PROMISE
IMPAACT 1077
Promoting Maternal and Infant Survival Everywhere

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Group

Pregnancy outcomes of women conceiving on ART compared to those commenced on ART during pregnancy

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FAMCRU

Disclosure

Gerhard Theron
has no financial relationships with commercial entities to disclose

Background

- The number of HIV-infected women conceiving on ART is increasing
- Evidence of ART safety at conception, during pregnancy and adverse pregnancy outcomes are conflicting
- The PROMISE 1077 BF&FF provide an opportunity for a post-hoc analysis

PROMISE 1077 HS
CID 2019; 68: 273-280

Clinical Infectious Diseases

MAJOR ARTICLE

Adverse Pregnancy Outcomes Among Women Who Conceive on Antiretroviral Therapy

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IMPAACT PROMISE Sites

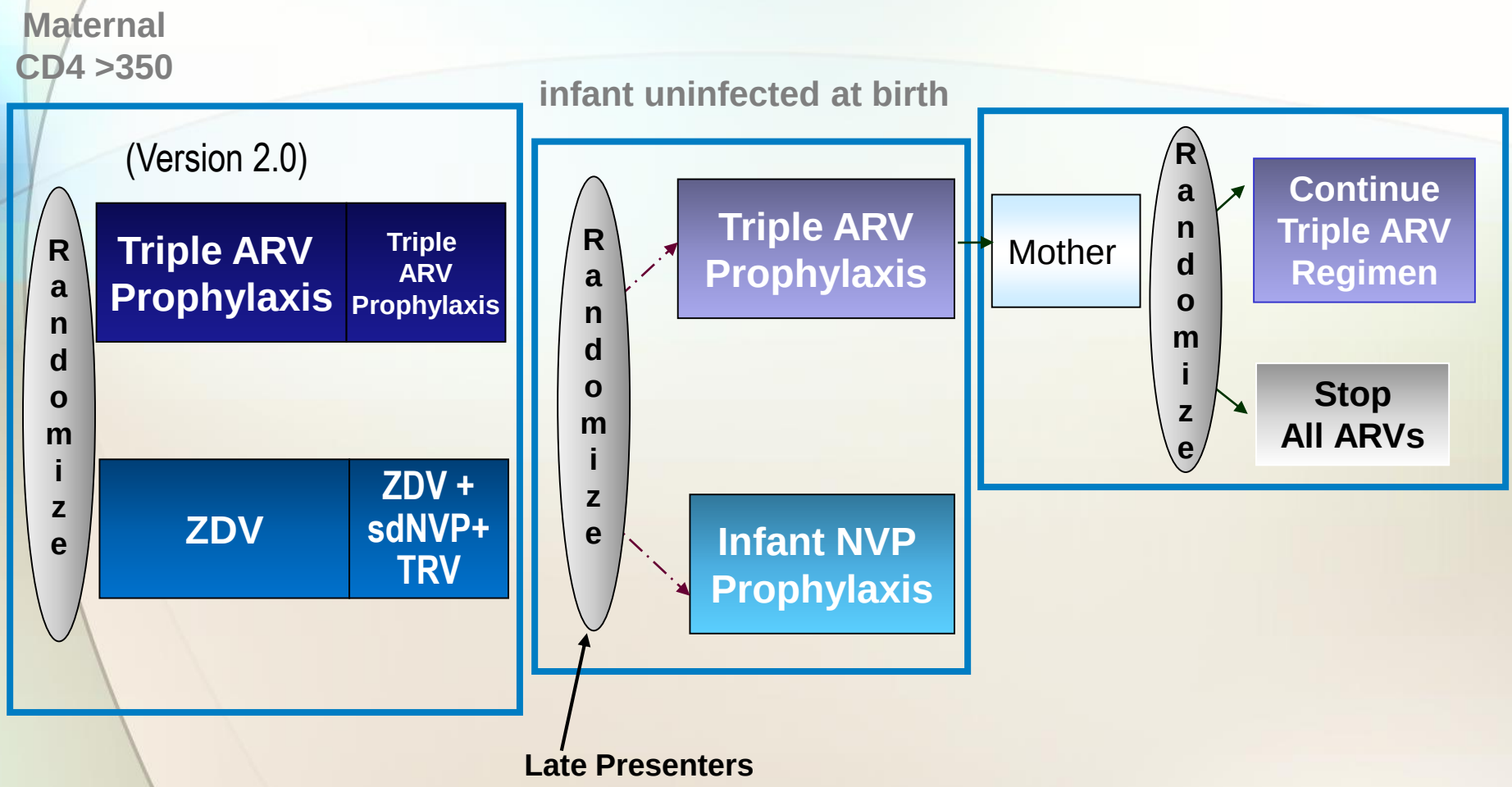
Includes NIH IMPAACT Clinical Research Sites in resource-limited international settings where the usual method of infant feeding is breastfeeding; and some sites (South Africa*, India*) where the option of formula feeding was also safe and available.

Sites in:

- *India* (1)*
- *Malawi (2)*
- *South Africa* (5)*
- *Tanzania (1)*
- *Uganda (1)*
- *Zambia (1)*
- *Zimbabwe (3)*

Three PROMISE Randomizations

Antepartum (14 wks-term) | **Labor/ Delivery** | **Postpartum** (for duration of BF) | **Maternal Health** (after BF cessation)



Methods

- **Pregnancy outcomes of women who became pregnant during follow-up:**

  FF & BF ~ randomized to ART following delivery

  BF ~ randomized to receive ART following breastfeeding cessation

- **Who conceived while on ART**

❖ **Compared to**

Women commenced on ART subsequent to diagnoses of pregnancy

Methods (cont)

ART regimen:

- **TDF, FTC or 3TC and LPV/r**
- **Regimens not provided by the study were allowed if definition cART met**
- **Follow-up of mothers ~ 96 weeks after the last delivery**
- **Infants follow-up ~ two years**

Methods (cont)

Maternal postpartum follow-up visits were:

- **1, 6, and 14 weeks after delivery**
- **Then every 12 weeks**

Pregnancy tests were done:

- **Week 14 postpartum**
- **Subsequently 12 weekly intervals when clinically indicated**
- **All women on EFV**

Methods (cont)

- **Women who became pregnant during follow-up, including more than one subsequent pregnancy remained in the study**
- **Pregnancy outcome recorded:**
  - **live births**
  - **neonatal death (≤28 days)**
  - **ectopic pregnancies**
  - **induced abortions**
  - **spontaneous abortions (<20 weeks)**
  - **stillbirths**

Methods (cont)

Pregnancy data included:

- **pregnancy complications**
- **birth weight**
- **gestational age at delivery**
- **type of delivery**

Statistical analysis

Two types of analyses conducted of pregnancy outcomes:

1. **By arm analyses in which data were restricted to pregnancies before July 7, 2015***

***Generalised estimating equations, account for multiple repeat pregnancies conducted by ITT, excluding cross overs, as treated**

2. **Time-to-event analyses that included all observed subsequent pregnancies****

****Cox proportional hazards regression clustered for multiple repeat pregnancies, adjusted for country and previous pregnancy complication**

Results

		By Arm Analyses (Conceptions prior to July 7, 2015 only)				
		Randomized at delivery		Randomized after breastfeeding		All mothers (N=760)
		Continue ART (N=97)	Discontinue ART (N=121)	Continue ART (N=41)	Discontinue ART (N=41)	
	N	96	121	41	41	755
Country	India	2	3	3	3	39 (5%)
	Malawi	35	43	15	17	240 (32%)
	South Africa	26	26	9	4	188 (25%)
	Tanzania	2	1	0	0	10 (1%)
	Uganda	21	23	8	10	135 (18%)
	Zambia	0	5	0	0	15 (2%)
	Zimbabwe	11	20	6	7	133 (18%)

Results (cont)

		By Arm Analyses (Conceptions prior to 7 July 2015)				
		Randomized at delivery		Randomized after breastfeeding		All mothers (N=760)
		Continue ART (N=97)	Discontinue ART (N=121)	Continue ART (N=41)	Discontinue ART (N=41)	
WHO Stage at or before estimated conception	Stage I	84 (88%)	112 (93%)	35 (85%)	36 (88%)	683 (90%)
	Stage II	11	8	6	4	61 (8%)
	Stage III	1	1	0	1	9 (1%)
	Stage IV	0	0	0	0	2 (0%)
CD4 (cells/mm^3)	N	96	121	41	41	755
	Min-Max	350-1,545	306-1,568	531-1,545	350-1,297	216-1,908
	Median	818	600	771	710	692
HIV RNA (copies/mL)	N	96	121	41	41	755
	Min-Max	20-89,755	20-975,501	20-27,372	30-203,421	20-975,501
	Median	40	3,726	40	565	200
	<400	62 (65%)	27 (22%)	37 (90%)	15 (37%)	413 (55%)

Subsequent pregnancy outcomes for the entire PROMISE follow-up cohort

Outcome	1st (N=837)	2nd (N=97)	3rd (N=5)	Total (N=939)
Ectopic or other non-viable pregnancy	11 (1%)	0 (0%)	0 (0%)	11 (1%)
Induced abortion	64 (8%)	10 (13%)	1 (33%)	75 (9%)
Spontaneous abortion (< 20 weeks)	100 (13%)	6 (8%)	0 (0%)	106 (12%)
Stillbirth (≥ 20 weeks)	25 (3%)	0 (0%)	0 (0%)	25 (3%)
Live birth	558 (72%)	57 (72%)	2 (67%)	617 (72%)
Live birth followed by neonatal death (≤ 28 days)	19 (2%)	6 (8%)	0 (0%)	25 (3%)
Missing data	60	18	2	80

Subsequent Pregnancy Birth Weights by Comparison Group (Conception date before July 7th, 2015)

		Randomized at delivery		Randomized after breastfeeding		Total (N=237)
		Continue ART (N=90	Discontinue ART (N=105)	Continue ART (N=39)	Discontinue ART (N=39)	
Birth Weight	VLBW (<1500g)	0 (0%)	1 (1%)	2 (7%)	0 (0%)	3 (2%)
	LBW (≥1500g-<2500g)	11 (17%)	4 (6%)	6 (22%)	4 (14%)	20 (13%)
	≥2500g	52 (83%)	63 (93%)	19 (70%)	24 (86%)	137 (86%)
Live birth missing BW		27	37	12	11	77

Analyses of LBW in continue ART and discontinue ART groups randomization at delivery (A) and after breastfeeding (B)

Group	Analysis Type	LBW cART	LBW dART	% LBW cART	% LBW dART	RR (95% CI) comparing cART to dART	p-value
A+B	ITT	16	7	21.2%	8.0%	2.65 (1.20, 5.81)	0.02
	Excluding crossovers	14	7	26.6%	9.0%	2.94 (1.24, 6.98)	0.01
	As treated	14	9	22.3%	9.0%	2.47 (1.00, 6.14)	0.05
A	ITT	11	6	17.9%	8.0%	2.24 (0.98, 5.11)	0.06
	Excluding crossovers	9	6	23.2%	9.1%	2.56 (0.98, 6.71)	0.06
	As treated	9	8	18.8%	9.0%	2.08 (0.76, 5.72)	0.15

Hazard Ratios for Time-Varying ART Exposure Indicator (Adjusted for Country and First PROMISE Pregnancy Outcome)

Endpoint	ART Exposure	Hazard Ratio (95% CI)	p-value
Spontaneous abortion, stillbirth, or neonatal death	No ART	Ref	
	On ART	1.40 (0.99, 1.98)	0.05

- Results are based on 1000 imputations of missing gestational ages
- Live births followed by neonatal deaths within 28 days were censored at the time of birth
- LBW is defined as < 2500g
- Model was adjusted for country and for whether the mother's first PROMISE pregnancy resulted in a spontaneous abortion, stillbirth, neonatal death, or low birth weight

Hazard Ratios for Time-Varying ART Regimen Group with no ARV Regimen as Reference

Endpoint	Regimen Group	Hazard Ratio (95% CI)	p-value
Spontaneous abortion, stillbirth, or neonatal death	No ARVs	Ref	
	ART including boosted/non-boosted PI	1.24 (0.79, 1.93)	0.35
	ART including NNRTI with no PI	1.48 (1.02, 2.14)	0.04
	Only NRTIs	3.11 (0.73, 13.33)	0.13

(Adjusted for Country and First PROMISE Pregnancy Outcome)

Results are based on 1000 imputations of missing gestational ages

LBW followed by neonatal deaths within 28 days were censored at the time of birth

LBW is defined as < 2500g

Model was adjusted for country and for whether the mother's first PROMISE pregnancy resulted in a spontaneous abortion, stillbirth, neonatal death, or LBW

Discussion

PROMISE 1077 HS*

- **Subsequent pregnancies = 277 (17%)**
  - **Spontaneous abortions**
  - **Stillbirths**

⇧ continue vs discontinue ART arms

- **23.6% vs 11.9%**
- **RR 2.0 (95%CI 1.1–3.5) p = 0.02**

*CID 2019;68

Discussion (cont)

Previous reports

- **Risk for LBW ⇧ more advanced HIV disease**
- **1077BF/FF study population >95% WHO clinical stage I**

  ⇧ CD4 counts ⇩ VL
- **Risk remains ~ all HIV-infected women conceiving on ART**

Discussion (cont)

Kourtis et al*

- **significant association between pre-pregnancy and 1st T vs 2nd or 3rd T initiation of ART and prematurity risk**

Meta-analysis by Uthman et al**

- **significantly increased risk PTD, very PTD and LBW conceiving on ART compared to initiating ART during pregnancy**

*PLOS ONE 2018; 13(7)

**Lancet HIV 2016

Discussion (cont)

Sub-study limitations

- **Missing gestational age and birth weigh**

Strengths

- **Data was collected in a carefully monitored trial**
- **Generalizability is increased by the multisite, multi-country design**

Conclusion

Progress towards

- **UNAIDS 90-90-90 targets by 2020**
- **⇧ proportion women conceiving on ART**

Ongoing research & surveillance

- **Possible adverse pregnancy outcomes ~ ART**

Including pregnant women in new ARV trials is crucial

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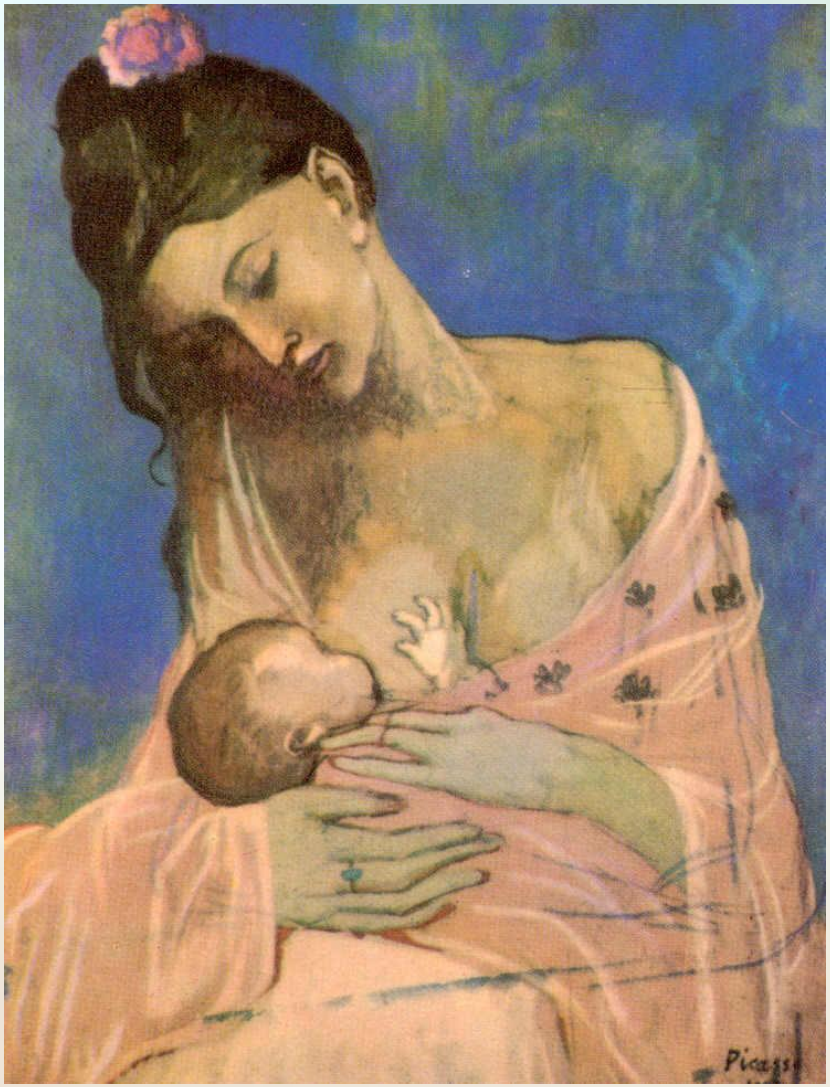

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