No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception

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Background. The efficacy of preventing perinatal transmission (PT) of human immunodeficiency virus type 1 (HIV-1) depends on both viral load (VL) and treatment duration. The objective of this study was to determine whether initiating highly active antiretroviral therapy (ART) before conception has the potential to eliminate PT.

Methods. A total of 8075 HIV-infected mother/infant pairs included from 2000 to 2011 in the national prospective multicenter French Perinatal Cohort (ANRS-EPF) received ART, delivered live-born children with determined HIV infection status, and did not breastfeed. PT was analyzed according to maternal VL at delivery and timing of ART initiation.

Results. The overall rate of PT was 0.7% (56 of 8075). No transmission occurred among 2651 infants born to women who were receiving ART before conception, continued ART throughout the pregnancy, and delivered with a plasma VL <50 copies/mL (upper 95% confidence interval [CI], 0.1%). VL and timing of ART initiation were independently associated with PT in logistic regression. Regardless of VL, the PT rate increased from 0.2% (6 of 3505) for women starting ART before conception to 0.4% (3 of 709), 0.9% (24 of 2810), and 2.2% (23 of 1051) for those starting during the first, second, or third trimester ($P < .001$). Regardless of when ART was initiated, the PT rate was higher for women with VLs of 50–400 copies/mL near delivery than for those with <50 copies/mL (adjusted odds ratio, 4.0; 95% CI, 1.9–8.2).

Conclusions. Perinatal HIV-1 transmission is virtually zero in mothers who start ART before conception and maintain suppression of plasma VL.

Keywords. HIV; pregnancy; antiretroviral therapy; treatment as prevention; mother-to-child transmission.

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The prevention of perinatal transmission (PT) of human immunodeficiency virus type 1 (HIV-1) had a major breakthrough 21 years ago, when the American-French randomized clinical trial ACTG076-ANRS024 [1] demonstrated a two-thirds reduction of mother-to-child transmission using the antiretroviral drug zidovudine during the second and third trimesters of pregnancy, at delivery, and in the neonatal period. Progressively lower PT rates were observed with increasingly potent antiretroviral therapy (ART) [2–6], and the current standard of care is triple antiretroviral combination therapy. The World Health Organization issued a goal of virtually eliminating mother-to-child (ie, perinatal plus breastfeeding) transmission of HIV worldwide by 2015. The use of ART to protect the exposed fetus from HIV transmission is a model for "treatment as prevention," which is now recommended on an individual as well as a population basis to prevent sexual transmission [7].

Three main factors are associated with a residual risk of PT despite ART, in the absence of breastfeeding: detectable maternal viral load (VL) at delivery, preterm delivery, and a short duration of ART before delivery [4, 8]. These factors are related, because starting ART earlier improves the chances of obtaining an undetectable VL before delivery, provided that the woman takes the medications. The relationship between the duration of ART during pregnancy and the risk of transmission is well established [6, 9]. Until recently, treatment guidelines indicated that for women who are not yet receiving therapy and have CD4 lymphocyte counts >500/μL, the indication for ART is mainly prophylactic to prevent PT, and one important issue is when to start therapy. Most guidelines in industrialized countries are to initiate ART as early as possible. However, other guidelines still recommend starting at some point between 12 and 24 gestational weeks, depending on the baseline VL and the estimated risk of premature delivery [10]. These guidelines were based on data from the United Kingdom indicating that women with a baseline VL <10 000 copies/mL can delay ART to 26 weeks without compromising their likelihood of achieving an undetectable VL by delivery [11]. Findings from other studies, however, including a case-control study of PT in which Tubiana et al [9] studied women with low VLs at delivery, suggested that the risk of in utero transmission was increased with delayed ART, particularly in women with high baseline VLs. Early and sustained control of maternal VL was associated with lower PT.

Women are increasingly starting ART before becoming pregnant. The most recent US guidelines for preconception counseling now suggest starting ART when planning pregnancy [12], and French HIV treatment guidelines are to offer ART to all HIV-infected persons regardless of CD4 cell counts and VL [13]. The objective of the current study was to quantify the reduction in the risk of PT associated with ART initiation before conception.

METHODS

The French Perinatal Cohort (ANRS CO1/CO11) is an ongoing, prospective, observational study involving 90 perinatal centers throughout France [4]. In each participating center, about 95% of all HIV-infected pregnant women are included, with informed consent. The study was approved by the Cochin Hospital Institutional Review Board and the French computer database watchdog commission. Clinicians are encouraged to follow current French national guidelines, which are updated at 2-year intervals [13]; these include monthly follow-up during pregnancy with plasma VL assessment and pediatric follow-up from birth to 18–24 months.

All HIV-1-infected women enrolled in the French Perinatal Cohort delivering in metropolitan France between 2000 and 2011 were included in the study if they received highly active ART, defined as a regimen containing ≥3 drugs or 1 drug other than a nucleoside reverse-transcriptase inhibitor, during pregnancy. Women who received only reverse-transcriptase inhibitor monotherapy or dual therapy were excluded. However, women who switched from a combination therapy to monotherapy or dual therapy were included, as were the small number of women who received monotherapy with ritonavir-boosted protease inhibitors (PIs) [14]. Breastfeeding women were also excluded.

Plasma VL testing was performed locally, using polymerase chain reaction (PCR)–based techniques in nearly all cases. No centralized testing was performed at the time of inclusion, nor were samples retested subsequently for the purpose of the study. Thus, the cutoffs for HIV RNA detection changed during the 11-year period, from 500 to 50 copies/mL, <50 copies/mL becoming the standard after 2005. The data for VL and the ART regimen at delivery were those recorded nearest to the date of delivery. A child was considered infected if HIV-1 DNA or RNA PCR results were positive for 2 consecutive samples or if HIV-1 antibodies were detected at ≥18 months of age. A child was considered uninfected if HIV-1 DNA or RNA PCR results were negative ≥2 months of age and ≥1 month after ceasing all antiretroviral prophylaxis and/or if results of HIV-1 serology became negative, as described elsewhere [15].

Statistical Analysis

We first compared maternal and infant characteristics according to the timing of ART initiation in 4 categories (before conception and at <14 , 24–27, and ≥28 gestational weeks), using χ^2 or Fisher exact tests for categorical variables and Student *t* tests or Wilcoxon rank tests for continuous variables. The estimated date of conception was determined by last menstrual period and/or ultrasound. When studying PT, we excluded children with undetermined HIV status. In cases of first-trimester interruption of the treatment present at conception, the timing of ART initiation was defined by the date of reintroduction.

Transmission rates were estimated with their binomial exact 95% confidence interval (CI). The analysis was then stratified according to timing at ART initiation and level of VL near delivery into 4 categories: <50 copies/mL or undetectable with a lower threshold (usually 20 copies/mL); undetectable with a threshold >50 copies/mL; detectable at 50–400 copies/mL; and ≥400 copies/mL. We used logistic regression to compare PT rates specifically between women with delivery VLs of <50 or 50–399 copies/mL, independent of timing of ART initiation, and then performed logistic regression for all VL categories. SAS statistical software (version 9.3; SAS, Institute) was used for analyses

RESULTS

From 2000 to 2011, a total of 12 284 mother/infant pairs were enrolled in EPF (Enquête Périnatale Française), among whom 8678 (including 218 twin pairs and 1 set of triplets) were eligible for the study (Figure 1).

Timing of ART Initiation (Table 1)

ART was initiated before conception in 47.2% of women (n = 4095), during the first trimester in 8.2% (n = 713), during the second trimester in 32.3% (n = 2803), and during the third trimester in 12.3% (n = 1067). Most ART regimens were PI-based triple therapy (82.5%) at the time of delivery. The overall proportion of women who were aware of their HIV diagnosis before becoming pregnant was 80.4%. The proportion was lower for those with treatment introduction beyond the first trimester; nonetheless, 59.8% of the women who started ART in the second or third trimester did know their HIV status before becoming pregnant. The majority of women (71.4%) maintained their initial ART regimen throughout the pregnancy.

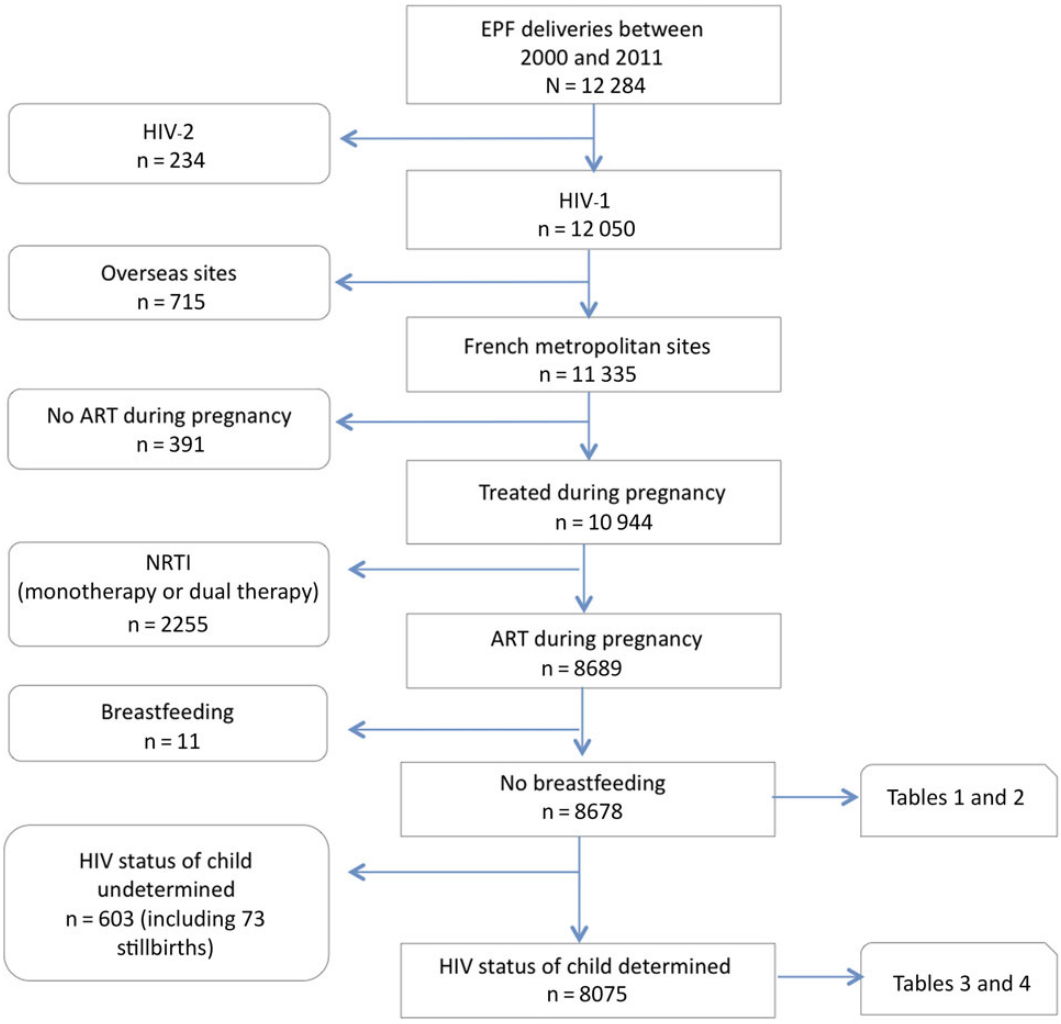

Figure 1. Flow chart. Abbreviations: ART, antiretroviral therapy; EPF, Enquête Périnatale Française; HIV, human immunodeficiency virus; HIV-1, HIV type 1; HIV-2, HIV type 2; NRTI, nucleoside reverse-transcriptase inhibitor.

Table 1. Maternal and Obstetrical Characteristics for Children Born to Human Immunodeficiency Virus-Infected Mothers in French Metropolitan Enquête Périnatale Française Sites in 2000–2011, Receiving Combined Antiretroviral Therapy During Pregnancy

			Time at First Antiretroviral Treatment During Pregnancy								
	All		Before Conception		1st Trimester (<14 GW)		2nd Trimester (14–27 GW)		3rd Trimester (≥28 GW)		
Characteristic	%	No.	%	No.	%	No.	%	No.	%	No.	*P* Value
All	. . .	8678	. . .	4095	. . .	713	. . .	2803	. . .	1067	. . .
Year of delivery											
2000–2002	14.8	1283	16.8	686	9.5	68	11.7	329	18.7	200	<.001
2003–2005	25.3	2197	20.5	839	24.8	177	27.3	764	39.1	417	
2006–2008	30.9	2681	29.2	1194	31.6	225	34	954	28.9	308	
2009–2011	29	2517	33.6	1376	34.1	243	27	756	13.3	142	
Maternal age, y											
<25	8.7	754	4.3	176	9.6	68	11	309	18.9	201	<.001
25–34	56.5	4899	51.6	2111	57.7	411	61.7	1727	61	650	
>34	34.8	3013	44.1	1803	32.7	233	27.2	762	20.2	215	
Missing	. . .	12	. . .	5	. . .	1	. . .	5	. . .	1	
Maternal geographic origin											
Metropolitan France	16.6	1432	20.4	830	17.2	121	13.2	368	10.7	113	<.001
Sub-Saharan Africa	71.6	6172	67.7	2751	71.2	501	75.1	2098	77.6	822	
Other	11.8	1015	11.8	481	11.7	82	11.7	328	11.7	124	
Missing	. . .	59	. . .	33	. . .	9	. . .	9	. . .	8	
HIV diagnosis before conception											
No	19.6	1694	0	0	14.9	106	37.5	1047	50.8	541	<.001
Yes	80.4	6954	100	4085	85.1	604	62.5	1742	49.2	523	
Missing		30		10		3		14		3	
Primiparous											
No	67.4	5849	72.1	2951	65.6	468	64.3	1801	59	629	<.001
Yes	32.6	2825	27.9	1142	34.4	245	35.7	1001	41	437	
Missing		4		2		0		1		1	
Gestational age at first antenatal maternity visit, wks gestation											
<14	45.6	3529	55.4	2060	64.2	408	34.5	845	23.3	216	<.001
14–27	44.9	3474	38.8	1444	30.3	193	59.3	1453	41.4	384	
≥28	9.4	730	5.8	216	5.5	35	6.2	151	35.3	328	
Missing		945		375		77		354		139	
First ART during pregnancy											
Triple NRTI	5.9	512	10.9	445	2.4	17	1.2	33	1.6	17	<.001
PI based	76.1	6606	59.3	2428	85.7	611	92.9	2603	90.3	964	
NNRTI based	15.8	1369	26.6	1090	10.5	75	5.1	143	5.7	61	
Three classes	1.2	104	2.0	81	0.8	6	0.5	13	0.4	4	
Other	1.0	87	1.2	51	0.6	4	0.4	11	2.0	21	
Last ART during pregnancy											
Zidovudine monotherapy[a]	0.4	37	0.7	28	0.0	0	0.2	7	0.2	2	<.001
Dual NRTI[a]	1.1	97	2.0	83	0.3	2	0.3	9	0.3	3	
Triple NRTI	3.1	267	5.0	203	2.0	14	1.1	32	1.7	18	
PI based	81.2	7046	71.3	2918	86.5	617	91.4	2561	89.0	950	
NNRTI based	10.9	942	17.2	703	7.3	52	4.6	129	5.4	58	
Three classes	1.3	114	2.1	86	1.3	9	0.5	14	0.5	5	
Other	2.0	175	1.8	74	2.7	19	1.8	51	2.9	31	

Table 1 continued.

Characteristic	All		Time at First Antiretroviral Treatment During Pregnancy								*P* Value
			Before Conception		1st Trimester (<14 GW)		2nd Trimester (14–27 GW)		3rd Trimester (≥28 GW)		
	%	No.	%	No.	%	No.	%	No.	%	No.	
Change in ART regimen during pregnancy											
No change	71.4	6192	56.7	2323	74.0	527	84.4	2367	91.4	975	<.001
1st-trimester interruption[b]	3.6	313	7.6	312	0	0	0	0	0	0	
Any ART change	25.0	2173	35.7	1460	26.0	186	15.6	436	8.6	92	
Last viral load before delivery, copies/mL											
<50[c]	68.0	5710	75.4	2994	74.2	512	64.8	1749	44.1	455	<.001
Undetectable 50–400 threshold	5.9	498	6.1	244	7.0	48	6.0	163	4.2	43	
50–399	15.2	1266	10.0	396	9.0	62	19.0	512	28.7	296	
≥400	10.9	918	8.4	335	9.9	68	10.3	277	23.0	238	
Missing		286	. . .	126	. . .	23	. . .	102	. . .	35	
CD4 cell count before delivery, cells/μL											
<200	9.0	751	7.8	308	14.3	99	9.4	251	9.2	93	<.001
200–349	21.0	1747	21.7	854	26.4	183	19.6	524	18.4	186	
350–499	28.0	2324	29.5	1158	25.4	176	26.0	695	29.2	295	
≥500	42.0	3486	41.0	1609	33.9	235	45.0	1204	43.3	438	
Missing	. . .	370	. . .	166	. . .	20	. . .	129	. . .	55	
Delivery mode											
Vaginal	42.7	3420	42.6	1639	44.1	290	45.0	1154	35.4	337	.002
Emergency cesarean delivery	22.0	1765	22.2	852	23.0	151	21.3	546	22.7	216	
Planned cesarean delivery	35.3	2832	35.2	1352	32.9	216	33.7	866	41.9	399	
Missing	. . .	661	. . .	252	. . .	56	. . .	237	. . .	116	
Intrapartum zidovudine											
No	4.0	335	4.5	180	3.9	27	3.7	100	2.7	28	.03
Yes	96.0	8113	95.5	3793	96.1	665	96.3	2638	97.3	1017	
Missing	. . .	230	. . .	122	. . .	21	. . .	65	. . .	22	

Abbreviations: ART, antiretroviral therapy; GW, gestational weeks; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

[a] Switch during pregnancy from triple ART to reverse-transcriptase inhibitor monotherapy or dual therapy.

[b] Interruption during first trimester, for >2 weeks, of ART underway at conception.

[c] VL undetectable with a technique with sensitivity above 50 copies/mL.

Proportion of Virological Success

The proportion of women with VLs of <50 copies/mL at delivery was highest when ART was initiated before conception (75.4%) or in the first trimester (74.2%) and significantly lower when ART was initiated later, during the second (64.8%) or third (44.1%) trimester ($P < .001$).

Pregnancy Outcomes (Table 2)

There were 16.1% preterm deliveries, of which most (12.7%) were moderately preterm (from 32 gestational weeks to 36 weeks + 6 days). The preterm delivery rate was similar in women who started ART before conception or during the 2 first trimesters ($P = .32$) and lower in those starting ART during the third trimester. We observed no difference in the incidence of stillbirths or in Apgar scores according to the timing of ART. The proportion of children with undetermined HIV status did not differ according to treatment timing.

PT of HIV-1 (Tables 3 and 4)

There was no PT (95% CI, .0%–.1%) among the 2651 women who started ART before conception, continued it during the pregnancy, and delivered with a VL of <50 copies/mL (Table 3). Furthermore, there was no case of transmission among the small subgroup of 212 women initiating ART before conception who had an undetectable VL using older-generation kits with limits of quantification >50 copies/mL.

Among the 4095 women receiving therapy before becoming pregnant, 7.6% (n = 312) had a treatment interruption in the

Table 2. Neonatal Characteristics of Children Born to Human Immunodeficiency Virus-Infected Mothers in French Metropolitan Enquête Périnatale Française Sites in 2000–2011, Receiving Combined Antiretroviral Therapy During Pregnancy[a]

			Timing at 1st Antiretroviral Treatment During Pregnancy								
	All		Before Conception		1st Trimester (<14 GW)		2nd Trimester (14–27 GW)		3rd Trimester ≥28 GW		
Characteristic	%	No.	%	No.	%	No.	%	No.	%	No.	*P* Value
All	. . .	8678	. . .	4095	. . .	713	. . .	2803	. . .	1067	
Live-born											
No	0.8	73	0.9	38	0.9	6	0.9	25	0.4	4	.22
Yes	99.2	8596	99.1	4055	99.2	707	99.1	2772	99.6	1062	
Birth weight, grams											
Median (IQR)	3020 (2670–3360)		3020 (2660–3360)		3065 (2645–3390)		3018 (2650–3360)		3040 (2740–3340)		.02
Missing	. . .	219	. . .	110	. . .	20	. . .	71	. . .	18	
Length at birth, cm											
Median (IQR)	48.0 (47–50)		48.0 (46–50)		48.0 (47–50)		48.0 (47–50)		49.0 (47–50)		<.001
Missing	. . .	476	. . .	243	. . .	49	. . .	148	. . .	36	
Head circumference, cm											
Median (IQR)	34.0 (33–35)		34.0 (33–35)		34.0 (33–35)		34.0 (33–35)		34.0 (33–35)		.003
Missing	. . .	537	. . .	279	. . .	44	. . .	161	. . .	53	
Gestational age at delivery, wk											
<32	3.4	294	4.0	164	3.2	23	3.6	100	0.7	7	.32[b]
32–36	12.7	1100	13.4	549	12.8	91	12.0	336	11.6	124	
≥37	83.9	7284	82.6	3382	84.0	599	84.4	2367	87.7	936	
5-min Apgar score											
0–3	0.6	50	0.6	25	0.7	5	0.6	15	0.5	5	.19
4–7	2.5	206	3.0	117	1.9	13	2.1	57	1.8	19	
8–10	96.9	8070	96.4	3776	97.3	659	97.3	2618	97.7	1017	
Missing	. . .	352	. . .	177	. . .	36	. . .	113	. . .	26	
Neonatal antiretroviral prophylaxis											
None	0.9	78	0.9	34	1.5	10	0.8	22	1.2	12	<.001
Zidovudine monotherapy	91.6	7635	92.0	3613	90.6	617	93.0	2504	87.1	901	
Other	7.5	623	7.2	281	7.9	54	6.2	166	11.8	122	
Missing	. . .	342	. . .	167	. . .	32	. . .	111	. . .	32	
Neonatal single-dose nevirapine											
No	95.8	8154	96.1	3855	97.6	679	96.2	2648	92.2	972	<.001
Yes	4.2	360	3.9	155	2.4	17	3.8	106	7.8	82	
Missing	. . .	164	. . .	85	. . .	17	. . .	49	. . .	13	
HIV infection status											
Not infected	92.4	8019	92.8	3798	91.9	655	92.7	2597	90.8	969	<.001
HIV infected	0.7	56	0.2	10[c]	0.4	3	0.8	22	2.0	21	
Undetermined	5.6	486	5.5	227	6.3	45	5.1	144	6.5	70	
Stillbirth	0.8	73	1.0	38	0.8	6	0.9	25	0.4	4	
Death before HIV diagnosis	0.5	44	0.5	22	0.6	4	0.5	15	0.3	3	

Abbreviations: ART, antiretroviral therapy; GW, gestational weeks; HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Values represent percentages and numbers of neonates except where otherwise indicated for median measurements.

[b] Comparison between groups initiating ART before conception or during the first or second trimester (because severe prematurity by definition would reduce the opportunity for initiation in the third trimester).

[c] Including 4 children whose mothers stopped taking ART when becoming pregnant.

first trimester. There were 4 cases of PT in this subgroup (1.3%); 2 of these children were born to mothers with VL <50 copies/mL near delivery.

The VLs and timing of highly active ART initiation were independently associated with PT in logistic regression (Table 4). Overall, the transmission rate increased from 0.2% (95% CI, .06%–.4%)

Table 3. Perinatal Human Immunodeficiency Virus Type 1 Transmission Rate According to Timing of Antiretroviral Therapy Initiation and Maternal Viral Load Near Delivery (Enquête Périnatale Française, Metropolitan France, 2000–2011): Stratified Analysis

	Timing of ART Initiation								
	Before Conception[a]		1st Trimester (<14 wk)		2nd Trimester (14–27 wk)		3rd Trimester (≥28 wk)		
Maternal VL	PT, % (95% CI)	No. With PT/Total No.	PT, % (95% CI)	No. With PT/Total No.	PT, % (95% CI)	No. With PT/Total No.	PT, % (95% CI)	No. With PT/Total No.	*P* Value
Maternal VL nearest delivery, copies/mL									
≥400	2.2 (.7–5.0)	5/230	1.5 (.04–7.8)	1/69	2.4 (1.0–4.9)	7/291	4.4 (2.1–7.9)	10/228	.37
50–400	0.3 (.01–1.8)	1/301	1.6 (.04–8.8)	1/61	1.4 (.5–2.8)	7/515	3.0 (1.4–5.7)	9/297	.06
Undetectable, threshold >50	0.0 (0–1.7)	0/212	0.0 (0–6.8)	0/52	0.6 (<.01 to 3.3)	1/169	0.0 (0–8.6)	0/41	.5
<50	0.0 (0–.1)	0/2651	0.2 (<.01 to 1.1)	1/507	0.5 (.2–1.0)	9/1735	0.9 (.2–2.3)	4/452	.002
Missing VL	. . .	0/111	. . .	0/20		0/100	. . .	0/33	. . .
Undetermined child HIV status	. . .	. . ./287	. . .	. . ./55	. . .	. . ./184	. . .	. . ./77	. . .

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; PT, perinatal transmission; VL, viral load.

[a] In case of treatment interruption of the first ART regimen for >2 weeks in the first trimester, the date of treatment initiation was defined as the time when ART was reintroduced.

for women starting ART before conception to 0.4% (.09%–1.2%), 0.9% (.5%–1.3%), and 2.2 (1.4%–3.3%) for those starting ART during the first, second, or third trimester, respectively ($P < .001$). The transmission rate increased with VL at delivery: from 0.3% (.1%–.4%) when the VL was <50 copies/mL to 1.5% (.9%–2.4%) for VL 50–399 copies/mL and 2.8% (1.8%–4.2%) when the VL was >400 copies/mL ($P < .001$). None of the other variables included in the multivariate analysis were significantly associated with PT; these included maternal age, geographic origin, mode of delivery, gestational age, first ART used (PI based vs nonnucleoside reverse-transcriptase inhibitor based), receipt of intrapartum intravenous zidovudine or peripartum nevirapine, type of postnatal prophylaxis, and sex of the child. In the multivariate analysis, PT remained significantly higher in women delivering with a VL of 50–400 copies/mL than in those delivering with a VL <50 copies/mL, independently of when ART was initiated (adjusted odds ratio, 4.0; 95% CI, 1.9–8.2), and this difference did not change when all of the VL categories were considered (Table 4).

Table 4. Perinatal Human Immunodeficiency Virus Type 1 Transmission Rate According to Timing of Antiretroviral Therapy Initiation and Maternal Viral Load Near Delivery (Enquête Périnatale Française, Metropolitan France, 2000–2011): Multivariate Logistic Regression[a]

Maternal VL and ART Timing	PT, % (95% CI)	No. With PT/Total No.	Adjusted OR (95% CI)	*P* Value
Overall PT (all infants with determined HIV status)	0.7 (.5–.9)	56/8075	. . .	. . .
Maternal VL nearest delivery, copies/mL				
≥400	2.8 (1.8–4.2)	23/818	6.2 (2.6–15.2)	<.001
50–399	1.5 (.9–2.4)	18/1174	4.3 (1.8–9.8)	
Undetectable, threshold >50	0.2 (<.01 to 1.2)	1/474	1.1 (.1–8.6)	
<50	0.3 (.1–.4)	14/5345	1	
Missing VL		0/264		
Timing of ART initiation				
3rd trimester (≥28 wks gestation)	2.2 (1.4–3.3)	23/1051	7.8 (2.1–28.8)	<.001
2nd trimester (14–27 wks gestation)	0.9 (.5–1.3)	24/2810	6.0 (1.7–20.7)	
1st trimester (<14 wks gestation)	0.4 (.09–1.2)	3/709	2.9 (.6–17.7)	
Before conception	0.2 (.06–.4)	6/3505	1	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PT, perinatal transmission; VL, viral load.

[a] Adjusted for maternal age, geographic origin, mode of delivery, gestational age, protease inhibitor–based versus nonnucleoside reverse-transcriptase inhibitor–based first combination ART regimen, zidovudine intrapartum prophylaxis, postnatal prophylaxis, postnatal nevirapine, and child's sex. The HIV status was unknown in 603 children.

DISCUSSION

Remarkably, we observed no case of PT among nearly 2700 women who started ART before conception and had a plasma VL <50 copies/mL at delivery. This contrasts with a "natural" PT risk of 15%–20% [16]. Numerous cohort studies have reported very low PT with antiretroviral prophylaxis [6], but this is the first to confirm that the virtual elimination of transmission is possible, with an upper 95% CI limit of 0.1%. The few cases of transmission in women who had VL <50 copies/mL at delivery occurred when therapy was started beyond the first trimester or interrupted during the pregnancy.

The main strengths of this cohort study are its large size, multicenter recruitment in routine clinical settings, high participation rates at each center, low proportion of infants lost to follow-up, and prospective data collection before knowledge of infant HIV status, thus limiting selection and differential classification biases. Our findings show that the earlier ART was started, the lower the rate of PT, whether or not VL at delivery was <50 copies/mL. When ART was started in the first trimester, it was nearly as effective as when it was started before pregnancy. The duration of therapy was shown elsewhere to be an important determinant of PT risk in our cohort [4, 9] and others [6]. Moreover, PT was significantly lower when maternal VL at delivery was <50 copies/mL than when it was 50–400 copies/mL, confirming a recent report on a cohort from the United Kingdom and Ireland [6].

There are several reasons to expect that long-term ART would optimize the prevention of in utero as well as intrapartum transmission, including the quality of immune restoration, reduction of proviral HIV-1 DNA in reservoirs, and better control of VL in various compartments, including the cervicovaginal tract. The relative contributions of ART duration and VL are difficult to investigate because they are highly associated, and statistical power is lacking because few cases of transmission are observed overall.

Our findings provide a strong argument for initiating therapy as soon as pregnancy is planned, even when there seems to be no immediate benefit for the woman's own health. In the French cohort in 2011, >40% of women were not yet receiving ART before becoming pregnant. Recent guidelines [13] recommend lifelong ART for all persons living with HIV, even when they are asymptomatic and have CD4 cell counts >500/μL. The rationale for this major change includes potential long-term benefit for the person's own health but also the prevention of transmission to sexual partners. The World Health Organization also endorsed in 2013 the objective of starting lifelong ART as early as possible in all HIV-infected pregnant women regardless of CD4 count and VL, referred to as Option B+ in the developing world [17]. In resource-poor settings with difficult access to care, starting ART as soon as possible can reduce the cascade of missed opportunities to eliminate PT, although there are obstacles to implementing such programs [18, 19]. More recently, the Panel on Treatment of HIV-Infected Pregnant Women in the United States recommended that all HIV-infected women contemplating pregnancy be placed on a maximally suppressive antiretroviral regimen [12].

Initiating ART before conception has several practical advantages. Antiretroviral drugs can be chosen in light of pregnancy issues, to assess tolerance, adherence, and efficacy and to allow for continuity between preconceptional and prenatal care. Another major benefit is to protect the male partner during attempts to conceive, if he is HIV uninfected [20]. PT prevention is the first example and model for treatment as prevention [7].

There are implications for perinatal management [12, 13, 21]. In the case of low maternal VL before delivery, Briand et al [22, 23] reported elsewhere that neither cesarean delivery [22] nor intrapartum preexposure prophylaxis with intravenous zidovudine [23] offer additional protection against PT. Regarding postnatal prophylaxis for the infant, future studies are required to evaluate whether treatment with several weeks of zidovudine or nevirapine is still necessary when the mother has long-term optimal VL control and does not breastfeed [24].

When ART is started earlier, safety is a crucial issue [25–27]. Because the rate of PT is already low, the incremental benefit for the child of moving toward systematic first-trimester ART exposure must take into consideration even rare toxic effects. The efficacy of ART to prevent PT depends solely on maternal VL, but tolerance differs according to the individual molecules used. Although no increase in the overall incidence of birth defects has been reported, Sibiude et al [28] reported an increase in congenital heart defects associated with first-trimester exposure to zidovudine, and there is controversy regarding the risk of central nervous system anomalies associated with efavirenz in the first trimester [29, 30]. Preterm birth was increased in numerous studies among women receiving ART [31–34], in addition to the role of maternal HIV infection itself [33]. In the present study, the incidence of preterm delivery was >16%, much higher than in the general population in high-income countries [34]. However, there was no difference in the incidence of preterm delivery according to the timing of treatment, before or after conception.

In conclusion, the present study provides evidence in favor of offering ART to all HIV-infected women planning to become pregnant and initiating ART as early as possible in pregnancy in women who become pregnant before being treated. These indications, as well as the specific antiretroviral drugs to be used, should be decided with the patient on an individualized basis, taking into consideration both safety and PT.

Notes

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