Increased Risk of Serious Bacterial Infections Due to Maternal Immunosuppression in HIV-Exposed Uninfected Infants in a European Country

Clement Taron-Brocard,[1] Jerome Le Chenadec,[1] Albert Faye,[2,3] Catherine Dollfus,[4] Tessa Goetghebuer,[5] Vincent Gajdos,[1,6,7] Jean-Marc Labaune,[8] Anais Perilhou,[1] Laurent Mandelbrot,[1,2,9] Stephane Blanche,[10,11,a] and Josiane Warszawski[1,7,12,a]; for the France REcherche Nord&Sud Sida-HIV Hepatites - Enquete Perinatale Francaise - CO1/CO11 Study Group[b]

[1]CESP INSERM U1018 - Univ Paris-Sud, Le Kremlin-Bicetre, [2]Univ Diderot Paris 7, [3]AP-HP Hôpital Robert Debré, and [4]AP-HP Hôpital Trousseau, Paris, France; [5]CHU St Pierre, Brussels, Belgium; [6]AP-HP Hôpital Antoine Béclère, Clamart, [7]Univ Paris-Sud, [8]Hôpital de la Croix Rousse, Lyon, [9]AP-HP Hôpital Louis Mourier, Colombes, [10]AP-HP Hôpital Necker, [11]EA 3620 Univ Paris Descartes 5, and [12]AP-HP Hôpital Bicetre, Paris, France

Background. Morbidity and mortality are higher among human immunodeficiency virus (HIV) exposed but uninfected (HEU) infants than unexposed infants, particularly if the mother had a low CD4 count. We investigated the possible association between maternal immune depression during pregnancy and the risk of infection in HEU infants in the national French Perinatal Cohort (EPF).

Methods. All neonates, born alive, to HIV-1–infected women enrolled in the EPF between 2002 and 2010 were included. The primary outcome was the first serious (hospitalization or death) infection during the first year of life. The main exposure variable was maternal CD4 cell count near delivery. The Kaplan–Meier method and multivariate Cox models were applied, with the different types of infections managed as competing events.

Results. Among 7638 HEU neonates, 699 had at least 1 serious infection (of which 159 were bacterial) with a Kaplan–Meier probability of 9.3% (95% confidence interval, 8.7–10.0) at 1 year. The risk of serious bacterial infection during the first year of life significantly increased with lower maternal CD4 cell count, before and after adjustment for maternal CD4 cell count <350 and 350–499 CD4/mm^3 (adjusted hazard ratio = 1.7 [1.2–2.6] and 1.2 [0.8–1.9], respectively; $P = .03$). This association mainly concerned infections involving encapsulated bacteria ($P = .03$). The risk of serious viral infection was, by contrast, independent of the mother's CD4 cell count.

Conclusions. Maternal CD4 count is significantly and specifically associated with the risk of serious infections with encapsulated bacteria in HEU infants.

Keywords. infants; HIV; pregnancy; mother-to-child transmission; CD4.

The widespread use of antiretroviral multitherapy during pregnancy has decreased the rate of mother-to-child transmission of human immunodeficiency virus (HIV) [1]. However, the number of HIV-exposed-but-uninfected (HEU) infants is increasing. Cohort studies in Africa [2–6] and India [7] report higher morbidity and mortality in HEU children than children born to HIV-uninfected mothers, specifically involving lower respiratory tract infections [3] and linked to maternal immune status [2]. Kuhn et al [8] report that infants born to mothers with <350 CD4 cells/mm^3 were 2.9 times more likely to die and 2.3 times more likely to be hospitalized than infants born to mothers with ≥350 CD4 cells/mm^3. Other similar studies confirm these findings [9]. Although there are no similar

Received 28 April 2014; accepted 11 July 2014; electronically published 22 July 2014.

[a]S. B. and J. W. contributed equally to this work.

[b]See France REcherche Nord&Sud Sida-HIV Hepatites Study Group members listed in the Appendix.

Correspondence: Clement Taron-Brocard, MSc, INSERM U1018 / Equipe 4, AP-HP Hôpital Bicêtre, 82 rue du Général Leclerc, 94276 Le Kremlin-Bicêtre Cedex (c.taron.brocard@gmail.com).

Clinical Infectious Diseases® 2014;59(9):1332–45

DOI: 10.1093/cid/ciu586

observations from large cohorts in industrialized countries, a Belgian study showed that streptococcus B infection was 19 times more frequent among HEU infants than other infants [10]. There are several possible reasons for these findings, including a social context of poverty and limited access to care, imbalanced maternal microbial ecology, or immunodeficiency in HEU infants. Several quantitative and qualitative immunological abnormalities have indeed been observed in these children [11], including altered dendritic cell phenotype [12, 13], CD4/8 lymphopenia [14–17], reduction of naive or memory T cells [14, 18, 19], reduced size of the thymus [20], cytokine production [14, 21], increased apoptosis of T cells [22], and altered cellular immune response to bacille Calmette-Guérin [23]. Data relevant to B lymphocyte function and production of specific antibodies after vaccination of HEU children are contradictory. Humoral immunity is, in some cases, apparently impaired [24]; however, in a large South African study, titers of antibodies against pertussis and pneumococcus after immunization were higher than in controls [25]. The main consistent finding is of impaired humoral immunity that is passively transferred from the mother to the child by placental transfer of maternal immunoglobulin (Ig) G [25–30]. Except for this passively transmitted humoral immune deficiency, it is difficult to dissect the role of the maternal disease itself from the potentially or putatively deleterious effects of HIV antigens to which the uninfected fetus is exposed [31], possible coinfections [32], and antiretroviral therapy (ART) [11, 33–36].

We used the national French Perinatal Cohort (EPF) to study the relationships between maternal immunological status and serious infectious morbidity of HEU infants living in a high-income country.

METHODS

The French Perinatal Cohort: France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11-EPF

Since 1986, EPF has prospectively enrolled pregnant HIV-infected women delivering in 90 centers throughout France. The methodology has been described elsewhere [37]. Mothers are followed until delivery and children are followed from birth to 1, 3, 6, 12, and 18–24 months after birth, and then, if HIV-infected, every 6 months. Clinicians are encouraged to follow current French national guidelines [38], without any specific recommendations from EPF, and there is no childhood immunization specifically given due to HIV exposure. The EPF is funded by the France REcherche Nord&Sud Sida-HIV Hepatites (ANRS) and has been approved by the Hôpital Cochin institutional review board and the French computer database watchdog commission.

Study Population

All neonates included in the EPF born to HIV-1–infected mothers between 1 January 2002 and 31 December 2010, at 28 weeks of gestational age or more, and not breastfed were eligible for this study if they were HIV-uninfected (N = 8216 infants). An infant was considered to be uninfected if serologically negative at ≥18 months and/or if 2 separate samples after the neonatal prophylactic treatment were HIV-1 polymerase chain reaction negative. Infants with undetermined HIV status, missing maternal CD4 cell count, or missing follow-up duration were excluded (Figure 1).

Primary Outcome

The primary outcome was the first serious infection during the first year of life. All clinical events and hospitalizations were recorded at each routine visit to the pediatric center, using standardized questionnaires that included items for infections, organ systems involved, and infectious agents responsible.

An infection was defined as "serious" if it was the main reason for hospitalization or death. Infections, as recorded prospectively by clinicians who reported them in standardized questionnaires, were retrospectively classified by both epidemiologists and pediatricians (blind to maternal and neonatal characteristics) into the following 3 categories: bacterial, viral, and fungal/parasitic. Infection categories were considered as proven if the causative agent was identified (from blood or local samples) or probable in cases of expert judgment alone. All infections with no reported causative agent and no unambiguous consensual identification were classified as "undetermined" (see Supplementary Table 1). Prenatal infections were not studied. Reasons for loss to follow-up, especially death, are reported in the EPF questionnaire when known by clinicians at participating centers.

Primary Exposure

The main exposure variable was the maternal CD4 cell count closest to (before or no later than 1 week after) delivery categorized into the following 3 classes: <350, 350–499, ≥500 cell/mm^3.

Statistical Analysis

Fisher exact or χ^2 tests were used to compare distributions of categorical variables. Student *t* test or Wilcoxon rank test was used to compare means of continuous variables.

The Kaplan–Meier survival method and proportional hazards survival Cox models were used to study the association between maternal CD4 cell count and the first occurrence of serious infection before age 1 year (event). Follow-up was censored at 12 months or the last available data before age 1 year. To study associations with each type of serious infection (bacterial, viral, fungal/parasitic, undetermined), follow-up was also censored at the first occurrence of any other type, considered as competing events. Adjusted hazard ratios (aHRs) measuring associations between maternal CD4 count and serious bacterial and viral infections were estimated in separate multivariate

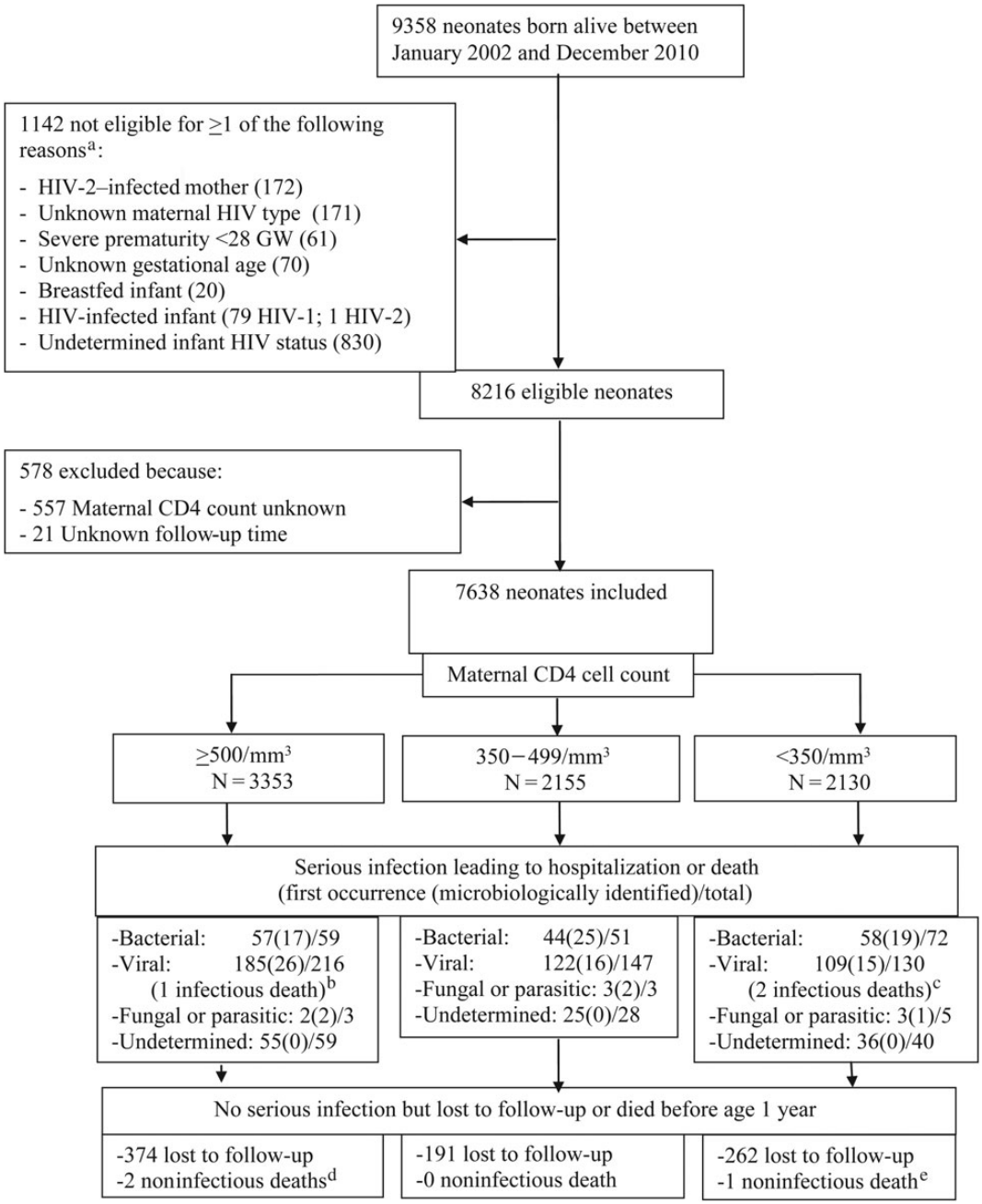

Figure 1. Flow chart identifying infants born to mothers infected with human immunodeficiency virus between 2002 and 2010 in the France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11. [a]Total may exceed the number not included because there was more than 1 reason for nonparticipation for several neonates. [b]One infant died at 9 months (severe diarrhea with dehydration). [c]Two infants died, 1 at 8 months (respiratory failure subsequent to viral infection and suffering from infantile spinal muscular amyotrophy) and 1 at 1 year (viral pericarditis). [d]One death of unknown cause at 5 months, 1 death from arterial pulmonary hypertension at 9 months. [e]One death due to cardiac failure at 6 months. Abbreviations: GW, gestational weeks; HIV, human immunodeficiency virus.

Cox models. The number of fungal/parasitic infections was too small to fit a specific model.

Multivariate models were adjusted for known risk factors of infections recorded in the EPF cohort, for type of ART (potentially linked to infant hematological parameters), and for other noncollinear variables found to be associated with $P < .2$ in bivariate analysis. We also adjusted for parity in order to account for correlations between infants born to the

Table 1. Characteristics of Human Immunodeficiency Virus (HIV)–Uninfected Neonates Born to HIV-1–Infected Mothers, According to Maternal CD4 Cell Count

Characteristic	Maternal CD4 Cell Count (cells/mm^3) ≥500 (N = 3353) % (n)	350–499 (N = 2155) % (n)	<350 (N = 2130) % (n)	*P* Value[a]
Maternal geographical origin				<.01
Other	35.8 (1181)	26.8 (569)	25.1 (533)	
Sub-Saharan Africa	64.2 (2121)	73.2 (1553)	74.9 (1587)	
Missing	51	33	10	
Maternal drug use during pregnancy (except cannabis)				.02
No	99.7 (3306)	99.5 (2123)	99.1 (2092)	
Yes	0.3 (11)	0.5 (10)	0.9 (19)	
Missing	36	22	19	
Maternal HIV stage				<.01
A or B	93.8 (1690)	92.5 (1042)	86.8 (902)	
C	6.2 (112)	7.5 (85)	13.2 (137)	
Missing	1551	1028	1091	
Maternal viral load during pregnancy				<.01
<400 cp/mL	90.0 (2952)	89.6 (1894)	81.8 (1707)	
400–9999 cp/mL	8.7 (286)	8.1 (171)	11.9 (249)	
≥10 000 cp/mL	1.3 (42)	2.3 (48)	6.3 (131)	
Missing	73	42	43	
First maternal antiretroviral during pregnancy				<.01
cART on conception	35.5 (1153)	41.0 (859)	40.9 (847)	
cART initiated during pregnancy	48.0 (1559)	46.7 (977)	51.4 (1065)	
NRTI mono-/bi-therapy	16.5 (536)	12.3 (257)	7.7 (161)	
Missing	105	62	57	
Last maternal ART during pregnancy				<.01
cART	84.8 (2810)	89.4 (1906)	94.3 (1982)	
NRTI mono/bi-therapy	15.2 (502)	10.6 (227)	5.7 (120)	
Missing	41	22	28	
Mode of delivery				<.01
Vaginal	46.3 (1437)	39.5 (785)	34.9 (690)	
Emergency cesarean section	19.8 (614)	22.6 (449)	25.0 (496)	
Planned cesarean section	33.9 (1051)	37.9 (752)	40.1 (793)	
Missing	251	169	151	
Premature delivery (<37 gestational weeks)				.24
No	86.3 (2895)	86.5 (1863)	84.9 (1808)	
Yes	13.7 (458)	13.5 (292)	15.1 (322)	
Post-natal antiretroviral prophylaxis drug type				<.01
No treatment	0.6 (15)	0.1 (2)	0.3 (5)	
Zidovudine	92.0 (2566)	92.5 (1659)	88.0 (1581)	
Zidovudine + Lamivudine	4.3 (121)	3.9 (71)	6.3 (114)	
Combination ART	2.3 (65)	2.7 (48)	4.0 (72)	
Other	0.8 (23)	0.8 (14)	1.4 (25)	
Missing	563	361	333	
Neonatal anemia				.25
>10 g/dL	98.8 (3048)	98.8 (1974)	98.3 (1929)	
≤10 g/dL	1.2 (38)	1.2 (24)	1.7 (34)	
Missing	267	157	167	

Table 1 continued.

Characteristic	Maternal CD4 Cell Count (cells/mm^3) ≥500 (N = 3353) % (n)	350–499 (N = 2155) % (n)	<350 (N = 2130) % (n)	*P* Value[a]
Neonatal neutropenia				.53
>1000/mm^3	98.2 (2919)	98.0 (1876)	97.8 (1827)	
≤1000/mm^3	1.8 (53)	2.0 (38)	2.2 (42)	
Missing	381	241	261	
Neonatal lymphopenia				
>2000/mm^3	92.6 (2276)	91.5 (1450)	92.3 (1439)	.47
≤2000/mm^3	7.4 (182)	8.5 (134)	7.7 (120)	
Missing	895	571	571	
Neonatal CD4 cell count				.24
Normal (≥35%)	98.6 (1651)	98.9 (1029)	98.0 (1005)	
Low (<35%)	1.4 (24)	1.1 (11)	2.0 (20)	
Missing	1678	1115	1105	
CD4 cell count at age 6 mo				.27
Normal (≥35%)	96.1 (1466)	95.0 (940)	94.9 (895)	
Low (<35%)	3.9 (59)	5.0 (49)	5.1 (48)	
Missing	1828	1166	1187	
Follow-up duration				.39
Lost to follow-up before 1 mo	0.1 (2)	0.0 (0)	0.1 (2)	
Still followed after 1 mo	99.9 (3351)	100.0 (2155)	99.9 (2128)	
Median (interquartile range)	365 (365; 365)	365 (365; 365)	365 (365; 365)	

Part of the France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11; 2002–2010.

Abbreviations: ART, antiretroviral therapy; cART, combination antiretroviral therapy; cp, copies; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor.

[a] Statistical test used: χ^2 test.

same mother. In the main analysis, we did not adjust for neonatal neutropenia or lymphopenia, including neonatal CD4, as these are potentially intermediate factors on the pathway between maternal immunity and infection risk. Sensitivity analyses were performed to check the robustness of results of the main analysis (see "Results" section).

SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC) was used for analyses; Proc FREQ was used for χ^2 and Fisher tests; Proc LIFETEST was used for Kaplan–Meier survival curves; and Proc PHREG was used for Cox proportional hazard ratios models. The cutoff for statistical significance was $P < .05$.

RESULTS

Population

Between January 2002 and December 2010, 7638 infants born to 5871 HIV-1–infected mothers were included in the analysis. Most (88.1%; n = 6729) were followed up for at least 365 days. Fourteen percent (n = 1072) of neonates were premature (<37 gestational weeks [GW]), including 154 who were severely premature (between 28 and 32 GW); maternal CD4 count was not associated with prematurity. Maternal CD4 count was ≥500/mm^3 for 43.9% (n = 3353) of these neonates, between 350 and 499/mm^3 for 28.2% (n = 2155), and <350/mm^3 for 27.9% (n = 2130); the median infant follow-up durations were similar in these 3 subgroups (Table 1). Low maternal CD4 count was significantly more frequent among women originating from sub-Saharan Africa, those who were active drug users, and those who delivered with higher maternal viral load or by caesarean section than among other women. CD4 count was also significantly lower among women receiving combination ART (cART) than those receiving mono or dual nucleoside reverse transcriptase inhibitors (NRTIs).

Frequency and Description of Serious Infection in Infants

Of the 7638 HEU infants, 699 experienced at least 1 serious infection (as the main reason for hospitalization or death) during their first year of life; there were 813 serious infections (1 to 5 per patient, mean 1.2). Of the 699 first serious infections, 59.5% were classified as viral (54 proven, 362 probable), 22.8% as

bacterial (60 proven, 99 probable), 1.1% as fungal or parasitic (5 proven, 3 probable), and 16.6% (n = 116) as undetermined (causative agent unknown or missing data, insufficient clinical data, or no consensual interpretation of the data available). The systems involved and infectious agents isolated are described in Supplementary Table 1. Twenty-nine percent (46/159) were lower respiratory tract infections (LRTI) (Table 2), with 24.5% (n = 39) being pneumonia. One opportunistic infection, that is, pneumocystis (confirmed by bronchioloalveolary lavage as "few cysts in lavage fluid"), was recorded in a 3-month-old infant born preterm (32 GW). An encapsulated germ was formally identified for 56.7% (34/60) of these confirmed bacterial infections. There were 3 deaths associated with infection—severe diarrhea with major dehydration, viral pericarditis, and respiratory failure associated with viral pneumonitis in a child with infantile spinal muscular atrophy.

The Kaplan–Meier probability of developing a serious infection during the first year of life was 9.3% (95% confidence interval, 8.7%; 10.0%), corresponding to an incidence of 10.1 per 100 person-years and stable throughout the study. The Kaplan–Meier probability at 1 year of life was 5.7% (5.2%; 6.3%) for viral infection, 2.2% (1.9%; 2.6%) for bacterial infection, 0.1% (0.1; 0.2%) for fungal or parasitic infection, and 1.6% (1.3%; 1.9%) for undetermined infections.

Relationships Between Maternal CD4 Count and Serious Infection in Infants: Bivariate and Multivariate Analysis

Maternal CD4 count was not significantly associated with the overall incidence of serious infections (log-rank $P = .59$). However, there was a specific association between maternal CD4 count and serious, proven, or probable bacterial infection ($P = .04$; Table 3) but not serious viral ($P = .76$), fungal or

Table 2. Description of the First Occurrence of Serious Infection, Defined as the Reason for Hospitalization or Cause of Death, in Human Immunodeficiency Virus (HIV)–Uninfected Infants Born to HIV-1–Infected Mothers

Characteristics	Bacterial 22.8% (n = 159)	Viral 59.5% (n = 416)	Fungal or Parasitic 1.1% (n = 8)	Undetermined 16.6% (n = 116)	*P* Value[a]
Organ					<.01
Renal and urinary system	44.0 (70)	0.0 (0)	0.0 (0)	2.6 (3)	
Bronchopulmonary	29.0 (46)	54.8 (228)	12.5 (1)	7.7 (9)	
Maternofetal infection	6.9 (11)	0.5 (2)	0.0 (0)	50.9 (59)	
Skin and mucous membranes	6.3 (10)	1.0 (4)	37.5 (3)	0.0 (0)	
Septicemia or septicemia-like symptoms	5.0 (8)	0.0 (0)	37.5 (3)	2.6 (3)	
Central nervous system	3.8 (6)	2.4 (10)	12.5 (1)	3.4 (4)	
Ear, nose, and throat	3.1 (5)	5.7 (24)	0.0 (0)	6.0 (7)	
Gastrointestinal	1.3 (2)	29.6 (123)	0.0 (0)	2.6 (3)	
Isolated fever	0.0 (0)	5.5 (23)	0.0 (0)	23.3 (27)	
Miscellaneous	0.6 (1)*	0.5 (2)†	0.0 (0)	0.9 (1)‡	
Age at onset					<.01
0–7 d	5.7 (9)	1.7 (7)	12.5 (1)	48.3 (56)	
8–28 d	13.2 (21)	10.1 (42)	37.5 (3)	10.3 (12)	
29–180 d	64.8 (103)	66.1 (275)	25.0 (2)	36.2 (42)	
181–365 d	16.3 (26)	22.1 (92)	25.0 (2)	5.2 (6)	
Median (interquartile range)	79 (41; 147)	96 (45; 169)	48 (14; 136)	11 (1; 68)	
Premature delivery (<37 gestational weeks)					.19
No	81.8 (130)	78.8 (328)	87.5 (7)	71.6 (83)	
Yes	18.2 (29)	21.2 (88)	12.5 (1)	28.4 (33)	
Maternal CD4 cell count during pregnancy					.11
≥500/mm^3	35.8 (57)	44.5 (185)	25.0 (2)	47.4 (55)	
350–499/mm^3	27.7 (44)	29.3 (122)	37.5 (3)	21.6 (25)	
<350/mm^3	36.5 (58)	26.2 (109)	37.5 (3)	31.0 (36)	
Maternal viral load during pregnancy					.32
<400 cp/mL	91.0 (142)	88.8 (365)	87.5 (7)	86.2 (100)	
400–9999 cp/mL	6.4 (10)	7.1 (29)	12.5 (1)	6.0 (7)	
≥10 000 cp/mL	2.6 (4)	4.1 (17)	0 (0)	7.8 (9)	
Missing	3	5	0	0	

Part of the France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11; 2002–2010. Serious infections included *, 1 arthritis; †, pericarditis; ‡, 1 bone pain.

[a] Statistical test used: Fisher test.

Table 3. Crude Associations Between Maternal CD4 Cell Count and Serious Infection, in Human Immunodeficiency Virus (HIV)–Uninfected Infants Born to HIV-1–infected Mothers, According to Type of Infection

	Maternal CD4 Cell Count								
	<350/mm^3 N = 3353			350–499/mm^3 N = 2155			≥500/mm^3 N = 2130		
	n	cHR	(95% CI)	n	cHR	(95% CI)	n		*P* Value[a]
All infections	206	1.1	(.9–1.3)	194	1.0	(.8–1.2)	299	Ref	.60
Bacterial infections									
All	58	1.6	(1.1–2.3)	44	1.2	(.8–1.8)	57	Ref	.04
Among infants born to sub-Saharan mothers	51	1.7	(1.1–2.5)	33	1.1	(.7–1.7)	41	Ref	.04
According to clinical type									
Bacterial pneumonia	18	2.0	(1.0–4.1)	7	0.8	(.3–1.9)	14	Ref	.04
Pyelonephritis	24	1.3	(.8–2.2)	17	0.9	(.5–1.7)	29	Ref	.46
According to age at occurrence									.21[b]
0–27 d	5	0.8	(.3–2.3)	15	2.3	(1.0–5.2)	10	Ref	.04
28–89 d	20	1.5	(.8–2.8)	18	1.3	(.7–2.5)	21	Ref	.41
90–365 d	33	2.0	(1.2–3.4)	11	0.7	(.3–1.3)	26	Ref	<.01
According to confirmed microbiological type									
Encapsulated bacteria[c]	12	2.7	(1.1–6.9)	15	3.3	(1.4–8.2)	7	Ref	.03
Nonencapsulated bacteria[d]	7	1.1	(.4–2.9)	11	1.7	(.7–4.0)	10	Ref	.43
Fungal or parasitic									
All	3	2.4	(.4–14.1)	3	2.3	(.4–13.9)	2	Ref	.58
Among infants born to sub-Saharan mothers	1	1.3	(.1–20.8)	3	4.1	(.4–38.5)	1	Ref	.38
Viral infections									
All	109	0.9	(.7–1.2)	122	1.0	(.8–1.3)	185	Ref	.76
Among infants born to sub-Saharan mothers	84	0.9	(.7–1.1)	102	1.1	(.8–1.4)	129	Ref	.33
Respiratory (bronchiolitis, rhinitis)	64	1.1	(.8–1.5)	68	1.2	(.9–1.6)	90	Ref	.58
Gastroenteritis	27	0.8	(.5–1.2)	39	1.1	(.7–1.6)	57	Ref	.35
Undetermined									
All	36	1.0	(.7–1.6)	25	0.7	(.4–1.1)	55	Ref	.28
Among infants born to sub-Saharan mothers	29	1.1	(.7–1.8)	20	0.8	(.5–1.4)	35	Ref	.48
Maternofetal infection suspected or with unknown germ	20	1.1	(.6–1.9)	9	0.5	(.2–1.0)	30	Ref	.09

Part of the France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11; 2002–2010.

Abbreviations: cHR, crude hazard ratio; CI, confidence interval; Ref, reference.

[a] Statistical test used: bivariate proportional hazards survival Cox models.

[b] Interaction between maternal CD4 cell count and follow-up time was computed with the time being coded as the log of time centered about its mean.

[c] *Staphylococcus pneumoniae, Haemophilus, S. agalactiae,* and *B. pertussis*.

[d] *Escherichia coli, Staphylococcus, Clostridium, Klebsiella,* and *Salmonella*.

parasitic ($P = .58$), or undetermined ($P = .28$) infections, suggesting that the absence of microbiological identification was not likely to be a differential bias (Figure 2). The association between lower maternal CD4 count and higher risk of serious bacterial infection remained constant (but tended to increase) during the first year of life; the interaction between maternal CD4 count and follow-up time was not significant ($P = .21$; Table 3).

We studied the association between maternal CD4 cell count and bacterial infection of the infant by stratifying for site of infection and type of microorganism. Maternal CD4 count was associated with LRTI but not with urogenital bacterial infection ($P = .04$ and .46, respectively) and with infections due to encapsulated bacteria (*Haemophilus, Streptococcus*, and *Bordetella*; $P = .03$) but not with those due to gram-negative enterobacteria ($P = .43$).

Infants excluded because of missing maternal CD4 values tended to have profiles (for the main covariates) similar to those of infants with known maternal CD4, and their overall risk of serious infections was not different ($P = .59$, data not shown). We found no evidence of a specific association between serious bacterial or viral infections and the type of treatment

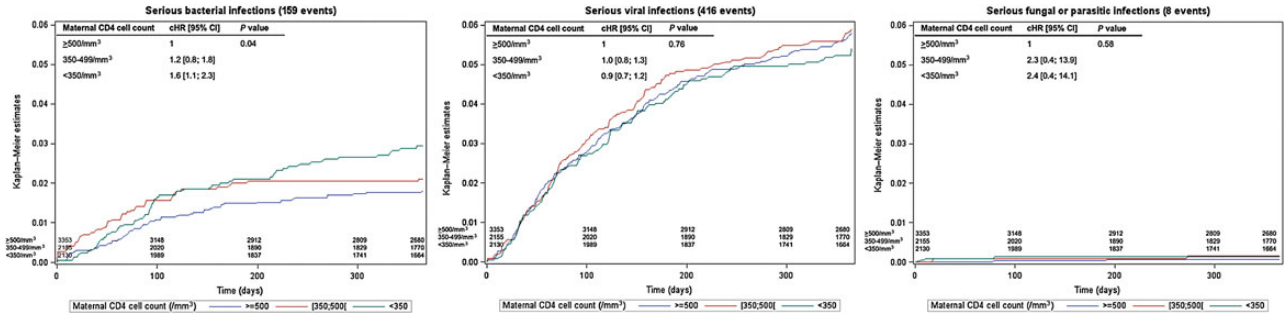

Figure 2. Kaplan–Meier probability estimates of serious infections in human immunodeficiency virus (HIV)–uninfected infants born to HIV-1–infected mothers, according to microbiological type of infection* and to maternal CD4 cell count (France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11 2002–2011). *The event was the first occurrence of a serious infection during the first year of life, the various types being considered as competing events. Association with each type of infection was studied separately, follow-up being censored at 12 months, at the time of loss to follow-up, or at the time of any other kind of first serious infection. Blood or local samples were used for microbiological identification of the causes of serious infections, according to clinical recommendations. No biological analyses were conducted specifically for this study. Abbreviations: cHR, crude hazard ratio; CI, confidence interval.

received by mothers—mono- and bi-therapies vs cART, nor zidovudine vs other NRTI-based combinations.

After adjustment in the multivariate Cox model (Tables 4 and 5), the maternal CD4 count remained associated with serious bacterial infections but not with viral infections. In particular, the risk of serious bacterial infection was significantly higher for infants of mothers with the lowest rather than the highest CD4 counts—aHR = 1.7 (1.2; 2.6) for CD4 <350/mm^3 and aHR = 1.2 (0.8; 1.9) for CD4 = 350–499/mm^3; $P = .03$. Also, bacterial infection remained associated with sub-Saharan maternal origin, vaginal delivery, prematurity, male gender, being small for gestational age, and neonatal anemia. Viral infection was independently associated with sub-Saharan maternal origin, multiparity, prematurity, fetal cardiac rhythm abnormalities, and male gender. More economical models gave similar results.

Maternal CD4 count was not associated with any of the following variables: neonatal anemia, neutropenia, lymphopenia, and low CD4 cell count at birth or at age 6 months, either before (Table 1) or after adjustment for maternal geographical origin. There was no interaction between maternal CD4 count and gestational age at delivery for the risk of bacterial infection (heterogeneity test $P = .50$, data not shown). The infant's CD4 cell count at birth was not associated with risk of serious infection (whether bacterial, viral, fungal or parasitic, undetermined, or any; data not shown).

Sensitivity Analysis

The relationship between maternal CD4 count and bacterial infection was not changed by restricting the analysis to term-born infants (overall $P = .02$) or excluding the 206 infants born to mothers with last maternal CD4 count measured more than 90 days before delivery ($P = .03$). The relationship between maternal CD4 count and serious bacterial and viral infections remained unchanged by restricting the analysis to the infants born to sub-Saharan mothers ($P = .04$ and .33, respectively).

In the main analysis, we dichotomized the 699 first serious infections into 4 types, considered as competing events for proportional hazards Cox modeling (159 bacterial, 416 viral, 8 fungal or parasitic, and 116 undetermined); subsequent serious infections were not included. However, 13 of the 540 infants who had a viral, fungal or parasitic, or undetermined first serious infection subsequently developed a serious bacterial infection. Inversely, a serious viral infection subsequently developed in 17 of the 283 infants who had other types of first serious infection. We performed a secondary survival analysis with the first occurrence of each type of infection as the events, ignoring previous history of other types of infection. The results were consistent; serious bacterial infections (aHR = 1.8 [1.2; 2.7] for CD4 < 350/mm^3 and aHR = 1.4 [0.9; 2.0] for CD4 = 350–499/mm^3; $P = .01$) but not viral infections (0.8 [0.6; 1.0] and 1.0 [0.8; 1.2]; $P = .18$) were associated with maternal CD4 values.

DISCUSSION

We report that the risk of serious bacterial infections among HEU infants during the first year of life is inversely associated with maternal CD4 values during pregnancy. This susceptibility to bacterial infection appears to involve mostly LRTI and infections with encapsulated pathogens, including *Haemophilus influenzae* and *Streptococcus pneumonia*. The risk is not limited to the neonatal period and seems to remain stable during the first year of life. In sharp contrast, there was no association between maternal CD4 count and the risk of viral infection. This is the first such study in an industrialized country. The findings suggest that, even in a context of easy and free access to

Table 4. Multivariate Analysis of the Relationships Between Maternal CD4 Cell Count and Serious Bacterial or Viral Infections in Human Immunodeficiency Virus (HIV)–Uninfected Infants Born to HIV-1–Infected Mothers

		Serious Bacterial Infection				Serious Viral Infection			
		Bivariate (N = 7638)		Multivariate (N = 6206)		Bivariate (N = 7638)		Multivariate (N = 6206)	
	N	cHR (95% CI)	*P* Value[a]	adjHR (95% CI)	*P* Value[a]	cHR (95% CI)	*P* Value	adjHR (95% CI)	*P* Value[a]
Maternal CD4 cell count									
≥500/mm^3	3353	1	*.04*	1	*.03*	1	*.76**	1	*.20*
350–499/mm^3	2155	1.2 (.8–1.8)		1.2 (.8–1.9)		1.0 (.8–1.3)		0.9 (.7–1.2)	
<350/mm^3	2130	1.7 (1.1–2.3)		1.7 (1.2–2.6)		0.9 (.7–1.2)		0.8 (.6–1.0)	
Year of birth									
2002–2004	2485	1	.11	1	.35	1	.57	1	.82
2005–2007	2606	1.3 (1.0–2.3)		1.3 (.8–2.0)		1.1 (.9–1.4)		0.9 (.7–1.2)	
2008–2010	2547	1.0 (.9–2.1)		1.0 (.6–1.6)		1.1 (.9–1.4)		0.9 (.7–1.2)	
Sub-Saharan maternal origin									
No	2283	1	<.01	1	.05	1	<.01	1	.02
Yes	5261	1.5 (1.2–2.6)		1.5 (1.0–2.4)		1.4 (1.1–1.8)		1.4 (1.1–1.8)	
Maternal parity									
Nulliparous	2684	1	.51	1	.34	1	<.01	1	<.01
1	2244	1.3 (.9–1.9)		1.3 (.9–2.0)		1.3 (1.0–1.7)		1.3 (1.0–1.7)	
2	1437	1.0 (.6–1.7)		0.9 (.5–1.5)		1.5 (1.2–2.0)		1.6 (1.2–2.2)	
3	1243	1.1 (.7–1.7)		1.0 (.6–1.6)		1.6 (1.2–2.2)		1.7 (1.2–2.3)	
Last antiretrovirals during pregnancy									
Mono-/bi-therapy	849	1	.01	1	.09	1	.37	1	.70
cART	6698	2.5 (1.2–5.1)		2.0 (.9–4.6)		1.2 (.8–1.6)		1.1 (.7–1.6)	
Type of nucleoside analogue									
Other	1868	1	.44	1	.62	1	.62	1	.30
Zidovudine	5679	1.1 (.8–1.7)		1.1 (.7–1.7)		1.1 (.8–1.3)		1.1 (.9–1.5)	
Maternal viral load near delivery									
<400 cp/mL	6553	1	.40	1	.89	1	.08	1	.12
400–9999 cp/mL	706	0.6 (.3–1.2)		1.0 (.5–2.0)		0.7 (.5–1.1)		0.7 (.5–1.1)	
≥10 000 cp/mL	221	0.9 (.3–2.3)		0.8 (.2–2.4)		1.4 (.9–2.3)		1.4 (.8–2.5)	
Mode of delivery									
Vaginal	2912	1	.06	1	.01	1	.15	1	.46
Emergency cesarean section	1559	0.6 (.4–1.0)		0.5 (.3–.8)		1.3 (1.0–1.7)		1.1 (.9–1.5)	
Planned cesarean section	2596	0.7 (.5–1.0)		0.7 (.5–1.0)		1.1 (.9–1.4)		1.2 (.9–1.5)	
Prematurity									
No (≥37 GW)	6566	1	.10	1	.03	1	<.01	1	<.01
Yes (<37 GW)	1072	1.4 (.9–2.1)		1.6 (1.0–2.6)		1.7 (1.3–2.2)		1.9 (1.4–2.4)	
Gender of neonate									
Male	3852	1	<.01	1	<.01	1	.03	1	.04
Female	3711	0.6 (.4–.8)		0.5 (.3–.7)		0.8 (.7–1.0)		0.8 (.7–1.0)	
Abnormal fetal cardiac rhythm									
No	7096	1	.15	1	.17	1	<.01	1	<.01
Yes	390	1.5 (.9–2.8)		1.4 (.8–2.7)		1.7 (1.2–2.4)		1.7 (1.1–2.4)	
Neonate small for gestational age									
No (> to 2 SD)	7196	1	<.01	1	<.01	1	.15	1	.11
Yes (≤ to 2 SD)	359	2.6 (1.6–4.3)		3.0 (1.8–5.1)		1.3 (.9–2.0)		1.4 (.9–2.2)	
Neonatal anemia									
>10 g/dL	6951	1	.03	1	.03	1	.66	1	.12
≤10 g/dL	96	2.6 (1.1–6.4)		2.7 (1.1–6.8)		0.8 (.3–2.1)		0.3 (.1–1.3)	

Part of the France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11; 2002–2010. Variables included in multivariate models.

Abbreviations: adjHR, adjusted hazard ratio; cART, combination antiretroviral therapy; cHR, crude hazard ratio; CI, confidence interval; cp, copies; GW, gestational weeks; SD, standard deviation.

[a] Statistical test used: proportional hazards survival Cox models.

Table 5. Bivariate Analysis of the Relationships Between Maternal CD4 Cell Count and Serious Bacterial or Viral Infections in Human Immunodeficiency Virus (HIV)–Uninfected Infants Born to HIV-1–Infected Mothers

		Serious Bacterial Infection Bivariate Analysis		Serious Viral Infection Bivariate Analysis	
	N	cHR (95% CI)	*P* Value[a]	cHR (95% CI)	*P* Value[a]
Maternal age*					
<25 y	711	1	.87	1	.78
25–29 y	1839	1.1 (.6–2.0)		1.0 (.7–1.5)	
30–34 y	2518	1.1 (.6–2.0)		0.9 (.7–1.3)	
≥35 y	2561	1.2 (.7–2.2)		0.9 (.6–1.3)	
Multiple pregnancy*					
No	7320	1	.52	1	.24
Twins or triplets	315	0.7 (.3–1.8)		1.3 (.8–2.0)	
ARV on conception*,†					
No	4464	1	.76	1	.78
Yes	3020	1.0 (.7–1.3)		1.0 (.8–1.2)	
First maternal antiretroviral during pregnancy					
NRTI mono-/bi-therapy	954	1	.04†	1	.55*
cART on conception	2859	2.1 (1.1; 4.2)		1.1 (.8; 1.6)	
cART initiated during pregnancy	3601	2.4 (1.2; 4.5)		1.2 (.9 1.6)	
HIV diagnosed before pregnancy*					
No	1705	1	.67	1	.26
Yes	5904	0.9 (.6–1.3)		1.1 (.9–1.5)	
Gestational age at booking*					
<14 GW	3057	1	.27	1	.24
14–27 GW	3023	0.8 (.5–1.1)		1.2 (1.0–1.5)	
≥28 GW	619	1.0 (.6–1.7)		1.0 (.7–1.5)	
Neonatal leucopenia‡,§					
No (>4000/mm$^{3)}$	5827	1	.27	1	<.01
Yes (≤4000/mm^3)	74	1.9 (.6–6.0)		2.5 (1.3–4.7)	
Neonatal neutropenia‡,§					
No (>1000/mm^3)	6622	1	.07	1	.32
Yes (≤1000/mm^3)	133	2.1 (.9–4.8)		1.4 (.7–2.6)	
Neonatal lymphopenia‡,§					
No (>2000/mm^3)	5165	1	.02	1	.41
Yes (≤2000/mm^3)	436	1.8 (1.1–3.1)		1.2 (.8–1.7)	
Neonatal thrombopenia*					
No (>100 G/L)	6916	1	.97	1	.28
Yes (≤100 G/L)	73	(Not available)		1.6 (.7–3.5)	
Neonatal CD4‡,§					
Normal (≥35%)	3685	1	.59	1	.56
Low (< 35%)	55	1.5 (.4–6.0)		0.7 (.2–2.6)	

Part of the France REcherche Nord&Sud Sida-HIV Hepatites CO1/CO11; 2002–2010.

Variables not included in multivariate models. Reason for exclusion from the multivariable model included the following: *, not associated; †, collinear with other variables included; ‡, on the causal pathway; or §, with too many missing values. Birth weight Z-scores, adjusted for gestational age at delivery and sex, were established using French standards, calculated from French Association of Users of Computerized Medical Records in Paediatrics, Obstetrics and Gynaecology Sentinel Network, Association des Utilisateurs de Dossiers Informatisés en Pédiatrie Obstétrique et Gynécologie. AUDIPOG (available at: http://www.audipog.net/). An infant was considered to be small for gestational age if the birthweight Z-score was more than 2 standard deviations below the mean, consistent with international recommendations.

Abbreviations: ARV, antiretroviral drugs; cART, combination antiretroviral therapy; cHR, crude hazard ratio; CI, confidence interval; GW, gestational weeks; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor.

[a] Statistical test used: proportional hazards survival Cox models.

healthcare, the relationship between maternal immunity and early pediatric infectious morbidity reported in low- or middle-income countries is a generalized phenomenon [2, 8, 9].

Our study has several strengths. We considered only infections that led to hospitalization or death, which minimized reporting heterogeneity and limited diagnosis errors and undetermined types. The association with degree of maternal immune suppression was strong for undoubtedly bacterial pneumonia and for infections involving encapsulated bacteria; however, it was not significant for pyelonephritis likely to be associated with gram-negative enterobacteria. Despite the larger number of viral infections compared with bacterial infections, thus with greater statistical power, no association could be detected between maternal CD4 count and gastroenteritis or bronchiolitis, undoubtedly of viral origin, or viral infections in general. The results were robust; they were largely unaffected in sensitivity survival analysis based on the first occurrence of each type of infection rather than the first occurrence of any serious infection primarily dichotomized into 4 types as competing events.

The association between low maternal CD4 count and neonatal bacterial infection was both specific and independent of potential confounding factors after adjustment in multivariate analysis. The sub-Saharan maternal origin, preterm delivery, being small for gestational age, vaginal delivery, male gender, and neonatal anemia remained significantly associated. Maternal origin, preterm delivery, and male gender were associated with both serious bacterial and serious viral infections, whereas high parity was associated only with serious viral infection, possibly due to the increased risk of viral contamination from other infants (brothers and sisters) in the home [9]. The association between bacterial infection and vaginal delivery may reflect obstetric factors that were not controlled for in this analysis. Healthcare is free for all pregnant women and infants (up to age 2 years) in France. We showed previously that more African immigrants than French-born women underwent HIV screening late in their pregnancies, but that access to mother-to-child transmission of HIV prevention, once the infection was diagnosed, is similar for the 2 groups [39]. These observations suggest that the association with serious bacterial infections is not solely due to differential access to care according to maternal geographical origin.

Our analysis provides strong evidence for a relationship between low maternal CD4 count and serious bacterial infections of the lung. Infections with encapsulated bacteria are clearly suggestive of weakened humoral immunity. The absence of association with viral infections suggests that cellular immunity is not clinically affected. Because the relationship remained significant in sensitivity analyses after adjustment for infant CD4 values, the association cannot be explained by a direct effect on newborn CD4 cell counts. The apparent humoral immune defect could be due to an altered mother-to-child IgG transfer through the placenta, as described previously [25], or to intrinsic humoral deficiency. In a well-designed study, the production of specific antibodies after immunization was normal or even higher in HEU infants than in control infants [25]. Although most events occurred during the first 3 months of life, the association with maternal CD4 count continued beyond the neonatal period and throughout the first year of life. The duration of protection by maternal antibodies has not been clearly established. The half-life of IgG is around 20 days, and the protective effect of such antibodies in infants is likely to last for several half-lives. Infectious morbidity in infants born to hypo- or agammaglobulinemic mothers, and before the child can develop effective humoral immunity, is well known but has never been rigorously described before the use of intravenous immunoglobulins. By contrast, the Bruton disease model is informative and well described [40]. Boys with this congenital X-linked disease are unable to produce antibodies and are agammaglobulinemic; the first infection rarely occurs before age 6 months and most patients present their first infection at age 6–12 months, clearly showing that maternal antibodies are protective until approximately this age.

The infectious-related mortality rate in France is low but may well be higher in low-resource settings and countries.

Prolonged antibacterial prophylaxis during infancy and/or maternal immunization against pneumococcus and haemophilus infection could be proposed during pregnancy. Early immunization for such infants may also be beneficial.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank other members of the coordinating center of France REcherche Nord&Sud Sida-HIV Hepatites - Enquete Perinatale Francaise (ANRS-EPF), Institut national de la santé et de la recherche médicale U1018-Centre d'épidémiologie et de santé publique, Le Kremlin-Bicetre, including Souad Belaggoun, Leïla Boufassa, Céline Ferey, Paulette Huynh, Julie Lamarque, Corinne Laurent, Jacques Ngondi, Marlène Pérès, Anaïs Perilhou, Marine Pytkowski, Elisa Ramos, and Thierry Wack. We thank all families who agreed to participate in this study. We also thank past contributors to ANRS-EPF: Assistance Publique Hôpitaux de Paris (APHP) Hôpital Louis Mourier, Colombes, France (Evelyne Hery); APHP Hôpital Beaujon, Clichy, France (Dominique Luton); Centre hospitalier des Feugrais, Elbeuf, France (Kamel Lahsinat); Hôpital d'Aix en Provence, Aix en Provence, France (Brahim Tadrist); APHP Hôpital Ambroise Paré, Boulogne Billancourt, France (Delphine Zenaty); CH Jean Rostand, Sèvres, France (Liliane Segard); Centre Hospitalier de Neuilly, Neuilly sur Seine, France (Bertrand Berterottière); Centre Hospitalier Intercommunal, Montreuil, France (Déborah Fried, Catherine Riehl); APHP Hôpital Saint-Antoine, Paris, France (Jacqueline Rodriguez, Eida Bui-Pha, Marie-Caroline

Meyohas); APHP Hôpital Bichat, Paris, France (Huguette Bastian); Centre Hospitalier Intercommunal, Créteil, France (Christine Pichon, Sophie Lemerle); Centre Hospitalier Pellegrin, Bordeaux, France (Véronique Schaeffer, Jean-Marie Ragnaud, Danièle Douard); Hôpital de Haute Pierre, Strasbourg, France (Jean-Jacques Favreau); Centre Hospitalier Général, Longjumeau, France (Aly Abbara); Centre hospitalier intercommunal, Villeneuve St Georges, France (François Guillot); CHRU, Dourdan, France (Valérie Ercoli); Hopital Foch, Suresnes, France (Anne-Marie Raison Boulley); Hôpital Esquirol, Saint-Maurice, France (Michel Robin); Institut Mutualiste Montsouris, Paris, France (Carole Carlus Moncomble); APHP Hôpital Necker, Paris, France (Sophie Parat, Véronique Cayol, Marie-Laure Chaix); CH, Gonesse, France (Jean-Bruno Lobut, Bénédicte Paindaveine, Didier Troisvallets); Centre Hospitalier Sud Francilien, Evry Corbeil, France (Adrien May, Isabelle Turpault); Clinique du Blanc Mesnil, Blanc Mesnil, France (Pierre Balde); APHP Groupe Hospitalier Pitié Salpêtrière, Paris, France (Inès de Montgolfier, Michèle Pauchard); APHP Hôpital Béclère, Clamart, France (Olivier Picone, Laurence Foix l'Hélias); Hôpital des Métallurgistes, Paris, France (Michel Rami); APHP Hôpital Avicennes, Bobigny, France (Michelle Bentata); Hôpital Max Fourestier, Nanterre, France (Benoît De Sarcus); Centre Hospitalier Général/, Evreux, France (Kadidia Toure); Centre Hospitalier Victor Jousselin, Dreux, France (Marie-France Denavit); APHP Hôpital Boucicaut, Paris, France (Marie-Christine Lafay-Pillet); Centre Hospitalier François Quesnay, Mantes La Jolie, France (Audoun Delanete); Hôpital Saint Michel, Paris, France (Christian Aufrant); APHP Hôpital Trousseau, Paris, France (Aude Wallet); Hôpital Charles Nicolle, Rouen, France (Véronique Brossard); APHP Hôpital Robert Debré, Paris, France (Aude Recoules, Annick Ottenwalter); APHP Hôpital de Bicêtre, Le Kremlin-Bicêtre, France (Marie-Thérèse Rannou); APHP Hôpital Hôtel Dieu, Paris, France (Jean-Paul Viard); Centre hospitalo universitaire de Nantes, Nantes, France (Françoise Mechinaud); Hôpital Jean Rostand, Ivry, France (Thierry Jault); Hôpital Hotel Dieu, Lyon, France (Marie-Christine Roussouly, Jérôme Massardier); Centre Hospitalier Général, Bastia, France (Olivier Pincemaille); Centre Hospitalier Régional, Orléans, France (Evelyne Werner); Hôpital Saint Claude, Basse Terre, France (Gérard Sibille); CHU -Maison de la Femme et de l'Enfant, Fort de France, France (William Cécile); Centre Hospitalier Louis Domergues, La Trinité, France (Nicole Hugon, Elisabeth Dussaix).

Financial support. This study was promoted and mainly sponsored by the France REcherche Nord&Sud Sida-HIV Hépatites. Funding was also received from the Agence Nationale de Sécurité du Médicament et des Produits de Santé.

Potential conflicts of interest. J. W. reports grants from Agence nationale de recherche sur le sida et les hépatites virales, agence autonome de l'INSERM and Agence Nationale de Sécurité du médicament et des produits de santé during the study; grants from Société Française de Lutte contre le cancer, ViiV Healthcare, Abbott, and Parexel; and nonfinancial support from Abbvie outside the submitted work. V. G. reports support from Institut Phisquare and Sanofi Pasteur MSD and grants from the French Health Ministry outside the submitted work. L. M. reports personal fees from Bristol Myers Squibb and Gilead outside the submitted work. The other authors report no conflict of interest. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med **1994**; 331:1173–80.
2. Marinda E, Humphrey JH, Iliff PJ, et al. Child mortality according to maternal and infant HIV status in Zimbabwe. Pediatr Infect Dis J **2007**; 26:519–26.
3. Koyanagi A, Humphrey JH, Ntozini R, et al. Morbidity among human immunodeficiency virus-exposed but uninfected, human immunodeficiency virus-infected, and human immunodeficiency virus-unexposed infants in Zimbabwe before availability of highly active antiretroviral therapy. Pediatr Infect Dis J **2011**; 30:45–51.
4. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. Mortality in HIV-infected and uninfected children of HIV-infected and uninfected mothers in rural Uganda. J Acquir Immune Defic Syndr **2006**; 41:504–8.
5. Landes M, van Lettow M, Chan AK, Mayuni I, Schouten EJ, Bedell RA. Mortality and health outcomes of HIV-exposed and unexposed children in a PMTCT cohort in Malawi. PloS One **2012**; 7:e47337.
6. Slogrove A, Reikie B, Naidoo S, et al. HIV-exposed uninfected infants are at increased risk for severe infections in the first year of life. J Trop Pediatr **2012**; 58:505–8.
7. Singh HK, Gupte N, Kinikar A, et al. High rates of all-cause and gastroenteritis-related hospitalization morbidity and mortality among HIV-exposed Indian infants. BMC Infect Dis **2011**; 11:193.
8. Kuhn L, Kasonde P, Sinkala M, et al. Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants? Clin Infect Dis **2005**; 41:1654–61.
9. Mussi-Pinhata MM, Freimanis L, Yamamoto AY, et al. Infectious disease morbidity among young HIV-1-exposed but uninfected infants in Latin American and Caribbean countries: the National Institute of Child Health and Human Development International Site Development Initiative Perinatal Study. Pediatrics **2007**; 119:e694–704.
10. Epalza C, Goetghebuer T, Hainaut M, et al. High incidence of invasive group B streptococcal infections in HIV-exposed uninfected infants. Pediatrics **2010**; 126:e631–8.
11. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL. HIV-exposed uninfected children: a growing population with a vulnerable immune system? Clin Exp Immunol **2014**; 176:11–22.
12. Chougnet C, Kovacs A, Baker R, et al. Influence of human immunodeficiency virus-infected maternal environment on development of infant interleukin-12 production. J Infect Dis **2000**; 181:1590–7.
13. Velilla PA, Montoya CJ, Hoyos A, Moreno ME, Chougnet C, Rugeles MT. Effect of intrauterine HIV-1 exposure on the frequency and function of uninfected newborns' dendritic cells. Clin Immunol Orlando Fla **2008**; 126:243–50.
14. Clerici M, Saresella M, Colombo F, et al. T-lymphocyte maturation abnormalities in uninfected newborns and children with vertical exposure to HIV. Blood **2000**; 96:3866–71.
15. Miles DJC, Gadama L, Gumbi A, Nyalo F, Makanani B, Heyderman RS. Human immunodeficiency virus (HIV) infection during pregnancy induces CD4 T-cell differentiation and modulates responses to bacille Calmette-Guérin (BCG) vaccine in HIV-uninfected infants. Immunology **2010**; 129:446–54.
16. Slogrove AL, Cotton MF, Esser MM. Severe infections in HIV-exposed uninfected infants: clinical evidence of immunodeficiency. J Trop Pediatr **2010**; 56:75–81.
17. Borges-Almeida E, Milanez HMBPM, Vilela MMS, et al. The impact of maternal HIV infection on cord blood lymphocyte subsets and cytokine profile in exposed non-infected newborns. BMC Infect Dis **2011**; 11:38.
18. Romano MF, Buffolano W, Bisogni R, et al. Increased CD154 expression in uninfected infants born to HIV-positive mothers exposed to antiretroviral prophylaxis. Viral Immunol **2006**; 19:363–72.
19. Vigano A, Saresella M, Schenal M, et al. Immune activation and normal levels of endogenous antivirals are seen in healthy adolescents born of HIV-infected mothers. AIDS Lond Engl **2007**; 21:245–8.
20. Kolte L, Rosenfeldt V, Vang L, et al. Reduced thymic size but no evidence of impaired thymic function in uninfected children born to human immunodeficiency virus-infected mothers. Pediatr Infect Dis J **2011**; 30:325–30.
21. Reikie BA, Adams RCM, Leligdowicz A, et al. Altered innate immune development in HIV-exposed uninfected infants. J Acquir Immune Defic Syndr **2014**; 66:245–55.
22. Economides A, Schmid I, Anisman-Posner DJ, Plaeger S, Bryson YJ, Uittenbogaart CH. Apoptosis in cord blood T lymphocytes from infants

of human immunodeficiency virus-infected mothers. Clin Diagn Lab Immunol **1998**; 5:230–4.
23. Mazzola TN, da Silva MTN, Abramczuk BM, et al. Impaired bacillus Calmette-Guérin cellular immune response in HIV-exposed, uninfected infants. AIDS Lond Engl **2011**; 25:2079–87.
24. Abramczuk BM, Mazzola TN, Moreno YMF, et al. Impaired humoral response to vaccines among HIV-exposed uninfected infants. Clin Vaccine Immunol **2011**; 18:1406–9.
25. Jones CE, Naidoo S, De Beer C, Esser M, Kampmann B, Hesseling AC. Maternal HIV infection and antibody responses against vaccine-preventable diseases in uninfected infants. J Am Med Assoc **2011**; 305:576–84.
26. De Moraes-Pinto MI, Verhoeff F, Chimsuku L, et al. Placental antibody transfer: influence of maternal HIV infection and placental malaria. Arch Dis Child Fetal Neonatal Ed **1998**; 79:F202–205.
27. Farquhar C, Nduati R, Haigwood N, et al. High maternal HIV-1 viral load during pregnancy is associated with reduced placental transfer of measles IgG antibody. J Acquir Immune Defic Syndr 1999 **2005**; 40:494–7.
28. Cumberland P, Shulman CE, Maple PAC, et al. Maternal HIV infection and placental malaria reduce transplacental antibody transfer and tetanus antibody levels in newborns in Kenya. J Infect Dis **2007**; 196:550–7.
29. Scott S, Moss WJ, Cousens S, et al. The influence of HIV-1 exposure and infection on levels of passively acquired antibodies to measles virus in Zambian infants. Clin Infect Dis **2007**; 45:1417–24.
30. Bunders M, Pembrey L, Kuijpers T, Newell M-L. Evidence of impact of maternal HIV infection on immunoglobulin levels in HIV-exposed uninfected children. AIDS Res Hum Retroviruses **2010**; 26:967–75.
31. Kuhn L, Coutsoudis A, Moodley D, et al. T-helper cell responses to HIV envelope peptides in cord blood: protection against intrapartum and breast-feeding transmission. AIDS Lond Engl **2001**; 15:1–9.
32. Slyker JA, Lohman-Payne BL, Rowland-Jones SL, et al. The detection of cytomegalovirus DNA in maternal plasma is associated with mortality in HIV-1-infected women and their infants. AIDS Lond Engl **2009**; 23:117–24.
33. Le Chenadec J, Mayaux M-J, Guihenneuc-Jouyaux C, Blanche S, Enquête Périnatale Française Study Group. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. AIDS Lond Engl **2003**; 17:2053–61.
34. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. J Infect Dis **2006**; 194:1089–97.
35. Bunders M, Thorne C, Newell ML, European Collaborative Study. Maternal and infant factors and lymphocyte, CD4 and CD8 cell counts in uninfected children of HIV-1-infected mothers. AIDS Lond Engl **2005**; 19:1071–9.
36. André-Schmutz I, Dal-Cortivo L, Six E, et al. Genotoxic signature in cord blood cells of newborns exposed in utero to a Zidovudine-based antiretroviral combination. J Infect Dis **2013**; 208:235–43.
37. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS Lond Engl **2008**; 22:289–99.
38. Morlat P, CNS, ANRS. Prise en charge médicale des personnes vivant avec le VIH [Internet], **2013**. Available at: http://www.sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf. Accessed 27 April 2014.
39. Jasseron C, Mandelbrot L, Tubiana R, et al. Prevention of mother-to-child HIV transmission: similar access for sub-Sahara African immigrants and for French women?. AIDS Lond Engl **2008**; 22:1503–11.
40. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) **2006**; 85:193–202.

APPENDIX

ANRS EPF-CO1/CO11 Study Group

Currently Active Contributors to ANRS-EPF

Assistance Publique - Hôpitaux de Paris (APHP) Hôpital Louis Mourier, Colombes, France (Laurent Mandelbrot, Catherine Crenn-Hebert, Corinne Floch-Tudal, Fabienne Mazy, Marine Joras, Françoise Meier, Emmanuel Mortier); APHP Hôpital Beaujon, Clichy, France (Pierre-François Ceccaldi, Maïa Banige, Agnès Villemant Uludag, Virginie Zarouk, Agnès Lefort); Hôpital Sainte Musse, Toulon, France (Gilles Hittinger, Jean-Marc Chamouilli, Christian Burle, Alain Lafeuillade); Centre Hospitalier (CH) Marechal Joffre, Perpignan, France (Marie Medus, Germaine Bachelard); Centre Hospitalo-Universitaire (CHU) Caremeau, Nîmes, France (Joëlle Dendale-Nguyen); CH les Oudairies, La Roche sur Yon, France (Thomas Guimard, Karine Guimard, Jean-Pierre Brossier, Philippe Perré, Jean-Luc Esnault, Olivier Bollengier Stragier, Sophie Leautez-Nainville); Centre Hospitalier William Morey, Châlon sur Saone, France (Sandrine-Anne Martha, Benoît Martha, Elise Maurel, Michel Françoise, Muriel Barat, Patricia Murger); Centre Hospitalier, Vernon, France (Mahfoud Rouha, Philippe Lumbroso, Alain Checoury); Centre Hospitalier Intercommunal de Cornouaille, Quimper, France (Pascale Perfezou, Gilles Blondin); Centre Hospitalier Universitaire, Brest, France (Séverine Ansart, Luc De Saint Martin, Philippe Le Moine); Centre Hospitalier, St Brieuc, France (Corinne Daniel, Christian Calvez, Emmanuelle Boutard); Centre Hospitalier Universitaire, Rennes, France (Cédric Arvieux, Estelle Bauville, Christelle Dupre); Centre Hospitalier Bretagne Atlantique, Vannes, France (Yves Poinsignon, Anne Grelier, Gaetane Mousset, Corinne Cudeville); Centre Hospitalier de Bretagne Sud, Lorient, France (Mathilde Niault, Isabelle Belzic, Philippe Moreau, Marie-Françoise Le Coz, Odile Luycx Vaillant); Centre Hospitalier de la région d'Annecy, Annecy, France (Virginie Vitrat, Didier Tardif, Jacques Gaillat, Anne Vanderbergh, Suzanne Braig); Centre Hospitalier Intercommunal, Montfermeil, France (Marion Dehlinger-Paul, Khaled Mohamed); Centre Hospitalier Intercommunal, Montreuil, France (Brigitte Heller-Roussin, Cécile Winter); APHP Hôpital Cochin-Port Royal, Paris, France (Ghislaine Firtion, Emmanuelle Pannier, Myriam Costa, Odile Launay, Dominique Salmon Ceron); APHP Hôpital Bichat, Paris, France (Sophie Matheron, Mandovi Rajguru, Neila Elaoun, Lahcene Allal, Elie Azria, Agnès Bourgeois Moine); Centre Hospitalier Intercommunal, Créteil, France (Valérie Garrait, Isabelle Hau, Claudine Touboul, Lanto Ratsimbazafy, Christiane Kommé, Brigitte Elharrar); Hôpital de la Croix Rousse, Lyon, France (Jean-Marc Labaune,

Laurent Cotte, René-Charles Rudigoz); Centre Hospitalier Pellegrin, Bordeaux, France (Christophe Elleau, Camille Runel-Belliard, Thierry Pistone); CHU Les Abymes, Pointe à Pître, France (Blandine Muanza, Elisabeth Broustal); Centre Hospitalier Général, Creil, France (Marc Duval-Arnould, Bénédicte Carpentier, Etienne Dienga); Hôpital de Haute Pierre, Strasbourg, France (MariaLuisa Partisani, Natacha Entz-Werle, Eric David, David Rey); Centre Hospitalier Général, Longjumeau, France (Hervé Seaume, Sarah Ducrocq, Philippe Bailly-Salin); Hôpital Paule de Viguier, Toulouse, France (Joëlle Tricoire, Alain Berrebi); Centre Hospitalier de la Côte Basque, Bayonne, France (Claudine Cayla); Centre hospitalier intercommunal, Villeneuve St Georges, France (Anne Chacé, Isabelle Metheron); Centre Hospitalier Intercommunal, Poissy Saint Germain en Laye, France (Anne Boutemy, Didier Armangaud, Sophie Couderc); Centre Hospitalier Général, Fontainebleau, France (Corinne Routier, Alain Alissa); Centre Hospitalier Robert Ballanger, Aulnay, France (Elisabeth Questiaux, Ahmed Zakaria, Hélène Dauphin, Céline Goissen, Marie Belloy, Jean-Luc Delassus); Hôpital Civil, Strasbourg, France (MariaLuisa Partisani, Christine Cheneau, Jean-Marie Lang); Centre Hospitalier Victor Dupouy, Argenteuil, France (Dominique Brault, Christine Allisy); APHP Hôpital Tenon, Paris, France (Marie-Gisèle Lebrette, Lise Selleret, François Hervé); Centre Hospitalier Général, Saint-Denis, France (Pascal Bolot, Marie-Aude Khuong-Josses, Dieudoné Ekoukou, Stéphane Bounan); APHP Hôpital Necker, Paris, France (Stéphane Blanche, Delphine Lemercier, Pierre Frange, Florence Veber, Alain Fisher); Centre Hospitalier Sud Francilien, Evry Corbeil, France (Michèle Granier, Alain Devidas, Rose Nguyen, Adrien May, Amélie Chabrol, Pierre Chevojon, Zaitoun Abdallah Moussa); Centre Médico-Chirurgical et Obstétrical, Schiltigheim, France; Centre Hospitalier Régional (CHR) American Memorial Hospital, Reims, France (Claire Pluchart, Christine Rouger); APHP Groupe Hospitalier Pitié Salpêtrière, Paris, France (Roland Tubiana, Manuela Bonmarchand, Luminata Shneider, Fabienne Caby, Ruxandra-Oana Calin); Centre Hospitalier René Dubos, Pontoise, France (Anne Coursol); APHP Hôpital Béclère, Clamart, France (Véronique Chambrin, Philippe Labrune, Laure Clech); Centre Hospitalier Marc Jacquet, Melun, France (Isolde Pauly-Ravelly, Raghad Moalim, Lydie Sanchez); Centre Hospitalier Général, Evreux, France (Ama Johnson); APHP Hôpital Jean Verdier, Bondy, France (Eric Lachassine, Laurence Benoist, Vincent Jeantils, Joel Gaudelus, Amélie Benbara, Anne Borgne); Centre Hospitalier de Meaux, Meaux, France (Leïla Karaoui, Véronique Lefevre Elbert); CHU de l'Archet, Nice, France (André Bongain, Fabrice Monpoux, Anne Deville, Eliane Galiba); Centre Hospitalier François Quesnay, Mantes La Jolie, France (Antoine Doumet); CHU Hôpital Nord, Amiens, France (Jean-Luc Schmidt); Hôpital de la Conception, Marseille, France (Ludovic Cravello); CHU de Brabois-Hôpital des Adultes, Vandoeuvre les Nancy, France (Claire Hubert); APHP Hôpital Trousseau, Paris, France (Catherine Dollfus, François Hervé, Marie-Dominique Tabone, Mary-France Courcoux, Guy Leverger, Bruno Carbonne); Hôpital Charles Nicolle, Rouen, France (Didier Pinquier, Brigitte Clavier, Gaelle Pinto-Cardoso); APHP Hôpital Robert Debré, Paris, France (Albert Faye, Sophie Matheron, Martine Levine, Erianna Bellaton Marouts, Constance Borie, Christine Boissinot); APHP Hôpital de Bicêtre, Le Kremlin-Bicêtre, France (Delphine Peretti, Corinne Fourcade); CHU Hôpital Saint Jacques, Besançon, France (Catherine Chirouze, Cécile Hafner Mauvais); CHU de Nantes, Nantes, France (Véronique Reliquet, Cécile Brunet-Cartier, Norbert Winer, Edouard Vaucel); CHU Hôpital du Bocage, Dijon, France (Claire Briandet); CHU Hôpital Clemenceau, Caen, France (Jacques Brouard); Centre Hospitalier de Lagny, Lagny, France (Arnaud Chalvon Demersay); Hôpital André Mignot, Le Chesnay, France (Véronique Hentgen, Fabienne Messaoudi); CHU de Tours, France (Louis, Bernard, Zoha Maakroun, Pascale Nau); Institut d'Hémato-Oncologie Pédiatrique, Lyon, France (Kamila Kebaïli); Hôpital Nord, Saint Etienne, France (Kareen Billiemaz); Centre Hospitalier Général, Bastia, France (Ramona Abrudan); Centre Hospitalier Universitaire, Angers, France (Pascale Fialaire, Stéphanie Proust); CHR, Orléans, France (Philippe Arsac, Louis Mesnard, Evelyne Werner); APHP Hôpital Lariboisière, Paris, France (Nicole Ciraru-Vigneron, Geneviève Mouchnino, Dominique Ayral); CHR Arnaud de Villeneuve, Montpellier, France (Emmanuelle Vintejoux, Muriel Lalande, Jacques Reynes, Michel Segondy); Centre Hospitalier Général, Orsay, France (Christiane De Gennes); Centre Hospitalier de Saint Martin, St Martin, France (Cyril Clavel); CHR Jeanne de Flandres, Lille, France (Françoise Mazingue, Yamina Hammou); Centre Hospitalier Dron, Tourcoing, France (Faïza Ajana); CHU - Maison de la Femme et de l'Enfant, Fort de France, France (Yves Hatchuel, Imad Nahri); CHU Dupuytren, Limoges, France (Claire Genet, Sophie Ducroix-Roubert, Yves Aubrard, Anne Constanty, Pierre Weinbreck); Hôpital Intercommunal Sud Léman Valserine, Saint Julien, France (Emilie Piet, Françoise Jacquier); Centre Hospitalier Saint Nazaire Cité Sanitaire, Saint Nazaire, France (Christophe Michau, Hassan Safwan, Arnaud Boutet); Groupe Hospitalier Saint Joseph, Paris, Centre Hospitalier Léon Binet, Provins (Mohamed Abdelhadi); Centre Hositalier Andrée Rosemon, Cayenne (Narcisse Elenga); Hôpital Calmette, Lille, France.

Steering Commitee Members of ANRS-EPF

Stéphane Blanche, Sandrine Delmas, Catherine Dollfus, Albert Faye, Jérôme Le Chenadec, Laurent Mandelbrot, Anaïs Perilhou, Christine Rouzioux, Jeanne Sibiude, Jean-Paul Teglas, Roland Tubiana, Josiane Warszawski.