AIDS 2016

Randomized Trial of Stopping or Continuing ART among Postpartum Women with Pre-ART CD4 ≥ 400 cells/mm^3 (PROMISE 1077HS)

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ACTG AIDS CLINICAL TRIALS GROUP

PROMISE IMPAACT 1077 Promoting Maternal and Infant Survival Everywhere

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Background

- The health benefits of antiretroviral therapy (ART) for women in the postpartum period with high CD4 cell counts have not been evaluated in randomized trials
- The aim of our study was to assess the risks and benefits of continued ART vs stopping ART among non-breastfeeding women after delivery

Study Design: Randomized Trial

- Key Eligibility
  - HIV-infected postpartum women
  - No clinical indication for ART based on local guidelines
  - CD4 cell count 400 cells/mm^3 or higher (prior to ART and at delivery)
  - ART naïve except for PMTCT
  - Received ART for PMTCT during current pregnancy (at least 4 weeks)
  - Not breastfeeding or planning to breastfeed
- Study Follow-up
  - Participants were randomized to continue or stop ART within 42 days of delivery; those who stopped were restarted when CD4 dropped below 350 cells/mm^3 or when clinically indicated
  - Participants were seen 4 weeks after enrollment and every 12 weeks thereafter through 84 weeks after the last enrollment.
  - ART was provided by the study (Lopinavir/r +TDF/FTC preferred regimen)

Study Design: Endpoints

- **Primary Composite Endpoint:**
  - Time to AIDS event (WHO Stage 4 Condition), serious cardiovascular, renal, hepatic event or death
- **Primary Safety Endpoint:**
  - Time to first targeted Grade 2, Grade 3 or 4 event
- **Key Secondary Endpoints:**
  - Composite endpoint of HIV/AIDS-related event or WHO Clinical Stage 2 or 3 event
  - Time to WHO Clinical Stage 2 or 3 events

Study Design: Sample Size and Monitoring

- Sample size of 2000 participants provided 90% power to detect a 50% reduction from an annualized primary event rate of 2.07%
- Intent-to-treat analysis included all women randomized
- Comparisons between treatment groups based on log rank tests and Cox regression models for estimation of treatment effect sizes
- Enrollment from January 2010-November 2014
- November 2014 - DSMB approved curtailing enrollment at 1,630 participants
- Analyses reflect follow-up until July 7, 2015
  - Participants were informed about the START results and all were offered ART

Study Sites

- *Argentina*
- *Botswana*
- *Brazil*
- *China*
- *Haiti*
- *Peru*
- *Thailand*
- *US*

52 clinical research sites in 8 countries

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Results

1917 Screened

1653 Enrolled

1 withdrew

R

n=827

n=825

CONTINUE ART

(median = 2.31 years)

79 (9.6%) premature d/c

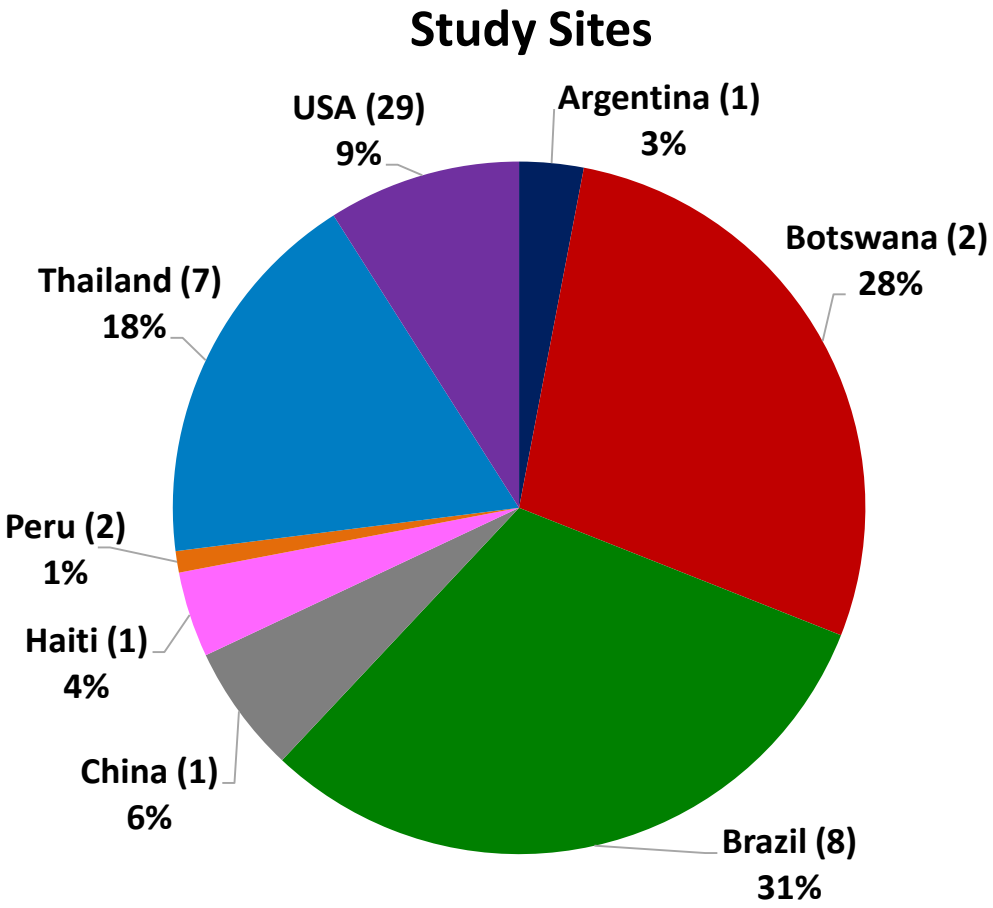
15% d/c ART

STOP ART

(median = 2.35 years)

70 (8.5%) premature d/c

12 % restarted ART prior to study threshold



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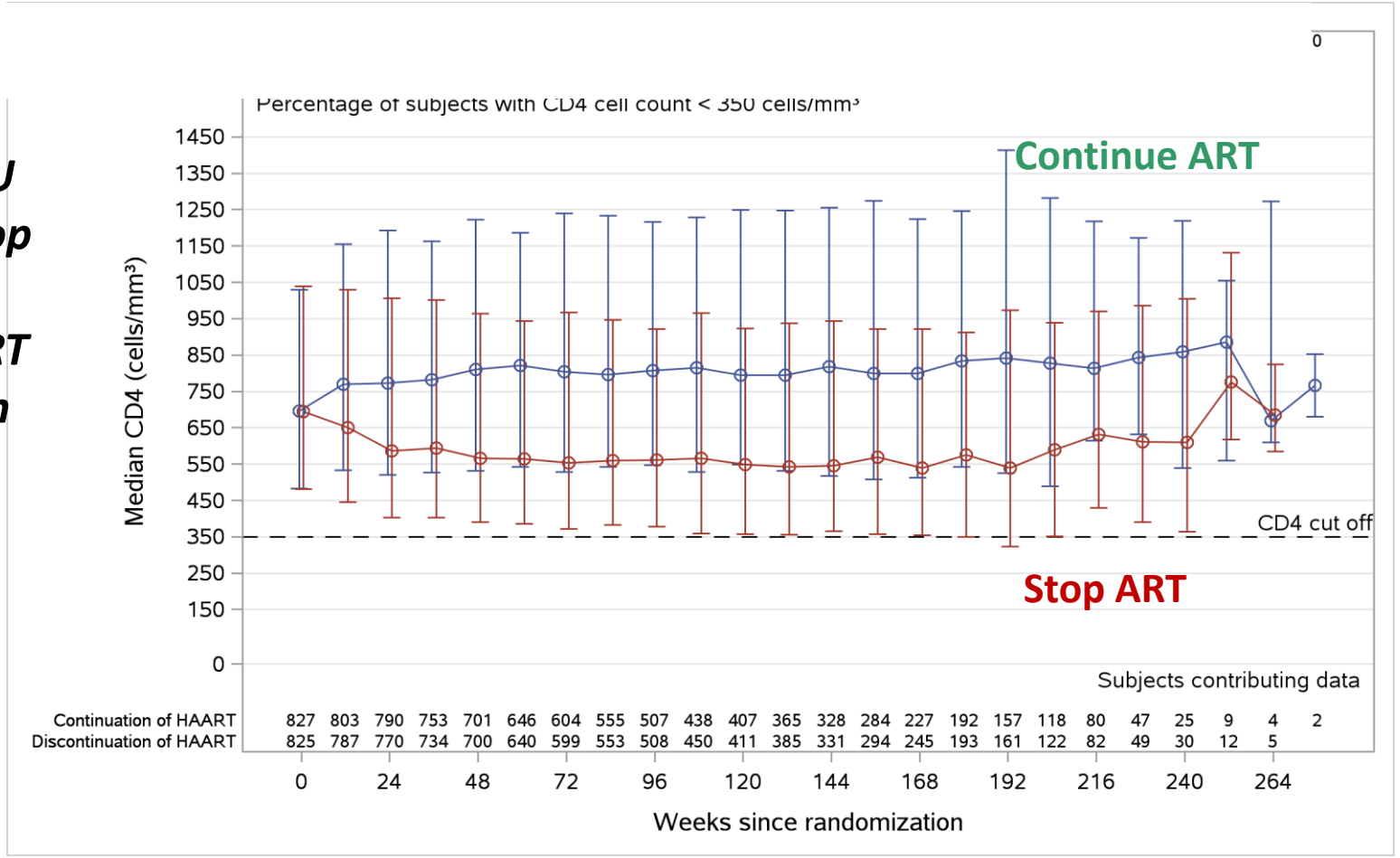
Baseline Characteristics

	CONTINUE ART n=827	STOP ART n=825
Median age	27 years	28 years
Median Screening CD4	696 cells/mm^3	695 cells/mm^3
Median Pre-ART CD4	550 cells/mm^3	548 cells/mm^3
WHO Stage 1	98%	99%
HIV-1 RNA <400	91%	91%
PMTCT ART PI-based	77%	76%
NNRTI-based	22%	21%
On Study ART **LPV/r based** **ATV/r based**	**74%** **19%**	**NA**

CD4 Counts by Study Arm

During F/U 31% of Stop arm started ART at median CD4 372 cells/mm³



Median, 10th and 90th percentiles of CD4 Cell Counts over Time

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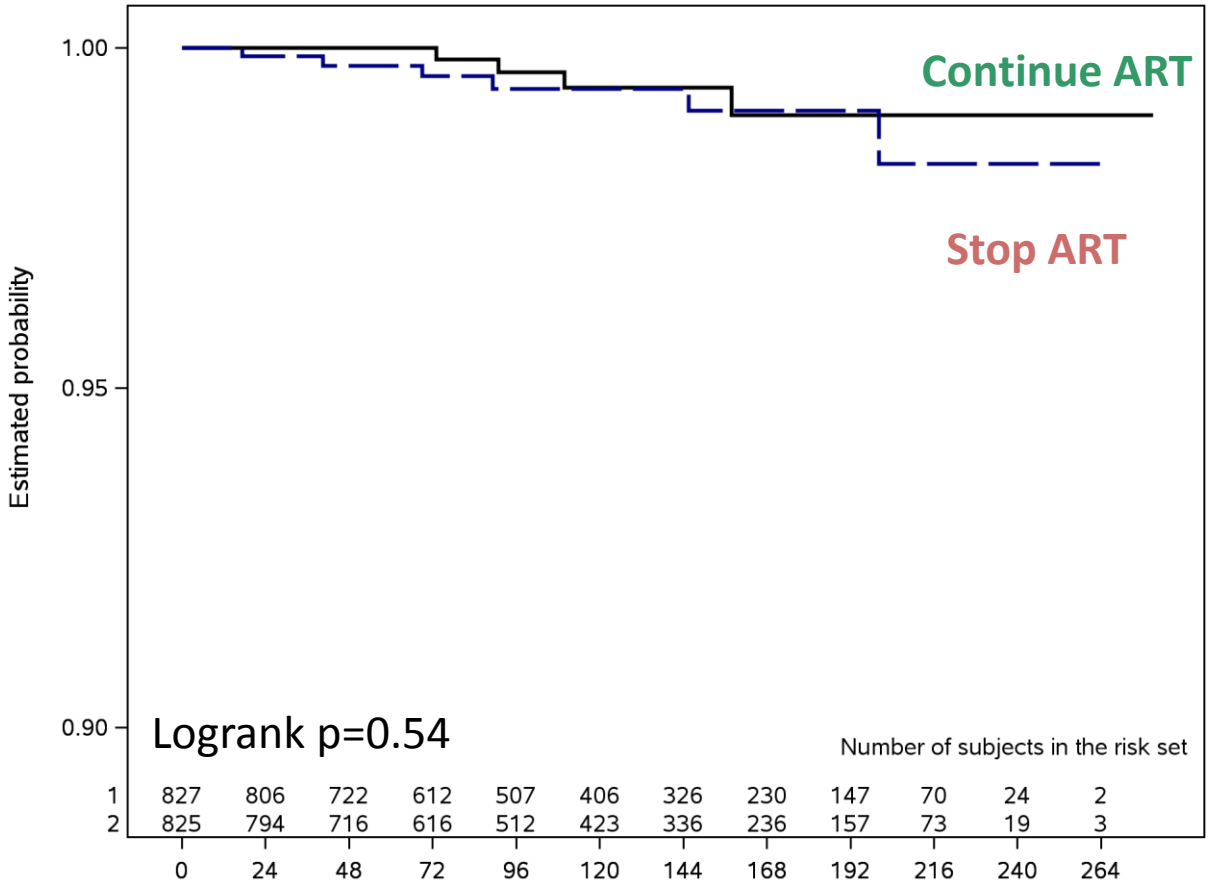
Primary Efficacy Outcome

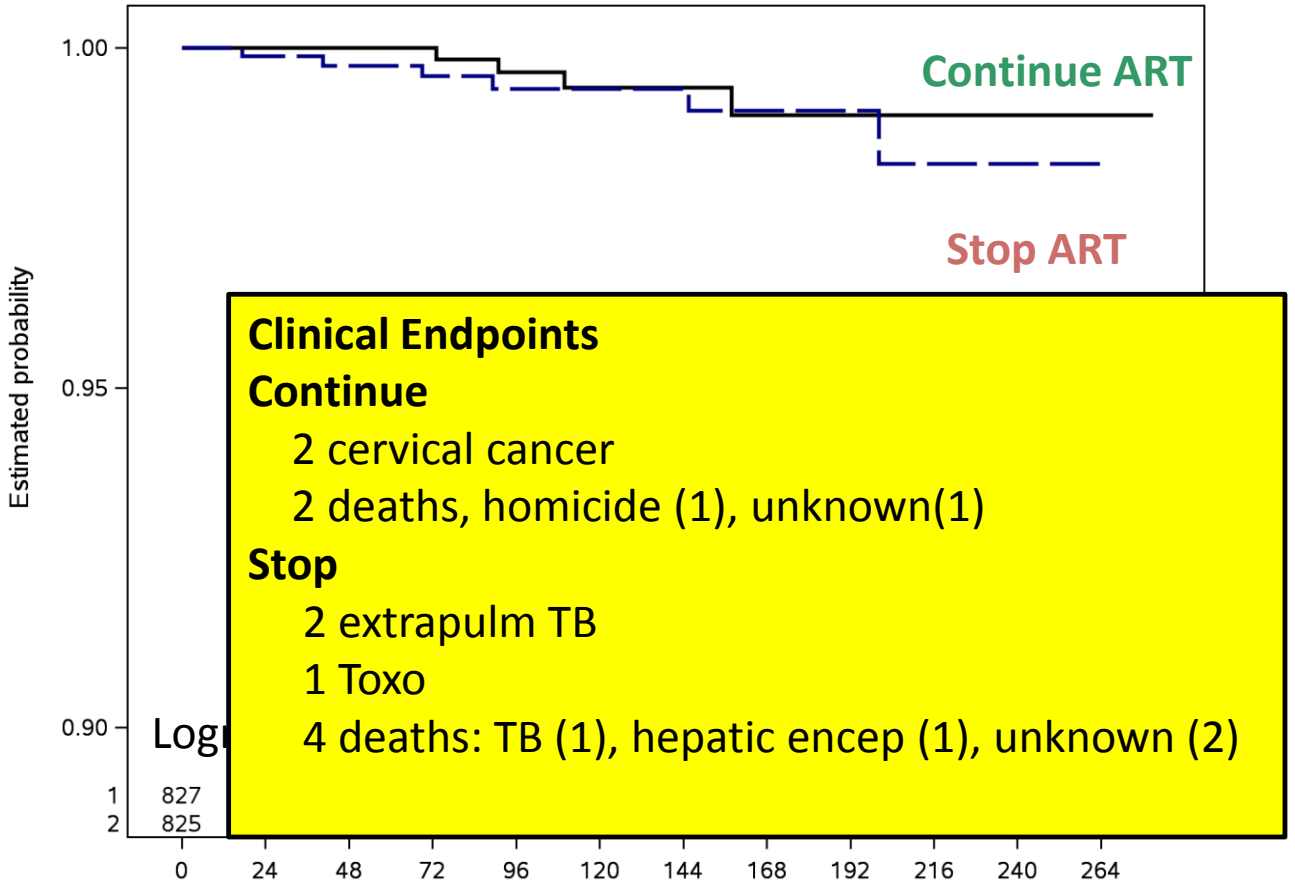
AIDS-defining event, serious non-AIDS event, or death due to any cause



Outcome	Continue ART		Stop ART		Hazard Ratio (95% CI)
	No	Rate per 100 py	No	Rate per 100 py	
Primary Efficacy Composite Endpoint	4	0.21	6	0.31	0.68 (0.19, 2.40)
AIDS Defining Event	2	0.10	3	0.15	0.67 (0.11, 4.02)
Serious Non-AIDS Event	0		0		
Death	2	0.10	4	0.20	0.52 (0.09, 2.81)

Primary Efficacy Outcome

AIDS-defining event, serious non-AIDS event, or death due to any cause



Clinical Endpoints

Continue

2 cervical cancer

2 deaths, homicide (1), unknown(1)

Stop

2 extrapulm TB

1 Toxo

4 deaths: TB (1), hepatic encep (1), unknown (2)

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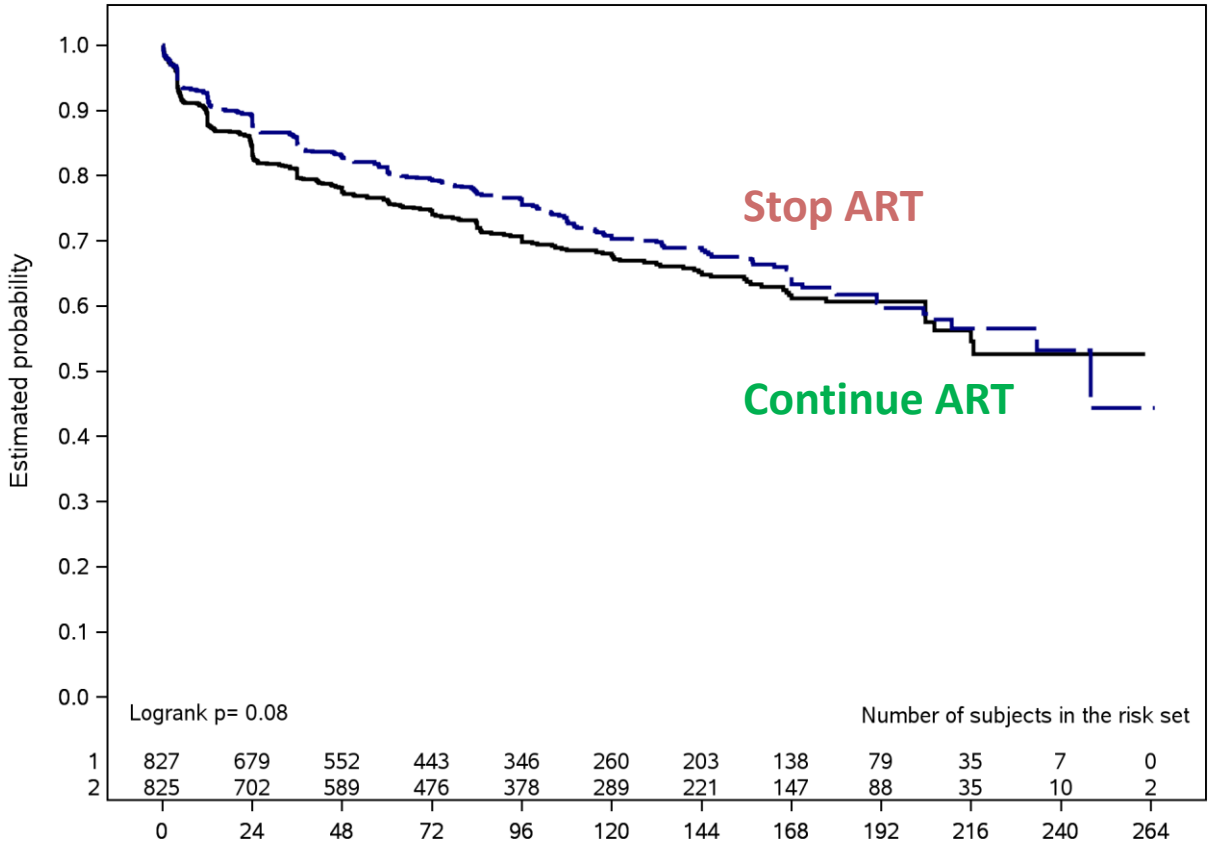
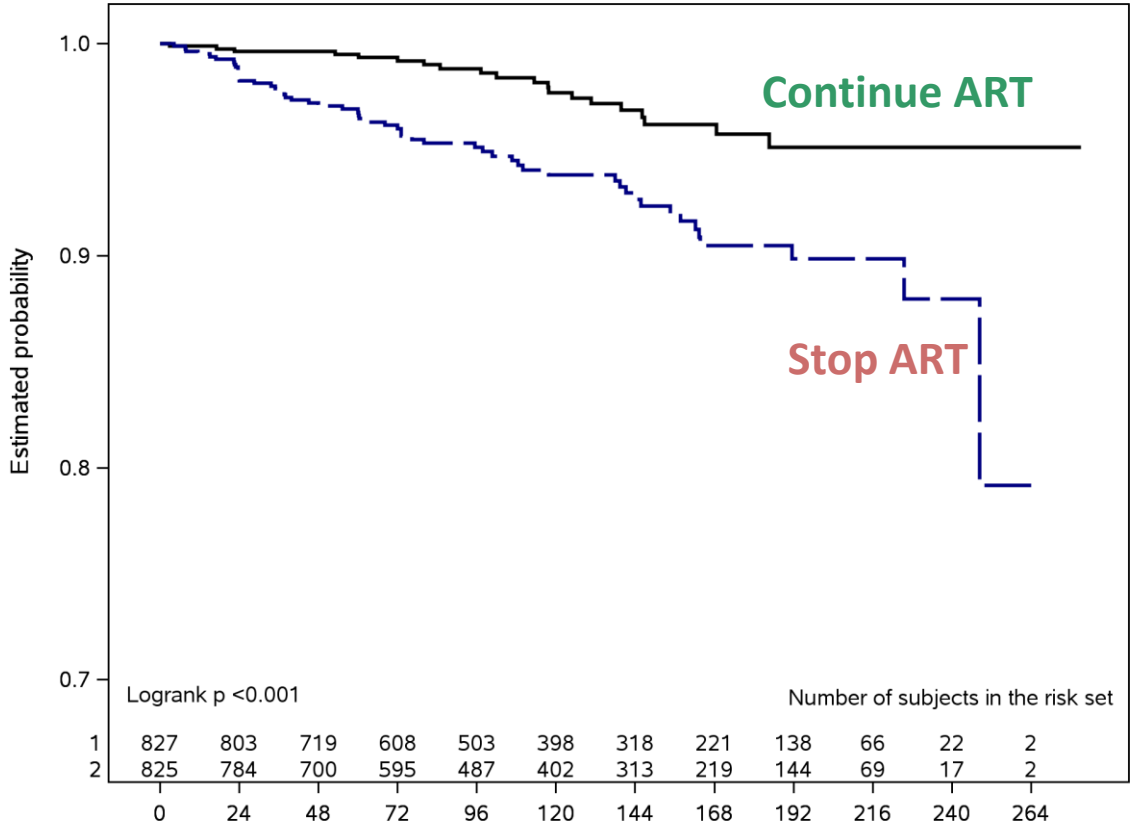
Primary Safety Endpoint

Composite of time to first Grade 3 or 4 sign or symptom or Grade 2, 3 or 4 chemistry or hematology result



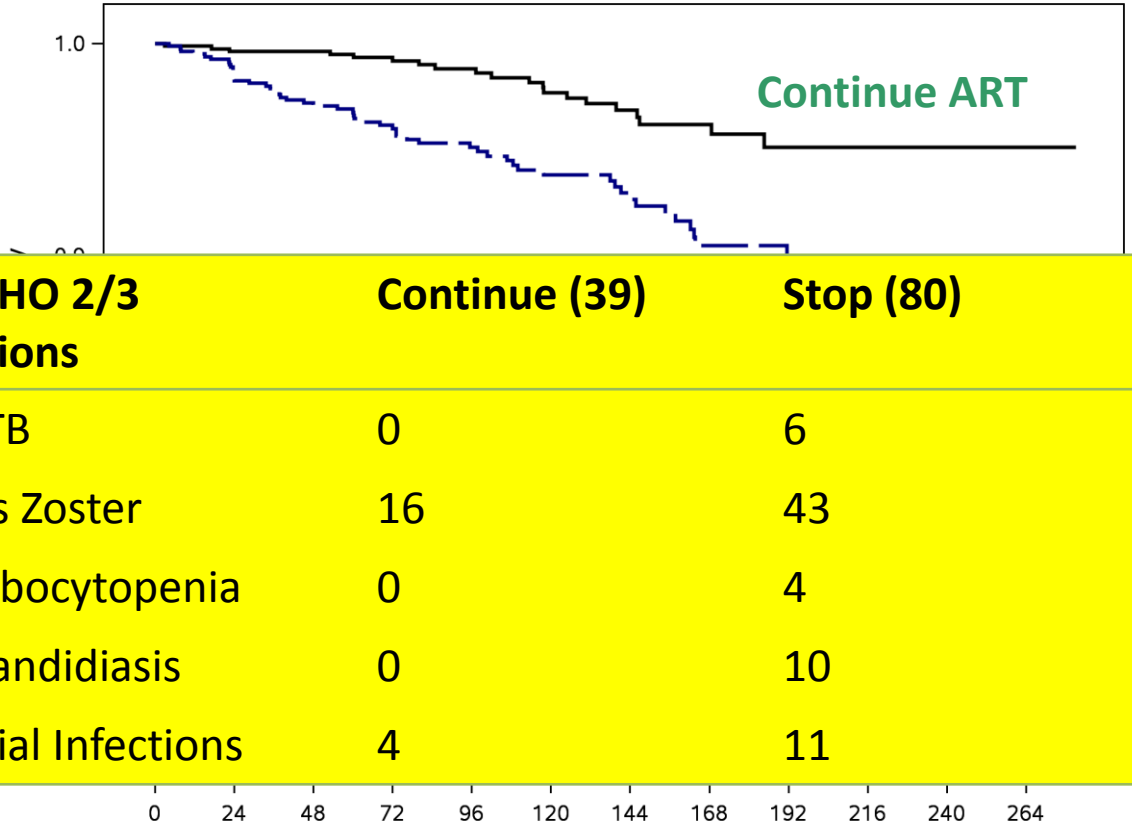
Outcome	Continue ART		Stop ART	
	No	Rate per 100 py	No	Rate per 100 py
Primary Safety Composite Endpoint	260	18.4 (15.7,21.4)	232	15.4 (13.1, 18.2)

Time to WHO Clinical Stage 2 or 3 Condition



Outcome	Continue ART		Stop ART		Hazard Ratio (95% CI)
	No	Rate per 100 py	No	Rate per 100 py	
Composite of HIV/AIDS Related Event or WHO Stage 2 or 3 Event	57	3.09	99	5.49	0.56 (0.41, 0.78)
WHO Stage 2 or 3 Event	39	2.02	80	4.36	0.47 (0.32, 0.68)

Time to WHO Clinical Stage 2 or 3 Condition



Key WHO 2/3 conditions	Continue (39)	Stop (80)
Pulm TB	0	6
Herpes Zoster	16	43
Thrombocytopenia	0	4
Oral Candidiasis	0	10
Bacterial Infections	4	11

Outcome	Continue ART		Stop ART		Hazard Ratio (95% CI)
	No	Rate per 100 py	No	Rate per 100 py	
Composite of HIV/AIDS Related Event or WHO Stage 2 or 3 Event	57	3.09	99	5.49	0.56 (0.41, 0.78)
WHO Stage 2 or 3 Event	39	2.02	80	4.36	0.47 (0.32, 0.68)

Virologic Failure (VF) and Resistance

- VF: Confirmed HIV-1 RNA > 1000 copies/ml at or after 24 weeks of ART
  - Among the 827 initially randomized to continue ART:
    - 76 (9%) experienced a single VL > 1000 copies/ml and re-suppressed
    - 15 had single VL > 1000 copies/ml and were lost to F/U
    - **189 (23%) experienced confirmed VF**
- Resistance Testing
  - Available for 155 (82%) of those with VF:
    - 103 (66%) had no evidence of resistance at the time of failure*
    - Among the 52 with evidence of resistance
      - 22 had resistance to one of the drugs in the failing regimen
      - 11 % (14/125) failing PI regimen
      - 30% (8/27) failing NNRTI regimen

*Note: overall 90% of participants were on PI based ART

Summary

- ART was safe and well-tolerated among post-partum women with CD4 cell counts ≥ 400
- Rates of AIDS defining and serious non-AIDS events were lower than expected and did not differ significantly by randomized arm
  - Rates of WHO Stage 2 and 3 events were halved with continued ART
- Virologic failure occurred in 23%, reflecting challenges with adherence in this population

Conclusions

- The safety and clinical benefit of continued ART observed in this randomized trial supports the use of continued ART (Option B+) for postpartum women
- Interventions to improve adherence as well as studies to examine newer regimens with a high genetic barrier to resistance are needed to insure maximal long term benefit.

Protocol Team and Site Investigators

The 1077 PROMISE study team gratefully acknowledges the dedication and commitment of the 1652 participants without whom this study would not have been possible.

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* In Memoriam
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