

PROMISE TRIAL: RESULTS OF CONTINUED VS DISCONTINUED ART AFTER END OF BREASTFEEDING

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INTRODUCTION

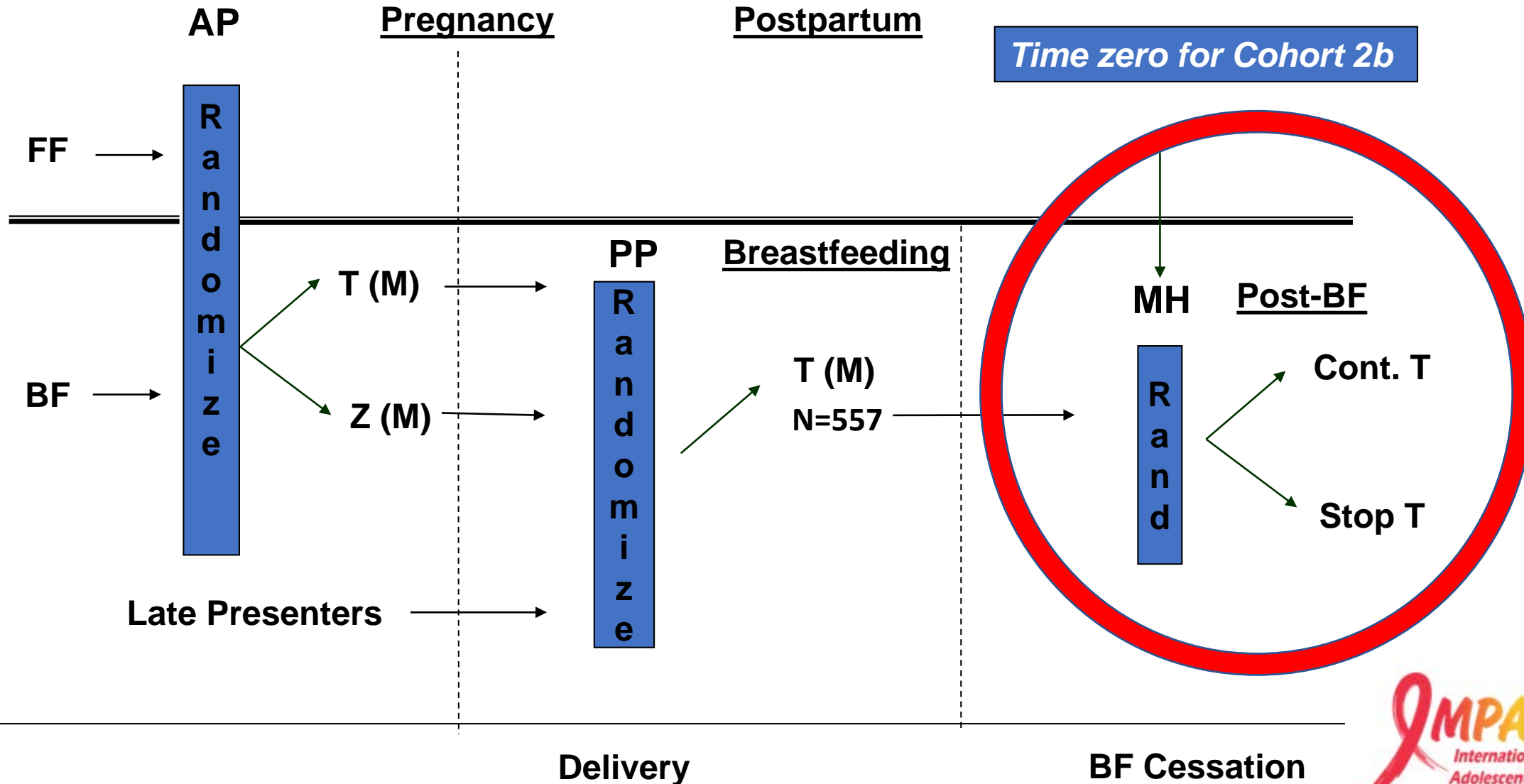
- The PROMISE multi-country randomized trial showed that use of triple antiretroviral drug regimens antepartum and postpartum substantially reduce transmission of HIV from HIV-infected mothers to their children.
- As use of antiretroviral treatment (ART) becomes universal, evaluation of extended use remains important.
- **This analysis, part of the PROMISE Maternal Health (MH) component, compares efficacy and safety between women who were randomized to continue or discontinue use of combined ART after cessation of risk of mother-to-child transmission (MTCT) of HIV during breastfeeding.**

METHODS

- This randomized trial, comprising eligible HIV-infected women from the postpartum component of PROMISE trial, was conducted during the period November 2011 and September 2014.
- Women who were originally randomized to triple ART for prevention of MTCT and maintained CD4 cell counts ≥ 350 cells/mm³ were randomized at the end of breastfeeding risk (cessation of breastfeeding) to two study arms: **continue with use of ART** or **discontinue use of ART**. Women who needed ART for their own health were not randomized.

Post-breastfeeding Maternal Health Randomization

What is the effect of extending the postpartum maternal triple ARV regimen after cessation of BF versus discontinuing the regimen with cessation of BF?



METHODS (CONT.)

- Study procedures at scheduled visits included completion of study forms, physical examination and collection of samples to perform laboratory tests – including hematology, chemistry, CD4 count, and viral load.
- Women randomized to continue ART were provided with lopinavir-ritonavir plus a fixed dose combination of emtricitabine-tenofovir disoproxil fumarate as the preferred regimen.
- Women who became pregnant were followed during the study and continued to receive combined ART as part of the study with modifications as necessary.
- Women in the discontinue ART arm received the local standard of care during follow-up. Women re-started ART for their own health, if needed.

METHODS (CONT.)

- The primary study efficacy endpoint was a composite measure of progression to AIDS-defining illness (WHO stage IV clinical event) or death.
- An Endpoint Review Committee reviewed all diagnoses identified as potential endpoints.
- Secondary safety outcome: Grade 3 or greater laboratory results or signs and symptoms and selected Grade 2 renal and hepatic laboratory results.
- An intent-to-treat analyses based on the randomization study arms was used.

METHODS (CONT.)

- The analyses are based on data collected before July 7, 2015 when the study sites were instructed to offer ART to all participants based on new findings from another study (START trial).
- Comparisons for categorical outcomes used Fisher's exact test.
- Comparisons between randomization arms with a survival outcome used the log-rank test and Cox regression models for estimation of treatment effect sizes.
- Time to event distributions were summarized using Kaplan-Meier (K-M) estimators.
- Incidence rates were calculated per 100 person-years (PYs).

RESULTS

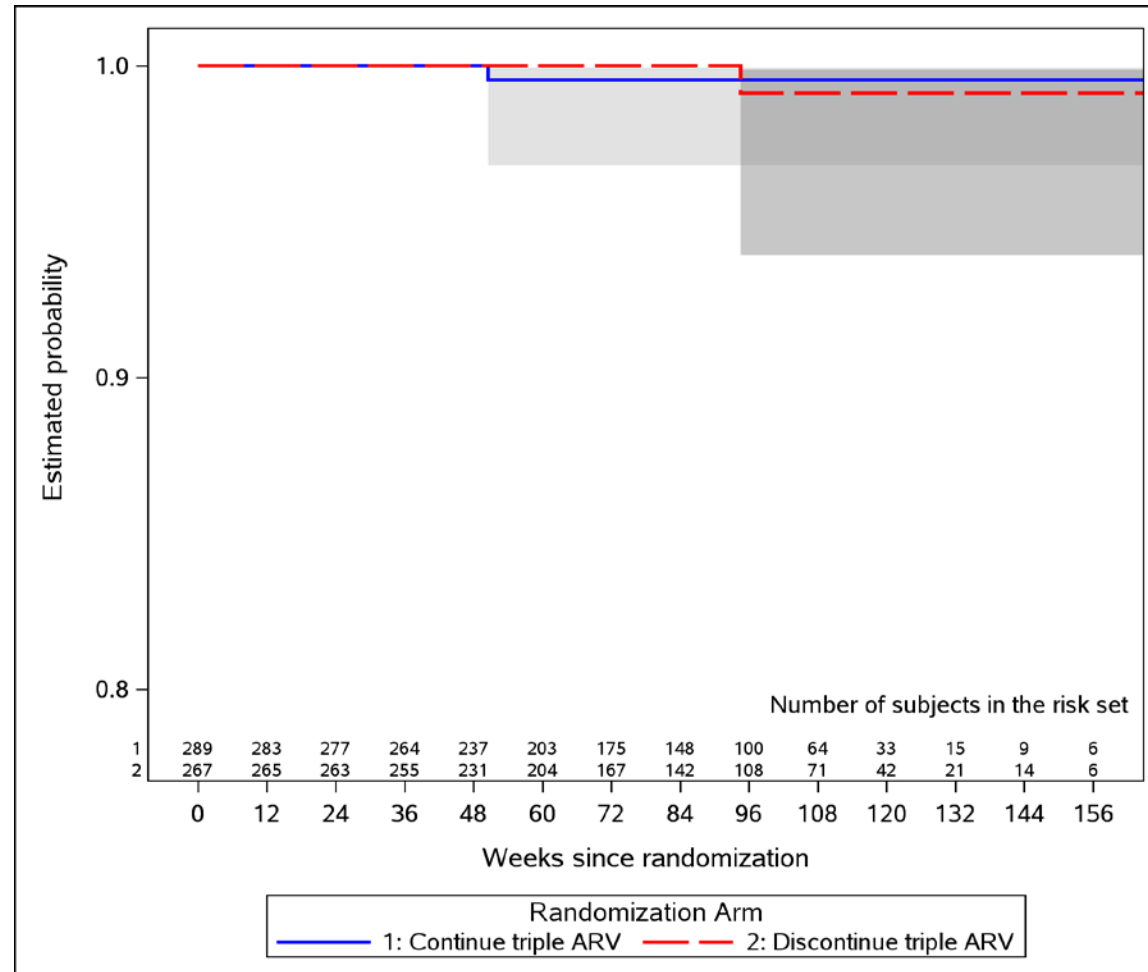
- In total, 557 women were randomized: 289 to continue ART and 268 to discontinue ART from the following sites: Malawi (33%), Zimbabwe (25%), South Africa (21%), Uganda (13%), India (7%), Tanzania (1%), and Zambia (1 participant).
- Baseline characteristics were similar at randomization: most women were black Africans (94%); median age was 28 years; BMI was 23.1 kg/m²; most were WHO clinical stage I (93%); and the majority had a CD4 \geq 500 cells/mm³ (95%).
- The overall median follow-up was 84 weeks (range: 4-171) and was not different between the two arms:
Follow-up (person-years sum of values): 438.4 in continue ART arm
433.0 weeks in discontinue ART arm

RESULTS (CONT.)

- ***Primary efficacy comparisons:*** There were two maternal deaths, one in each arm. The rates were comparable and not statistically significant; hazard ratio=1.04 (95% CI 0.06-16.59).
- Reported causes of death: Continue ART - ruptured ectopic pregnancy; Discontinue ART - chronic renal insufficiency.

Primary Efficacy: Time to first AIDS-defining illness or death

Randomization Arm	Incidence rate (95% CI)	Hazard ratio (95% CI)	Log Rank p-value
Continue triple ARV	0.23 (0.15, 0.34)	1.04 (0.06, 16.59)	0.98
Discontinue triple ARV	0.23 (0.16, 0.35)		

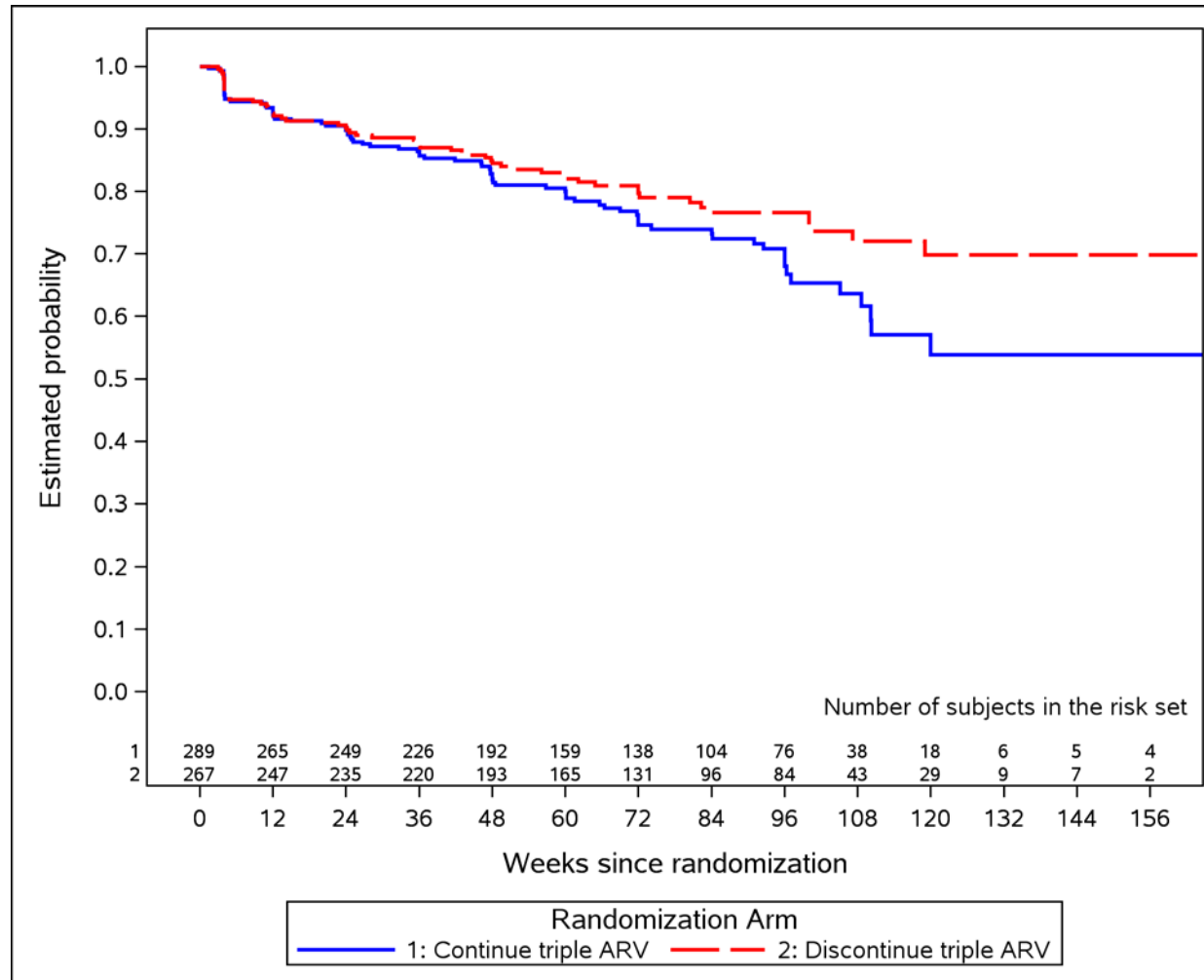


RESULTS – SAFETY

- **Secondary safety comparisons:** There were 78 composite safety events in the continue arm and 57 in the discontinue arm (p-value = 0.08).
- **Restricting the analysis to only signs and symptoms:** There were 20 grade 3 or higher signs and symptoms in the continue arm and 7 in the discontinue arm (p-value = 0.01). The most common sign and symptom was weight loss: 16 in continue arm and 5 in discontinue arm.

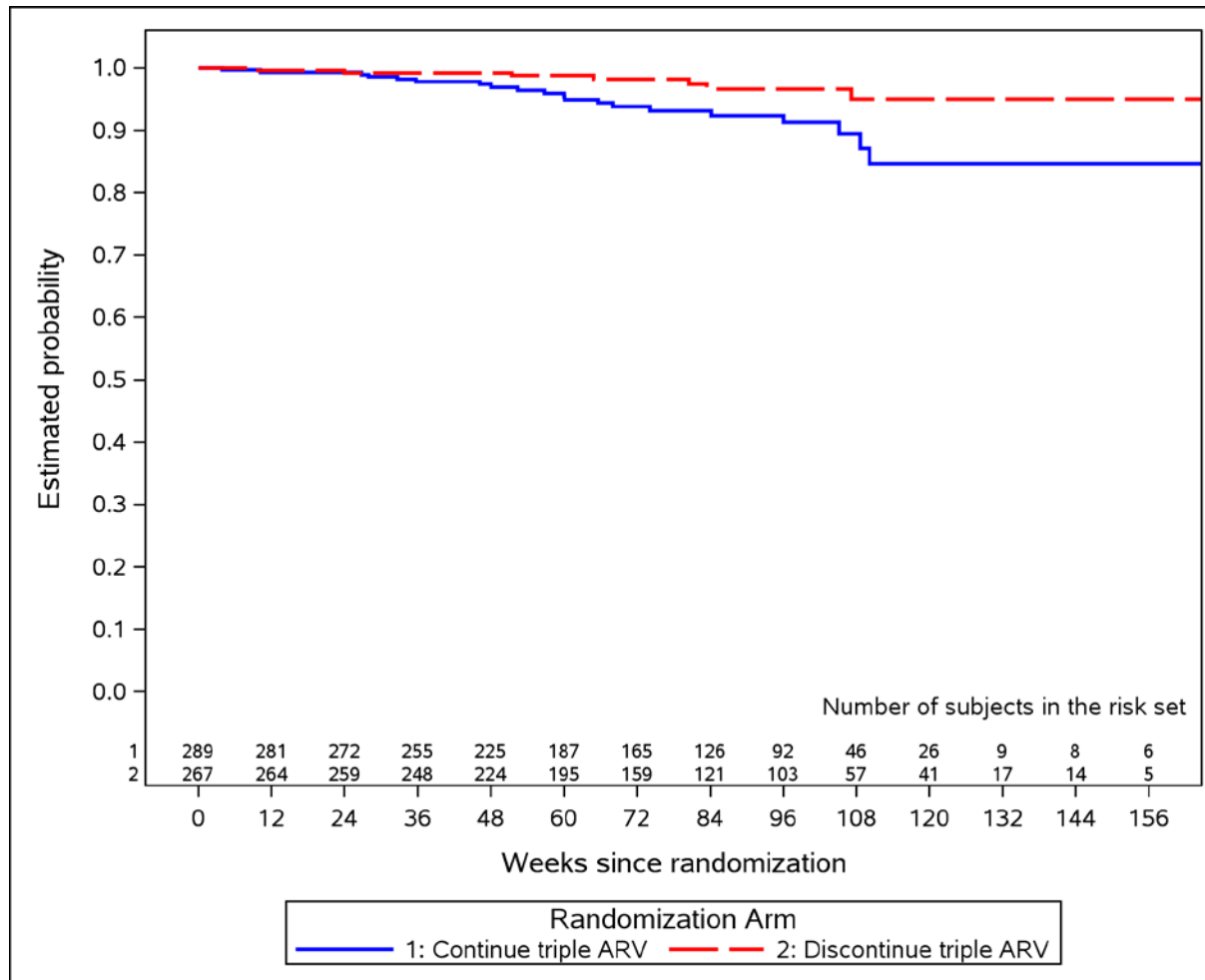
Time to first grade 2, 3 or 4 adverse events – Composite endpoint of Chemistries, Signs and Symptoms

Randomization arm	Subjects	Cumulative events	Total person - Years	Incidence rate (95% CI) *	p-value
Continuation triple ARV	289	78	359.1	21.7 (17.1, 27.7)	0.08
Discontinue triple ARV	267	57	356.1	16.0 (12.1, 21.3)	



Time to first grade 3 or 4 signs or symptoms

Randomization arm	Subjects	Cumulative events	Total person - Years	Incidence rate (95% CI) *	p-value
Continuation triple ARV	289	20	408.9	4.9 (3.8, 6.3)	0.01
Discontinue triple ARV	267	7	411.3	1.7 (1.1, 2.6)	



RESULTS – SUBSEQUENT PREGNANCIES

- Of the 557 women in this analysis, 81 (15%) had a record of at least one subsequent pregnancy, 42 in continue ART arm and 39 discontinue ART arms:

Delivery Outcome	Continue arm N=42	Discontinue arm N=39	Total N=81
Live birth	28 (67%)	28 (72%)	56
Induced abortion	6 (14%)	5 (13%)	11
Spontaneous abortion	4 (10%)	2 (5%)	6
Stillbirth	2 (5%)	2 (5%)	4
Live birth followed by neonatal death	1 (2%)	1 (3%)	2
Ectopic pregnancy	0	1	1

These differences were not statistically significant (p=0.59)

RESULTS – SUMMARY

	Rates of Adverse Events per 100 PY		P-value
	Continue ART	Discontinue ART	
Primary			
AIDS defining illness or death*	0.23 (1/435.1)	0.23 (1/430.5)	0.98
Secondary			
Composite grade 2, 3 or 4 adverse events**	21.7 (78/359.1)	16.0 (57/356.1)	0.08
Composite grade 3 or 4 serious adverse events***	9.7 (38/391.4)	5.5 (22/400.3)	0.03
Grade 3 or 4: signs or symptoms***	4.9 (20/408.9)	1.7 (7/411.3)	0.01
Grade 2, 3, 4 hematology or chemistry***	15.4 (57/370.9)	12.3 (45/365.1)	0.28
Composite endpoint of HIV/AIDS-related event or WHO stage II/III event**	4.28 (18/420.2)	2.37(10/422.8)	0.12

* Pre-specified analysis: only two deaths; no AIDS-defining illness. ** Pre-specified secondary outcome; *** Post-hoc analysis

CONCLUSIONS

- After cessation of breastfeeding, rates of clinical events remained very low in both groups.
- However, the rates of some secondary post-hoc AE analyses were significantly higher in the continue ART arm compared to discontinue ART arm.
- Studies of newer ART regimens are needed to improve the long-term outcomes for post-partum women

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