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Lopinavir/Ritonavir Monotherapy as a Nucleoside Analogue–Sparing Strategy to Prevent HIV-1 Mother-to-Child Transmission: The ANRS 135 PRIMEVA Phase 2/3 Randomized Trial

Roland Tubiana,[1,2] Laurent Mandelbrot,[3,4,5] Jérome Le Chenadec,[3] Sandrine Delmas,[3,6] Christine Rouzioux,[7,8] Deborah Hirt,[7,9] Jean-Marc Treluyer,[7,9] Dieudonné Ekoukou,[10] Eda Bui,[11] Marie-Laure Chaix,[7,8] Stéphane Blanche,[7,12] and Josiane Warszawski;[3,6,13] for the ANRS 135 PRIMEVA (Protease Inhibitor Monotherapy Evaluation) Study Group[a]

[1]AP-HP, Hôpital Pitié Salpêtrière, Service de maladies infectieuses, Paris, [2]INSERM U 943, Paris, [3]INSERM, Centre for research in Epidemiology and Population Health, U1018, Equipe VIH et IST, Le Kremlin Bicêtre, [4]AP-HP, Hôpital Louis Mourier, HUPNVS, Service de Gynécologie et d'obstétrique, Colombes, [5]Université Diderot Paris 7, [6]AP-HP, Hôpital Bicêtre, Service d'Epidemiologie et Santé Publique, Le Kremlin-Bicêtre, [7]EA 3620 Université Paris Descartes 5, [8]AP-HP, Hôpital Necker, Service de Virologie, Paris, [9]AP-HP Hôpital Cochin, Paris, [10]Centre Hospitalier General, Service de Gynécologie et d'obstétrique, Saint-Denis, [11]AP-HP, Hôpital Saint-Antoine, Paris, [12]AP-HP, Hôpital Necker, Unité d'Immunologie Hématologie Pédiatrique, Paris, and [13]Université Paris Sud, UMRS 1018, Le Kremlin-Bicêtre, France

Background. Prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) is usually based on zidovudine-containing regimens, despite potential toxicities. This multicenter trial evaluated whether lopinavir/ritonavir (LPV/r) monotherapy in HIV type 1–infected women not requiring antiretrovirals for themselves could control maternal viral load (VL).

Methods. Overall, 105 pregnant women with baseline VL <30 000 copies/mL and CD4 ≥350 cells/μL were randomized to start open-label LPV/r 400/100 mg twice daily alone (monotherapy group, n = 69) or combined with zidovudine/lamivudine 300/150 mg twice daily (triple therapy group, n = 36) from 26 gestational weeks to delivery. According to a Fleming 2-stage phase 2 design, monotherapy was considered to be efficacious if at least 59 patients achieved VL <200 copies/mL at 8 weeks of treatment (primary endpoint). Secondary endpoints were VL at delivery and tolerance.

Results. Monotherapy was efficacious as defined: 62 women in the monotherapy group achieved VL <200 copies/mL at 34 weeks' gestation (ie, 8 weeks of treatment; 89.9%; 95% confidence interval [CI], 80.2%–95.8%). At delivery, proportions with VL <200 copies/mL were similar in the monotherapy and triple therapy groups (92.8% vs 97.2%; $P = .66$); however, fewer had VL <50 copies/mL in the monotherapy group (78.3% vs 97.2%; $P = .01$). Changes for intolerance were less frequent in the monotherapy than in the triple therapy group (1.4% vs 11.1%, respectively; $P = .046$). Cesarean delivery and preterm delivery rates did not differ. All children were liveborn; 1 case of HIV-1 transmission occurred in the triple therapy group, none in the monotherapy group (95% CI upper limit = 5.2%).

Conclusions. LPV/r monotherapy achieved satisfactory virologic efficacy in women treated solely for PMTCT, providing proof of concept for future nucleoside-sparing strategies.

Clinical Trials Registration. NCT00424814; Afssaps AIDS Clinical Trial Group A61176-34.

Keywords. HIV; PMTCT; zidovudine; lopinavir/ritonavir; monotherapy.

Rates of mother-to-child transmission (MTCT) of human immunodeficiency virus type 1 (HIV-1) are <1% in industrialized countries where combination

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Correspondence: Roland Tubiana, MD, Service de Maladies Infectieuses et Tropicales, AP-HP Groupe Hospitalier Pitié–Salpétrière, Paris 75013, France (roland.tubiana@psl.aphp.fr).

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antiretroviral therapy (cART) is recommended for all HIV-infected pregnant women, regardless of whether they require therapy for their own health [1–3]. The benefit of cART is based on the finding that suppression of HIV-1 replication is the major determinant of perinatal transmission reduction [4–6].

A combination of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a ritonavir-boosted protease inhibitor (PI/r) is recommended for prevention of MTCT (PMTCT) in Europe and the United States, of which the most widely used combination is zidovudine/lamivudine (ZDV/3TC) with lopinavir/ritonavir (LPV/r) [1–3, 7].

There is ongoing debate regarding safety issues for newborns exposed to NRTIs in utero [8]. Nucleosides and nucleotides cross the placenta, with an affinity for both mitochondrial and nuclear human DNA [9, 10]. ZDV is even considered to be a possible class 2B carcinogen for humans [11]. To date the only "evidence-based" ZDV in utero exposure–related toxicity was transient macrocytic anemia, observed in the pivotal AIDS Clinical Trial Group (ACTG) 076 randomized study [12]. However, more recent observational studies in large cohorts have suggested other toxicities such as rare neurological diseases associated with persistent mitochondrial dysfunction [13, 14], long-term mild hematopoietic inhibition [15], and modified ultrasound measurements of cardiac function up to adolescence [16, 17]. In parallel, a series of genotoxicity biomarkers were identified in neonates exposed to ZDV alone or with lamivudine, corroborated by experiments in primates [18, 19]. Although their clinical significance remains unknown, they raise concern for potential long-term toxicity.

For these reasons, we evaluated a nucleoside-sparing regimen for PMTCT. LPV/r was chosen because it is widely prescribed in pregnancy [20], and its use as monotherapy was shown to be potent in nonpregnant naive adults, with a VL reduction on the order of 2.15 log by 4–8 weeks [21]. In a randomized trial, VL was <400 copies/mL at 24 weeks in 78% of patients, a proportion not different from those on cART [22]. Viral resistance is unlikely to emerge in case of failure of a short antepartum treatment as the genetic barrier is high for lopinavir. Furthermore, in case of insufficient response to PI/r monotherapy, adding NRTIs is effective in rapidly suppressing HIV-1 load [23, 24], allowing, in our specific situation, to achieve a controlled VL at delivery. The low placental transfer of LPV/r limits the potential for in utero toxicities [25], and, finally, using fewer drugs may reduce cost, side effects, and drug interactions and facilitates adherence.

The primary objective of ANRS 135 PRIMEVA was to assess whether LPV/r monotherapy during pregnancy in HIV-1–infected women who do not require ART for themselves is able to control maternal viral load (VL) <200 copies/mL.

METHODS

Study Population

ANRS 135 PRIMEVA was a phase 2/3 randomized, open-label, multicenter trial, approved by the ethics committee of Pitié Salpétrière Hospital and by the French Drug Authority (Afssaps). Pregnant women were enrolled in 19 sites in mainland France participating in the French Perinatal Cohort (EPF ANRS-CO1) [5]. Patients aged ≥18 years with documented HIV-1 infection were eligible if they fulfilled the following criteria at 20–24 gestational weeks (GW): no serious pregnancy complication or major risk of premature delivery; not on ART and naive for PIs except during a previous pregnancy; no mutations conferring resistance to LPV; plasma HIV-1 RNA <30 000 copies/mL and CD4 count of ≥350 cells/μL, the CD4 cutoff for treatment initiation at the time of the study design; no contraindication to the study drugs; and written informed consent.

Procedures

Centralized randomization was performed up to 25 GW. Women were allocated (2:1) to receive open-label treatment from 26 GW (±1 GW) with LPV/r (Kaletra) alone in the monotherapy group or combined with ZDV/3TC (Combivir) in the triple therapy group. Treatment group assignment was immediately communicated to the site investigator via fax. Patients and physicians were not masked to treatment group assignment.

Standard doses were used for LPV/r (400/100 mg twice daily) and ZDV/3TC (300/150 mg twice daily in controls). If plasma VL was ≥200 copies/mL at 8 weeks of treatment (34 ± 1 GW), treatment adherence was discussed and therapy intensified. According to French guidelines at the time of the study [1], all women in both study groups were to receive intravenous ZDV during labor and all infants to receive 4–6 weeks of ZDV chemoprophylaxis, breastfeeding was discouraged, and elective cesarean delivery was recommended in case of maternal VL >400 copies/mL.

Maternal clinical examination and laboratory tests were performed at screening, treatment initiation (26 ± 1 GW), at 2, 4, 8 (primary endpoint evaluation), and 12 weeks of treatment (28, 30, 34, and 38 GW, respectively), at delivery, and at 4 and 12 weeks postpartum. Standard tests including HIV-1 RNA polymerase chain reaction (PCR), and CD4 cell count, hematology, and biochemistry measurements were performed locally at each scheduled visit. HIV genotype for resistance testing was performed at the screening and postpartum visits. Maternal blood samples for LPV pharmacokinetic assessment (trough level) at week 8 were collected the morning after the last evening dose. Maternal blood, cord blood, and amniotic fluid samples were collected at delivery when possible, to study LPV concentrations and quantify HIV-1 RNA. Adherence was assessed on the basis

of pill count at each visit and a self-administered questionnaire at week 8.

Children were followed according to the usual guidelines, at birth and at 4, 12, 24, 48, and 72 or 96 weeks, with physical examination, blood cell counts, chemistry including lactates except at birth, and HIV-1 DNA and RNA PCR. HIV serology was performed at the last visit. Gastric aspirates were collected at birth when feasible and frozen for centralized HIV-1 RNA quantification.

Clinical and laboratory adverse events were graded according to the classifications of the ANRS for adults and ACTG for children [26].

Study Endpoints

This study was designed to evaluate the efficacy of LPV/r monotherapy to obtain an HIV-1 plasma load <200 copies/mL at 8 weeks of treatment, that is, at 34 ± 1 GW (primary endpoint). It was not designed to demonstrate the equivalence of LPV/r monotherapy compared to triple therapy, as this would require a very large sample size. Cases without HIV-1 RNA quantification between 33 and 35 GW (missing data) were considered to have failed treatment.

Secondary efficacy endpoints were the proportion of assigned regimen maintained until delivery, VL <50 copies/mL at delivery, new antiretroviral resistance mutations 4 and 12 weeks postpartum, and detectable HIV-RNA in newborn gastric fluid. Safety endpoints were pregnancy outcomes and maternal and infant clinical and biological adverse events.

Statistical Analysis

The number of patients to be enrolled in the "monotherapy group" was originally estimated to be 100 over 2 years, and was reduced before the interim analysis to 70 over 3 years, due to lower enrollment than expected. A Fleming 2-stage phase 2 design was planned to prematurely terminate the trial in case of insufficient efficacy according to the primary endpoint ($P_0 \leq 75\%$ of VL <200 copies/mL at week 8), with expected proportion $P_A > 90\%$. The LPV/r monotherapy would be stopped with fewer than 42 successes among the first 50 patients at the end of stage 1, and would be consideredto be effective with at least 59 of 70 successes at the end of stage 2, with a risk of error of 0.041. Otherwise, the strategy would be considered ineffective, with a risk of error of 0.07. The trial would also be stopped if 2 cases of MTCT occurred at any moment in the monotherapy group. Following interim analysis on the first 50 inclusions showing 43 virological successes, the data safety monitoring board allowed the pursuit of the trial.

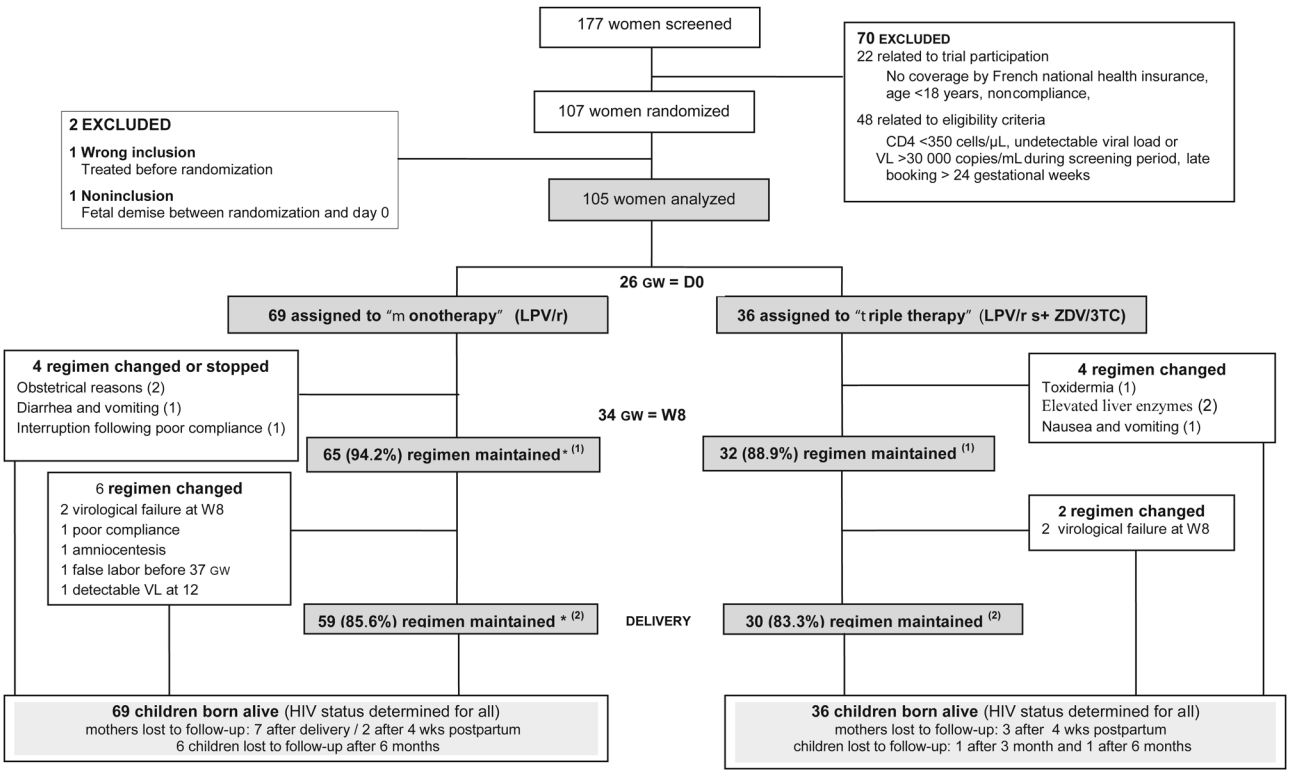

Figure 1. PRIMEVA trial profile (ANRS 135 PRIMEVA). *Included 2 estimated low LPV concentration; (1) first per protocol set; (2) second per protocol set. Abbreviations: D0, day 0; GW, gestational weeks; HIV, human immunodeficiency virus; LPV/r, lopinavir/ ritonavir; VL, viral load; W8, week 8; ZDV/3TC, zidovudine/lamivudine.

Table 1. Baseline Characteristics of Pregnant Women at Enrollment (ANRS 135 PRIMEVA)

Characteristic	Monotherapy (n = 69)		Triple Therapy (n = 36)		*P* Value[a]
	Median [Range] or % (No.)		Median [Range] or % (No.)		
Maternal age, y					
Median, range	30	[18–44]	29	[18–42]	.23
Country of birth					
Metropolitan France	14.5	(10)	11.1	(4)	.96
French overseas department	1.4	(1)	0.0	(0)	
Sub-Saharan Africa	72.5	(50)	77.8	(28)	
Other countries	11.6	(8)	11.1	(4)	
Marital status					
Living in couple	58.0	(40)	55.6	(20)	.81
Tobacco use					
≥10 cigarettes/d	2.9	(2)	2.8	(1)	1
Gestational age, wk from last menstrual period					
At booking visit in maternity	14.0	[5–25]	12.0	[5–23]	.28
At screening	21.0	[20–25]	21.0	[19–26]	.43
At enrollment	26.0	[24–27]	26.0	[25–27]	.76
Gravidity					
Primigravida	7.3	(5)	11.1	(4)	.49
HIV diagnosis					
Known before conception	84.1	(58)	80.6	(29)	.65
History of antiretroviral therapy					
Any, including PI[b]	36.2	(25)	22.2	(8)	.14
Any, not including PI	20.3	(14)	13.9	(5)	
None	43.5	(30)	63.9	(23)	
Resistance-associated mutations					
ZDV	1.5	(1)	0.0	(0)	
3TC/FTC	0.0	(0)	0.0	(0)	
LPV/r	0.0	(0)	0.0	(0)	
HIV subtype					
B	26.5	(18)	26.5	(6)	.50
CRF02AG	38.4	(26)	38.2	(11)	
Other	35.3	(24)	35.3	(15)	
CD4 cell percentage					
At screening	32	[15–49]	31	[20–43]	.93
At day 0	31	[11–52]	31	[17–43]	.87
CD4 cell count, cells/μL					
Nadir	447	[310–1320]	443	[219–893]	.66
At screening	525	[350–1320]	523	[360–938]	.65
At day 0	498	[222–1020]	504	[243–881]	.66
Plasma HIV-1 RNA, copies/mL					
Zenith	9915	[256–151 000]	6887	[350–234 200]	.92
At screening	2952	[231–27 782]	2928	[210–20 672]	.24
At enrollment	2687	[70–28 258]	1887	[48–46 100]	.41

Abbreviations: 3TC/FTC, lamivudine/emtricitabine; ANRS, French National Agency for Research on AIDS and Viral Hepatitis; HIV, human immunodeficiency virus; LPV/r, lopinavir with ritonavir; PI, protease inhibitor; PRIMEVA, Protease Inhibitor Monotherapy Evaluation; ZDV, zidovudine.

[a] *P* values were obtained with χ^2 test or 2-sided Fisher exact test for categorical variables, and Student *t* test or 2-sided Wilcoxon 2-samples test for continuous variables.

[b] Previous antiretroviral therapy regimens containing PIs were all during previous pregnancy.

With a 2:1 randomization, 35 patients were planned in the triple therapy group. The proportion of VL <200 copies/mL at week 8 was also compared with the monotherapy group. For neonates, the trial was designed to detect differences between the 2 groups of 1.4 g/dL hemoglobin, 49 000 platelets, 1500 neutrophils, or 950 lymphocytes/μL, with a power of 80%, based on standard deviations estimated in the EPF cohort between 2000 and 2004 [5]. Estimates of percentages with 95% confidence intervals (categorical variables), medians with interquartile range (continuous variables), and appropriate 2-tailed parametric or nonparametric tests were used for the comparison of baseline and secondary endpoints between the 2 groups.

Main analysis was performed on intent to treat (ITT), after excluding 1 patient included by mistake and another with a fetal demise before starting treatment. Per-protocol (PP) analysis compared women in each group who did not change from the assigned regimen (whatever the reason) until primary evaluation (week 8), and until delivery for the secondary outcome measures. For safety in children, we also excluded infants who received 2 or more drugs as neonatal prophylaxis, and the child who was HIV-infected.

RESULTS

From 14 June 2007 to 29 June 2010, 107 pregnant women were randomized; among them 105 were eligible for analysis, 69 in the LPV/r monotherapy and 36 in the triple therapy group, all of whom gave birth to liveborn singletons (Figure 1). The 2 groups did not differ in terms of baseline demographics or obstetrical or HIV infection status (Table 1). Women in the monotherapy group tended to have less prior antiretroviral use, in particular PIs in a previous pregnancy, than those in the triple therapy group (43.5% vs 63.9%), but the difference was not statistically significant and no genotypic resistance to LPV was found. Screening median VL and CD4 cell count were 2952 copies/mL and 525 cells/μL, respectively.

Treatment was changed or stopped before 8 weeks in 4 patients in the monotherapy group (poor digestive tolerance, premature rupture of membranes, preterm labor without delivery, and poor compliance) and 4 in the triple therapy group, all for grade 3/4 toxicities. Changes after 8 weeks were due to virological failure at week 8 in accordance with the protocol (2 in each group), or for other reasons, all in the monotherapy group (poor compliance, addition of ZDV for an amniocentesis, false labor, detectable VL at week 12). At delivery, 59 (85.6%) women in the monotherapy group and 30 (83.3%) in the triple therapy group remained on the assigned regimen. All women received intrapartum ZDV except 1 in the monotherapy group. After delivery, 97% of women stopped ART.

The primary efficacy criterion was achieved (ITT analysis), as 62 women had VL <200 copies/mL at 34 GW in the monotherapy group (89.9%; 95% confidence interval [CI], 80.2%–95.8%; Table 2). The corresponding proportion in the triple therapy group was 94.4% (95% CI, 81.3%–99.3%), which was not significantly different.

Table 2. Maternal Virological Outcomes—Intent-to-Treat Analysis (ANRS 135 PRIMEVA)

Outcome	Monotherapy (n = 69)		Triple Therapy (n = 36)		*P* Value[a]
At 8 wk (primary endpoint)					
VL <200 copies/mL, % (No.) [95% CI][b]	89.9 (62)	[80.2–95.8]	94.4 (34)	[81.3–99.3]	.72
Not measured, % (no./No.)	4.3	3/69	0.0	0/36	
Max value	6900		1901		
Delivery					
VL <200 copies/mL, % (No.) [95% CI][b]	92.8 (64)	[83.9–97.6]	97.2 (35)	[85.5–99.9]	.66
VL <50 copies/mL, % (No.) [95% CI][b]	78.3 (54)	[66.7–87.3]	97.2 (35)	[85.5–99.9]	.01
Not measured, % (no./No.)	1.4	1/69	0.0	0/36	
Max value	890		2112		
4 wk postpartum[c]					
Median VL (range)	7661	(20–376 000)	1109	(18–23 896)	.01
Not measured, % (no./No.)	14.9	(10/67)[c]	5.9%	(2/34)[c]	
12 wk postpartum[c]					
Median VL (range)	3641	(77–368 000)	1903	(47–24 014)	.16
Not measured, % (no./No.)	14.9	(10/67)[c]	8.8	(3/34)[c]	

Abbreviations: ANRS, French National Agency for Research on AIDS and Viral Hepatitis; CI, confidence interval; PRIMEVA, Protease Inhibitor Monotherapy Evaluation; VL, viral load.

[a] *P* values were obtained with χ^2 test or 2-sided Fisher exact test for categorical variables, and Student *t* test or 2-sided Wilcoxon 2-samples test for continuous variables.

[b] 95% CI: exact confidence intervals for binomial variable.

[c] Among women who stopped antiretroviral therapy at delivery.

At delivery, the proportion did not differ between the 2 groups for VL <200 copies/mL (92.8% in the monotherapy group and 97.2% in the triple therapy group; $P = .66$). It was lower in the monotherapy group for VL <50 copies/mL (78.3% vs 97.2%; $P = .01$), with the same trend in the PP analysis (Supplementary Table 1). At 4 weeks postpartum after stopping treatment, the median VL was significantly higher in the monotherapy group than in the triple therapy group, a difference that was decreased at 12 weeks. No resistance to LPV/r was detected at 4 or at 12 weeks postpartum.

Gastric aspirates were tested for 67% of neonates (46 of 69 and 24 of 36, respectively) and there was no case of detectable HIV-1 RNA.

The median plasma trough LPV concentration was 4280 ng/mL (interquartile range [IQR], 2540–6130 ng/mL) at week 8 and 3615 ng/mL (IQR, 2487–5850 ng/mL) at delivery in the monotherapy group (Table 3). The concentration at delivery tended to be higher than in the triple therapy group. Nevertheless, the median ratios did not differ for cord/maternal blood between the monotherapy and triple therapy groups (0.18 vs 0.25, respectively; $P = .81$) or for amniotic fluid/cord blood (0.87 vs 0.99, respectively; $P = .55$). At 8 weeks of treatment, 20.8% of women reported having missed at least 1 pill during the 4 previous days or the 4 previous weeks (24.6% vs 13.9%; $P = .2$).

Changes in treatment due to toxicity were less frequent in the monotherapy than the triple therapy group (1.4% vs 11.1%; $P = .046$): 1 woman in each group for diarrhea and/or vomiting, 1 for toxidermia, and 2 for elevated liver enzymes in the triple therapy group (Table 4). Gestational age, mode of delivery, postnatal prophylaxis, maternal and infant severe adverse events, and grade 3/4 laboratory abnormalities did not differ between groups (Tables 4–6). Median maternal and neonatal mean corpuscular volumes at delivery were significantly lower in the monotherapy than in the triple therapy group, whereas median neonatal hemoglobin concentration at birth and number of leukocytes at month 3 were higher (Table 6).

Table 3. Lopinavir Plasma Concentrations and Adherence Indicators—Intent-to-Treat Analysis (ANRS 135 PRIMEVA)

Indicator	Monotherapy (n = 69)		Triple Therapy (n = 36)		*P* Value[a]
Maternal plasma trough LPV concentration at 8 study weeks (33–35 GW)					
Undetectable: % (no./No.)	3.6	(2/55)	10.3	(3/29)	.33
Concentration, ng/mL: median [IQR]	4280	[2540–6130]	3420	[2425–4180]	.14
Time gap, min: median [IQR]	780	[710–860]	810	[740–930]	.07
Maternal plasma trough LPV concentration at delivery					
Undetectable: % (no./No.)	9.3	(5/54)	7.7	(2/26)	1.0
Concentration, ng/mL: median [IQR]	3615	[2487–5850]	2475	[1470–4276]	.09
Time gap, min : median [IQR]	670	[350–975]	615	[370–930]	.92
Cord blood LPV concentration at delivery					
Undetectable: % (no./No.)	22.9	(11/48)	23.8	(5/21)	1.0
Concentration, ng/mL: median [IQR]	663	[100–1395]	290	[132–530]	.06
Time gap, min: median [IQR]	675	[375–900]	665	[435–859]	.78
Amniotic fluid LPV concentration at delivery					
Undetectable: % (no./No.)	27.9	(12/43)	25.0	(4/16)	1.0
Concentration, ng/mL: median [IQR]	300	[50–824]	344	[95–487]	.39
Time lag (minutes): median [IQR]	653	[375–944]	615	[385–735)	.62
Cord blood/maternal plasma ratio at delivery					
Both performed: % (no./No.)	53.6	(37/69)	44.4	(16/36)	.37
Ratio: median [IQR]	0.18	[0·08–0·35]	0·25	[0.05–0.41]	.81
Amniotic fluid/cord blood ratio at delivery					
Both performed: % (no./No.)	52.2	(36/69)	38.8	(14/36)	.20
Ratio: median [IQR]	0.87	[0.32–1.31]	0.99	[0.8–1.0]	.55
W8 self-reported missed pills in the last 4 d or in the last 4 wk					
At least once: % (no./No.)	24.6	(16/65)	13.9	(5/36)	.20
LPV/r drug dispensation between enrollment and delivery					
Below needed: % (no./No.)	8.7	(6/69)	17.1	(6/35)	.20

Abbreviations: ANRS, French National Agency for Research on AIDS and Viral Hepatitis; GW, gestational weeks; IQR, interquartile range; LPV, lopinavir.

[a] *P* values were obtained with χ^2 test or 2-sided Fisher exact test for categorical variables, and Student *t* test or 2-sided Wilcoxon 2-samples test for continuous variables.

Table 4. Maternal Adverse Events and Obstetrical and Delivery Outcomes—Intent-to-Treat Analysis (ANRS 135 PRIMEVA)

	Monotherapy (n = 69)		Triple Therapy (n = 36)		
Adverse Event/Outcome	Median	[Range] or % (No.)	Median	[Range] or % (No.)	*P* Value[a]
Duration of therapy, d					
All regimens	90	[50–111]	90	[57–111]	.92
LPV/r	90	[23–111]	88	[14–111]	.17
Change ARV for toxicity	1.4	(1)	11.1	(4)	.046
Any SAE between enrollment and delivery	26.1	(18)	38.9	(14)	.18
Obstetrical SAE	15.9	(11)	16.7	(6)	.92
Preeclampsia	0		2.8	(1)	
Gestational diabetes	1.4	(1)	5.6	(2)	
Placenta previa	4.3	(3)			
Gestational proteinuria	1.4	(1)			
HELLP syndrome	1.4	(1)			
Liver disorders	2.8	(2)	2.8	(1)	
Oligohydramnios			2.8	(1)	
Intrauterine hypoxia, unspecified			2.8	(1)	
Maternal care due to uterine scar	1.4	(1)			
False labor	2.8	(2)			
Complications of labor and delivery	1.4	(1)			
Preterm labor without delivery	1.4	(1)			
Preterm spontaneous labor and delivery	1.4	(1)	2.8	(1)	
Gestational age at delivery, wk					
Term delivery (≥37 wk)	89.9	(62)	88.9	(32)	.82
Moderate prematurity (33–36 wk)	8.7	(6)	11.1	(4)	
Severe prematurity (<32 wk)	1.5	(1)	0.0	(0)	
Median gestational age, wk	39	[32–41]	39	[35–41]	.88
Premature rupture of membranes	21.7	(15)	11.1	(4)	.18
Mode of delivery					
Vaginal	49.3	(34)	52.8	(19)	.62
Emergency cesarean delivery	21.7	(15)	13.9	(5)	
Planned cesarean delivery	29.0	(20)	33.3	(12)	
Reason for cesarean delivery					
Previous cesarean delivery	23.2	(16)	25.0	(9)	
Fetal heart rate anomalies	8.6	(6)	11.1	(4)	
Arrested labor or malpresentation	13.0	(9)	8.3	(3)	
MTCT prevention	2.9	(2)	2.8	(1)	
Instrumental delivery	2.9	(2/69)	5.6	(2/36)	.61
Intrapartum intravenous ZDV	98.6	(68/69)	100	(36/36)	1
Duration of intravenous ZDV, min	292	[50–1220]	373	[40–1165]	
Continued ART at 4 wk postpartum	1.5	(1/68)	5.6	(2/36)	.24
Reason for continuing ART					
HIV-negative partner		(1)			
Maternal indication				(2)	
SAE in postpartum period	26.1	(18)	36.1	(13)	.29
CD4 count at delivery, cells/mm^3					
Median [range]	610	[278–1150]	659	[391–1266]	.92
Mean difference since enrollment (SD)	166	(SD = 189)[b]	165	(SD = 189)[b]	.89
PP resistance-associated mutations					
ZDV	4.2	(2/48)	4.3	(1/23)	1

Table 4 continued.

Adverse Event/Outcome	Monotherapy (n = 69)		Triple Therapy (n = 36)		*P* Value[a]
	Median	[Range] or % (No.)	Median	[Range] or % (No.)	
3TC/FTC	0.0	(0/48)	4.4	(1/23)	.32
LPV/r	0.0	(0/48)	0.0	(0/23)	1

Abbreviations: 3TC/FTC, lamivudine/emtricitabine; ANRS, French National Agency for Research on AIDS and Viral Hepatitis; ART, antiretroviral therapy; ARV, antiretroviral; HELLP, hemolysis, elevated liver enzymes, and low platelet count; HIV, human immunodeficiency virus; LPV/r, lopinavir with ritonavir; MTCT, mother-to-child transmission; PP, postpartum; SAE, severe adverse event; SD, standard deviation; ZDV, zidovudine.

[a] *P* values were obtained with χ^2 test or 2-sided Fisher exact test for categorical variables, and Student *t* test or 2-sided Wilcoxon 2-samples test for continuous variables.

[b] $P < .001$, as tested by paired Student *t* test.

No transmission occurred in the monotherapy group (95% CI upper limit = 5.2%), but 1 case occurred in the triple therapy group (2.8%; 95% CI, .07%–14.5%). The mother's VL was 7730 copies/mL at baseline and <50 copies/mL at 8 weeks of LPV/r + ZDV/3TC, confirmed <50 copies /mL on day 1 postpartum. After spontaneous labor at 39 GW under

Table 5. Infant Outcomes—Intent-to-Treat Analysis (ANRS 135 PRIMEVA)

Outcome	Monotherapy (n = 69)		Triple Therapy (n = 36)		*P* Value[a]
	Median	[Range] or % (No.)	Median	[Range] or % (No.)	
Liveborn	100.0	(69/69)	100.0	(36/36)	1
Male sex	44.0	(31/69)	36.1	(13/36)	.38
Birthweight, g	3175	[1700–4110]	3143	[2255–3760]	.6
Height, cm	49	[40–53]	48	[44–54]	.43
Head circumference, cm	34	[30–37]	34	[30–37]	.94
Apgar score at 5 min	10	[7–10]	10	[8–10]	.72
Type of postnatal prophylaxis					
ZDV monotherapy ± NVP sd[a]	87.0	(59 + 1)	100	(36 + 0)[b]	.16
3TC monotherapy ± NVP sd[a]	1.4	(1 + 0)		0	
ZDV/3TC ± NVP sd[c]	8.7	(2 + 4)		0	
ZDV/3TC/LPV/r ± NVP sd[c]	2.·9	(1 + 1)		0	
Duration of PNP, d	37	(21–49)	42	[17–57)	.99
Hospitalization in first week	14.5	(10/69)	11.1	(4/36)	.77
Adverse events in first week					
Any	29.0	(20/69)	25.0	(9/36)	.66
Any in infants term born	20.3	(14/68)	19.4	(7/36)	.92
SAE	17.4	(12/69)	8.3	(3/36)	.21
Adverse events before 6 mo					
Any	49.3	(34/69)	47.2	(17/36)	.84
Any in infants term born	40.6	(28/68)	41.7	(15/36)	.91
SAE	26.1	(18/69)	22.2	(8/36)	.66
Congenital birth defects					
Reported by 6 wk of life	8.7	(6)	16.7	(6)	.33
Reported by 6 mo	14.5	(10)	22.2	(8)	.42

Abbreviations: 3TC, lamivudine; Apgar, appearance, pulse, grimace, activity, respiration; LPV/r, lopinavir/ritonavir; NVP, nevirapine; PNP, postnatal prophylaxis; SAE, severe adverse event; sd, single dose; ZDV, zidovudine.

[a] No. of neonates who received NVP sd in addition to regimen.

[b] Including 1 HIV-infected child who subsequently received LPV/r + ZDV/3TC.

[c] *P* values were obtained with χ^2 test or 2-sided Fisher exact test for categorical variables, and Student *t* test or 2-sided Wilcoxon 2-samples test for continuous variables.

Table 6. Maternal and Infant Biological Parameters—Intent-to-Treat Analysis (ANRS 135 PRIMEVA)

Parameter	Monotherapy (n = 69)				Triple Therapy (n = 36)				*P* Value[a]
	No.	Grade 3/4, % (No.)	Median	[Range]	No.	Grade 3/4, % (No.)	Median	[Range]	
Mothers									
Hemoglobin, g/dL									
Baseline (≤day 0)	69	0.0	10.7	[8.3–13.7]	36	0.0	10.7	[8.3–13.6]	.74
Delivery	69	0.0	10.2	[7.2–13.6]	36	2.8 (1)	10.5	[6.8–13.0]	.98
MCV, mm^3									
Baseline (≤day 0)	69		86	[62–99]	36		86	[59–94]	.31
Delivery	69		86	[71–104]	36		97	[69–110]	<.01
Leukocytes, cells/mm^3									
Baseline (≤day 0)	69	0.0	7090	[3600–11 420]	36	0.0	6655	[4000–11 420]	.23
Delivery	69	0.0	8000	[4290–13 970]	36	0.0	6755	[4100–11 400]	.03
Platelets, $10^3/mm^3$									
Baseline (≤day 0)	69	0.0	248	[111–394]	36	0.0	221	[123–314]	.02
Delivery	69	0.0	227	[123–458]	36	0.0	220	[115–461]	.81
Infants									
Hemoglobin, g/dL									
Birth	68	0.0	16.4	[10.9–21.6]	36	0.0	15.2	[12.1–20.4]	.09
12 wk	66	1.5 (1)	11.0	[8.4–13.0]	34	0.0	11.1	[9.3–13.5]	.71
MCV, mm^3									
Birth	67		98	[80–115]	35		113	[90–124]	<.01
12 wk	66		81	[69–92]	33		84	[64–91]	.80
Leukocytes, cells/mm^3									
Birth	67	0.0	9080	[3590–21 700]	36	0.0	8430	[5400–20 600]	.88
12 wk	66	0.0	10 100	[6600–22 200]	33	0.0	8690	[4950–15 800]	.03
Platelets, $10^3/mm^3$									
Birth	67	0.0	286	[108–499]	35	0.0	290	[175–440]	.30
12 wk	66	0.0	454	[258–765]	33	0.0	457	[239–787]	.90
AST, U/L									
Birth	68	0.0	51	[30–117]	33	0.0	44	[6–89]	.04
12 wk	61	0.0	38	[20–84]	29	0.0	34	[23–94]	.24
ALT, U/L									
Birth	68	0.0	15	[5–47]	34	0.0	18	[6–44]	.77
12 wk	61	0.0	26	[9–68]	30	0.0	26	[13–97]	.58
Bilirubin, mmol/L									
Birth	42	0.0	68	[7–197]	23	0.0	99	[12–204]	.05
12 wk	34	0.0	6	[2–17]	16	0.0	5	[2–8]	.09
Lactate, mmol/L									
12 wk	43		2.3	[0.9–5.2]	27		2·5	[1.2–5.5]	.45
Lipase, U/L									
Birth	57	0.0	22	[4–202]	29	0.0	27	[6–185]	.40
12 wk	61	0.0	16	[4–255]	28	0.0	16	[7–170]	.96
LDH, U/L									
Birth	43		706	[338–1311]	24		728	[342–1499]	.65
12 wk	45		423	[215–860]	24		446	[147–1035]	.99
Creatinine, mmol/L									
Birth	58	0.0	46	[15–67]	29	0.0	47	[8.9–71]	.47
12 wk	63	0.0	26	[4–49]	30	0.0	23	[10–40]	.27

Table 6 continued.

Parameter	Monotherapy (n = 69)				Triple Therapy (n = 36)				*P* Value[a]
	No.	Grade 3/4, % (No.)	Median	[Range]	No.	Grade 3/4, % (No.)	Median	[Range]	
CPK, U/L									
Birth	49	0.0	364	[103–1874]	28	0.0	262	[71–647]	.10
12 wk	47	0.0	146	[67–295]	24	0.0	139	[65–283]	.80

Abbreviations: ALT, alanine aminotransferase; ANRS, French National Agency for Research on AIDS and Viral Hepatitis; AST, aspartate aminotransferase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; MCV, mean corpuscular volume.

[a] Comparison of quantitative values: *P* values were obtained with Student *t* test or 2-sided Wilcoxon 2-samples test.

intravenous ZDV, the mother vaginally delivered a healthy female after 8 hours of membrane rupture. The neonate was diagnosed with HIV at 4 weeks with a VL of 11 000 copies/mL while taking ZDV prophylaxis. Combination ART was quickly started with good tolerance and efficacy. The sample from day 4, initially tested negative, was retested weakly positive for HIV DNA, suggesting late in utero transmission. No gastric aspirate was available for this child.

DISCUSSION

This is the first randomized trial to evaluate an NRTI-sparing strategy of antiretroviral monotherapy during pregnancy for PMTCT of HIV-1. We showed that this strategy achieved satisfactory virologic efficacy at 8 weeks of treatment, with 90% of women achieving VL <200 copies/mL at 34 GW. Moreover, although the trial was not designed to show equivalence, the proportion was on the same order as with triple therapy.

When considering a VL <50 copies/mL at delivery, the result was better in the triple than in the monotherapy group (97.2% vs 78.3%; $P = .01$). Nonetheless, all but 1 patient in the monotherapy group achieved a VL <200 copies/mL. This is consistent with results reported for LPV/r monotherapy in a randomized trial conducted among nonpregnant patients failing nonnucleoside reverse transcriptase inhibitor–based cART [27]. Concerning pregnant women, these results compare favorably with those from the French Perinatal Cohort [20] and other observational cohorts from high-income countries, where the proportion with VL>50 copies/mL at delivery ranged from 13% to 44% [28, 29]. Although increasingly sensitive methods for HIV-1 RNA quantification have led clinicians to request VL <50 copies/mL before delivery, there is no evidence that it is more effective to prevent MTCT in comparison with the thresholds of 200 or 400 copies/mL [5]. Cutoffs to recommend elective cesarean delivery vary in guidelines from 1000 copies/mL in the United States and 400 copies/mL in France to 50 copies/mL in the United Kingdom [30]. Benchmarks for virological success in nonpregnant patients are <400 copies/mL after 3 months of ART and 50 copies/mL within 6 months according to French guidelines [1], and virologic responses do not differ between pregnant and nonpregnant women [31]. One approach to maximize the likelihood of obtaining a VL below the limit of quantification of available assays would be to select women with lower VL, as suggested by our results, which showed that 32 of 34 women with baseline VL <3000 copies/mL in the monotherapy group achieved VL <50 at delivery (data not shown). However, this criterion would exclude a majority of women. Another approach with larger indications would be to initiate monotherapy earlier than 26 GW to allow for earlier control of maternal VL, which has been shown to be an important determinant of PMTCT efficacy [5, 29, 32]

With the standard 400/100 mg dosage of LPV/r, median plasma trough concentrations of LPV were above the recommended level in both groups [33]. This contrasts with previous observational reports [34, 35].

Unexpectedly, maternal plasma LPV concentrations at delivery were higher in the monotherapy than in the triple therapy group, although the interval between drug intake and delivery did not differ between the 2 groups. Interactions have not been described between LPV/r and ZDV/3TC. This difference might reflect better adherence in the monotherapy group, but self-reported adherence and pill count were similar in both groups. There is controversy concerning dosage of LPV/r, because plasma concentrations have been shown to decrease during pregnancy [1–3]. Our findings suggest that a standard dose is sufficient in women harboring wild-type HIV strains. Our results confirm the low placental transfer of LPV, as well as the lack of drug placental accumulation [25, 36]

The benefit in terms of tolerance is a low drug exposure for the fetus. The disadvantage would be the lack of pre/postexposure prophylaxis. Decades ago, when using ZDV monotherapy despite its small impact on maternal HIV-RNA, it was shown that PMTCT required transfer of ZDV to the fetus [12, 37]. This paradigm could be different using boosted PIs, which

effectively control HIV replication and thus reduce perinatal exposure to the virus. It is reassuring to note that we did not detect HIV in any available neonatal gastric aspirate, contrary to what was reported following ZDV monotherapy [38]. This suggests that most infants in the LPV/r monotherapy group were not exposed to HIV during delivery.

The proportion of women who changed therapy because of toxicity was significantly higher with triple therapy, possibly reflecting the cumulative risk of several antiretrovirals. Hemoglobin at birth was lower in infants exposed to NRTI, which is consistent with the original placebo-controlled randomized study [12]. Concerning long-term effects of in utero exposure, our study was limited by the fact that all children received postnatal ZDV prophylaxis. A potential weakness was the risk of detecting spurious instances of $P < .05$ resulting from the large number of comparisons performed in relation to the number of patients; however, the only differences we found were expected. Further substudies are under way to test for mitochondrial damage and genotoxicity.

In France, as well as in other industrialized countries, most HIV-infected women are now treated before becoming pregnant, as therapy is recommended for CD4 cell counts <500 cells/μL. The ANRS 135 Primeva results are a step toward the proof of concept that PMTCT without NRTIs might be an alternative for pregnant immunocompetent women with spontaneously low VLs. Further research directions include the removal of ZDV in its intrapartum and postnatal components and the evaluation of boosted PI monotherapy as treatment simplification or as a switch-therapy in women successfully treated with cART before conception. From the perspective of resource-poor settings, where PMTCT of HIV is a major public health challenge, strategies requiring serial VL monitoring appear unrealistic. However, the present study may open the way for other novel nucleoside-sparing strategies, which could be more widely applicable to prevent infant HIV infections worldwide.

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

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Author contributions. R. T., L. M., S. B., and J. W. designed the trial and wrote the draft of the report. R. T., J. W., and S. D. coordinated the trial and the monitoring of the study. J. W. and J. L. analyzed the data and did the statistical analysis. R. T., L. M., D. E., and E. B. recruited patients and obtained the data. C. R. and M.-L. C. coordinated the virological analysis. D. H. and J.-M. T. coordinated the pharmacological analysis. All authors contributed to interpretation of data and reviewed the report.

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