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Maintenance darunavir/ritonavir monotherapy to prevent perinatal HIV transmission, ANRS-MIE 168 MONOGEST study

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Objectives: Because NRTIs can have fetal toxicities, we evaluated a perinatal NRTI-sparing strategy to prevent perinatal HIV transmission. Our primary objective was to determine the proportion maintaining a viral load (VL) of <50 copies/mL up to delivery on darunavir/ritonavir monotherapy, without requiring treatment intensification.

Methods: In a one-arm, multicentre Phase 2 clinical trial, eligible patients in the first trimester of pregnancy on ART with plasma VL < 50 copies/mL received maintenance monotherapy with darunavir/ritonavir, 600/100 mg twice daily. VL was monitored monthly. ART was intensified in the case of VL > 50 copies/mL. Neonates received nevirapine prophylaxis for 14 days.

Results: Of 89 patients switching to darunavir/ritonavir monotherapy, 4 miscarried before 22 weeks' gestation, 2 changed treatment for elevated liver enzymes without virological failure, and 83 were evaluable for the main outcome. Six had virological failure confirmed on a repeat sample (median VL = 193 copies/mL; range 78–644), including two before switching to monotherapy. In these six cases, ART was intensified with tenofovir disoproxil fumarate/emtricitabine. The success rate was 75/83, 90.4% (95% CI, 81.9%–95.7%) considering two patients with VL missing at delivery as failures, and 77/83, 92.8% (95% CI, 84.9%–97.3%) when considering them as successes since both had undetectable VL on darunavir/ritonavir throughout pregnancy. In ITT, the last available VL before delivery was <50 copies/mL in all of the patients. There was no case of perinatal HIV transmission.

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Conclusions: Darunavir/ritonavir maintenance monotherapy required intensification in nearly 10% of cases. This limits its widespread use, thus other regimens should be evaluated in order to limit exposure to antiretrovirals, particularly NRTIs, during pregnancy.

Introduction

Viral suppression throughout pregnancy with ART eliminates perinatal transmission (PT) of HIV, regardless of the number or type of antiretroviral drugs.[1] Current guidelines recommend triple therapy with two NRTIs for pregnant women living with HIV, associated with a boosted PI (PI/ritonavir), an NNRTI or an integrase strand transfer inhibitor (INSTI).[2–4] In France, the first-line association was two NRTIs and a PI/ritonavir since the early 2000s.[5]

However, NRTI-related toxicities are reported in fetuses and neonates,[6] including mitochondrial toxicities following exposure to zidovudine and lamivudine in clinical[7,8,9,10] and experimental studies.[11,12] Nuclear DNA alterations are reported in cord blood cells with zidovudine and tenofovir.[13,14] Long-term follow-up of children exposed to zidovudine *in utero* has shown conflicting evidence of subclinical myocardial dysfunction.[15,16,17] Exposure to didanosine, an NRTI which is no longer used, was associated with some childhood cancers.[18] There are conflicting reports of an association between tenofovir exposure and altered growth and bone mineral content.[19,20] Also, postnatal zidovudine as prophylaxis is related to haematological abnormalities [21,22] and hyperlactataemia[23] in infants.

Paradoxically, despite known toxicities, NRTIs are still recommended in pregnancy and for neonatal prophylaxis. No NRTI-sparing regimen has yet been studied in pregnant women, except for a randomized controlled trial of lopinavir/ritonavir monotherapy.[24,25]

The intrapartum component of PT prevention with zidovudine is not required when maternal plasma viral load (VL) is suppressed.[26] For postnatal prophylaxis, zidovudine remains standard care in most countries, but nevirapine prophylaxis is now an option in France,[5,27] based on reassuring neonatal data.[28,29,30,28,31]

After *in utero* exposure to PIs, no fetal toxicity was described except for increased bilirubinaemia with atazanavir/ritonavir.[32] Placental transfer of PIs is lower than for NRTIs.[33] There is now a long experience on the use of darunavir/ritonavir during pregnancy.[34–38,39,40] Dual therapy with darunavir/ritonavir and lamivudine or emtricitabine was reported in a small retrospective study.[41]

Ritonavir-boosted darunavir monotherapy has been used in non-pregnant persons for its virological potency, tolerability and high genetic barrier to resistance NRTI-sparing therapy but has not been previously studied in pregnancy. With darunavir/ritonavir monotherapy, 80% to 90% of patients[42,43] maintained viral suppression at 48 to 96 weeks. In cases of virological failure, the risk of emergence of drug-resistance mutations was low and resumption of triple therapy was effective.

The purpose of this study was to evaluate, in women starting pregnancy with suppressed viraemia on combination ART, an NRTI-sparing maintenance strategy using darunavir/ritonavir monotherapy during pregnancy and nevirapine monotherapy as neonatal prophylaxis.

The primary objective was to estimate the proportion of women maintaining a VL of <50 copies/mL until delivery after switching to darunavir/ritonavir monotherapy early in pregnancy, without requiring treatment intensification for virological failure. Secondary objectives were to estimate the proportion of women with VL < 50 copies/mL at delivery in ITT, the proportions of miscarriage, of treatment changes for intolerance or other reasons, to identify factors associated with virological failures, and to determine darunavir and ritonavir plasma concentrations.

Methods

A one-arm, open-label, multicentre Phase II clinical trial was performed in 24 ANRS-MIE EPF centres in France.

Study population and intervention

Patients in the first trimester of pregnancy with HIV-1 and long-term antiretroviral success were informed about the study by their providers; those who consented were assessed for eligibility at the screening visit, and if eligible were offered enrolment with informed written consent.

Eligibility

Inclusion criteria were pregnancy, gestational age under 15 weeks, maternal age ≥18 years, documented HIV-1 infection, current treatment with at least two ARVs, viral suppression for at least 12 months, defined by VL < 50 copies/mL (a single value between 50 and 399 copies/mL was not an exclusion criterion if followed by two successive VL < 50 copies/mL at least 1 month before enrolment), CD4 cells ≥250 cells/mm^3, healthcare coverage and informed written consent. The inclusion criteria for enrolment of the neonate in the paediatric component of the study were enrolment of the mother in the trial, and informed written consent by both parents or legal guardians.

Non-inclusion criteria were infection with HIV-2, age <18 years, HIV-1 plasma VL of (i) >50 copies/mL at screening; or (ii) >400 copies/mL or between 50 and 399 copies/mL on two consecutive measurements in the last 12 months, CD4 count <250 cells/mm^3, history of CD4 count nadir <200 cells/mm^3, history of treatment failure, intolerance to darunavir or ritonavir, HBV coinfection (HBsAg positive and/or detectable HBV DNA), history of resistance to any PI or to nevirapine, intended absence from the study centre, or person under a legal guardianship. Infants were excluded from the paediatric component of the study in the absence of consent by both parents or legal guardians.

Study regimen and follow-up

The maternal regimen was darunavir/ritonavir (600/100 mg orally twice daily). Women on darunavir/ritonavir-based ART combination therapy switched directly to darunavir/ritonavir monotherapy. Women who were taking other ART combinations replaced their third antiretroviral (PI/ritonavir, NNRTI or INSTI) with darunavir/ritonavir 600/100 mg twice daily, while maintaining the previous NRTI backbone to check for tolerance. If clinical tolerance of darunavir/ritonavir was satisfactory after 2 weeks, the NRTIs were stopped. In the case of intolerance, another ART was decided by the investigator, and follow-up was continued.

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Plasma HIV VL was monitored monthly, according to usual pregnancy guidelines. In the case of VL ≥ 50 copies/mL, testing was repeated within 14 days. If the VL was <50 copies/mL, darunavir/ritonavir monotherapy was continued, whereas if it remained ≥50 copies/mL, treatment was intensified. The choice of the intensified regimen was left up to the clinicians.

At delivery, no intrapartum zidovudine was added if the most recent maternal VL was below 50 copies/mL, except for complications such as chorioamnionitis or intrapartum haemorrhage, according to French guidelines.[5]

After delivery, the choice of maternal ART was left up to the clinician and patient. As recommended in France, there was no breastfeeding.

Neonatal prophylaxis

Neonates received prophylaxis with nevirapine once daily for 14 days at a fixed dose: 15 mg for birthweights of >2.5 kg, 10 mg for between 2 and 2.5 kg and 2 mg/kg/day for <2 kg, according to French[5] and WHO guidelines.[44] Preterm neonates (before 37 weeks of gestation, WG) received 4 weeks of zidovudine prophylaxis. In the case of maternal virological failure, usual guidelines were to be applied.[5] Enrolment of neonates required additional consent from both parents. In the case of the co-parent not signing consent, particularly when the mother did not accept to inform the co-parent of her HIV status, infant prophylaxis was prescribed by their paediatrician following usual guidelines.

Maternal study visits were monthly with the obstetrician and HIV specialist as per usual care, with physical examination and biology, including plasma HIV-1-RNA, blood cell counts, liver enzymes, creatinine, urine albumin, CD4/CD8 counts at each trimester, first-trimester TORCH screening, and hepatitis C and hepatitis B, with HBV DNA testing in the case of positive anti-HBc antibodies, even when HBsAg was negative. Gestational diabetes was screened with a 75 g oral glucose challenge test at 24–28 WG. A six-point self-completed questionnaire for adherence was administered at each visit. Additional visits were performed in the case of VL increase or biological or clinical anomalies.

Total HIV-1 DNA was quantified on stored samples by ultrasensitive quantitative PCR (qPCR) in blood samples collected at enrolment and at delivery with the Generic DNA cell Biocentric assay.[45] Plasma HIV-1 RNA was quantified by ultrasensitive RT–PCR on large plasma volumes adapted on the Alinity m HIV-1 assay (Alinity m HIV-1) (quantification threshold: 6 copies/mL).

Infants' follow-up was according to practice guidelines[46] until 6 months, with physical and biological tests including HIV-1-RNA and/or DNA PCR for diagnosis of HIV status.[47]

Endpoints

The primary endpoint was the rate of maternal plasma VL < 50 copies/mL maintained until delivery after switching to darunavir/ritonavir monotherapy, without requiring treatment intensification for virological failure.

Secondary endpoints were the proportion of plasma VL < 50 copies/mL at delivery in an ITT analysis, treatment changes for intolerance, toxicity or other reasons, and factors associated with virological failure. Pregnancy outcomes were described. Any case of mother-to-child transmission was to be considered as a serious adverse event and analysed immediately.

Determination of darunavir and ritonavir plasma concentrations

Total darunavir and ritonavir and unbound (darunavir only) plasma concentrations were determined at Day 0, Week (W)4, W24–28, W32 and delivery, 12 h after the last drug intake (C_{min}) by UPLC coupled with tandem MS (Waters Acquity UPLC-TQD, Milford, MA, USA).[48,49]

Plasma protein binding analysis involved an ultrafiltration assay (Centrifree®; Millipore, Molsheim, France). Limits of quantification (LOQs) were 5 ng/mL for darunavir and 10 ng/mL for ritonavir. Total darunavir C_{min} values were interpreted according to the 10-fold *in vitro* protein binding-corrected median effective concentration required to induce 50% virological response (EC_{50}) of 550 ng/mL.[49]

Statistical methods

The trial was designed as a one-stage Phase 2 trial, with an expected observed success rate of 95%, power set at 80% and a two-sided alpha of 5% for the exact test of the comparison of the observed proportion of success against the minimum bound of success set at 85%. The 95% CI of proportions was estimated using the exact Clopper–Pearson method for binomial proportion. We initially planned to recruit 120 evaluable patients, but based on the accrual rate, the protocol was amended to enrol a minimum of 80 evaluable patients.

The primary analysis concerned the proportion of virological success defined by a VL of <50 copies/mL at childbirth among women who remained on darunavir/ritonavir monotherapy, excluding miscarriages before 22 WG and/or treatment changes for intolerance. The protocol planned to consider values not measured within 7 days of delivery as failures in the primary analysis and to perform a case-by-case review of such cases if all VLs during the pregnancy were <50 copies/mL.

The proportion of virological success was also estimated in a secondary ITT analysis among all women who were enrolled to monotherapy, regardless of subsequent changes.

Initial characteristics potentially associated with virological failure were analysed by comparing percentages (categorical variables), means and medians (continuous variables) between women with failure and women whose darunavir/ritonavir monotherapy was maintained until delivery. Analyses were carried out with the software SAS® V9 and STATA® V11.

Ethics

All women were enrolled with their informed, written consent. The trial was registered (EudraCT # 2015-002542-31, Clinicaltrials.gov #NCT02738502) and was approved by the Committee for Protection of Persons (CPP Ile de France VII) on 22 January 2016 and the French Medicines Agency on 17 December 2015.

Results

We enrolled 91 women between 6 June 2016 and 4 June 2019 (Figure 1), at a median of 14 WG (IQR 12–15). Ten women who started their pregnancies with regimens not containing darunavir/ritonavir first switched to darunavir/ritonavir-based triple therapy for 2 weeks before stopping the NRTI component. Another 81 with darunavir/ritonavir-based regimens at screening switched directly to darunavir/ritonavir monotherapy. Two patients did not proceed to darunavir/ritonavir monotherapy, one for elevated liver enzymes at enrolment, and another because of a miscarriage. Overall, 89 women started darunavir/ritonavir monotherapy, among whom 4 had miscarriages before 22 WG.

Among 85 women who delivered at 22 WG or later, 2 had elevated liver enzymes and switched to tenofovir disoproxil fumarate/emtricitabine + raltegravir (400 mg twice daily), including one who withdrew her consent at 26 WG, so no subsequent data are available. Both had VL < 50 copies/mL at the time of switch. Thus, 84 patients were followed until delivery and 83 were evaluable for the primary endpoint.

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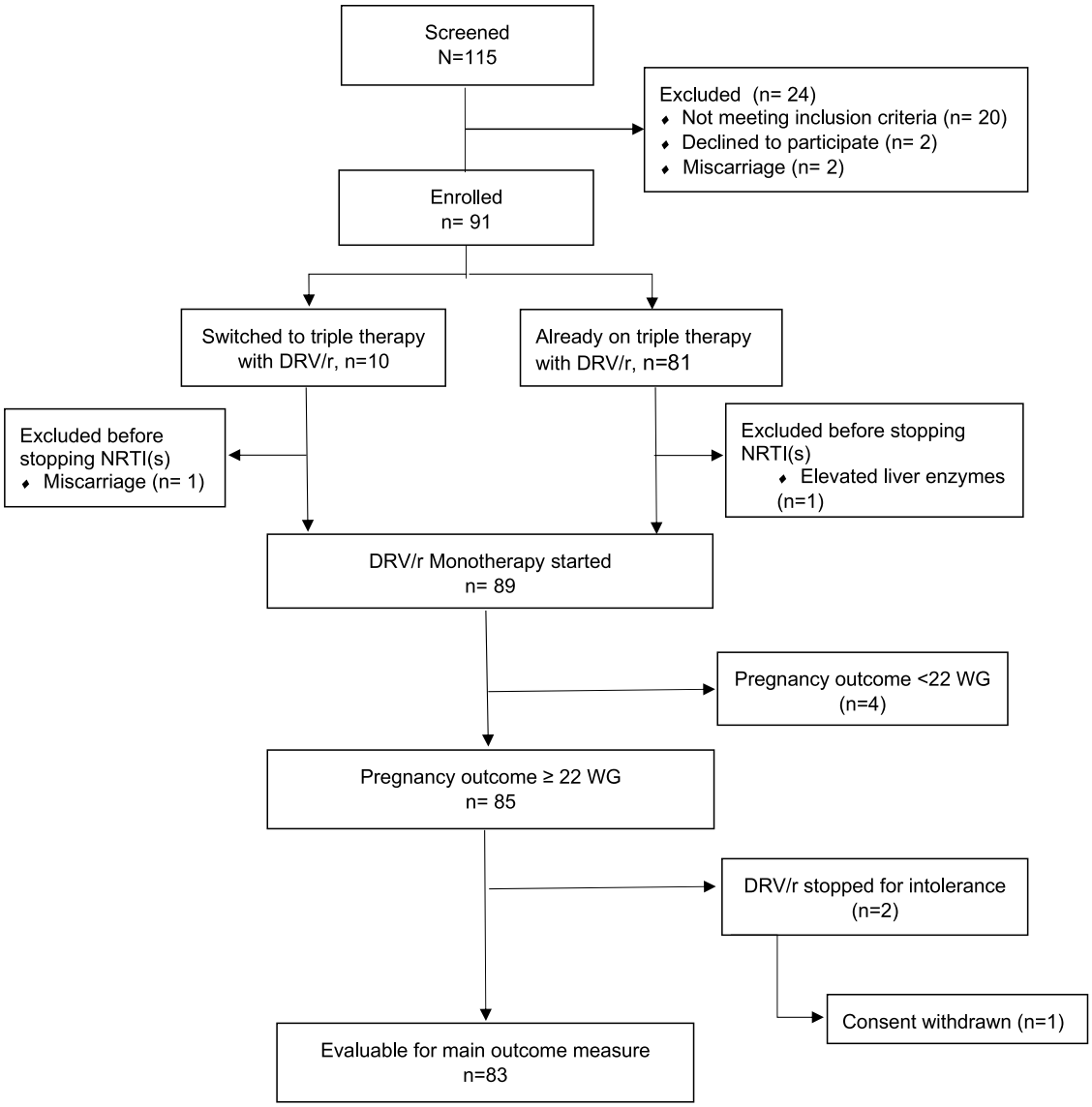

Figure 1. Flow chart for Monogest ANRS 168 study.

Characteristics at enrolment are described in Table 1. Baseline characteristics of women who miscarried did not differ from the overall population and none stopped darunavir/ritonavir monotherapy for adverse effects or virological failure.

Pregnancy outcomes were unremarkable, including preterm birth, birthweight, (Table 2). In two cases, IV zidovudine was administered because of placental bleeding during labour.

Virological endpoints

Treatment was intensified for virological failure in 6/83 (median VL = 193 copies/mL; range 78–252, confirmed on a second sample with a median VL of 178 copies/mL, range 64–1703) (Table 3). Another two patients had VL missing at delivery; both had monthly undetectable VL on darunavir/ritonavir throughout their pregnancies, including 33 and 13 days before delivery. When considering them as failures, the success rate was 75/83, 90.4% (95% CI with the binomial exact method, 81.9%–95.7%), which was not significantly greater than the minimum success rate, which we had set at 85% (exact two-sided test, $P = 0.22$). When considering them as successes, the success rate was 77/83, 92.8% (95% CI with the binomial exact method, 84.9%–97.3%). This 92.8% success rate was greater, according to the exact two-sided test, than the minimum success rate as defined in the study protocol ($P = 0.047$).

Among women who maintained viral suppression through delivery, five had a single VL measurement ≥50 copies/mL during the pregnancy with subsequent values <50 copies/mL without ART change, thus considered as viral blips.

For three patients, VL was already ≥50 copies/mL on the day of starting monotherapy (Table 4). When checked within the following 2 weeks according to the protocol, one virological failure

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Table 1. Characteristics of 89 women starting nucleoside-sparing therapy with darunavir/ritonavir, Monogest ANRS 168 study

	% or median (IQR)	*N*
Demographics		
Maternal age, years	35 (31–39)	89
Maternal weight at starting pregnancy, kg	68 (60–77)	87
Country of birth		
France, mainland	20.2	18
Sub-Saharan Africa	70.8	63
Other	9.0	8
Professional activity		
No	28.1	25
Yes	69.7	62
Unknown	2.2	2
Marital status		
Single	12.4	11
Cohabitating	87.6	78
Gravidity at enrolment		
Primigravida	9.0	8
Secundigravida	19.1	17
Multigravida	71.9	64
Parity at enrolment		
Nullipara	23.7	21
Primipara	27.0	24
Multipara	49.4	44
History of preterm delivery		
No	87.6	78
Yes	7.9	7
Unknown	4.5	4
HIV infection characteristics		
Time since first ARV regimen, months	72 (42–112)	89
Time with plasma HIV-RNA <50 copies/mL, months	43 (26–73)	89
CD4 count (cells/mm^3)		
Lowest recorded in patient's history	367 (297–482)	89
CD4 at screening	685 (534–850)	89
HIV-RNA at screening		
<50 copies/mL	100.0	89
HIV-RNA at start of monotherapy		
< 50 copies/mL	94.4	84
≥50 copies/mL	3.4	3
Not measured	2.2	2
Total HIV-DNA at start of monotherapy, log copies/10^6 PBMCs	2.45 (2.16–2.90)	80
Type of ART regimen at conception		
Dual	4.5	4
Triple	95.5	85
Duration of ART regimen used at the time of conception, months	17 (9–28)	89
NRTI at conception		
Tenofovir disoproxil fumarate + emtricitabine	79.8	71
Abacavir + lamivudine	15.7	14
Lamivudine	2.2	2
Emtricitabine	1.1	1
No NRTI	1.1	1
Associated antiretrovirals at conception		
Darunavir/ritonavir	33.7	30
Atazanavir/ritonavir	5.6	5
Nevirapine	2.2	2
Rilpivirine	31.5	28
Raltegravir	2.2	2
Dolutegravir	9.0	8
Elvitegravir/cobicistat	14.6	13
Etravirine + raltegravir	1.1	1
Darunavir introduction		
Before conception	33.7	30
Between conception and enrolment	56.2	50
Started at enrolment (switch)	10.1	9

was confirmed and treatment was intensified (with a delay of 56 days) and two patients had VL < 50 copies/mL, one of whom had virological failure 140 days later requiring treatment intensification, while the other maintained virological success on monotherapy. Among the six patients with virological failure, the time from darunavir/ritonavir monotherapy to virological failure ranged from 0 to 139 days (Table 4).

Treatment intensification consisted of adding tenofovir disoproxil fumarate/emtricitabine to darunavir/ritonavir and was successful in all six patients. In ITT analysis, the last VL during the pregnancy was below 50 copies/mL for all (88/88) patients enrolled on darunavir/ritonavir monotherapy (excluding one who withdrew consent).

The 6 women who required ART intensification had a lower median baseline CD4 cell count (516 versus 725 cells/mm^3, respectively; $P = 0.027$), and had a higher proportion of highly sensitive VL ≥ 6 copies/mL at enrolment (50% versus 11.8%, $P = 0.038$), compared with the 77 women who maintained virological suppression on monotherapy (Table 5). The PBMC-associated HIV-DNA concentration was not significantly higher in the failure group. Genotyping resistance testing was performed for the six cases of virological failure, showing no acquisition of resistance-associated mutations. There were one or more issues with treatment adherence in all six patients who had virological failure; however, adherence issues did not differ significantly from the patients who maintained virological success (data not shown).

Pharmacological results

Total and unbound darunavir C_{min} post darunavir/ritonavir (600/100 mg twice daily) regimen were stable throughout pregnancy (Table 6). They were adequate, with total darunavir C_{min} > 550 ng/mL in all women except two at W4 and one at W24–28. Unbound darunavir C_{min} values were >55 ng/mL in all women except one at W4, one at W24–28, one at W32 and one at

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Table 2. Pregnancy outcomes in 89 women starting nucleoside-sparing therapy with darunavir/ritonavir, Monogest ANRS 168 study

	% or median (IQR)	*N*
Clinical events during pregnancy		
Pre-eclampsia	5.6	5
Diabetes mellitus	16.9	15
Cholestasis (grade ≥3)	2.2	2
HELLP syndrome	1.1	1
Elevated liver enzymes (grade ≥3) without cholestasis or HELLP	7.9	7
Anaemia (grade ≥3)	0	0
Outcomes		
Miscarriages <22 WG	4.5	4
Live births	95.4	84
Unknown (consent withdrawn)		1
Among 88 women[a]		
Post-partum haemorrhage	5.7	5
Among 84 deliveries >22 WG[a]		
Birth defects		
No birth defects	96.4	81
Congenital diaphragmatic hernia and pulmonary sequestration	1.2	1
Hydronephrosis	1.2	1
Skin haemangioma	1.2	1
Gestational age at delivery		
Preterm deliveries (32–36 WG)	9.5	8
Term deliveries (≥37 WG)	90.5	76
Mode of delivery		
Vaginal delivery	69.0	58
Emergency Caesarean section	15.5	13
Planned Caesarean section	15.5	13
Intrapartum prophylaxis		
None	95.2	80
Zidovudine	4.8	4
Neonate		
Weight (g)	3170 (2820–3465)	84
Length (cm)	50 (48–51)	73
Head circumference (cm)	35 (33–36)	76
Low birthweight (< 2500 g)	9.5	8
Small for gestational age (<10th centile)	8.3	7

HELLP, haemolysis/elevated liver enzymes/low platelets.
[a]Follow-up beyond 26 WG not reported for one patient who withdrew consent.

delivery. Trough darunavir concentrations in the six failures, at enrolment, W4 and nearest to the failure, were not lower than in patients who maintained virological success.

Adverse events

In addition to the 2 cases where darunavir/ritonavir was stopped for intolerance, there were 10 cases of liver enzyme elevation, of which 3 were attributable to pregnancy-related conditions (1 case of pre-eclampsia with HELLP syndrome and 2 cases of cholestasis of pregnancy) and 7 that were not explained by hepatitis or pregnancy-related conditions. The rate of preterm delivery was 9.5% and the rate of birth defects was 3.6%. No cases of mother-to-child transmission were reported.

Discussion

Main findings

Treatment with darunavir/ritonavir monotherapy was successful in 90.4% when considering two missing VLs at delivery as failures, and 92.8% in the sensitivity analysis counting the two patients with missing VLs at delivery as successes since they had virological suppression throughout the pregnancy. The success rate was significantly higher than the minimal success rate set in the study protocol in the sensitivity analysis, but not in the primary analysis.

ITT analysis showed that no patient had plasma HIV-RNA above 50 copies/mL near delivery. This is reassuring regarding the risk of PT, providing monthly monitoring of maternal VL, as recommended for all pregnant women with HIV.[5]

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Table 3. Virological outcomes in 85 women starting nucleoside-sparing therapy with darunavir/ritonavir and pregnancy outcome ≥22 WG, Monogest ANRS 168 study

	N	%	95% CI
Darunavir/ritonavir monotherapy changes before delivery			
No change	77	90.6	82.3–95.8
Changed for intolerance	2	2.4	
Changed for inefficacy	6	7.1	
HIV-RNA at delivery (−8 to +7 days)			
<50 copies/mL	82	96.5	90.0–99.3
>50 copies/mL	0	0.0	
Unknown at delivery (−8 to +7 days)[a]	3	3.5	
Last HIV-RNA at, or before, delivery			
<50 copies/mL	85	100.0	95.8 to <100
Primary endpoint among 83 evaluable patients			
With missing HIV-RNA at delivery = failure			
Success	75	90.4	81.9–95.7
Failure (including 2 missing VL)	8	9.6	
With missing HIV-RNA at delivery as success			
Success (VL < 50 copies/mL with no darunavir/ritonavir change)	77	92.8	84.9–97.3
Failure	6	7.2	

[a]One for consent withdrawn at 26 WG with last HIV-RNA <50 copies/mL at 26 WG; two with last available HIV-RNA at 13 and 33 days before delivery (both <50 copies/mL).

Table 4. Characteristics of six patients with virological failure on darunavir/ritonavir monotherapy in pregnancy, Monogest ANRS 168 study

Conception	Therapy at conception	1 DRV/r + TDF/FTC	2 DRV/r + TDF/FTC	3 RPV/TDF/FTC	4 EVG/r + TDF/FTC	5 RPV/TDF/FTC	6 NVP + TDF/FTC
Screening	HIV RNA, copies/mL	<40	<40	<40	<20	<40	<20
	CD4 nadir, cells/mm^3	282	467	271	394	224	631
	CD4, cells/mm^3	435	619	5071	530	503	621
	Time on ART, months	93	15	34	37	39	112
At start of DRV/r	Time from screening, days	7	46	17	6	8	21
	HIV-RNA, copies/mL	225[a]	<40	<40	<20	<40	425[b]
	Ultrasensitive HIV RNA, copies/mL	133	+ <6	+ <6	+ <6	8	not measurable[c]
	HIV DNA, copies/10^6 PBMCs	272	882	243	55	811	1544
Virological failure	Gestational age at viral failure, weeks	15	33	26	37	29	37
	First VL > 50 copies/mL	225	161	644	78	252	126
	Days from start of DRV/r	0	126	74	149	98	139
	Second VL > 50 copies/mL	613	267	1703	64	89	70
	Days from start of DRV/r	7	131	88	162	112	141
	Darunavir C_{min}, ng/mL[d]	1859	3200[e]	2150	1427	2358	4161
	Ritonavir C_{min}, ng/mL[d]	161	1023[e]	218	72	321	88
	Time to intensification, days	56	134	88	165	119	141
	ART intensification after virological failure	DRV/r + TDF/FTC	DRV/r + TDF/FTC	DRV/r + TDF/FTC	DRV/r + TDF/FTC	DRV/r + TDF/FTC	DRV/r +TDF/FTC
At delivery	HIV RNA at delivery, copies/mL	<40	<40	<40	<40	<40	<20
	Ultrasensitive HIV RNA, copies/mL	< 6	Not done	<6	< 6	22	10

DVR, darunavir; r, ritonavir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; RPV, rilpivirine; EVG, elvitegravir; NVP, nevirapine.
[a]VL 225 at DRV/r initiation, 612 copies/mL 7 days later and <50 copies/mL at 35 days, intensification requested by Centre de Méthodologie et de Gestion.
[b]VL 425 at DRV/r initiation, then <20 copies/mL 7 days later. Failure 139 days after start of DRV/r.
[c]PCR inhibitor.
[d]At time of second VL sampling.
[e]Interval between last drug intake and sampling was unknown.

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Table 5. HIV and treatment history in 83 patients evaluable for virological success of darunavir/ritonavir monotherapy (monotherapy maintained until delivery), Monogest ANRS 168 study

	Virological failure (*N* = 6)		Virological success (*N* = 77)		
	n	% or median (IQR)	*n*	% or median (IQR)	*P*
Time since first ARV regimen, months	6	38 (34–93)	77	70 (46–109)	0.19
Duration of ART regimen used at the time of conception, months	6	22 (8–34)	77	17 (9–27)	0.66
HIV					
Time since HIV diagnosis, years	6	3 (3–8)	77	7 (4; 10)	0.06
Time with plasma HIV-RNA <50 copies/mL, months	6	32 (19–36)	77	44 (26–70)	0.26
CD4 lymphocytes at screening/mm^3	6	519 (503–619)	77	725 (597–911)	0.03
HIV-RNA at screening					
<50 copies/mL	6	100.0	77	100.0	
HIV-RNA at start of monotherapy					
<50 copies/mL	4	66.7	75	97.4	0.01
≥50 copies/mL	2	33.3	1	1.3	
Unknown	0		1	1.3	
Viraemia (copies/mL) if ≥50	2	325 (225–425)	1	185	
Ultra-sensitive HIV-RNA at start of monotherapy					
<6 copies/mL	3	50.0	67	87.0	0.04
≥6 copies/mL	3	50.0	9	11.7	
Unknown	0		1	1.3	
HIV-DNA at start of monotherapy					
HIV-DNA copies/10^6 PBMCs	6	542 (243–882)	73	280 (144–775)	0.50
Unknown	0		4		
ART at conception, number of drugs					
Dual	0	0.0	4	5.2	1.00
Triple	6	100.0	73	94.8	
NRTI at conception					
TDF + FTC	6	100.0	60	77.9	0.80
ABC + 3TC	0	0.0	13	16.9	
3TC	0	0.0	2	2.6	
FTC	0	0.0	1	1.3	
No NRTI	0	0.0	1	1.3	
Associated antiretrovirals at conception					
Darunavir	2	33.3	25	32.5	0.54
Atazanavir	0	0.0	5	6.7	
Nevirapine	1	16.7	1	1.3	
Rilpivirine	2	33.3	23	29.9	
Raltegravir	0	0.0	2	2.6	
Dolutegravir	0	0.0	8	10.4	
Elvitegravir	1	16.7	12	15.6	
Etravirine + raltegravir	0	0.0	1	1.3	
Time of darunavir introduction					
Before conception	2	33.3	25	32.5	0.88
Between conception and enrolment	3	50.0	44	57.1	
Started at enrolment (switch)	1	16.7	8	10.4	

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine.

The treatment regimen was chosen on the basis of data showing plasma concentrations of darunavir decreased in the second and third trimesters of pregnancy and target concentrations were best attained with twice-daily dosage.[38,50] Plasma concentrations of darunavir monotherapy were above the antiviral efficacy threshold in most patients from enrolment through to delivery, suggesting overall good adherence to this regimen, despite the twice-daily regimen. The virological failures did not seem clearly related to insufficient concentrations. Inter-individual plasma pharmacokinetics variability was as expected for boosted PIs, and low compared with the integrase inhibitor raltegravir.[51] Protein binding of darunavir was stable

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Table 6. Total and unbound DRV C_{min} post darunavir/ritonavir (600/100 mg twice daily) regimen

	N	Total DRV C_{min} ng/mL, median (IQR)	Unbound DRV C_{min} ng/mL, median (IQR)
Week 4	85	2429 (1801–3217)	182 (124–261)
Week 24–28	80	2250 (1414–3132)	180 (115–237)
Week 32	73	2332 (1604–3107)	174 (123–265)
Delivery	61	2746 (1771–3490)	176 (137–293)

DRV, darunavir.

throughout pregnancy despite small changes related to plasma protein concentrations.

The rate of virological failure in our study was lower than observed in the French perinatal cohort in the same period among women taking classical triple combination therapies, where over 10% had VLs above 50 copies/mL near delivery.[1,52] In pregnant women, as well as other populations, the main determinant of treatment failure is poor adherence. An important consideration when making any change to an ART regimen is whether this will improve or impair adherence. Among women switching ART in pregnancy for concern about fetal safety, previous reports showed contrasting findings.[53,54]

The factors predictive of success were undetectable ultrasensitive HIV-1 RNA and high baseline CD4 cell count, as previously reported outside pregnancy.[55] In non-pregnant persons, other factors predictive of virological success of boosted-PI monotherapy were good compliance, low HIV-1 proviral DNA and prolonged control of viral replication.[55,56,57]

Regarding safety, monotherapy avoids issues related to nucleoside analogue exposure, but not those related to darunavir/ritonavir. Liver enzyme elevation, which has been previously reported with boosted-PI therapy,[58] was observed in the absence of common pregnancy-related conditions (cholestasis of pregnancy or pre-eclampsia) in seven of our patients. While boosted-PI regimens have been associated with preterm delivery,[59,60] the incidence was 9%, which is unremarkable and below the rate of 14% in women receiving triple ART in the French EPF cohort.[59] One hypothesis could be that preterm delivery was associated with lopinavir, which was widely used in the previous studies,[61] rather than a class effect of PIs or a general effect[62] of therapy, or possibly with other time-related changes in management.

Strengths and weaknesses

This is the first study to date to evaluate a regimen of PT prevention without any exposure to NRTIs during pregnancy, delivery or the neonatal period. The other strengths are the prospective multicentre design and high standards of follow-up and monitoring.

An important limitation of the study was the high-resource setting and the highly selected population, which may not reflect real-world programmes, thus reducing the external validity in other settings,[63] especially in the case of breastfeeding.[64] Also, we had to limit the number of patients to enrol, leading to loss of power. We chose an open-label one-arm interventional design, since a randomized equivalence trial would require a much larger enrolment and was not feasible.

Perspectives

Current guidelines do not recommend PI monotherapy in non-pregnant individuals. The rationale for NRTI-free strategies is to reduce the risk of toxicities in the special context of pregnancy, where it may be preferable to limit exposure of the fetus to multiple medications. Such decisions should be based on consideration of the benefits and risks according to each patient's individual virological history and personal preferences and priorities, in a framework of shared decision-making. The place for darunavir/ritonavir monotherapy would be in limited circumstances, such as pregnant HIV-1 or HIV-2 controllers having undetectable plasma HIV RNA without ART, or patients with a strong preference to not use NRTIs in pregnancy who can be expected from our findings to have an acceptably low risk of virological failure on darunavir/ritonavir monotherapy. This pilot study paves the way for the evaluation of other simplified regimens during pregnancy, which could offer optimal viral control while reducing maternal and fetal NRTI exposure.

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References

1 Sibiude J, Le Chenadec J, Mandelbrot L *et al*. Update of perinatal HIV-1 transmission in France: zero transmission for 5482 mothers on continuous ART from conception and with undetectable viral load at delivery. *Clin Infect Dis* 2022; **76**: e590–8. https://doi.org/10.1093/cid/ciac703

2 EACS. Guidelines, Version 11.0, October 2021. 2021. https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf.

3 WHO. Update of Recommendations on First- and Second-line Antiretroviral Regimens. 2019. https://www.who.int/publications/i/item/WHO-CDS-HIV-19.15.

4 Clinical Info HIV.gov. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/recommendations-arv-drugs-pregnancy-prevent-hiv-improve-maternal-health?view=full.

5 Morlat P. Prise en charge médicale des personnes vivant avec le VIH. Désir d'enfant et grossesse (May 2018). https://cns.sante.fr/wp-content/uploads/2017/11/experts-vih_grossesse.pdf.

6 Sibiude J, Warszawski J, Blanche S. Tolerance of the newborn to antiretroviral drug exposure in utero. *Expert Opinion on Drug Safety* 2015; **14**: 643–54. https://doi.org/10.1517/14740338.2015.1019462

7 Mandelbrot L, Landreau-Mascaro A, Rekacewicz C *et al*. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; **285**: 2083–93. https://doi.org/10.1001/jama.285.16.2083

8 Blanche S, Tardieu M, Rustin P *et al*. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999; **354**: 1084–9. https://doi.org/10.1016/S0140-6736(99)07219-0

9 Poirier MC, Divi RL, Al-Harthi L *et al*. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr* 2003; **33**: 175–83. https://doi.org/10.1097/00126334-200306010-00010

10 Barret B, Tardieu M, Rustin P *et al*. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS* 2003; **17**: 1769–85. https://doi.org/10.1097/00002030-200308150-00006

11 Liu Y, Shim Park E, Gibbons AT *et al*. Mitochondrial compromise in 3-year old patas monkeys exposed *in utero* to human-equivalent antiretroviral therapies. *Environ Mol Mutagen* 2016; **57**: 526–34. https://doi.org/10.1002/em.22033

12 Divi RL, Leonard SL, Kuo MM *et al*. Transplacentally exposed human and monkey newborn infants show similar evidence of nucleoside reverse transcriptase inhibitor-induced mitochondrial toxicity. *Environ Mol Mutagen* 2007; **48**: 201–9. https://doi.org/10.1002/em.20201

13 Andre-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. https://doi.org/10.1093/infdis/jit149

14 Vivanti A, Soheili TS, Cuccuini W *et al*. Comparing genotoxic signatures in cord blood cells from neonates exposed *in utero* to zidovudine or tenofovir. *AIDS* 2015; **29**: 1319–24. https://doi.org/10.1097/QAD.0000000000000564

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15 Lipshultz SE, Shearer WT, Thompson B *et al*. Cardiac effects of antiretroviral therapy in HIV-negative infants born to HIV-positive mothers: NHLBI CHAART-1 (National Heart, Lung, and Blood Institute Cardiovascular Status of HAART Therapy in HIV-exposed infants and children cohort study). *J Am Coll Cardiol* 2011; **57**: 76–85. https://doi.org/10.1016/j.jacc.2010.08.620

16 Cade WT, Waggoner AD, Hubert S *et al*. Reduced diastolic function and left ventricular mass in HIV-negative preadolescent children exposed to antiretroviral therapy *in utero*. *AIDS* 2012; **26**: 2053–8. https://doi.org/10.1097/QAD.0b013e328358d4d7

17 Sibiude J, Le Chenadec J, Bonnet D *et al*. In utero exposure to zidovudine and heart anomalies in the ANRS French perinatal cohort and the nested PRIMEVA randomized trial. *Clin Infect Dis* 2015; **61**: 270–80. https://doi.org/10.1093/cid/civ260

18 Hleyhel M, Goujon S, Delteil C *et al*. Risk of cancer in children exposed to didanosine *in utero*. *AIDS* 2016; **30**:1245–56. https://doi.org/10.1097/QAD.0000000000001051

19 Siberry GK, Jacobson DL, Kalkwarf HJ *et al*. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis* 2015; **61**: 996–1003. https://doi.org/10.1093/cid/civ437

20 Siberry GK, Williams PL, Mendez H *et al*. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. *AIDS* 2012; **26**: 1151–9. https://doi.org/10.1097/QAD.0b013e328352d135

21 Lahoz R, Noguera A, Rovira N *et al*. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J* 2010; **29**: 376–9. https://doi.org/10.1097/INF.0b013e3181c81fd4

22 Neubert J, Pfeffer M, Borkhardt A *et al*. Risk adapted transmission prophylaxis to prevent vertical HIV-1 transmission: effectiveness and safety of an abbreviated regimen of postnatal oral zidovudine. *BMC Pregnancy Childbirth* 2013; **13**: 22. https://doi.org/10.1186/1471-2393-13-22

23 Soler-Palacín P, Martín-Nalda A, Martínez-Gómez X *et al*. Hyperlactatemia and *in utero* exposure to antiretrovirals: is the control group the clue? *AIDS Res Hum Retroviruses* 2012; **28**: 752–8. https://doi.org/10.1089/aid.2011.0198

24 Tubiana R, Le Chenadec J, Rouzioux C *et al*. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/mL at delivery: a case-control study nested in the French Perinatal Cohort (EPF-ANRS CO1). *Clin Infect Dis* 2010; **50**: 585–96. https://doi.org/10.1086/650005

25 Tubiana R, Mandelbrot L, Le Chenadec J *et al*. 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. *Clin Infect Dis* 2013; **57**: 891–902. https://doi.org/10.1093/cid/cit390

26 Briand N, Mandelbrot L, Le Chenadec J *et al*. No relation between in-utero exposure to HAART and intrauterine growth retardation. *AIDS* 2009; **23**: 1235–43. https://doi.org/10.1097/QAD.0b013e32832be0df

27 Morlat P. Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'experts. Actualisation 2015, du Rapport 2013. https://cns.sante.fr/wp-content/uploads/2015/10/experts-vih_actualisation2015.pdf.

28 Nielsen-Saines K, Watts DH, Veloso VG *et al*. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med* 2012; **366**: 2368–79. https://doi.org/10.1056/NEJMoa1108275

29 Taha TE, Kumwenda NI, Gibbons A *et al*. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 2003; **362**: 1171–7. https://doi.org/10.1016/S0140-6736(03)14538-2

30 Gray GE, Urban M, Chersich MF *et al*. A randomized trial of two post-exposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS* 2005; **19**: 1289–97. https://doi.org/10.1097/01.aids.0000180100.42770.a7

31 Chasela CS, Hudgens MG, Jamieson DJ *et al*. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med* 2010; **362**: 2271–81. https://doi.org/10.1056/NEJMoa0911486

32 Mandelbrot L, Mazy F, Floch-Tudal C *et al*. Atazanavir in pregnancy: impact on neonatal hyperbilirubinemia. *Eur J Obstet Gynecol Reprod Biol* 2011; **157**: 18–21. https://doi.org/10.1016/j.ejogrb.2011.02.005

33 Chappuy H, Tréluyer JM, Rey E *et al*. Maternal-fetal transfer and amniotic fluid accumulation of protease inhibitors in pregnant women who are infected with human immunodeficiency virus. *Am J Obstet Gynecol* 2004; **191**: 558–62. https://doi.org/10.1016/j.ajog.2004.01.034

34 Colbers A, Moltó J, Ivanovic J *et al*. Pharmacokinetics of total and unbound darunavir in HIV-1-infected pregnant women. *J Antimicrob Chemother* 2015; **70**: 534–42. https://doi.org/10.1093/jac/dku400

35 Furco A, Gosrani B, Nicholas S *et al*. Successful use of darunavir, etravirine, enfuvirtide and tenofovir/emtricitabine in pregnant woman with multiclass HIV resistance. *AIDS* 2009; **23**: 434–5. https://doi.org/10.1097/QAD.0b013e32832027d6

36 Ivanovic J, Bellagamba R, Nicastri E *et al*. Use of darunavir/ritonavir once daily in treatment-naive pregnant woman: pharmacokinetics, compartmental exposure, efficacy and safety. *AIDS* 2010; **24**: 1083–4. https://doi.org/10.1097/QAD.0b013e32833653b2

37 Mandelbrot L, Duro D, Belissa E *et al*. Placental transfer of darunavir in an *ex vivo* human cotyledon perfusion model. *Antimicrob Agents Chemother* 2014; **58**: 5617–20. https://doi.org/10.1128/AAC.03184-14

38 Zorrilla CD, Wright R, Osiyemi OO *et al*. Total and unbound darunavir pharmacokinetics in pregnant women infected with HIV-1: results of a study of darunavir/ritonavir 600/100 mg administered twice daily. *HIV Med* 2014; **15**: 50–6. https://doi.org/10.1111/hiv.12047

39 Khoo S, Peytavin G, Burger D *et al*. Pharmacokinetics and safety of darunavir/ritonavir in HIV-infected pregnant women. *AIDS Rev* 2017; **19**: 16–23.

40 Pope R, Kashuba A. Darunavir for use in pregnant women with HIV. *Expert Rev Clin Pharmacol* 2017; **10**: 1317–27. https://doi.org/10.1080/17512433.2017.1390428

41 Gliga SS, Clavel CO, Alix AF *et al*. Dual therapy with lamivudine + protease inhibitor during pregnancy for prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr* 2013; **63**: e159–63. https://doi.org/10.1097/QAI.0b013e31829b2c4b

42 Arribas JR, Horban A, Gerstoft J *et al*. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS* 2010; **24**: 223–30. https://doi.org/10.1097/QAD.0b013e3283348944

43 Katlama C, Valantin MA, Algarte-Genin M *et al*. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS* 2010; **24**: 2365–74. https://doi.org/10.1097/QAD.0b013e32833dec20

44 WHO. Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Towards Universal Access. https://apps.who.int/iris/handle/10665/96350

45 Avettand-Fenoel V, Chaix ML, Blanche S *et al*. LTR real-time PCR for HIV-1 DNA quantitation in blood cells for early diagnosis in infants born to seropositive mothers treated in HAART area (ANRS CO 01). *J Med Virol* 2009; **81**: 217–23. https://doi.org/10.1002/jmv.21390

46 Morlat P. Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'experts. Rapport 2013. 2013. https://sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf.

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47 Warszawski J, Tubiana R, Le Chenadec J *et al*. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS* 2008; **22**: 289–99. https://doi.org/10.1097/QAD.0b013e3282f3d63c

48 Jung BH, Rezk NL, Bridges AS *et al*. Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry. *Biomed Chromatogr* 2007; **21**: 1095–104. https://doi.org/10.1002/bmc.865

49 Ortiz R, DeJesus E, Khanlou H *et al*. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS* 2008; **22**: 1389–97. https://doi.org/10.1097/QAD.0b013e32830285fb

50 Stek A, Best BM, Wang J *et al*. Pharmacokinetics of once versus twice daily darunavir in pregnant HIV-infected women. *J Acquir Immune Defic Syndr* 2015; **70**: 33–41. https://doi.org/10.1097/QAI.0000000000000668

51 Zheng Y, Hirt D, Delmas S *et al*. Effect of pregnancy on unbound raltegravir concentrations in the ANRS 160 RalFe trial. *Antimicrob Agents Chemother* 2020; **64**: e00759-20. https://doi.org/10.1128/AAC.00759-20

52 Albert AYK, Elwood C, Wagner EC *et al*. Investigation of factors associated with spontaneous preterm birth in pregnant women living with HIV. *AIDS* 2020; **34**: 719–27. https://doi.org/10.1097/QAD.0000000000002464

53 Peyronnet V, Warszawski J, Sibiude J *et al*. Does changing antiretroviral therapy in the first trimester of pregnancy for safety concerns have an impact on viral suppression? *J Acquir Immune Defic Syndr* 2019; **80**: 574–84. https://doi.org/10.1097/QAI.0000000000001954

54 Frange P, Tubiana R, Sibiude J *et al*. Rilpivirine in HIV-1-positive women initiating pregnancy: to switch or not to switch? *J Antimicrob Chemother* 2020; **75**: 1324–31. https://doi.org/10.1093/jac/dkaa017

55 Lambert-Niclot S, Flandre P, Valantin MA *et al*. Factors associated with virological failure in HIV-1-infected patients receiving darunavir/ritonavir monotherapy. *J Infect Dis* 2011; **204**: 1211–6. https://doi.org/10.1093/infdis/jir518

56 Avettand-Fenoel V, Flandre P, Chaix ML *et al*. Impact of 48 week lopinavir/ritonavir monotherapy on blood cell-associated HIV-1-DNA in the MONARK trial. *J Antimicrob Chemother* 2010; **65**: 1005–7. https://doi.org/10.1093/jac/dkq084

57 Guiguet M, Ghosn J, Duvivier C *et al*. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS* 2012; **26**: 2345–50. https://doi.org/10.1097/QAD.0b013e32835646e0

58 Douhnai D, Tassin M, Sibiude J *et al*. Prenatal diagnosis of intra hepatic arterio venous fistula: case report and review of the literature. *J Matern Fetal Neonatal Med* 2019; **32**: 2575–8. https://doi.org/10.1080/14767058.2018.1438400

59 Sibiude J, Warszawski J, Tubiana R *et al*. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? *Clin Infect Dis* 2012; **54**: 1348–60. https://doi.org/10.1093/cid/cis198

60 Eke AC, Mirochnick M, Lockman S. Antiretroviral therapy and adverse pregnancy outcomes in people living with HIV. *N Engl J Med* 2023; **388**: 344–56. https://doi.org/10.1056/NEJMra2212877

61 Theron G, Brummel S, Fairlie L *et al*. Pregnancy outcomes of women conceiving on antiretroviral therapy (ART) compared to those commenced on ART during pregnancy. *Clin Infect Dis* 2021; **73**: e312–e20. https://doi.org/10.1093/cid/ciaa805

62 Dunk CE, Serghides L. Protease inhibitor-based antiretroviral therapy in pregnancy: effects on hormones, placenta, and decidua. *Lancet HIV* 2021; **9**: e120–9. https://doi.org/10.1016/S2352-3018(21)00249-6

63 Myer L, Dunning L, Lesosky M *et al*. Frequency of viremic episodes in HIV-infected women initiating antiretroviral therapy during pregnancy: a cohort study. *Clin Infect Dis* 2017; **64**: 422–7. https://doi.org/10.1093/cid/ciw792

64 Van de Perre P, Goga A, Ngandu N *et al*. Eliminating postnatal HIV transmission in high incidence areas: need for complementary biomedical interventions. *Lancet* 2021; **397**: 1316–24. https://doi.org/10.1016/S0140-6736(21)00570-5

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