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HIV Drug Resistance at Mother-to-Child Transmission & Emergence During Breastfeeding

Presented by Ceejay Boyce, PhD Student

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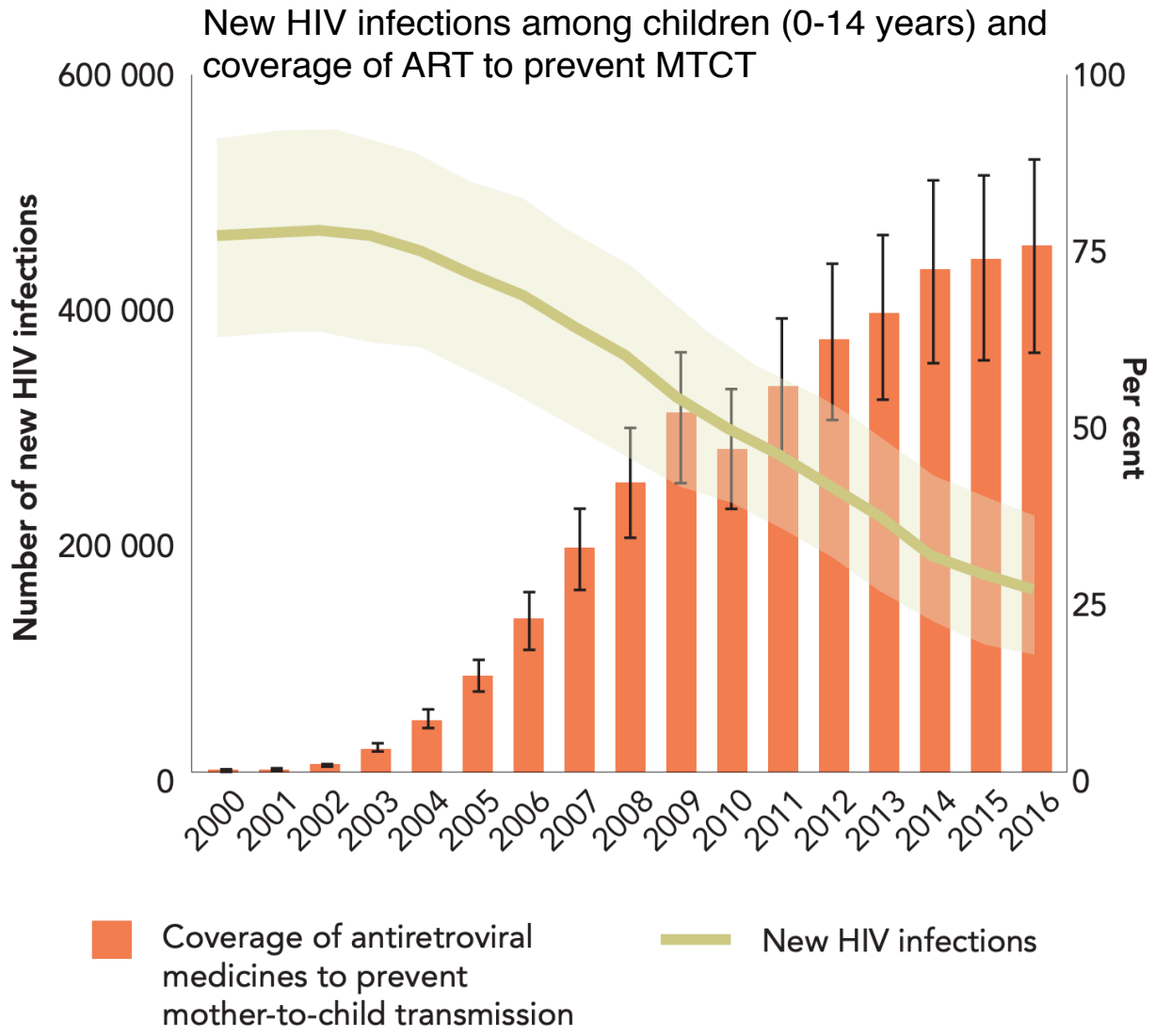
Disclosures

- No conflicts of interest to disclose

HIV Mother-to-Child Transmission (MTCT)

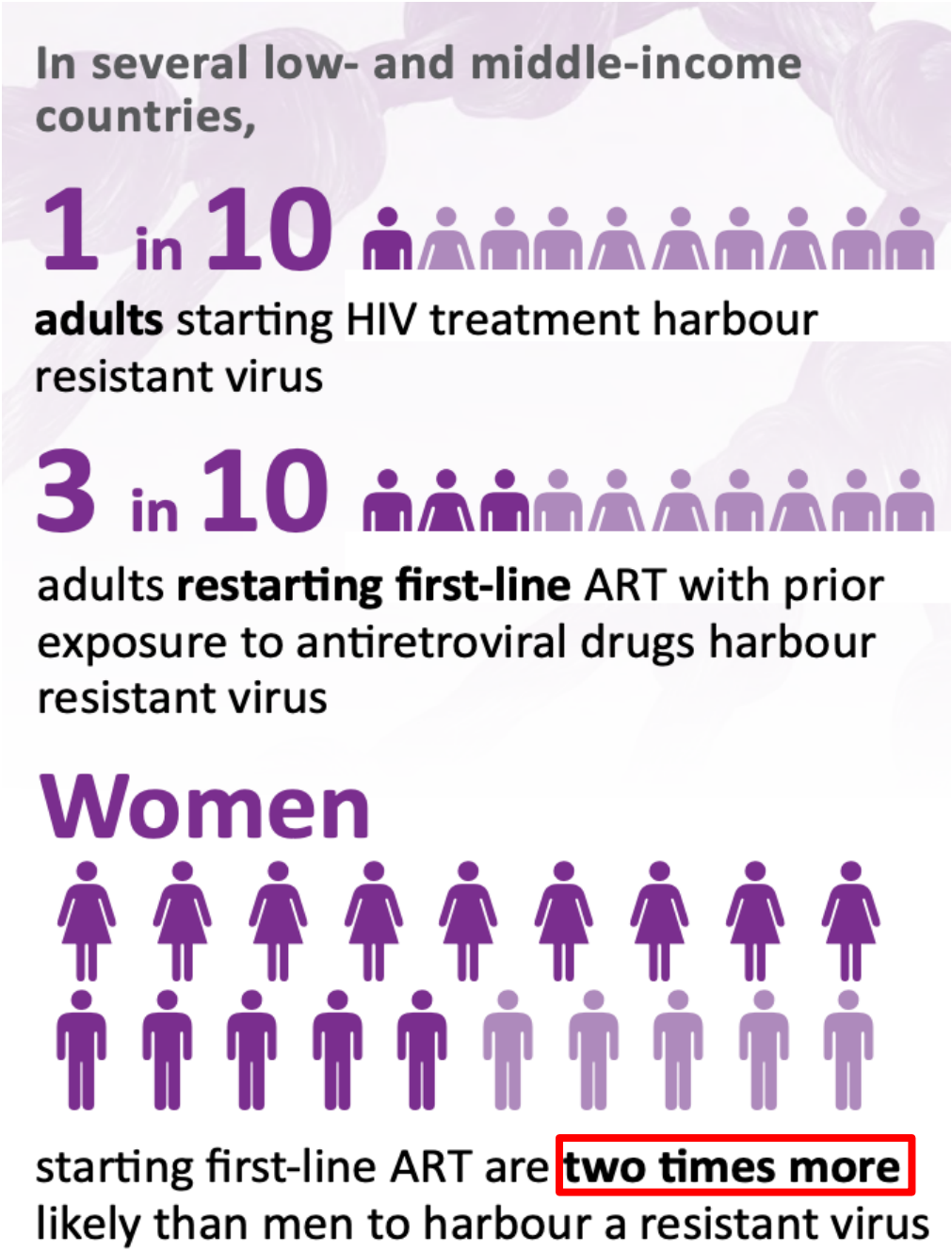
- Global effort to eliminate HIV MTCT to reduce the total number of new HIV infections annually
- Without ART, HIV MTCT rates range from 15-45%
- ⇡ ART coverage = ⇣ in MTCT



2017 estimates | UNAIDS

HIV Drug Resistance

- ↟ ART coverage = ↟ rates of pre-treatment drug resistance
- Women have higher rates of pre-treatment drug resistance
  - Diagnosed earlier in course of infection due to pregnancy
- Unknown if drug resistance (**DR**) in mothers increases the risk of MTCT



2017 HIV drug resistance report | WHO

Study Goals

Aim 1: Assess the association of maternal DR with the risk of MTCT

Aim 2: Describe DR in HIV-infected infants

Study Population & Case-Control Design

- **Population**: mother-infant pairs from the PROMISE 1077 BF Study
  - Trial across 14 clinical sites in Malawi, South Africa, Zimbabwe, Tanzania, Uganda, Zambia, & India

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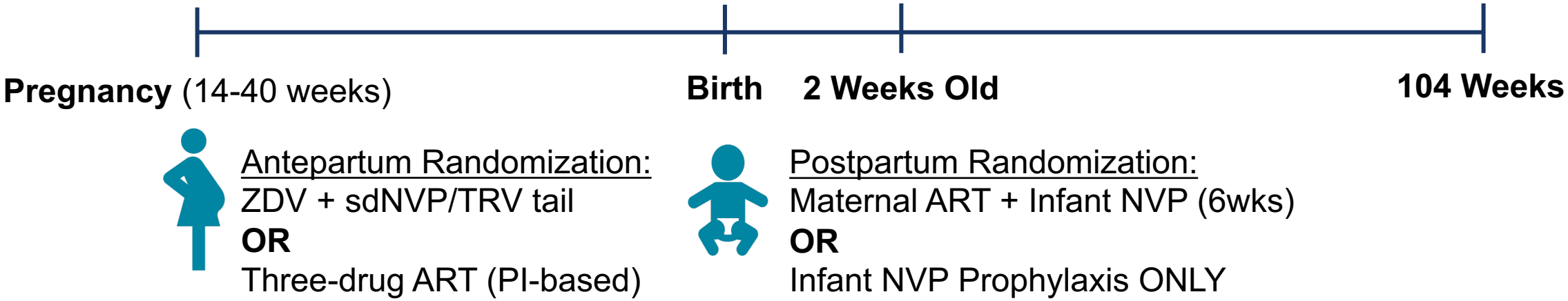

Study Population & Case-Control Design

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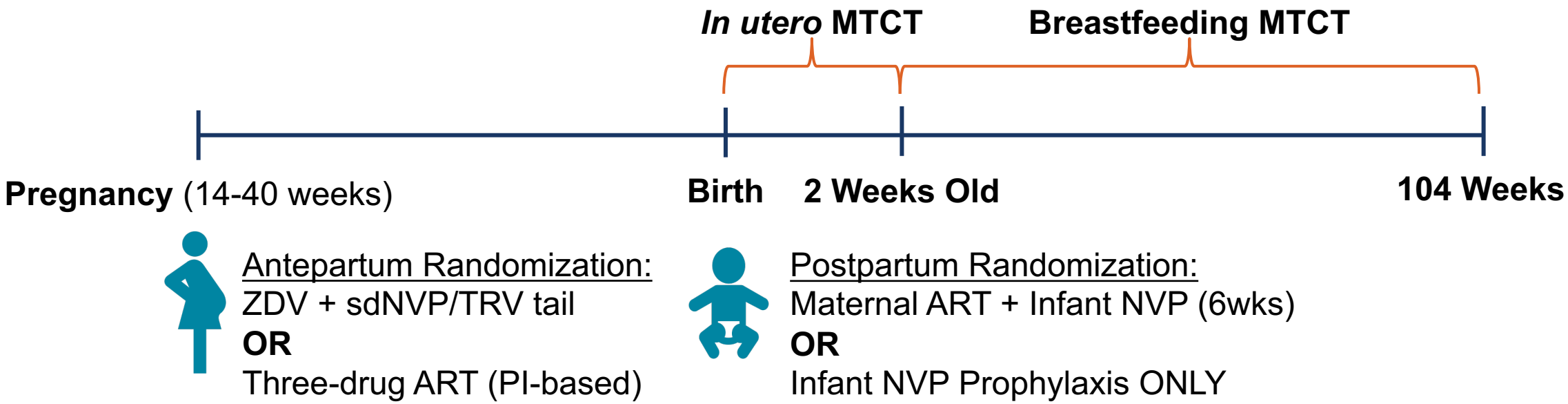


- **Design of case-control study**:
  - 1:3 case-control ratio of HIV-infected mothers, matched by delivery date and clinical site
    - Cases = transmitting mothers and their infants (n = 85)
      - 48 *in utero*/peripartum infections
      - 37 breastfeeding infections
    - Controls = non-transmitting mothers (n = 254)

Study Design

Aim 1: Assess the association of maternal DR with the risk of MTCT

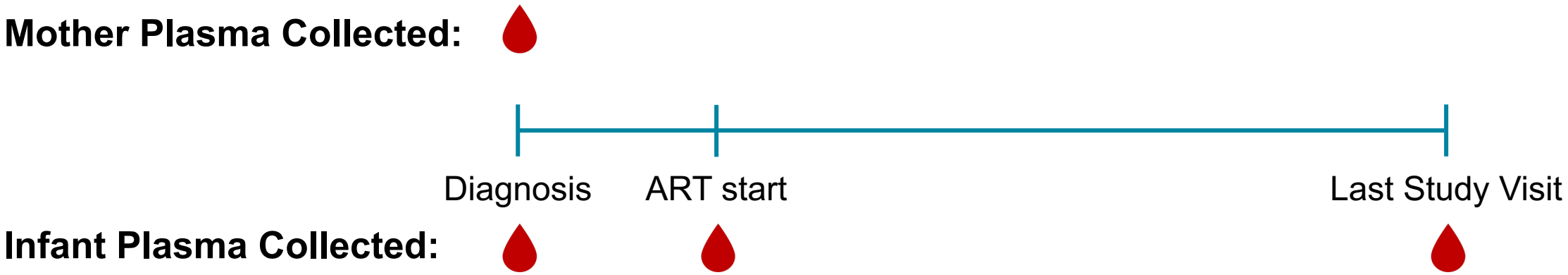
- ↳ Compare rate of HIV DR in case (MTCT) vs control (no MTCT) mothers; adjusting for HIV RNA viral load and antepartum treatment regimen

Aim 2: Describe DR in HIV-infected infants

- ↳ Compare rate of HIV DR in infants with *in utero* MTCT vs breastfeeding MTCT at HIV diagnosis and over time

Study Methods

- Genotypic HIV drug resistance by consensus sequencing of HIV *pol*



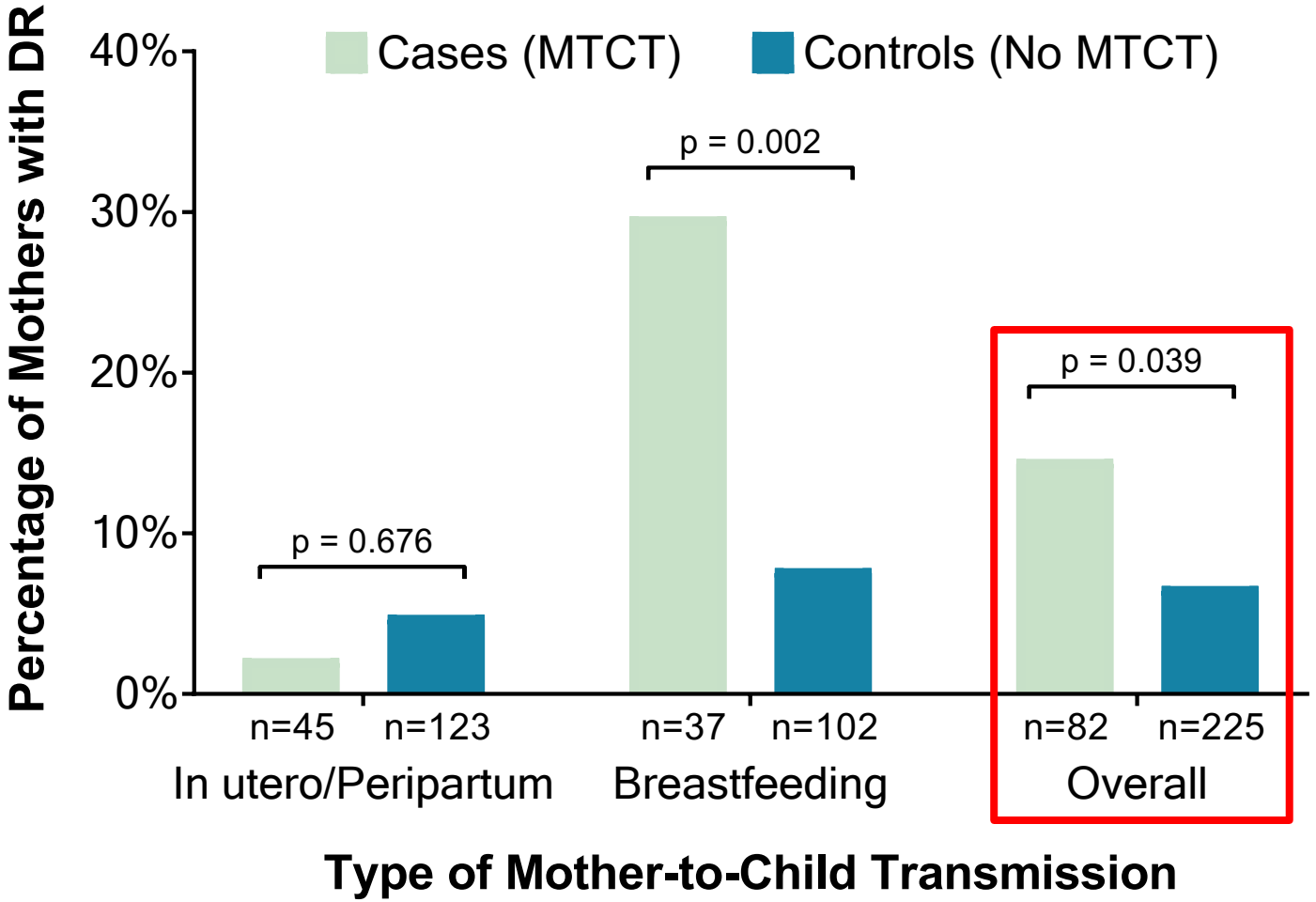
- Mothers and infants categorized as wild-type (**WT**) or drug resistant (**DR**) using major drug resistance mutations defined by Stanford HIV Database

Aim 1: Assess the association of maternal DR with the risk of MTCT

Hypothesis: Presence of DR HIV in maternal plasma will be associated with increased risk of MTCT compared to mothers with WT HIV

Results: DR greater in maternal cases vs controls at infant HIV diagnosis

- Overall, transmitting mothers had a higher probability of DR at infant HIV diagnosis (14.6% vs 6.2%, p=0.039)



Compared using Fisher's Exact test

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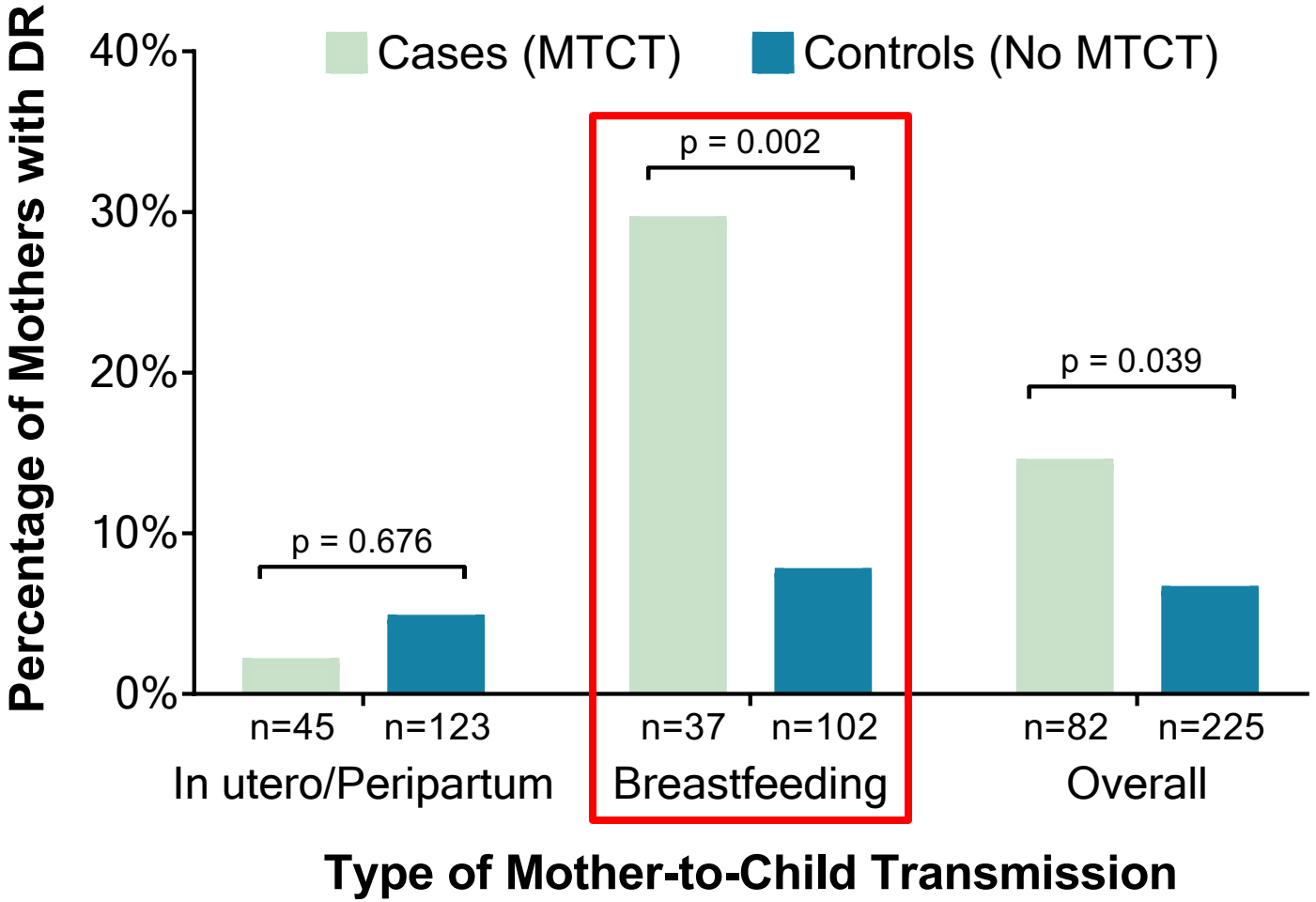

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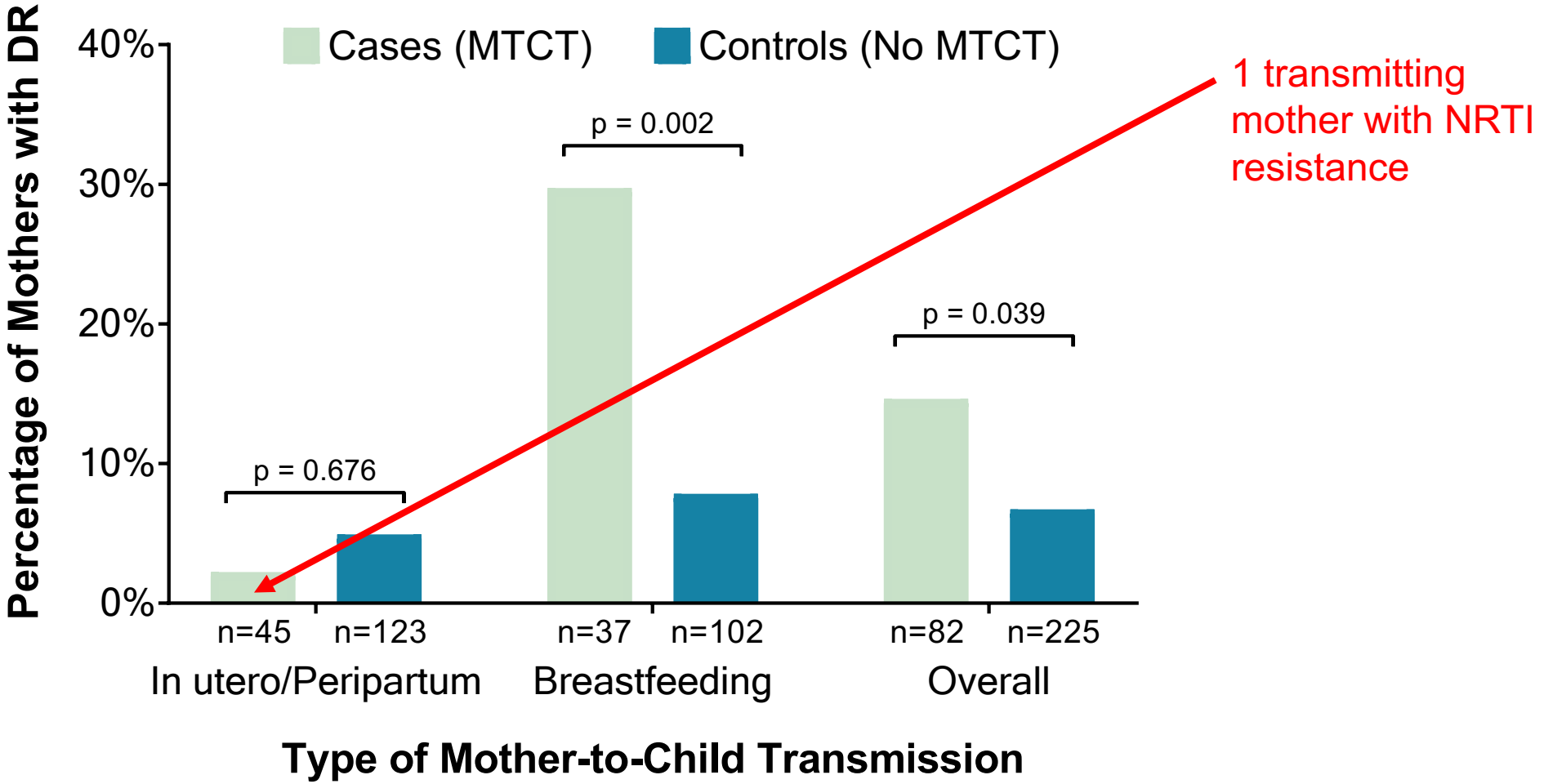

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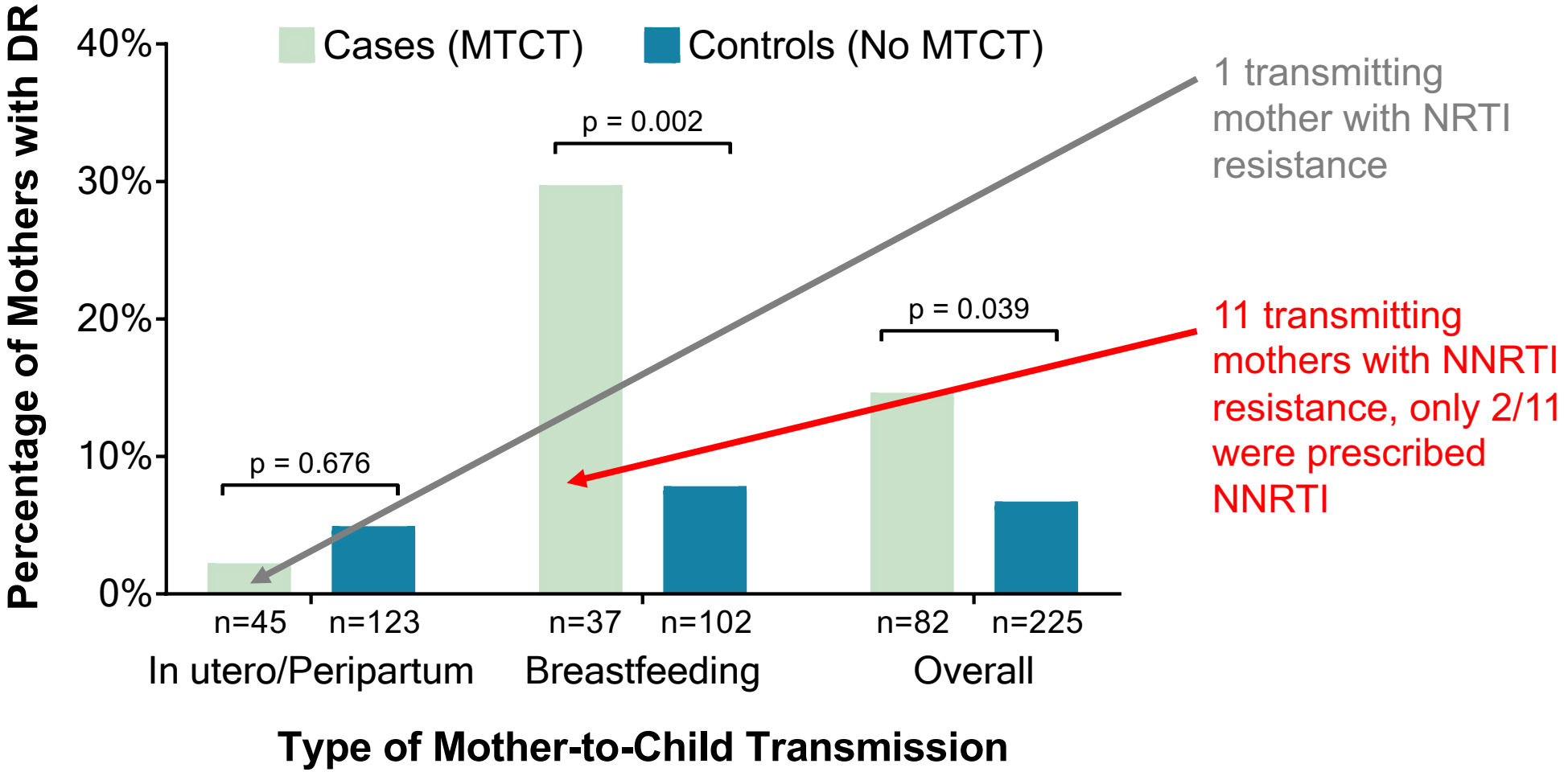

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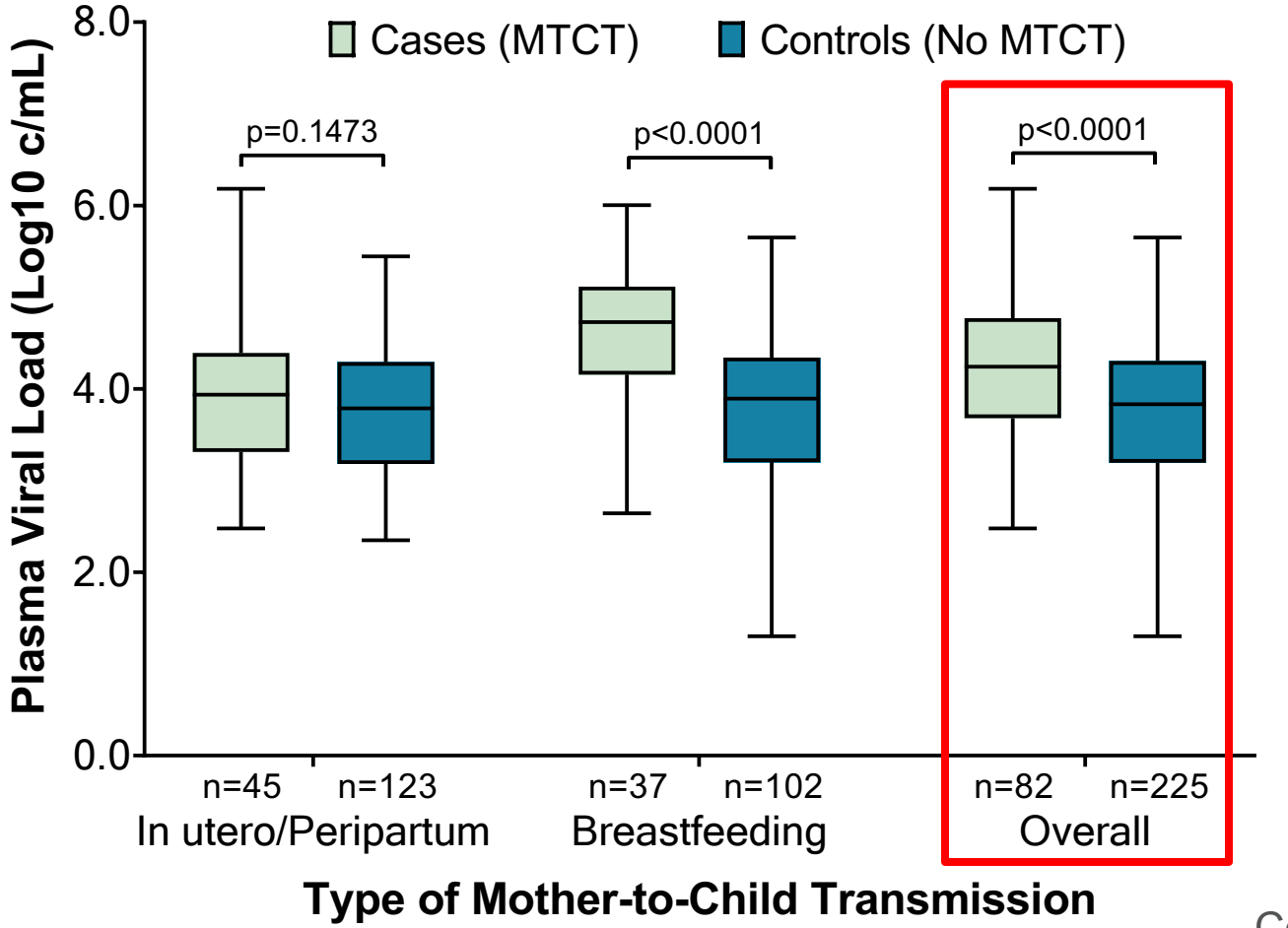
Results: DR mutations detected in maternal cases and controls at infant HIV diagnosis

- Most common DR mutation was K103N in both cases and controls

Drug Class	Mutation	# Cases (%) n = 82	# Controls (%) n = 225
PI	M46I	-	2 (0.9%)
NRTI	M41L	-	1 (0.4%)
	D67N	-	2 (0.9%)
	K70R	-	1 (0.4%)
	K219N	1 (1.2%)	-
NNRTI	A98G	-	1 (0.4%)
	K101E	1 (1.2%)	2 (0.9%)
	K103N	7 (8.5%)	6 (2.7%)
	V179D	1 (1.2%)	-
	Y181C	1 (1.2%)	-
	Y188C	1 (1.2%)	-
	G190A/E	2 (2.4%)	2 (0.9%)
Total # of Mothers with ≥1 DR Mutation		**12 (14.6%)**	**14 (6.2%)**

Results: Plasma HIV RNA higher in maternal cases vs controls at infant HIV diagnosis

- Overall, transmitting mothers had higher median HIV RNA levels at infant HIV diagnosis (4.28 vs. 3.86 log10 copies/mL, p<0.0001)



Compared using Mann-Whitney test

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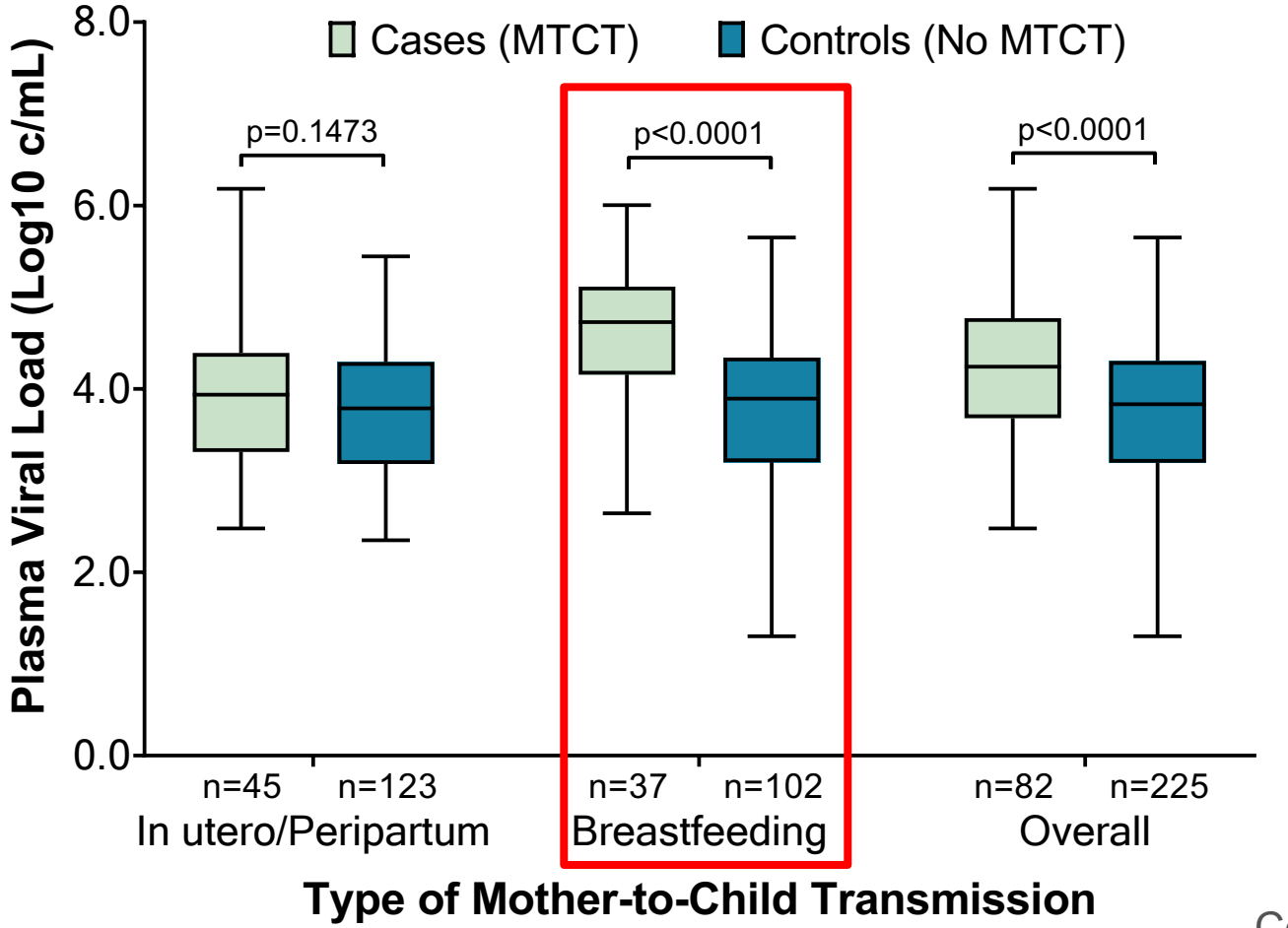

Compared using Mann-Whitney test

Results: Maternal DR associated with increased risk of MTCT during breastfeeding and “overall”

- Multivariable analysis adjusted for maternal plasma HIV RNA, genotype, and antepartum treatment regimen

Covariate (Reference)	**OR (95% CI)**	**p-value**
≥4 Log c/mL Plasma Viral Load (<4 Log c/mL)	2.33 (1.29-4.21)	0.005
DR Genotype (WT Genotype)	2.45 (1.03-5.81)	0.042

Compared using Conditional Logistic Regression

Results: Maternal DR associated with increased risk of MTCT during breastfeeding and “overall”

- Multivariable analysis adjusted for maternal plasma HIV RNA, genotype, and antepartum treatment regimen
- Adjusting for maternal plasma HIV viral load at infant diagnosis, DR was still significantly associated with increased risk of MTCT

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Compared using Conditional Logistic Regression

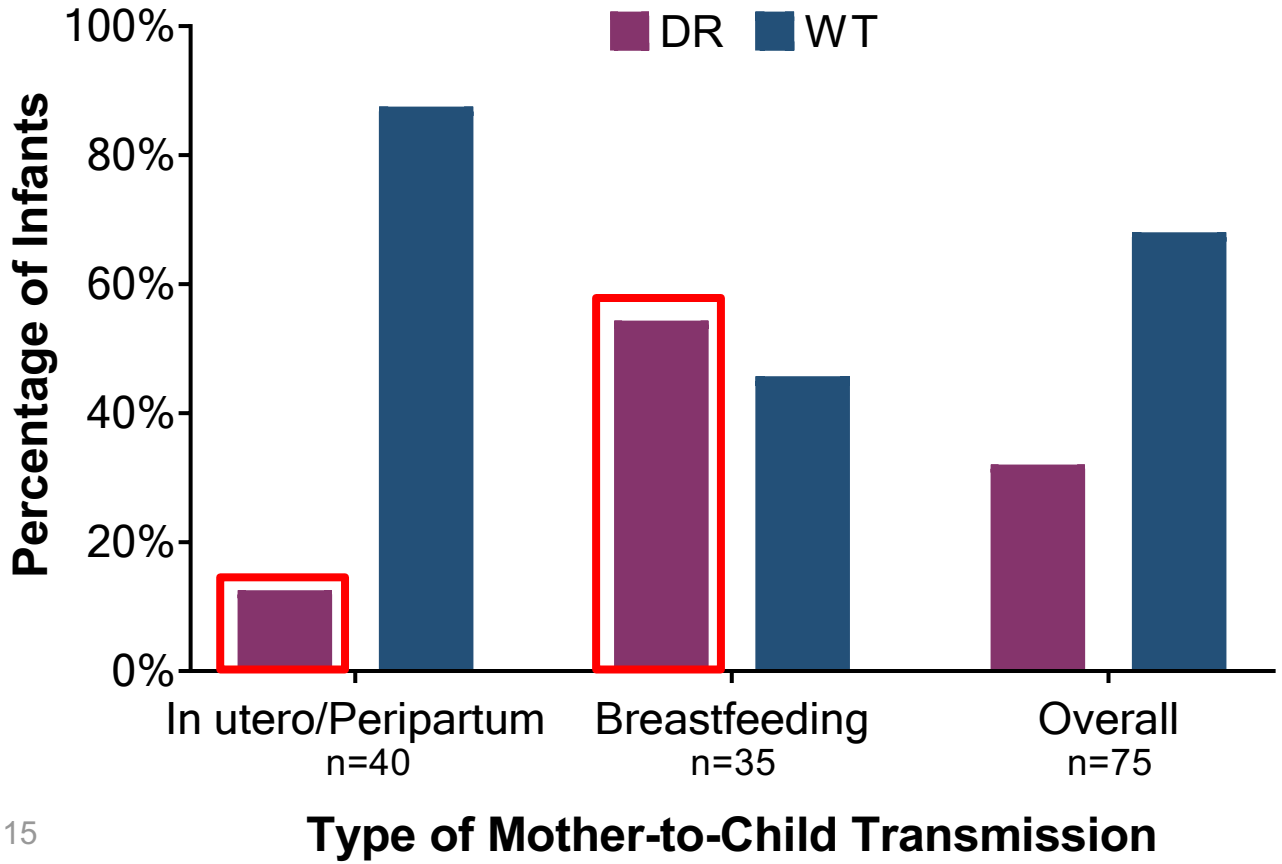
Aim 2: Describe DR in HIV-infected infants

Hypotheses:

1. Resistance mutations detected at HIV diagnosis will persist over time
2. Prolonged selective pressure from infant nevirapine (NVP) prophylaxis or maternal and/or infant ART could select DR mutations

Results: HIV DR was less frequent in infants with *in utero* MTCT vs. breastfeeding MTCT

- At HIV diagnosis, prevalence of DR was lower in infants with *in utero*/peripartum MTCT vs breastfeeding MTCT (12.5% vs 54.3%, p<0.001)



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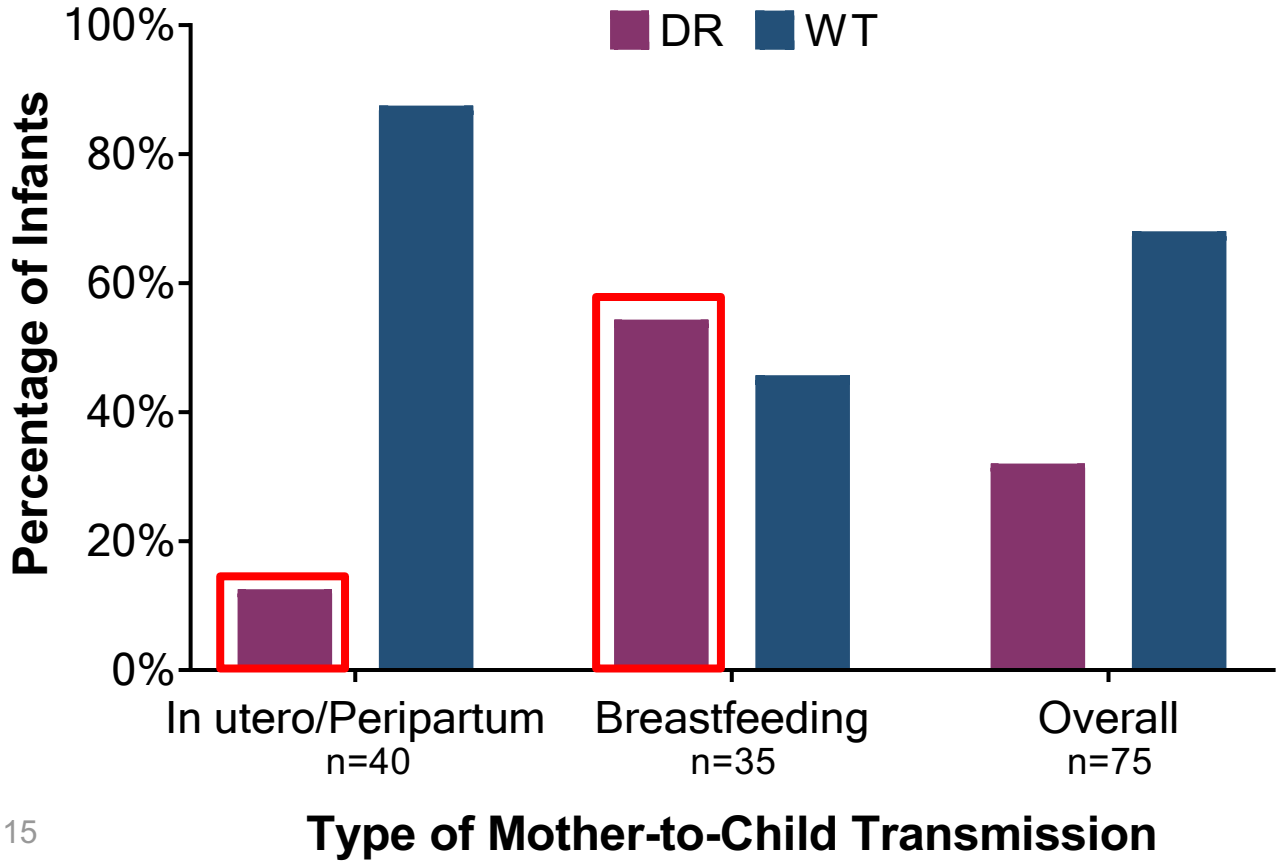
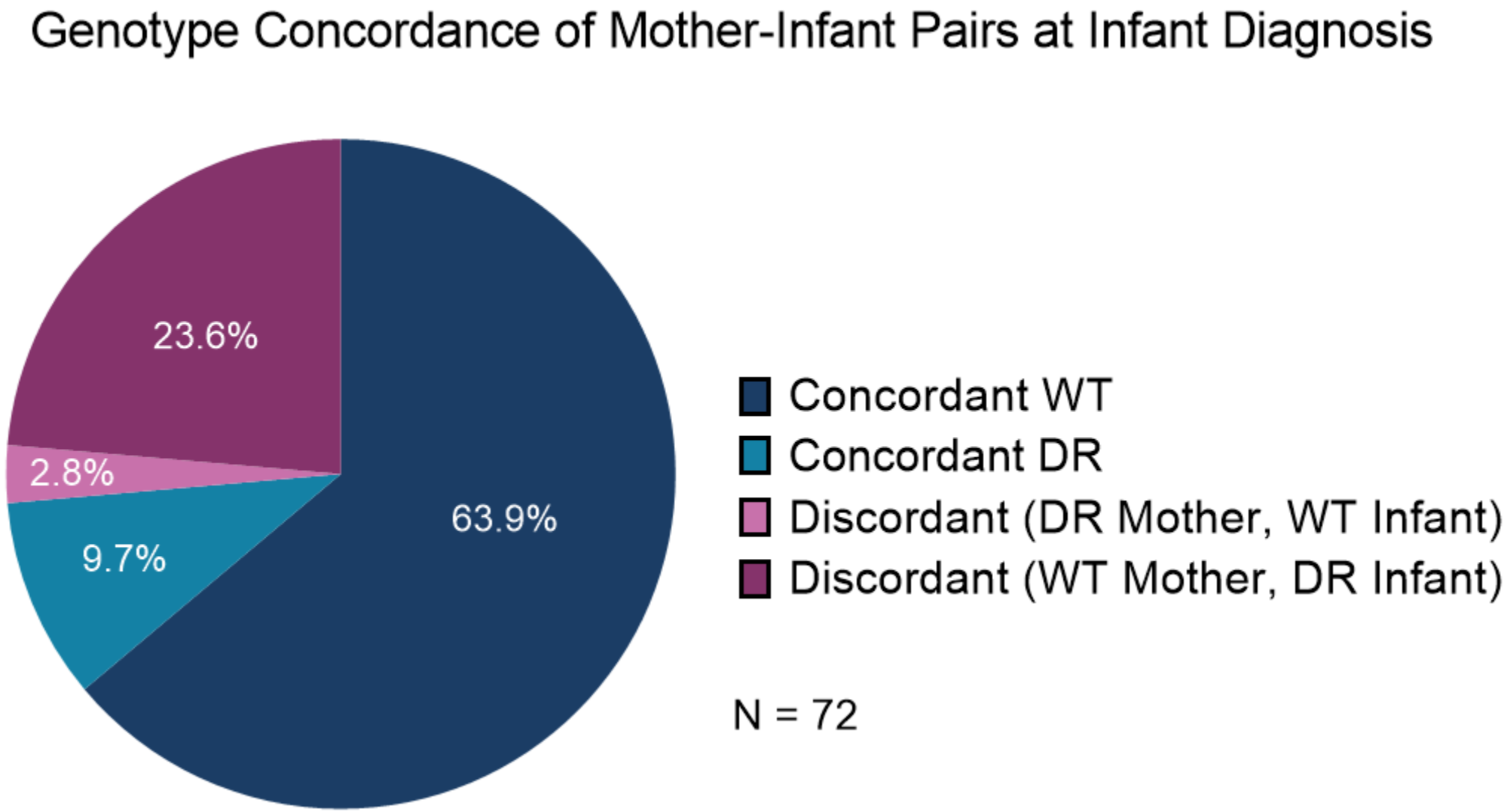
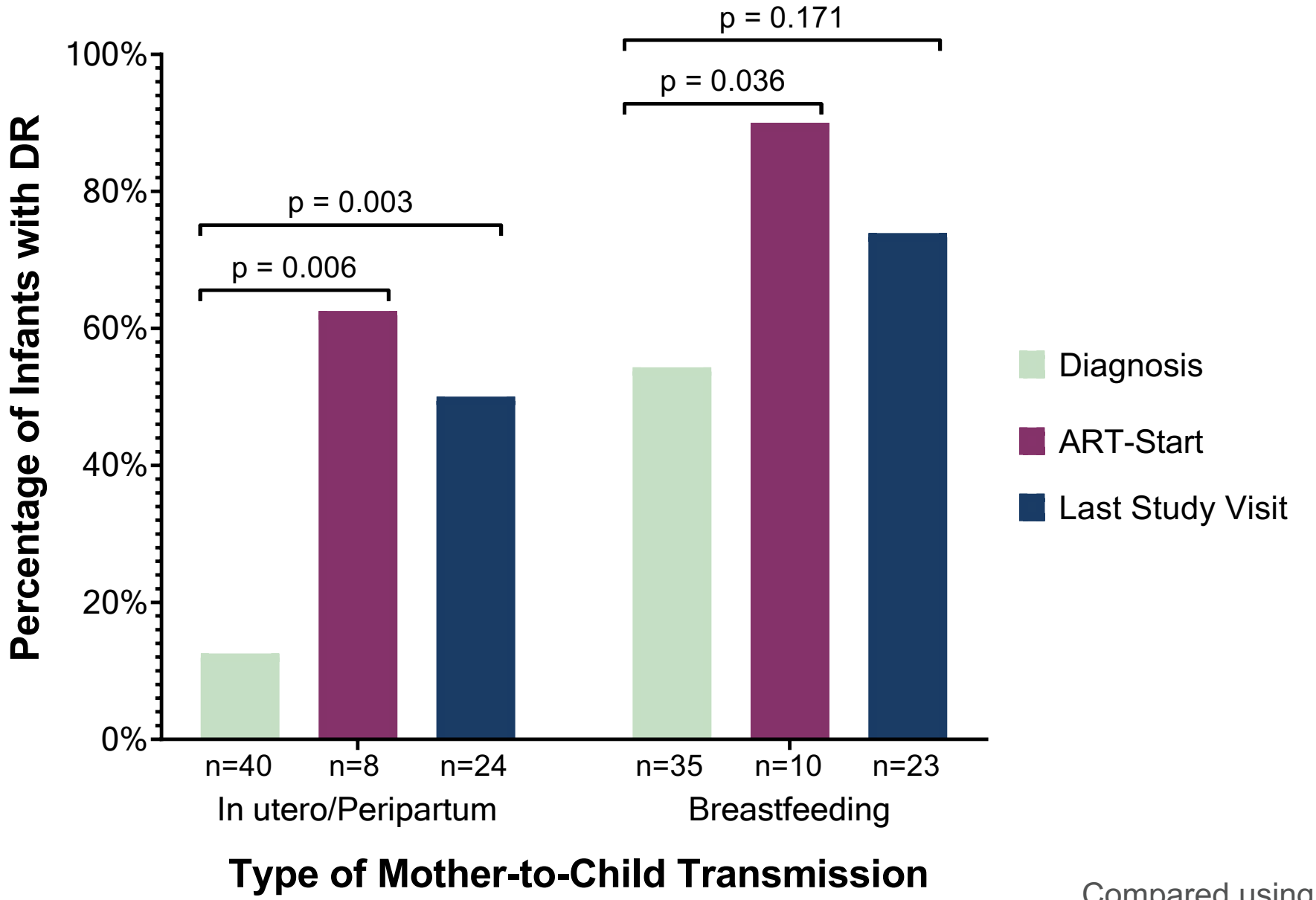


Mutations Detected	*In utero* or Peripartum n = 40	Breastfeeding n = 35
NRTI		
Single	-	3
Multiple	-	-
NNRTI		
Single	5	8
Multiple	-	7
NRTI & NNRTI	-	1
Total # of DR infants	**5 (12.5%)**	**19 (54.3%)**

Results: ~25% of mother-infant pairs had discordant genotypes, 90% were WT moms with DR infants



Results: HIV DR emerged in infants over time during breastfeeding



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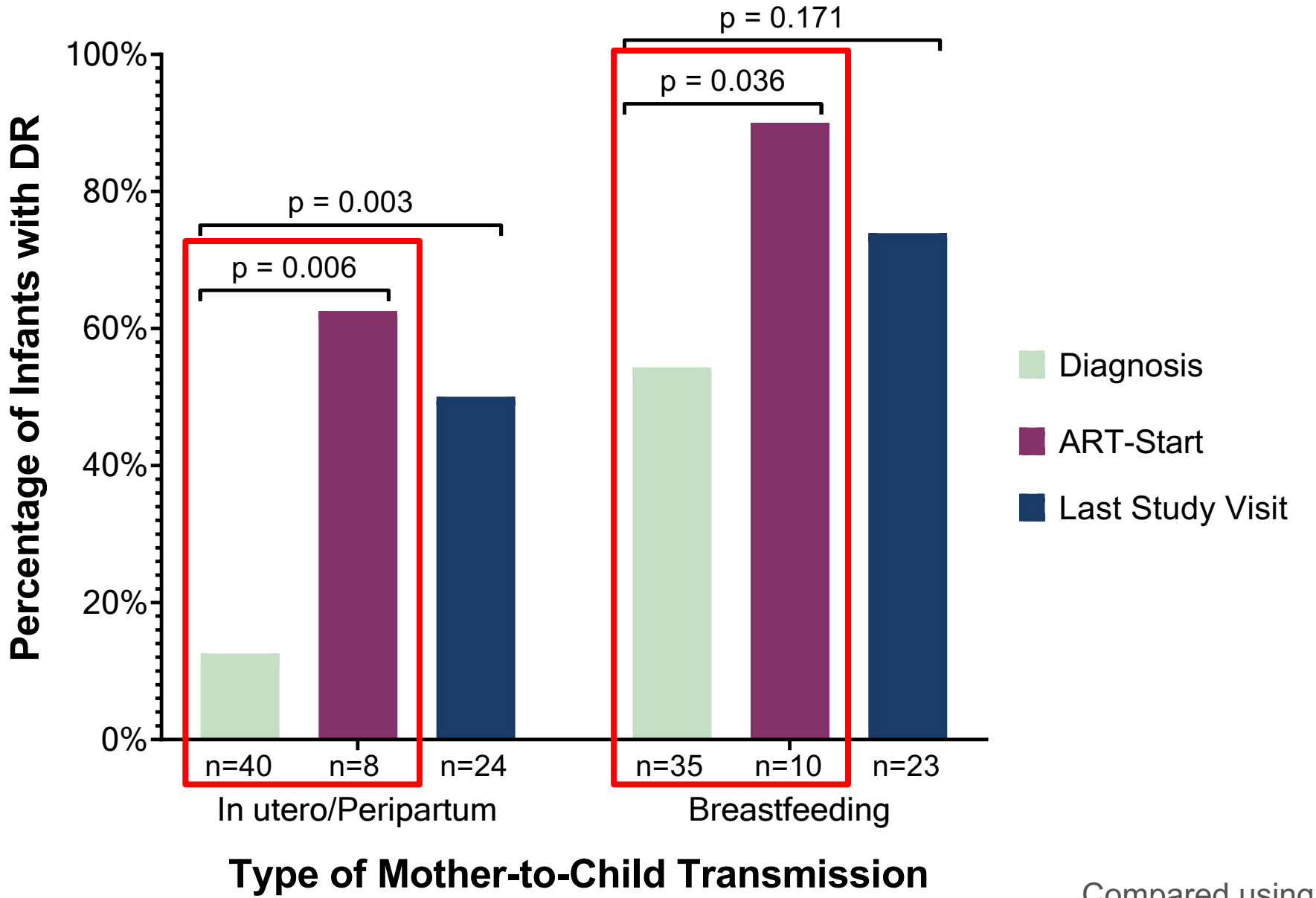

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Conclusions & Future Directions

- **Finding**: At infant HIV diagnosis, maternal plasma HIV RNA and HIV DR were both independently associated with increased risk of MTCT
- **Interpretation**: In addition to non-suppression of HIV replication, HIV DR in mothers appears reduce effectiveness of infant NVP prophylaxis
  - ↳ Maternal NNRTI DR appears transmitted as 9/11 (82%) did not have a history of NNRTI

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- **Interpretation**: Prolonged exposure to NVP prophylaxis or maternal ART during breastfeeding led to the emergence of DR in infants
- **Our conclusion**: Replacement of NVP prophylaxis for MTCT with regimens that have a greater barrier to DR and would retain NNRTI susceptibility in infected infants

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