reactivation observed in immunosuppressed individuals [24, 25]. CMV replication was detected in 30%–50% of HIV-1–infected patients with $CD4^+$ cell counts <100 cells/mm^3. In our study, low $CD4^+$ cell counts close to the time of delivery (<200 cells/mm^3) were strongly associated with CMV transmission, even in children without HIV-1 coinfection.

We found that, during 1997–2004, the prevalence of congenital CMV infection was higher among patients for whom antiretroviral therapy was initiated during the second trimester of pregnancy than among those for whom it was initiated earlier. French guidelines recommend initiating antiretroviral treatment as soon as possible in pregnant women with low $CD4^+$ cell counts [16–18]. For these patients, early initiation of HAART may have increased protection against CMV reactivation, thereby decreasing rates of transmission to the fetus; after HAART initiation, CMV viremia has been shown to decrease rapidly, with a median half-life of 5.2 days and a rapid normalization of $CD8^+$ functions before $CD4^+$ cell count recovery [26, 27]. In our survey, the prevalence of congenital CMV infection was similar among children exposed to HAART in utero and children exposed to NRTI monotherapy. This may reflect the fact that monotherapy is recommended for mothers with a favorable initial immunovirological status and lower risk of CMV transmission to their fetus. Conversely, HAART was more frequently administered to mothers with $CD4^+$ cell counts <200 cells/mm^3 and a higher risk of CMV transmission. Adjustment for initial immunovirological status was not possible because $CD4^+$ cell count and viral load early during pregnancy were not recorded in our routine questionnaires.

The prevalence of congenital CMV infection tended to increase among HIV-1–infected newborns over the course of the study period, whereas it notably decreased among HIV-1–uninfected children between 1997 and 2004, especially after 2000. The prevalence of congenital CMV infection decreased from 3.2% in 1997–1998 to 1.2% in 2003–2004, which is close to the prevalence expected for the general population. Many changes in sociodemographic characteristics and HIV-1 infection care occurred during this period, with increases in the proportion of mothers originating from sub-Saharan Africa, maternal age at delivery, multiparity, and HAART use and decreases in HIV-1 loads at delivery. Nevertheless, CMV prevalence decreased over time, even after adjustment for these factors. This decrease cannot be accounted for by changes in laboratory methods, which became more sensitive over time [28]. It also cannot be accounted for by broader systematic screening, because the proportion of neonates tested remained stable after 1997, and factors associated with screening (geographic origin and gestational age) were included in multivariate analysis. This decrease in CMV prevalence is also unlikely to be attributable to changes in the environmental reservoir of CMV in the contact population, because the study period is too short for such changes to have occurred. Instead, our results strongly suggest that the risk of CMV transmission in utero

decreased because of more effective and earlier control of the immunological status of HIV-1–infected pregnant women, which is attributable to the more widespread use of HAART in more recent periods; 9.6% of HIV-1–infected pregnant women received HAART in 1997, compared with 73.3% who received HAART in 2004. The stability of $CD4^+$ cell counts close to the time of delivery during the period 1997–2004, contrasted with the large decrease in viral load, may reflect the earlier prescription of effective multidrug therapy in mothers with a poorer immunological status.

CMV-related symptoms occurred frequently in children coinfected with CMV and HIV-1 (23.1%), consistent with previous findings [13]; symptoms that were potentially CMV-related could also be attributable to HIV-1 infection; however, these symptoms tended to occur less frequently in children who were only infected with HIV-1 (8.2%; $P = .11$). Conversely, the percentage of newborns without HIV-1 coinfection who experienced CMV-related symptoms (6.8%) was only one-half that reported in previous studies [8]. In our study, the frequency of symptomatic congenital CMV infection may have been underestimated, because not all CMV-related symptoms were systematically recorded in a standardized manner in the questionnaires. However, recurrent maternal infection, the most likely origin of CMV transmission in our population, has been associated with lower morbidity rates [7] and may account for the lower frequency of symptomatic infections. Long-term evaluation of sensorineurological sequelae was not possible in this survey, because follow-up of HIV-1–uninfected children was stopped at the 2 years of age. Moreover, hearing loss was not systematically evaluated in congenitally CMV-infected children.

In conclusion, congenital CMV infection was highly prevalent among children born to HIV-1–infected mothers from 1993 through 2004. The prevalence of this infection remained high and was associated with frequent morbidity in newborns who were coinfected with HIV-1. Systematic screening for CMV infection should therefore be recommended in these children. In newborns not coinfected with HIV-1, the proportion of symptomatic cases of CMV infection tended to be lower than that expected on the basis of published results, and the prevalence of congenital CMV in 2003–2004 tended to be similar to the prevalence reported for the general population [2]. This strongly suggests that the strategies that have proved so effective for preventing the mother-to-child transmission of HIV-1 also appear to be efficient at preventing congenital CMV infection.

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