Similar Clinical Outcomes Between Formula and Breastfeeding Women in PROMISE

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Background: PROMISE

- Study of antiretroviral strategies in pregnant and postpartum women with high CD4 cell counts
  - Implemented in 2010, prior to results of studies of ART in men and non-pregnant women with high CD4 cell counts
  - 1077HS: Performed in locations where standard of care was ART in pregnancy & postpartum formula feeding (single randomization postpartum to continue or discontinue ART)
  - 1077BF/FF: Performed in locations where standard of care included short course antiretrovirals in pregnancy & postpartum breastfeeding. Randomizations antepartum, postpartum, and at cessation of breastfeeding to examine a range of infant and maternal outcomes
- Focus today: Maternal health outcomes of postpartum breastfeeding women (1077BF/FF)
  - Presentation of results from PROMISE 1077BF/FF ("predominately breastfeeding")
  - Review the study design of PROMISE 1077HS ("formula feeding")
  - Cross study comparison: breastfeeding (1077BF/FF) versus formula feeding women (1077HS)

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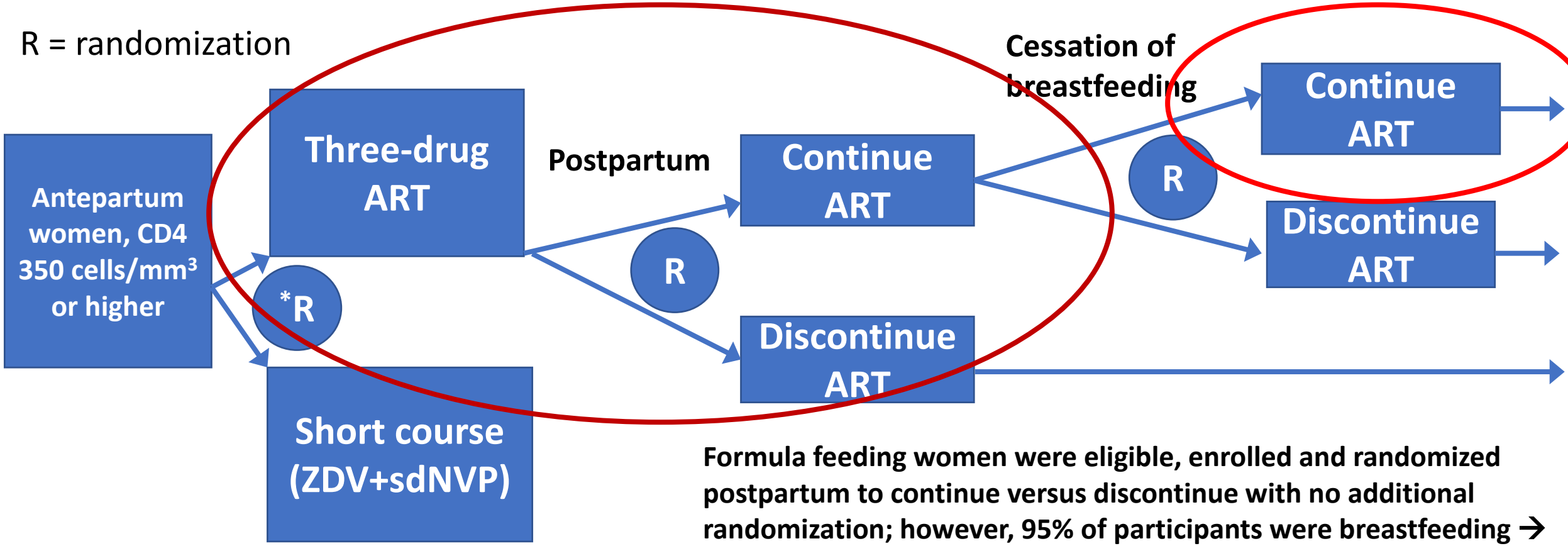
PROMISE 1077BF/FF Study Design



Formula feeding women were eligible, enrolled and randomized postpartum to continue versus discontinue with no additional randomization; however, 95% of participants were breastfeeding → "Breastfeeding PROMISE study"

*Fowler MG et al; NEJM Nov 2016;
Flynn M et al, JAIDS Apr 2018

Study Design PROMISE BF/FF ("Breastfeeding"): Randomized Trial

- Key Eligibility for this Analysis
  - HIV-infected postpartum women
  - No clinical indication for ART based on local guidelines
  - CD4 cell count 350 cells/mm^3 or higher (prior to ART and at delivery)
  - ART naïve except for PMTCT
  - Randomized to receive ART for PMTCT during current pregnancy in the PROMISE antepartum component
- Study Follow-up
  - Participants were randomized within 42 days after delivery to continue or discontinue ART; those who stopped were restarted when CD4 dropped below 350 cells/mm^3 or when clinically indicated (per protocol)
  - Participants were seen 4 weeks after enrollment and every 12 weeks thereafter
  - ART was provided by the study (Lopinavir/r +TDF/FTC preferred regimen)

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Study Design: Endpoints

- **Primary Composite Endpoint:**
  - Time to AIDS event (WHO Clinical Stage 4 Condition) or death

- **Key Secondary Endpoints:**
  - Time to composite endpoint of HIV/AIDS-related event* or WHO Clinical Stage 2 or 3 Condition
  - Time to WHO Clinical Stage 2 or 3 events (post-hoc)
  - Safety Endpoint: Time to first targeted Grade 2, Grade 3 or 4 event**

* WHO Clinical Stage 4 illnesses, pulmonary tuberculosis (TB) and other serious bacterial infections

**Selected Grade 2 lab abnormalities (renal, hepatic and hematologic) and all Grade 3 or higher lab values and signs and symptoms

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Study Design: Sample Size and Monitoring

- Sample size determined by enrollment to PROMISE antepartum component; power calculations assumed an annualized primary event rate of 3.33%
- Intent-to-treat analysis included all women randomized in the postpartum component
- Comparisons between treatment groups based on log rank tests and Cox regression models for estimation of treatment effect sizes
- Enrollment from June 2011-October 2014
- Analyses reflect follow-up until July 7, 2015
    - Participants were informed about the START results and all were offered ART

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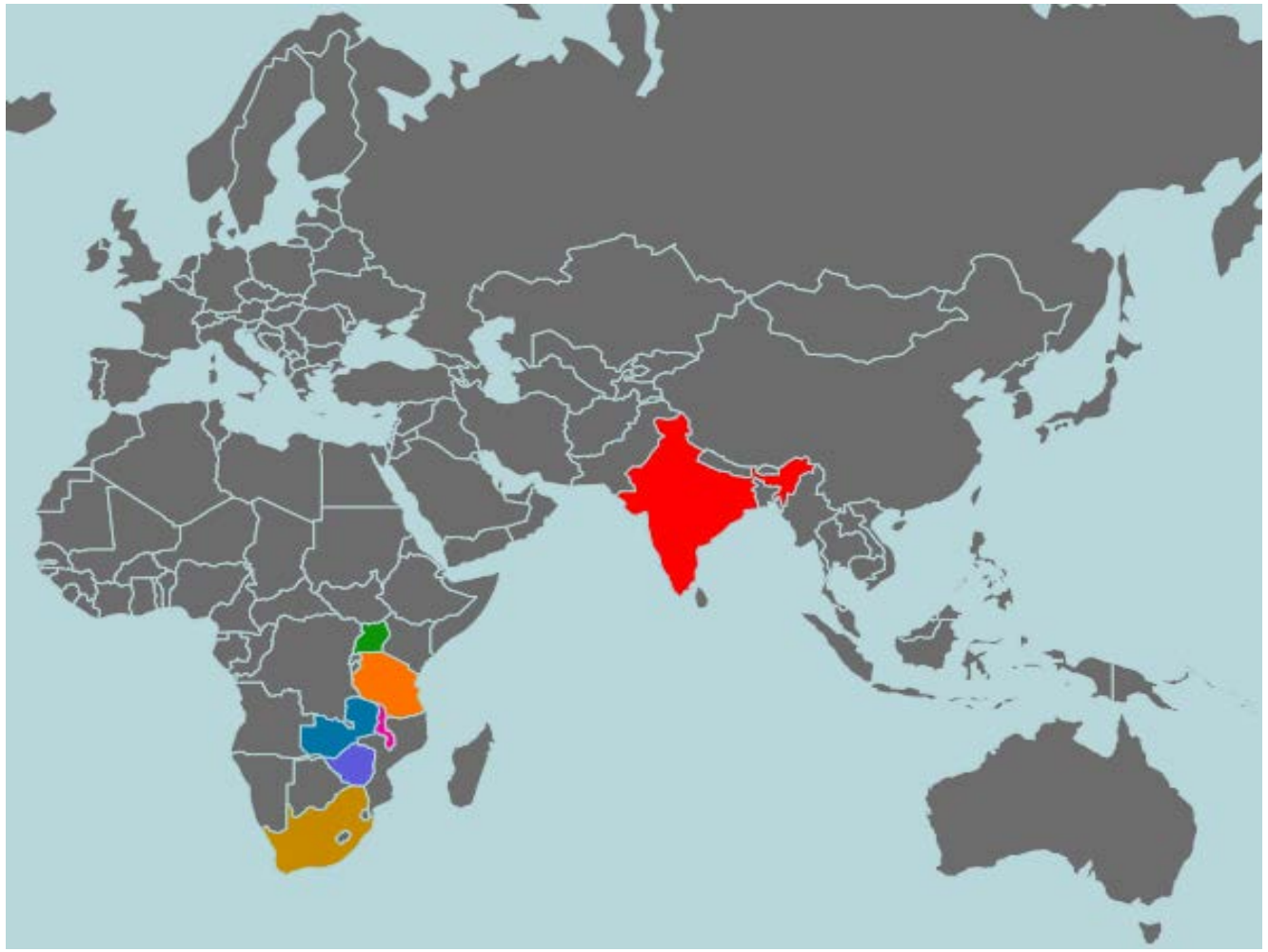
Study Sites



- India
- Malawi
- South Africa
- Tanzania
- Uganda
- Zambia
- Zimbabwe

15 clinical research sites in 7 countries

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Results

328 not enrolled
-32% missed timeline
-13% clinical indication for ART
-10% infant ineligible
-4% lab out of range
-55% other/no reason given

1,994 received antepartum ART

1,612 eligible

1 excluded

R

n=801

n=811

CONTINUE ART

(median = 1.38 years)

23 (3%) premature d/c from study follow-up

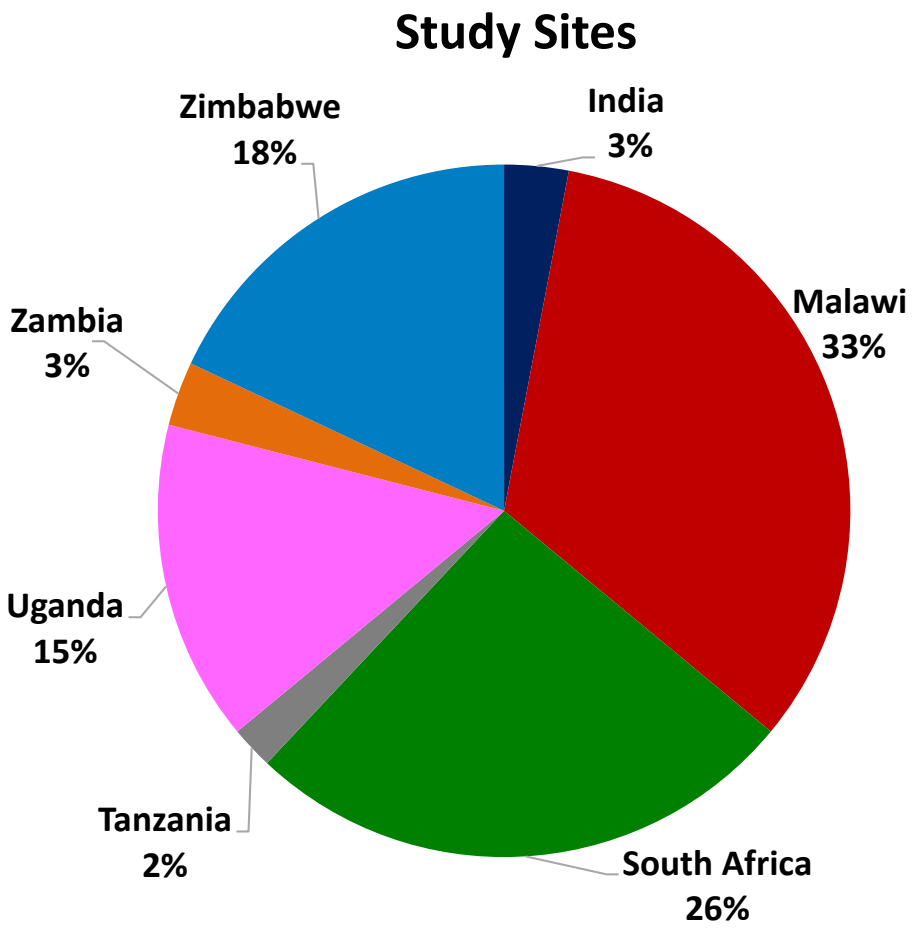
14% discontinued ART

DISCONTINUE ART

(median = 2.04 years)

34 (4%) premature d/c from study follow-up

6% restarted ART prior to study threshold



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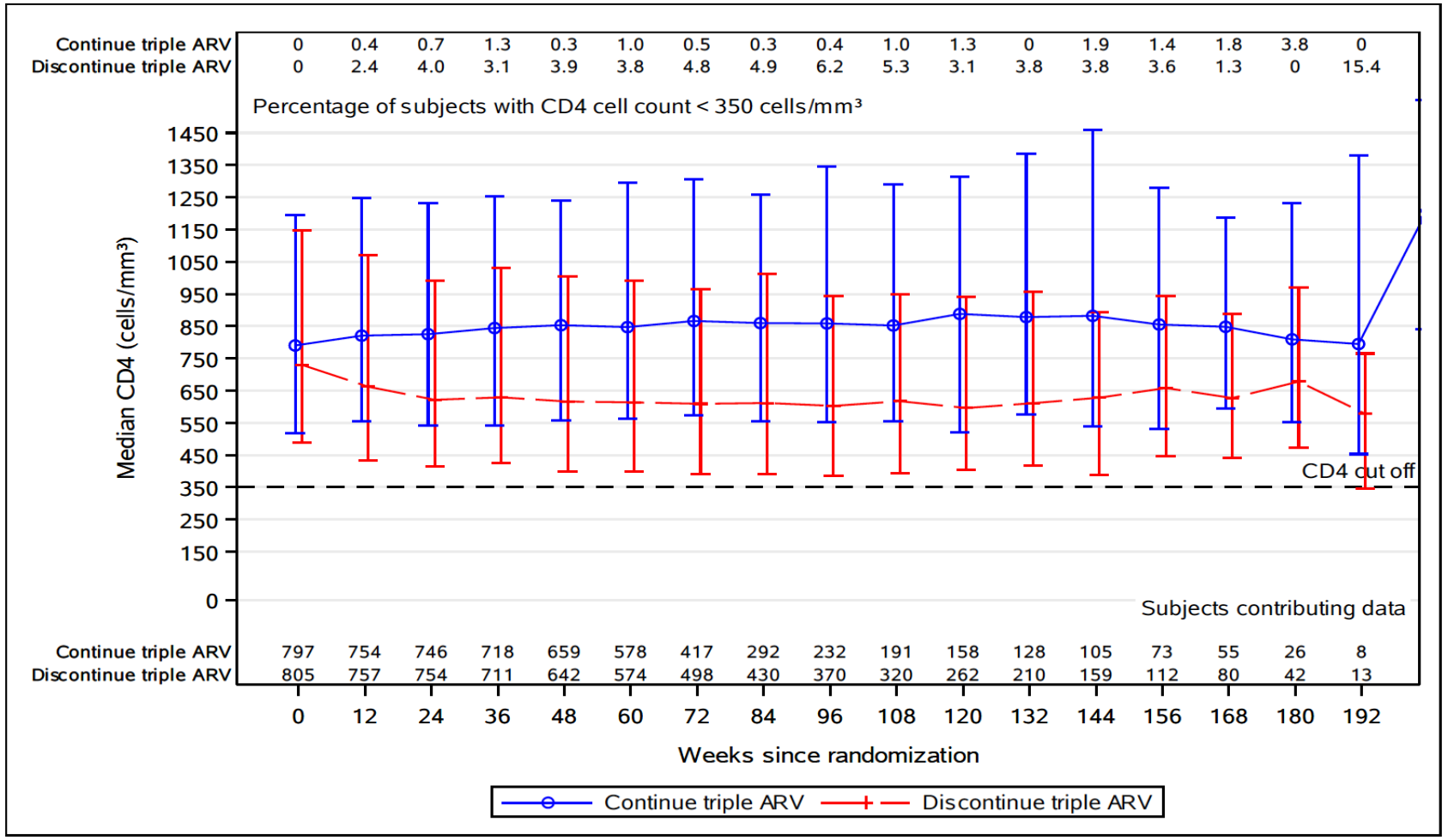
Baseline Characteristics

	CONTINUE ART n=801	DISCONTINUE ART n=811
Median age (IQR)	27 years (23-31)	27 years (24-31)
Race		
Asian	0 (0%)	1 (0%)
Black African	781 (98%)	787 (97%)
Indian	20 (2%)	22 (3%)
Median Screening CD4 count (IQR)	726 cells/mm^3 (593-911)	730 cells/mm^3 (586-902)
WHO Stage 1	96%	98%
HIV-1 RNA <1,000 copies/ml	93.6%	94.0%
On Study ART regimen		
LPV/r based	98%	
NNRTI	<1%	N/A

CD4 Counts by Study Arm

During F/U 11% of women in the discontinue arm started ART for CD4 <350 cells/mm³ (median 316 cells/mm³)



Median, 10th and 90th percentiles of CD4 T-cell counts over time

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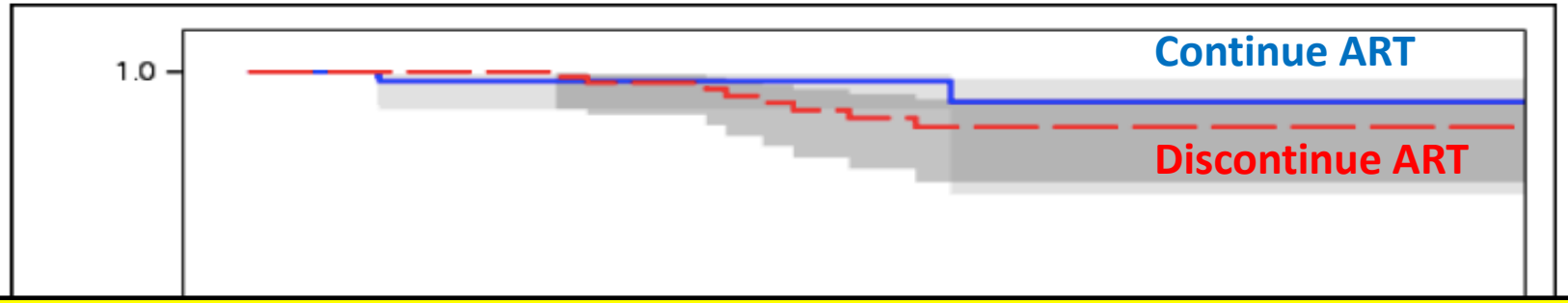
Primary Efficacy Outcome

AIDS-defining event or death

Shading: 95% Cis



p=0.37

Clinical Endpoints

Continue

3 deaths: disseminated/miliary TB (1), suicide (1), ruptured ectopic pregnancy (1)

Discontinue

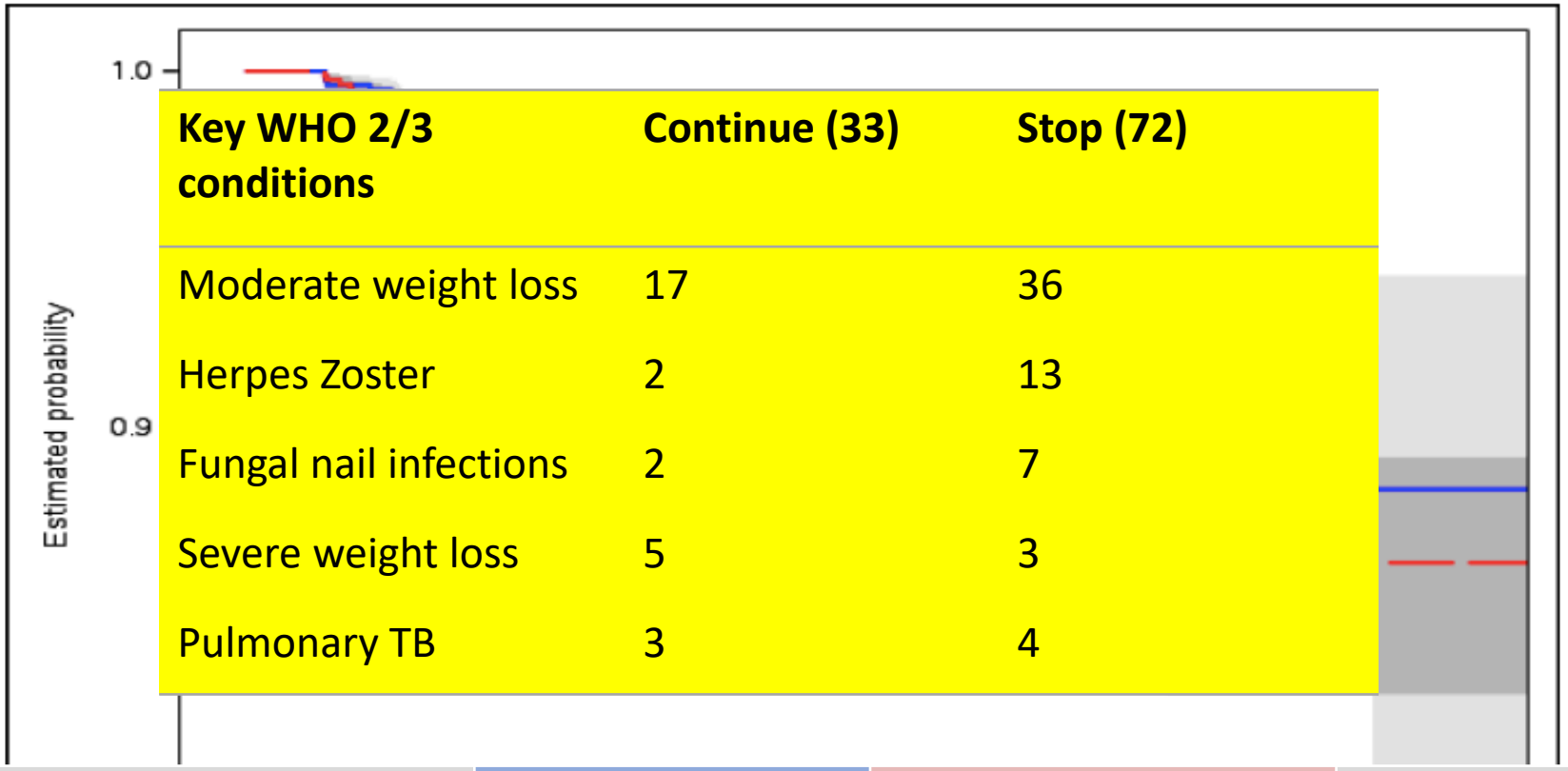
1 extrapulmonary TB

7 deaths: bacterial pneumonia (1), bacterial sepsis (2), pulmonary hypertension(1), pulmonary TB (1), diabetic ketoacidosis (1), hepatitis (unknown etiology) with fulminant liver failure (1)

Outcome*	Continue ART		Discontinue ART		Hazard Ratio (95% CI)
	No	Rate per 100 py	No	Rate per 100 py	
Primary Efficacy Composite Endpoint	3	0.24	8	0.49	0.55 (0.14, 2.08)
AIDS Defining Event	1	0.08	4	0.25	0.36 (0.04, 3.30)
Death	3	0.24	7	0.43	0.65 (0.17, 2.53)

*Sensitivity analysis excluding formula feeding women (n=85) did not change results

Time to WHO Clinical Stage 2 or 3 Condition



Key WHO 2/3 conditions	Continue (33)	Stop (72)
Moderate weight loss	17	36
Herpes Zoster	2	13
Fungal nail infections	2	7
Severe weight loss	5	3
Pulmonary TB	3	4

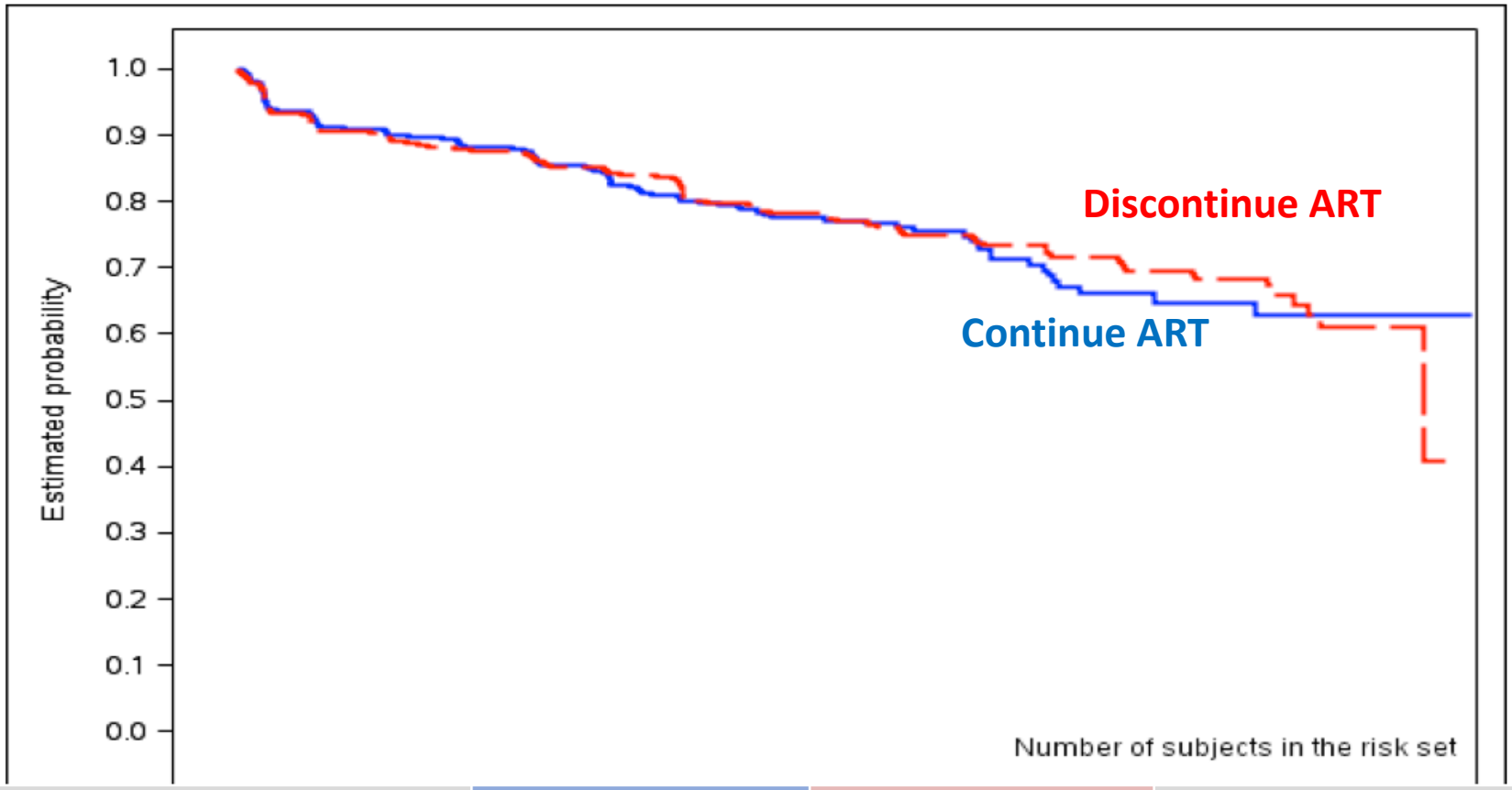
p=0.01

*Outcome	Continue ART		Discontinue 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	42	3.47	86	5.61	0.63 (0.43, 0.91)
WHO Stage 2 or 3 Event	33	2.70	72	4.66	0.60 (0.39, 0.90)

*Sensitivity analysis excluding formula feeding women (n=85) did not change results

Primary Safety Endpoint

Composite of the time to the first grade 3 or 4 sign or symptom, or grade 2, 3, or 4 hematology or chemistry event, whichever comes first



p=0.61

Outcome	Continue ART		Discontinue ART		Hazard Ratio (95% CI)
	No	Rate per 100 py	No	Rate per 100 py	
Grade 2, 3, and 4 Toxicity	160	15.3	189	13.9	0.95 (0.76, 1.17)
Grade 3 and 4 Toxicity	70	6.0	93	6.2	1.01 (0.74, 1.38)

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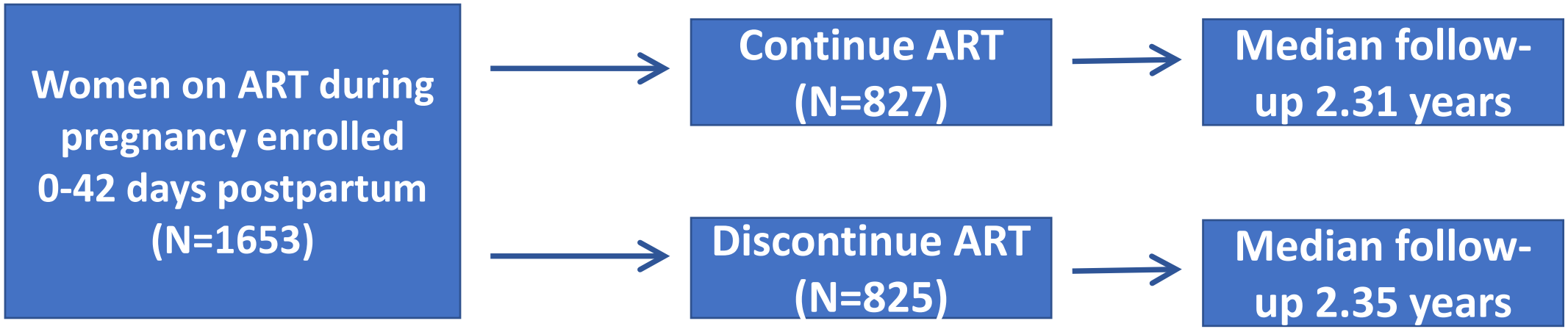
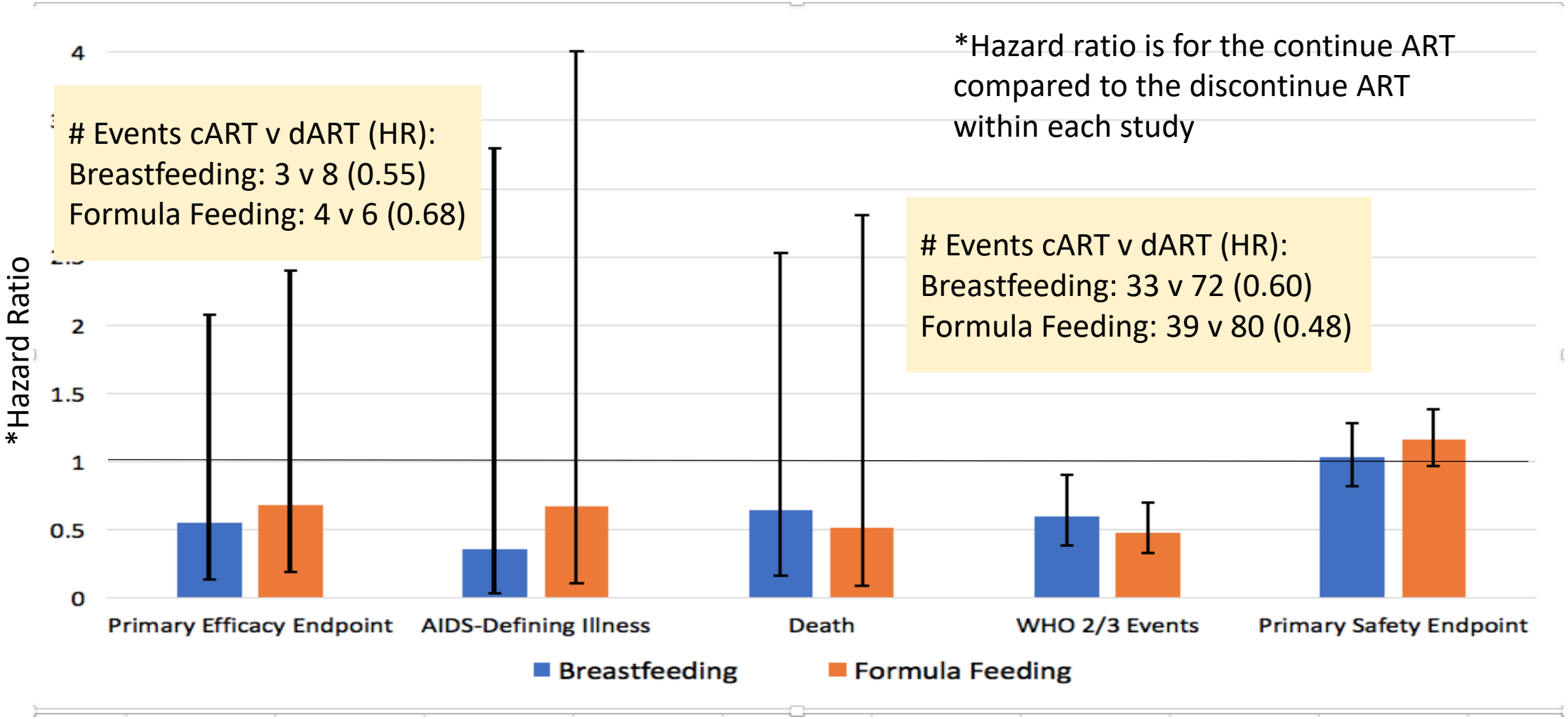
Formula Feeding Study: PROMISE 1077HS



- Sites where three drug ART was standard in pregnancy, along with formula feeding postpartum
- Enrolled Jan 2010-Nov 2014 in Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand, and the United States
- Similar pre-specified outcomes as PROMISE breastfeeding women
- Published: Currier, JS et al. PLoS One. 2017 May 10;12(5)
- Provides contemporary comparison cohort (breastfeeding versus formula feeding women)

Hazard ratios and 95% confidence intervals for PROMISE outcomes: breastfeeding compared to formula feeding women



Limitations and Conclusions

- Limitations include lower than expected number of events, use of LPV/r, and relatively short follow-up
- ART was safe and well-tolerated among postpartum women with CD4 cell counts $\geq$ 350 cells/mm^3
- Rates of AIDS defining events were low, more common in women who discontinued, but not statistically significant by randomized arm
  - Rates of WHO Stage 2 and 3 events were approximately halved with continued ART
- Comparable outcomes between breastfeeding and formula feeding women (>3,000 women from 15 countries)
- Studies that provide longer follow-up and newer regimens are needed to further inform strategies for optimizing health outcomes in reproductive-age women

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