

Timing of initiation of ART before or after conception is not associated with adverse pregnancy outcomes: findings from the ANRS 12136 TEMPRANO trial in Côte d'Ivoire.

Thierry TIENDREBEOGO¹, Anani BADJE², Shino ARIKAWA¹, Marie-Louise NEWELL³, Christine DANIEL², Delphine GABILLARD¹, Serge EHOLIE², Xavier ANGLARET^{1,2}, Renaud BECQUET¹ and the ANRS 12136 TEMPRANO trial team
1. Université de Bordeaux, INSERM, Bordeaux Population Health Research Center, UMR 1219, Bordeaux, France, 2. Programme PAC-CI, French National Agency for Research on AIDS and Viral Hepatitis (ANRS) Research Center, Abidjan, Cote D'Ivoire, 3. University of Southampton, Global Health Research Institute, Southampton, United Kingdom.

Background & Objectives

Lifelong combination antiretroviral therapy (ART) as early as possible Lifelong combination antiretroviral therapy (ART) started immediately after HIV diagnosis is now the norm for all individuals infected with HIV. It implies that all women should now be on treatment before conception or should start ART from early pregnancy for those who had not been diagnosed until they got pregnant. A recent meta-analysis pointed out an increased risk of adverse pregnancy outcomes associated with ART initiation before or early in pregnancy. However these findings were confounded by strong methodological issues. The ANRS TEMPRANO trial provides a unique opportunity to better address this topic thanks to a randomized design.

This study aimed at assessing adverse pregnancy outcomes associated with ART initiated before conception or early pregnancy compared with that of ART started after conception.

Methods

Study design and setting:

Analysis were done using data from the TEMPRANO trial, an unblinded, multicenter, individual-randomized controlled, 2-by-2 factorial, 1:1 superiority trial conducted in Abidjan, Côte d'Ivoire. In this trial, newly diagnosed HIV-infected women were assigned to either early (irrespective of CD4 count) or deferred (WHO standard) TDF-based ART. Pregnancy was determined at each follow-up visit and confirmed by urine test. Gestational age was based on ultrasound.

Study Population:

All women included in the TEMPRANO trial and who got pregnant before the end of the 30 months follow-up.

Study outcomes:

- We investigated adverse pregnancy outcomes in first pregnancies:
- Stillbirth
 - small for gestational age (SGA) (below 10th percentile of the reference curves)
 - preterm delivery (PTD) (Birth before 37 week of gestational age)
 - low birthweight (LBW) (birthweight under 2500 g)
 - A composite outcome was calculated as any adverse pregnancy outcome.

Statistical analyses:

Characteristics of the study population were described as median for continuous variables and as frequencies for categorical variables. All pregnancy issues were described and compared according to randomization arms. Risks of adverse pregnancy outcomes were analyzed by randomisation arms in an intent-to-treat analysis to account for timing of ART initiation in relation to conception. Further, in a per-protocol analysis, we excluded women in the deferred ART strategy who became ART eligible and initiated ART before conception (e.g. before the end of the first pregnancy trimester). Adjusted Odds Ratios (aOR) were estimated in logistic regression allowing for women's age, parity, and the nearest CD4 cell count before conception.

Results

Study population selection

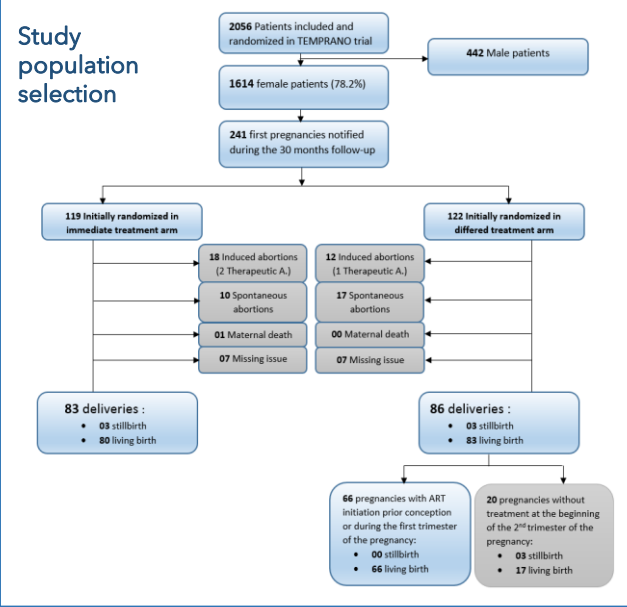


Table 1. Baseline characteristics of pregnant women. TEMPRANO trial, Abidjan, Ivory Coast, 2008-2015

	Early ART		Deferred ART		p-value
	n	%	n	%	
Age - no. (%)					0.865
Less than 25 Years	21	17.6	26	21.3	
25-30 Years	48	40.3	48	39.3	
31-40 Years	47	39.5	44	36.1	
> 40 Years	3	2.5	4	3.3	
Educational level - no. (%)					0.546
None	37	31.1	29	23.8	
Primary school	35	29.4	39	32.0	
Secondary school	36	30.3	38	31.1	
> secondary school	11	9.2	16	13.1	
INH prophylaxis					0.171
No INH	69	58.0	60	49.2	
INH	50	42.0	62	50.8	
Last CD4 count before conception - cell/mm³					<0.001
Mean (S)	627.2 (199)		460.4 (157)		
Median (Q1-Q3)	604 (497-742)		449 (338-568)		

Table 2. Risk of adverse pregnancy outcome by study randomization strategy or by timing of ART initiation to conception. TEMPRANO trial, Abidjan, Ivory Coast, 2008-2015

	Intent to treat (ITT)				Per-Treatment (PT)			
	n/N	%	aOR [95% CI]*	p-value	n/N	%	aOR [95% CI]*	p-value
DELIVERIES	N=169				N=149			
Stillbirth				0.52				0.17
Deferred ART Arm (ITT), ART post-conception (PT)	3/86	3.5	1.00		0/66	0.0	-	
Early ART Arm (ITT), ART pre-conception (PT)	3/83	3.6	1.91 [0.26-14.08]		3/83	3.6	-	
LIVE BIRTHS	N=163				N=146			
Low birthweight				0.63				0.68
Deferred ART Arm (ITT), ART post-conception (PT)	18/83	21.7	1.00		14/66	21.2	1.00	
Early ART Arm (ITT), ART pre-conception (PT)	16/80	20.0	0.81 [0.34-1.90]		16/80	20.0	0.83 [0.34-2.02]	
Preterm delivery				0.68				0.79
Deferred ART Arm (ITT), ART post-conception (PT)	15/83	18.1	1.00		13/66	19.7	1.00	
Early ART Arm (ITT), ART pre-conception (PT)	17/80	21.3	1.20 [0.50-2.88]		17/80	21.3	1.13 [0.46-2.74]	
Small for gestational age				0.75				0.75
Deferred ART Arm (ITT), ART post-conception (PT)	20/83	24.1	1.00		16/66	24.2	1.00	
Early ART Arm (ITT), ART pre-conception (PT)	19/80	23.8	0.87 [0.38-1.98]		19/80	23.8	0.87 [0.37-2.03]	
COMPOSITE VARIABLE	N=169				N=149			
Any of the above adverse outcomes				0.71				0.74
Deferred ART Arm (ITT), ART post-conception (PT)	38/86	44.2	1.00		30/66	45.4	1.00	
Early ART Arm (ITT), ART pre-conception (PT)	38/83	45.8	0.87 [0.44-1.75]		38/83	45.8	0.88 [0.43-1.81]	

* Adjusted for women's age, parity, and the most recent CD4 cell count before conception

- In total, 119 and 122 pregnancies were reported, with 83 and 86 deliveries leading to 80 and 83 live births, in the early and deferred ART strategy respectively; 17 women in the deferred ART strategy started ART before conception, their exclusion resulted in 66 live births in this group.
- High prevalence of induced abortions (27 voluntary abortions in both arms (certain declared "spontaneous abortions" was probably induced)
- When comparing the characteristics of pregnant women, difference between the two arm is related to the last CD4 count before conception (probably due to CD4 count decline in deferred ART arm compared to Early ART arm
- Overall, about 3.5% of pregnancies resulted in stillbirths
- Among livebirths: 21% were LBW, 19% PTD and 23% SGA.
- Risk of adverse pregnancy outcomes did not differ significantly by randomisation strategy in either intent-to-treat or per-protocol analysis (Table 2). Risk of any of adverse pregnancy outcome (composite variable) was not associated with trial arm (intent-to-treat) or timing of ART initiation (before or after conception).

Conclusion

- Using data from women randomly allocated to immediate vs. deferred ART, our results provide reassuring evidence on the lack of association with timing of ART pre- or post-conception.
- Adverse pregnancy outcomes were common in this population however.

