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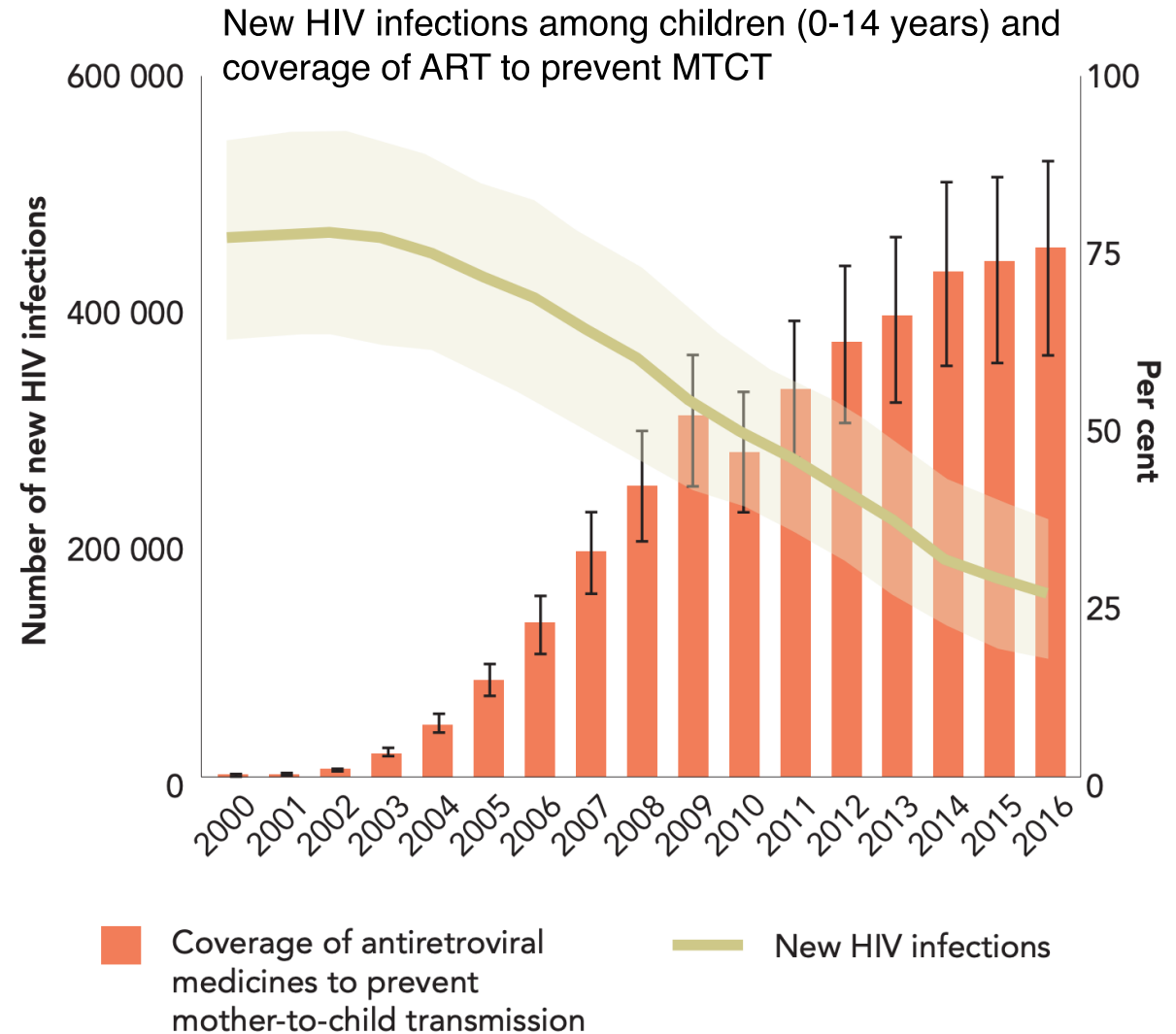
HIV Drug Resistance at Mother-to-Child Transmission & Emergence During Breastfeeding

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HIV Mother-to-Child Transmission (MTCT)

- Global effort to eliminate HIV MTCT to reduce the total number of new HIV infections annually
- Without antiretroviral therapy (**ART**), HIV MTCT rates range from 15-45%
- ↑ ART coverage = ↓ in MTCT



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
 - Challenging the elimination of MTCT
- Unknown if drug resistance (**DR**) in mothers increases the risk of MTCT

In several low- and middle-income countries,

1 in 10  **adults** starting HIV treatment harbour resistant virus

3 in 10  **adults restarting first-line ART** with prior exposure to antiretroviral drugs harbour resistant virus

Women



starting first-line ART are **two times more** likely than men to harbour a resistant virus

Study Goals



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



Aim 2: Describe the emergence of DR in HIV-infected infants

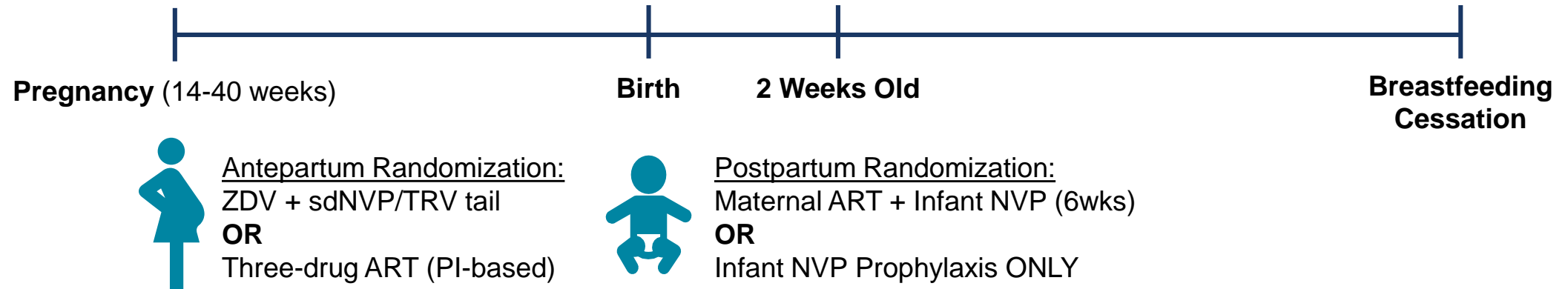
Study Population & Case-Control Design

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



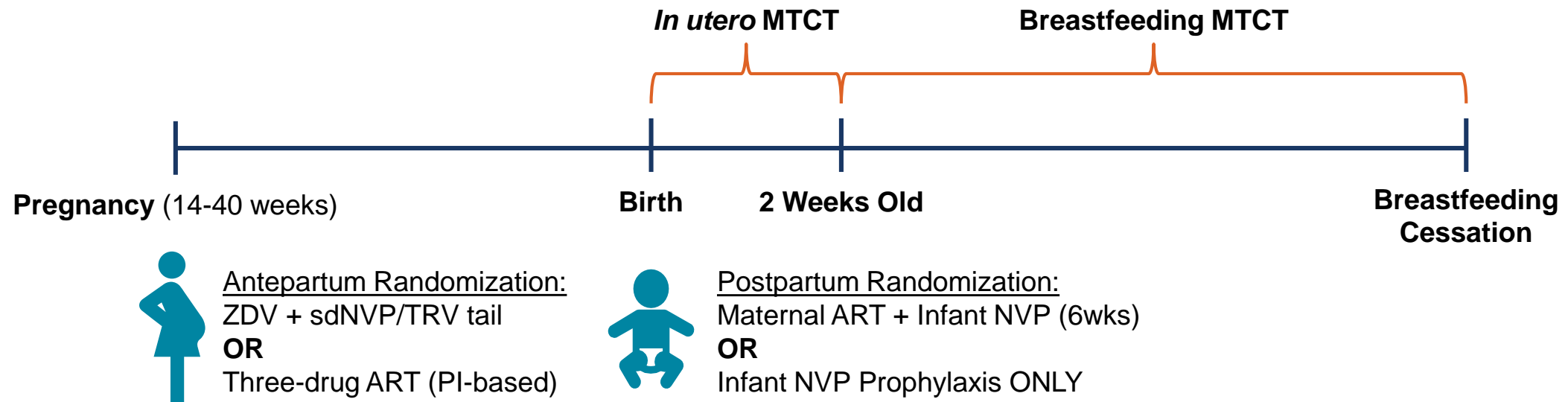
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- **Design of case-control study:**

- 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

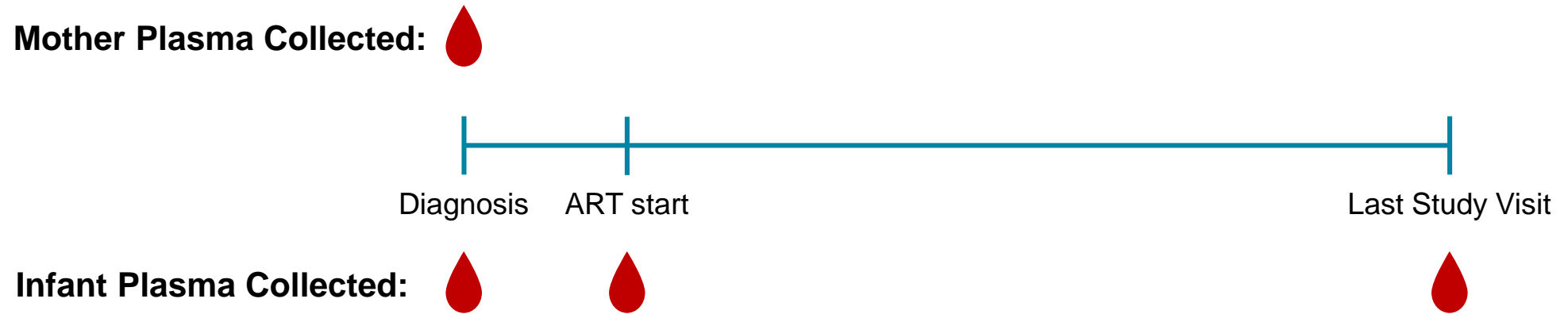
- ↳ Compare rate of HIV DR in case (MTCT) vs control (no MTCT) mothers; adjusting for HIV RNA viral load and antepartum treatment regimen



Aim 2: Describe the emergence of 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



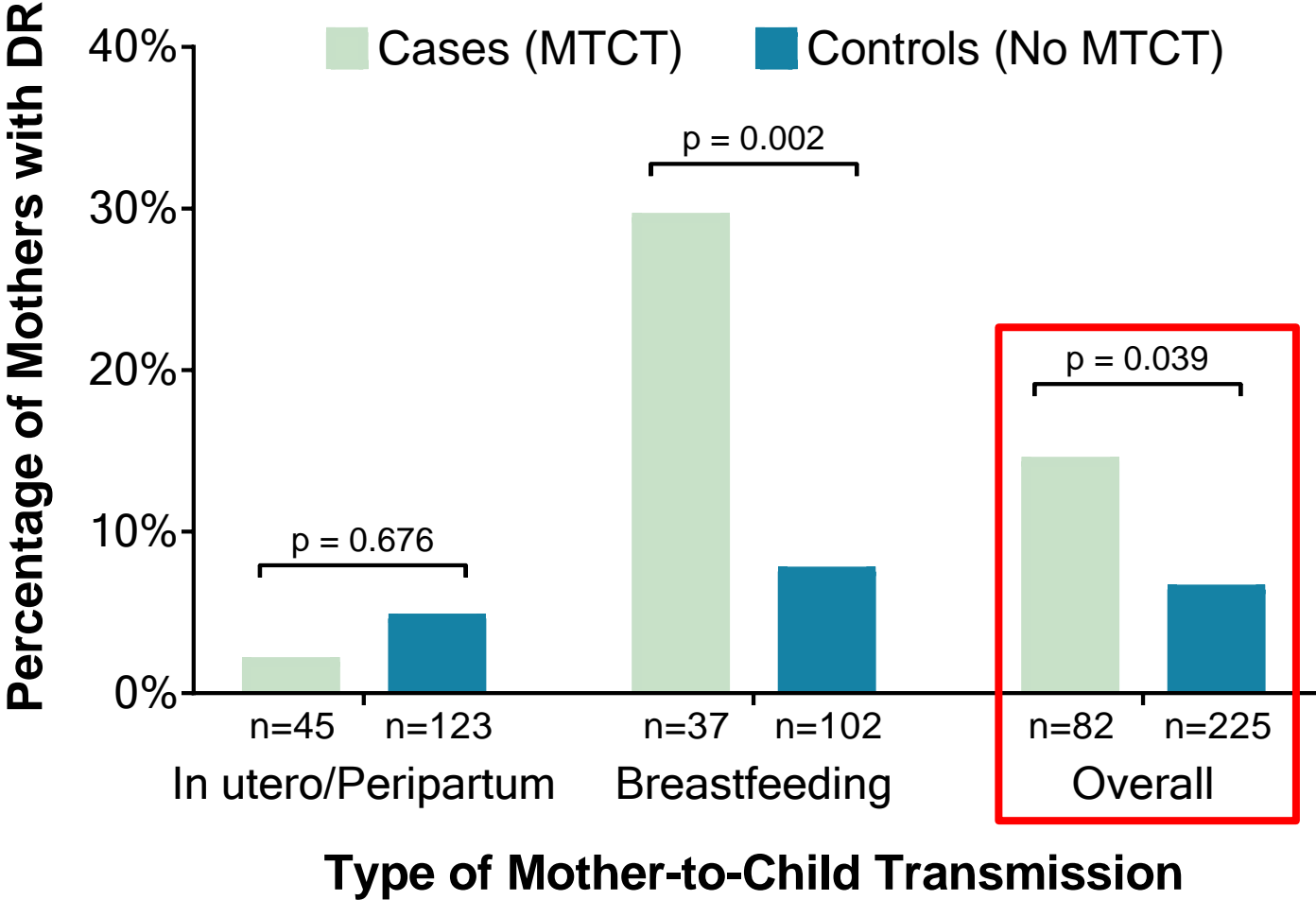
- Genotypic HIV drug resistance by consensus sequencing of HIV *pol*
- Mothers and infants categorized as wild-type (**WT**) or drug resistant (**DR**) using major drug resistance mutations defined by Stanford HIV Database

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

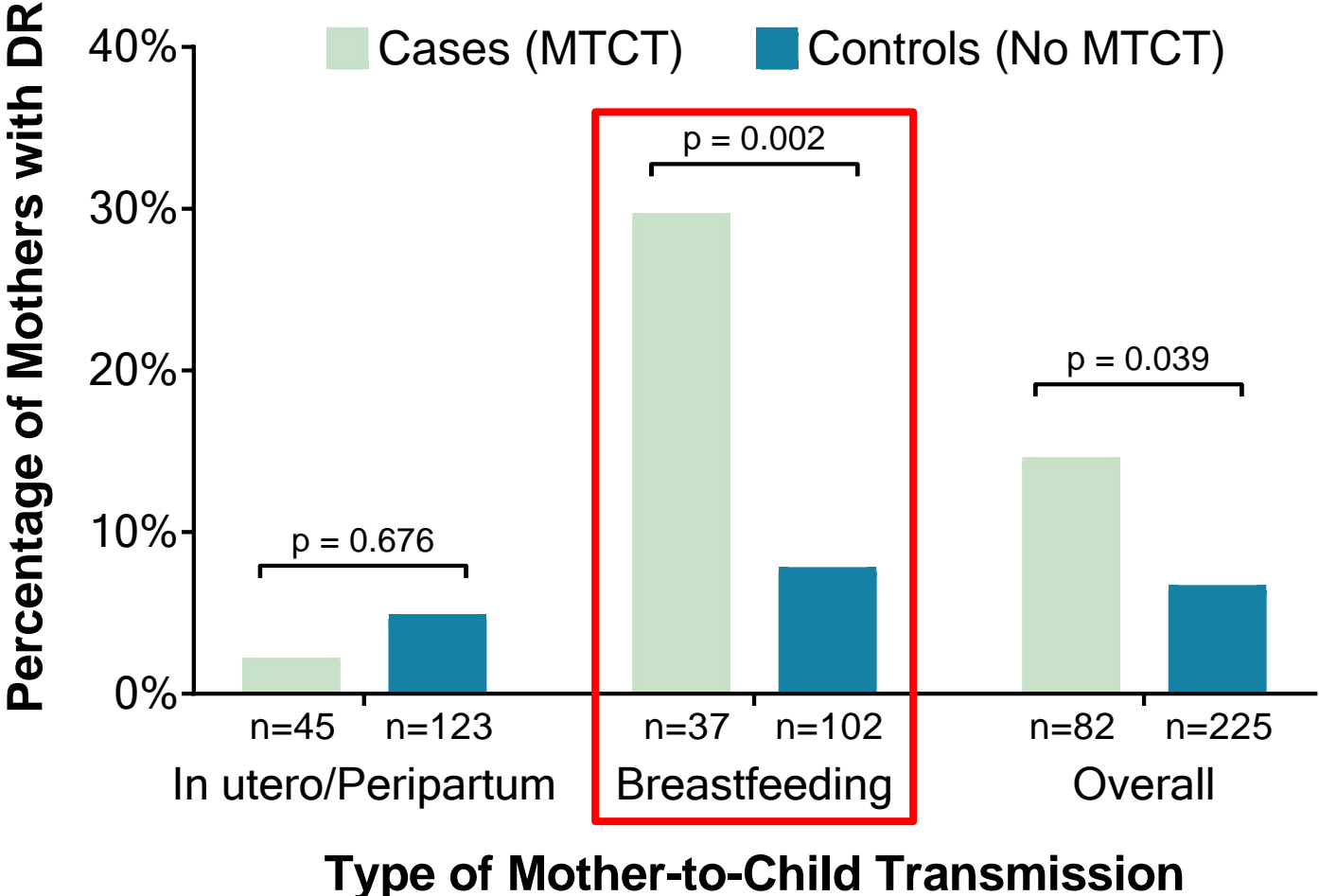
- Overall, transmitting mothers had a higher rate of DR at infant HIV diagnosis (14.6% vs 6.2%, $p=0.039$)



Compared using Fisher's Exact test

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

- Overall, transmitting mothers had a higher rate of DR at infant HIV diagnosis (14.6% vs 6.7%, $p=0.039$)



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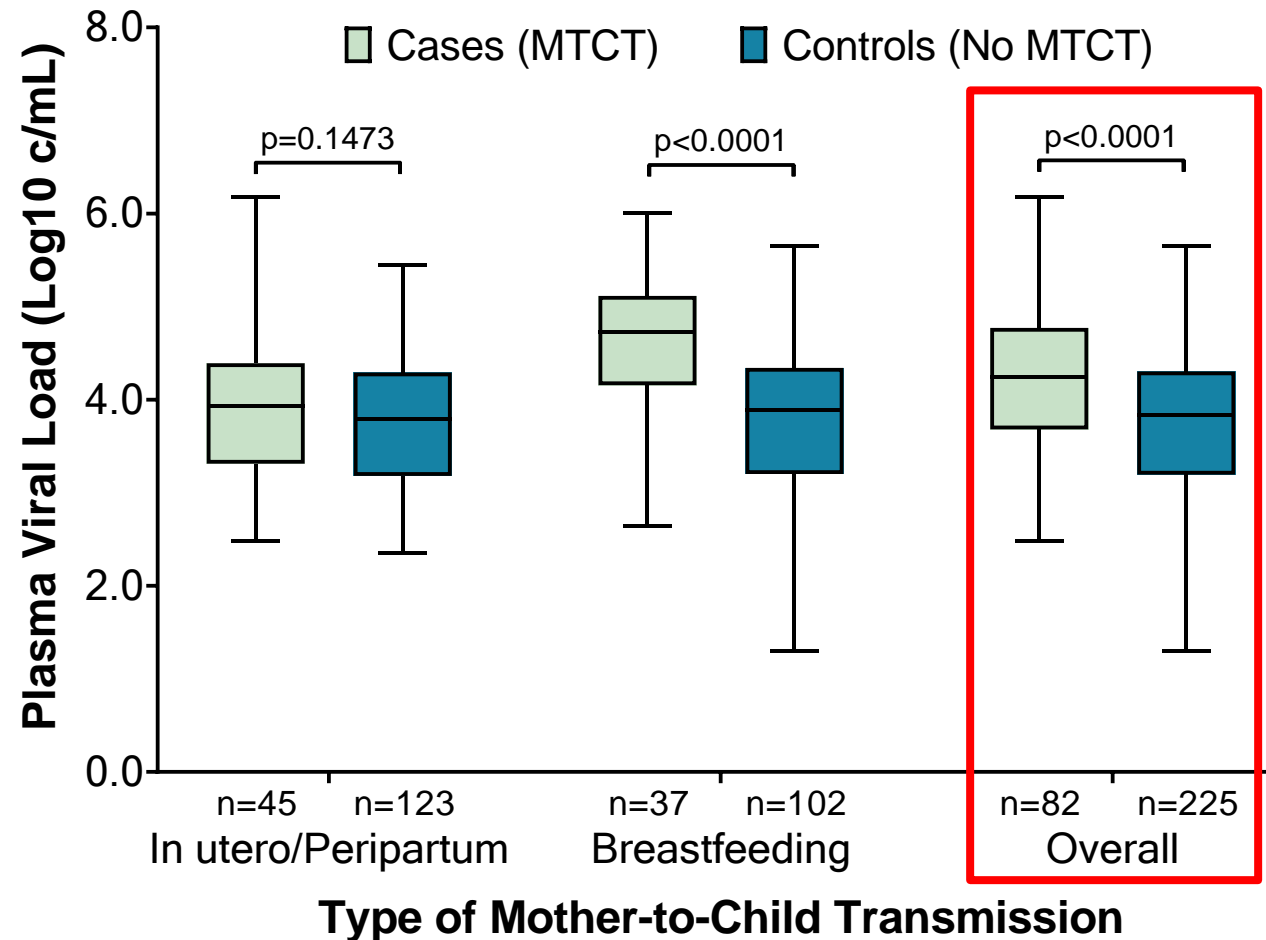
Results: DR greater in maternal cases vs controls at infant HIV diagnosis

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

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

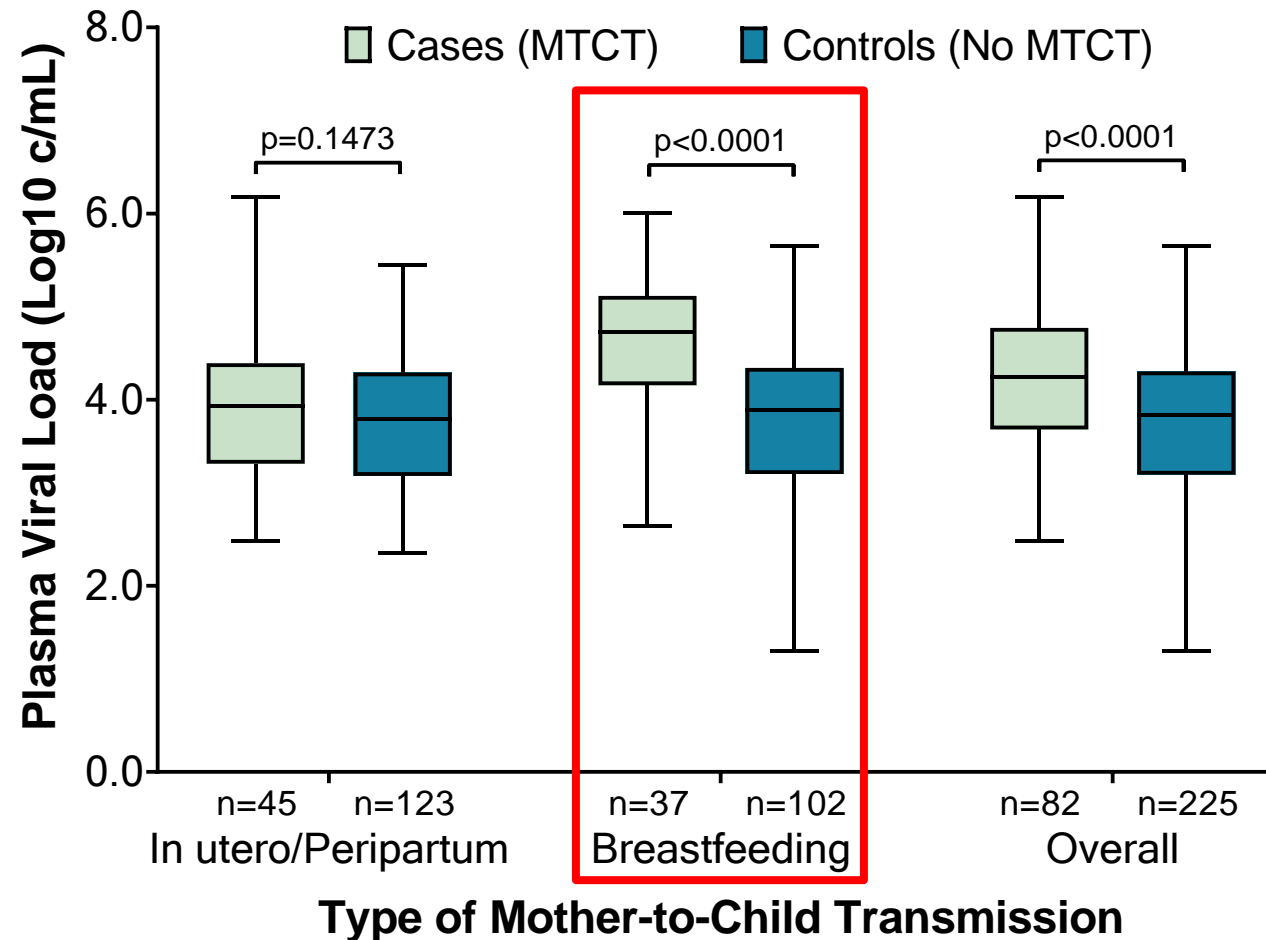
Results: HIV RNA higher in maternal cases vs controls at infant HIV diagnosis

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



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

- Adjusting for maternal plasma HIV viral load at infant diagnosis, **DR was significantly associated with increased risk of MTCT**
- Antepartum treatment with three-drug ART was associated with decreased risk of MTCT (compared to no treatment)

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
Antepartum Three-drug ART (Late Presenters = no treatment)	0.15 (0.04-0.56)	0.005
Antepartum ZDV-monotherapy (Late Presenter = no treatment)	0.35 (0.10-1.25)	0.106

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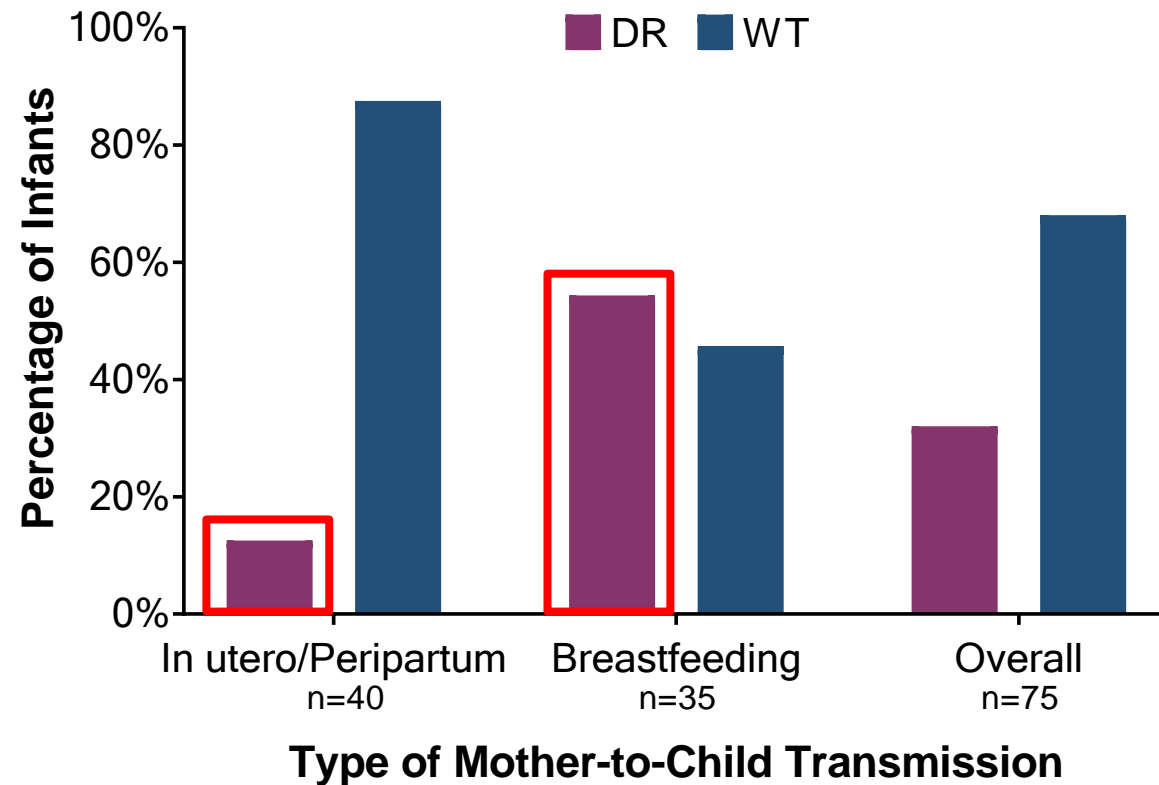
Aim 2: Describe the emergence of DR in HIV-infected infants

Hypotheses:

1. Resistance mutations detected at HIV diagnosis will persist over time
2. Prolonged selective pressure from maternal or infant ART could select DR mutations

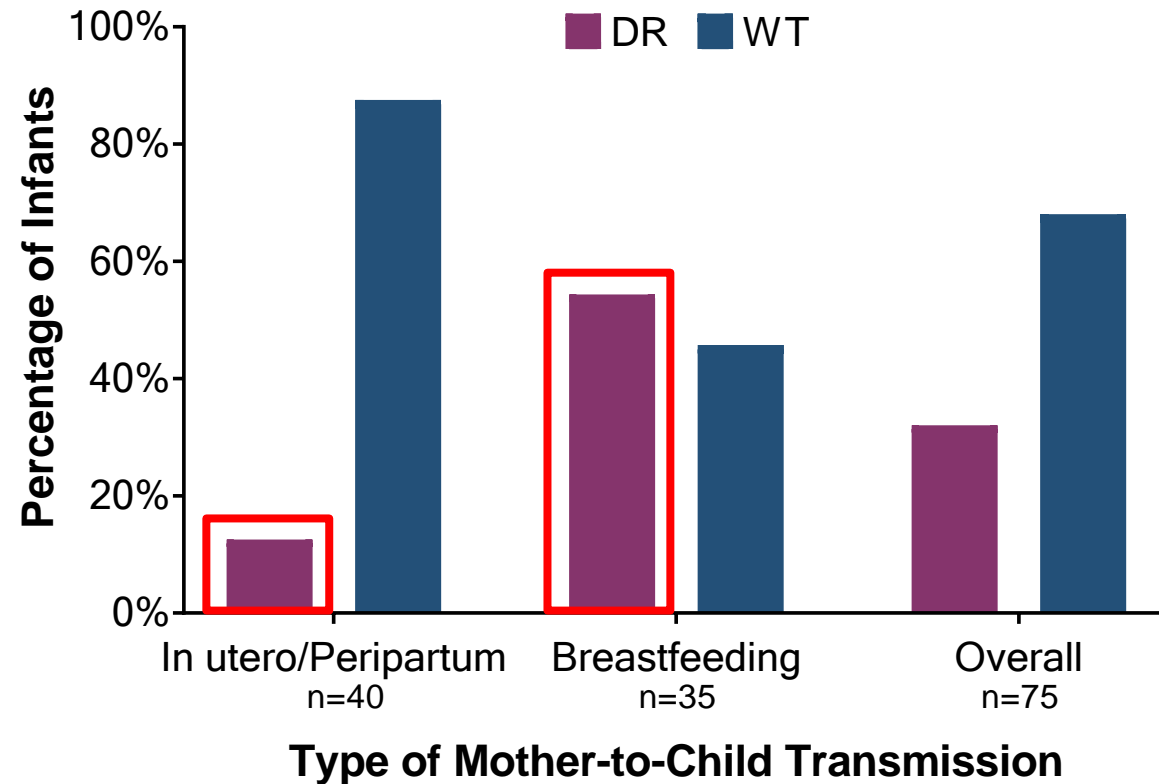
Results: HIV DR was less frequent in infants with *in utero* MTCT vs. breastfeeding MTCT

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



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

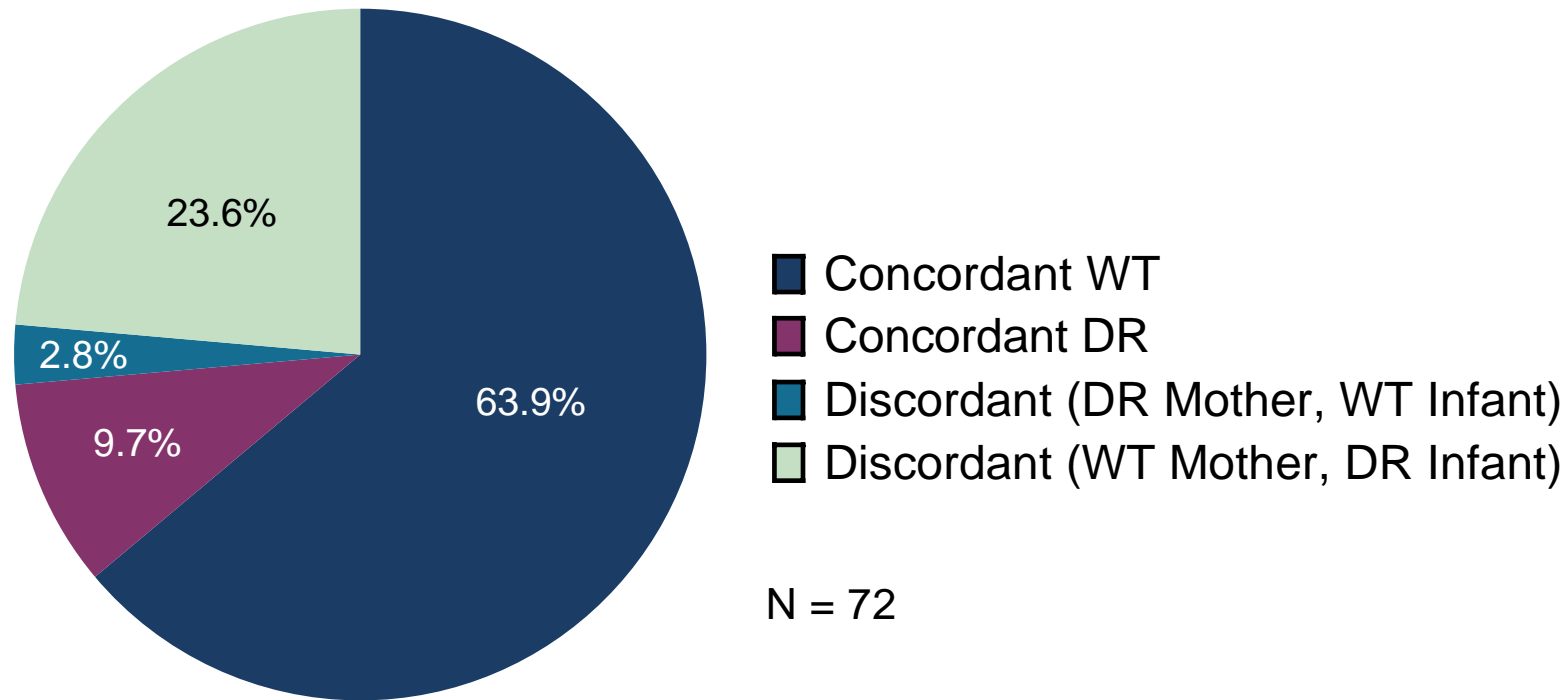
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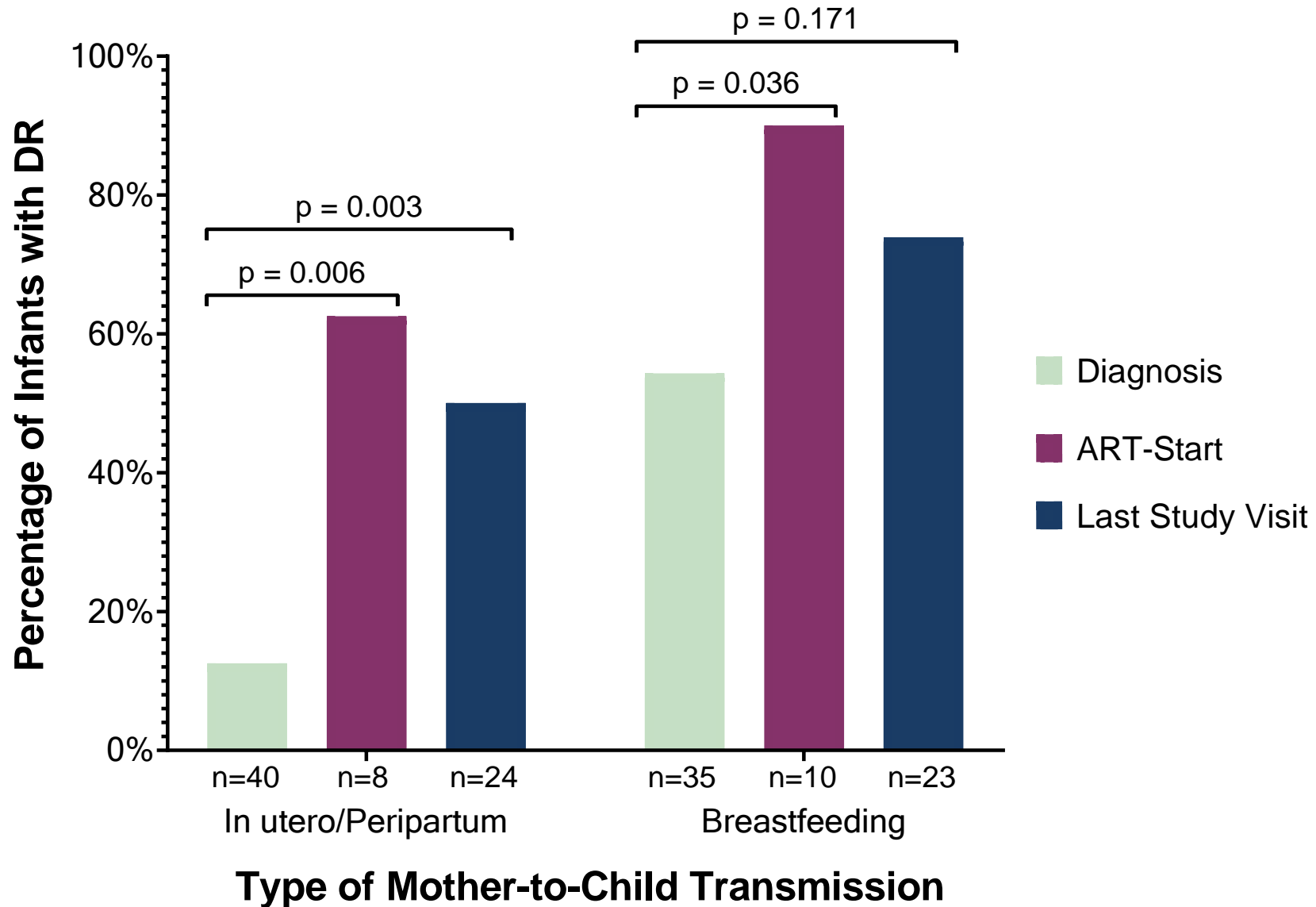
Mutations Detected	<i>In utero or Peripartum</i> n = 40	Breastfeeding n = 35
NRTI		
Single	-	3
Multiple	-	-
NNRTI		
Single	5	8
Multiple	-	7
NRTI & NNRTI		
	-	1
Total # of DR infants	5 (12.5%)	19 (54.3%)

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

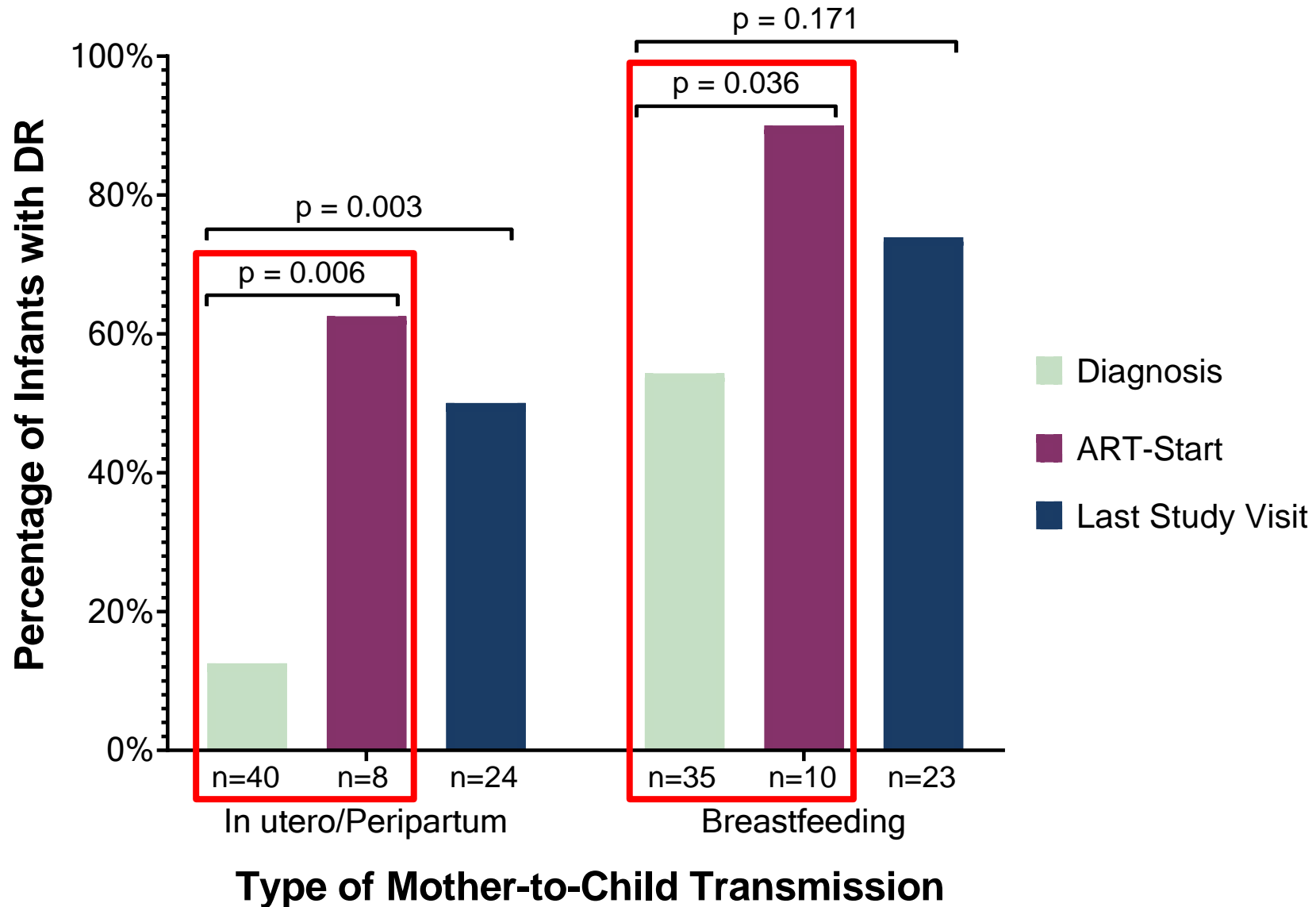
Genotype Concordance of Mother-Infant Pairs at Infant Diagnosis



Results: HIV DR emerged in infants over time during breastfeeding



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Conclusions & Future Directions

- **Finding:** At infant HIV diagnosis, maternal viral load 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 may reduce effectiveness of infant prophylaxis explaining association with MTCT
 - ↳ We are investigating how much maternal DR was transmitted vs selected prior to MTCT
- **Finding:** DR was less prevalent at diagnosis in infants with *in utero* MTCT vs breastfeeding MTCT, but over time DR emerged in both groups
- **Interpretation:** Prolonged exposure to maternal ART or NVP prophylaxis during breastfeeding led to the emergence of DR in infants
- **Our conclusion:** It may be time to replace single-drug (e.g. NVP) prophylaxis for MTCT with other strategies that have a greater barrier to drug resistance

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Results: Specific HIV DR Mutations Detected in Infants at HIV Diagnosis by Type of MTCT

HIV DR Mutations Detected by Type of MTCT

Mutation	<i>in utero or Peripartum</i> n = 40	Breastfeeding n = 35
M184I/V	-	4
A98G	-	1
K101E	-	1
K103N	-	5
V106M	1	3
V108I	1	-
V179D	-	1
Y181C	2	9
Y188C	-	1
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Total # of DR infants	5 (12.5%)	19 (54.3%)

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