Randomized Trial Of Raltegravir-ART vs. Efavirenz-ART When Initiated During Pregnancy (NICHD P1081)

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Background

- Pregnant women living with HIV require effective antiretroviral therapy (ART) for their own health and to prevent HIV infection of their infants

- Integrase inhibitors are potent and well tolerated, but randomized trials comparing their efficacy and safety to efavirenz containing ART initiated during pregnancy are lacking

Methods

- NICHD P1081 is a Phase IV multicenter, randomized, open-label trial comparing raltegravir (RAL) vs. efavirenz (EFV) in combination with ZDV and 3TC in ART-naïve pregnant women

- Outcomes: HIV virologic response, tolerability, and safety

- Study timeline:
  - Opened in September 2013 for women 28 to <37 weeks gestation
  - Entry gestational age limit reduced to 20 weeks in August 2016 after 22% of sample enrolled
  - Enrollment completed in February 2018

Methods (1)

- Enrollment sites in Brazil, Tanzania, South Africa, Thailand, Argentina and US

- Eligibility criteria: Pregnant women living with HIV who were between 20 to <37 weeks gestation and were naïve to ART

- Randomized to receive RAL or EFV with ZDV/3TC
  - A change to different nucleoside analogs was allowed if clinically indicated

- Samples were collected at entry for HIV RNA PCR, viral resistance testing, history/physical exam and hematology/chemistry testing

Methods (2)

- Participants followed until 24 weeks postpartum
- Primary outcome measures:
  - Efficacy: Plasma HIV-1 RNA PCR (VL) <200 copies/mL at delivery
  - Tolerability: Remaining on EFV or RAL (whichever was assigned) through delivery
  - Maternal and Infant Safety: Adverse events ≥grade 3
- Secondary Outcome Measures:
  - Efficacy/Tolerance: Rapid, sustained viral load reduction while staying on study drug until delivery
  - Adverse pregnancy outcome: Stillbirth, preterm birth
  - Infant HIV infection

Methods (3)

- The randomization and primary statistical comparisons were stratified by gestational age at entry
- Sample size target: 334 evaluable women
    - Primary efficacy population (n=307):
        - Screening/entry VL ≥200 copies, AND
        - No HIV genotypic resistance to any study ARV at screening/entry, AND
        - Valid VL result at delivery (or ≤ 21 days prior)
    - Sensitivity analyses:
        a) Added the women with HIV genotypic resistance to any study ARV at screening/entry or no genotype test result (n=362)
   b) Also added the women with screening/entry VL < 200 copies/mL (n=387)

Study Population

Mean (SD) or N (%)

|	EFV (N=202)	RAL (N=206)	Total (N=408)
Age	26.7 (6.2)	27.6 (6.2)	27.2 (6.2)
Race (Asian/Black/Hispanic/White)	12%/37%/51%/1%	11%/35%/53%/1%	12%/36%/52%/1%
Entry HIV RNA (log 10 copies/mL)	3.9 (0.9)	3.9 (0.9)	3.9 (0.9)
Entry HIV RNA <200 copies/mL	14 (7%)	9 (4%)	23 (6%)
Absolute CD4 count (cells/mm3)	460.1 (262.7)	411.3 (214.5)	435.3 (240.3)
NRTI background regimen			
ZDV/3TC	170 (84%)	171 (83%)	341 (84%)
TDF/FTC	31 (15%)	33 (16%)	64 (16%)
Gestational age (wks) at entry	26.9 (4.8)	26.8 (4.8)	26.9 (4.8)
Gestational age strata at entry			
20-<28 wks	102 (50%)	103 (50%)	205 (50%)
28-<37 wks	100 (50%)	103 (50%)	203 (50%)
Viral resistance at entry (RTI/INSTI)	14 (7%)/0(0%)	21 (11%)/0(0%)	35 (9%)/0(0%)

Results – Primary Outcomes

Efficacy: Proportion with Delivery VL <200 copies/mL Overall and by Gestational Age at Entry (n=307 women*)
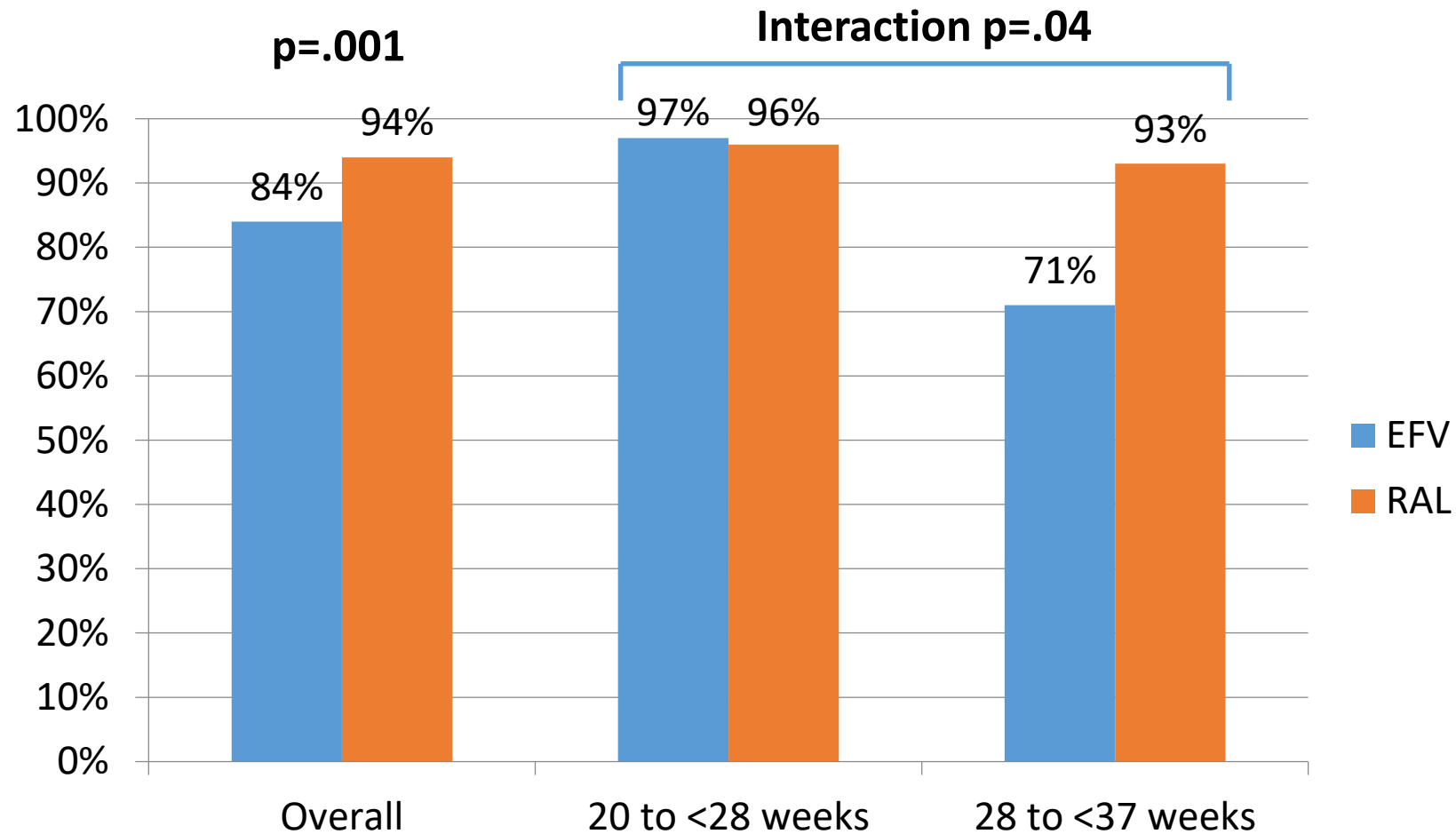
*Women with entry VL > 200 copies/ml and no HIV genotypic resistance to any study ART at entry
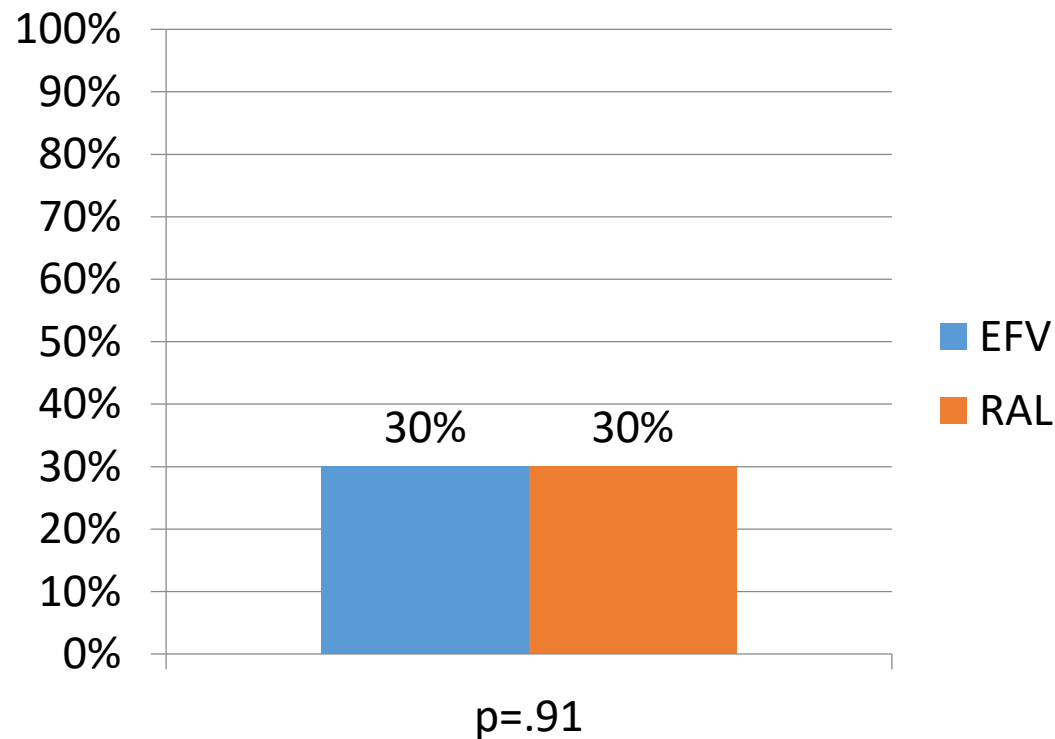
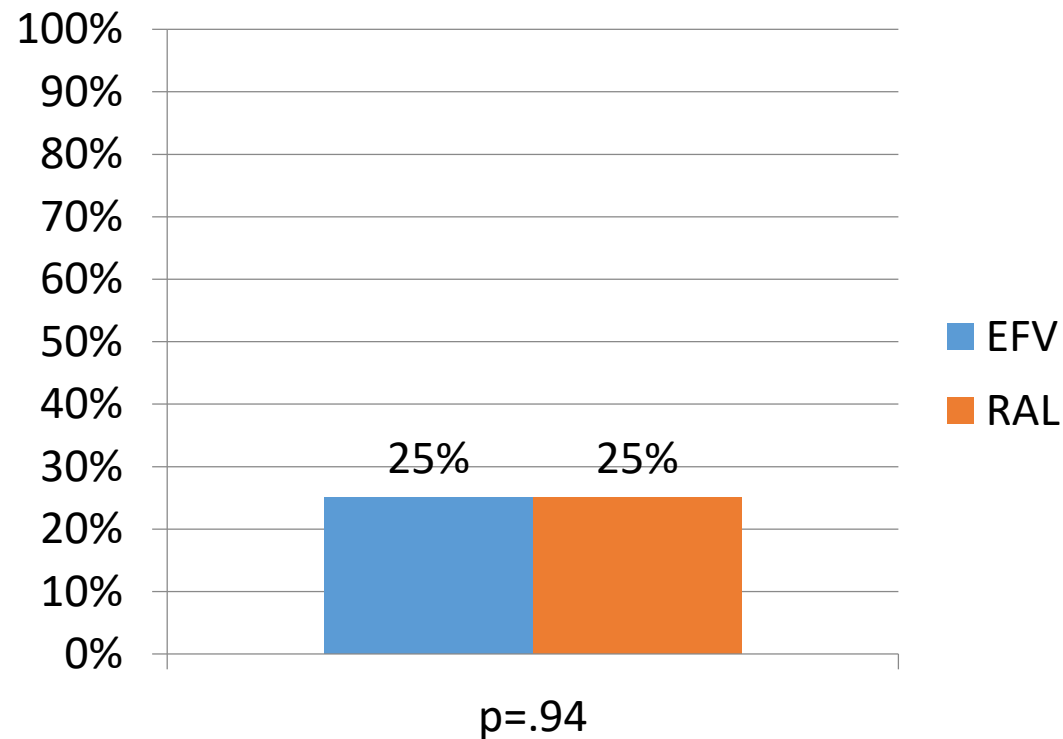# Tolerability: Proportion of Women who Remained on Assigned ARV (RAL or EFV) through Delivery (n=394 women*)
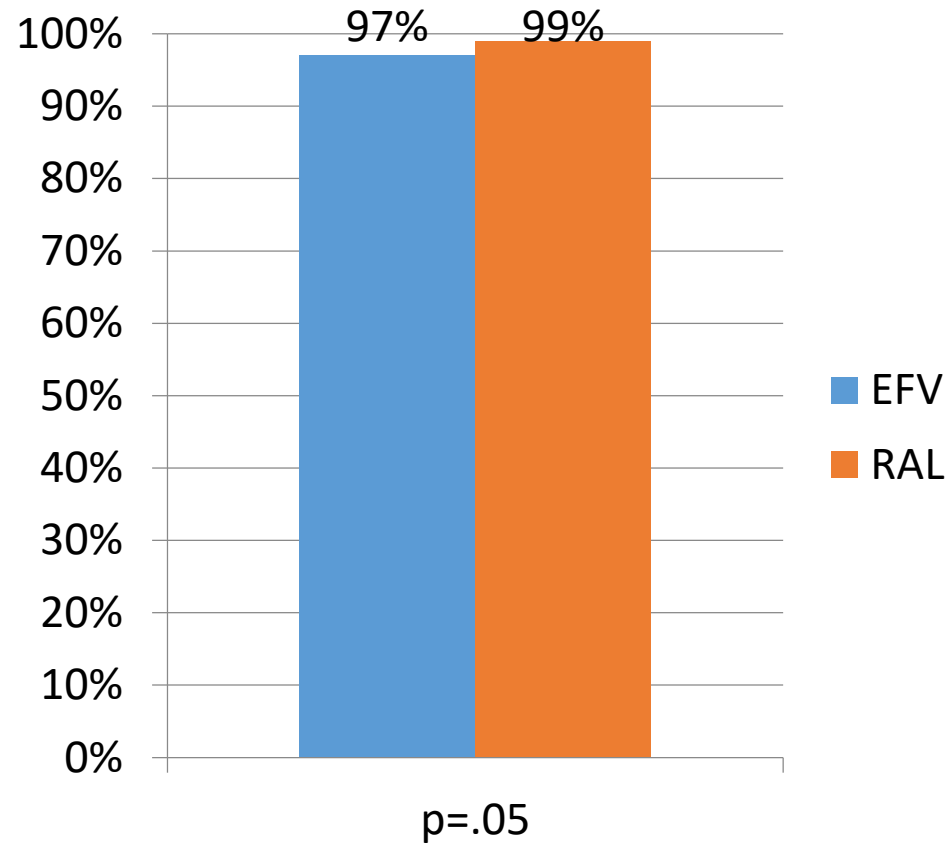
*Women who received at least one dose of study ARV and delivered on-study

Maternal and Infant Safety: Proportion with an Adverse Event ≥ Grade 3

Women (n=403*)

p=.91

Infants (n=393[a])

p=.94

*Women who received at least one dose of study ARV
[a]Live-born infants whose mother received at least one dose of study ARV and delivered on-study

Secondary Efficacy/Tolerance Outcome Measure

	EFV arm	RAL arm	P-value*
Rapid and sustained virologic response while remaining on study drug through delivery[a]	84/131 (64%)	121/132 (92%)	<.001
Viral load ≥2.0 log decline or <200 copies/mL by wk 2	91/131 (69%)	123/132 (93%)	
Viral load <1,000 copies/mL all time points after wk 4	117/123 (95%)	115/120 (96%)	
Remained on study drug through delivery	129/131 (98%)	131/132 (99%)	

*Cochran-Mantel-Haenszel test stratified by gestational age at entry (20-<28, 28-<31, 31-<34, or 34-<37 wks)

[a]Secondary composite outcome for all women in the primary virologic response and tolerability analyses with a VL result at study week 2 (day 11-17) and at least one subsequent VL result after study week 4.

Estimated Proportion with VL <200 copies/mL by Number of Days since Randomization
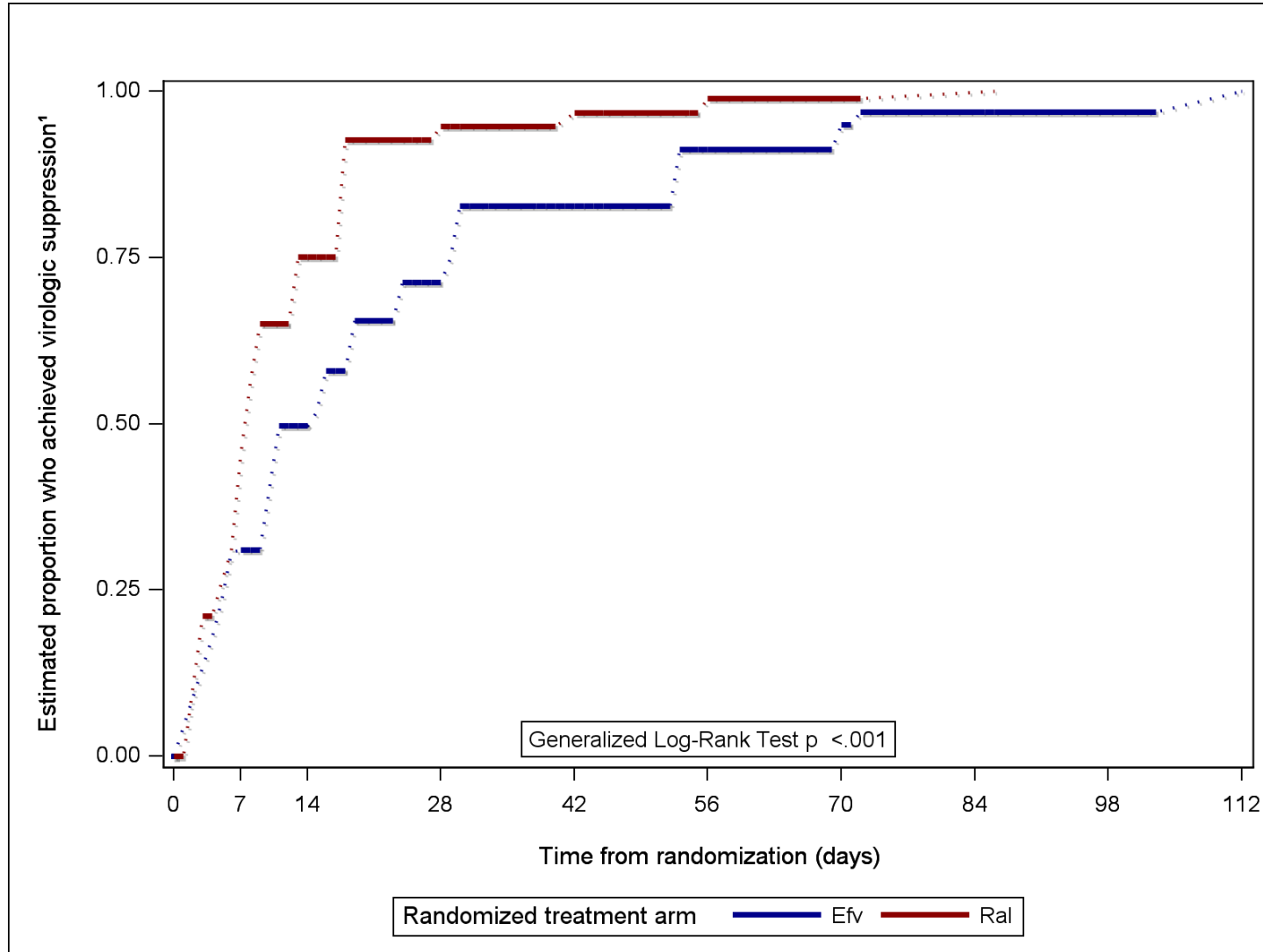
Median Time to VL <200 copies/mL:
RAL: 8 days
EFV: 15 days

Adverse Pregnancy Outcomes and Infant HIV Infection

	EFV arm	RAL arm	P-value*
Stillbirth	1/194 (1%)	3/200 (2%)	.62
Preterm delivery (<37 wks gestation)	20/190 (11%)	24/195 (12%)	.63
Infant HIV infection	6/184 (3%)	1/190 (1%)	.06

* Fisher exact test

Conclusions

- Both RAL and EFV were safe and well tolerated in women initiating ART during pregnancy
- Women receiving RAL had:
  - Faster viral load reduction
  - Greater proportion with viral load <200 copies/mL at delivery, mainly among those who enrolled later in gestation
- These data support the use of RAL-ART during pregnancy, especially for women starting ART after 28 weeks gestation

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