

HIV Drug Resistance at Perinatal Transmission and Accumulation During Breastfeeding

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Introduction

BACKGROUND

- Perinatal transmission of HIV has decreased with the increased coverage of antiretroviral (ARV) drugs
- Pre-treatment HIV drug resistance to 1st-line non-nucleoside reverse transcriptase inhibitors (NNRTI) is increasing in low-resource communities due to transmitted or selected drug resistance mutations (DRM) and in women from treatment to prevent mother-to-child HIV transmission (MTCT)
- However, whether HIV DR in mothers increases the risk of MTCT or resistance in the infant has not been well studied

AIMS OF THIS STUDY

- Assess the association of maternal HIV DR with the risk of MTCT
- Describe the acquisition or emergence of DR in HIV-infected infants

Methods

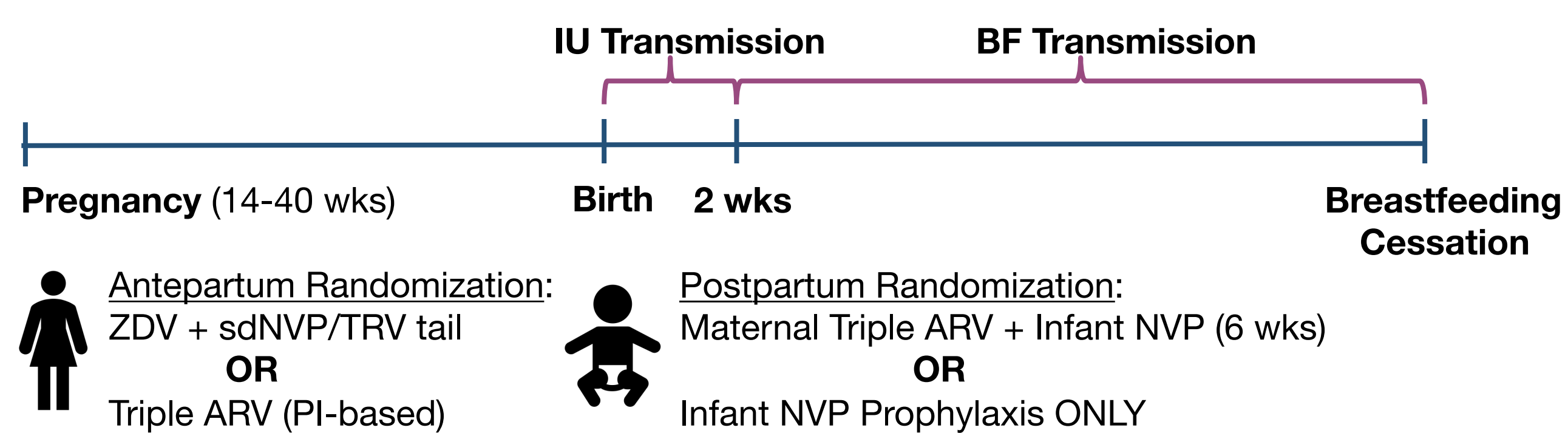
STUDY POPULATION & DESIGN

Parent Study: PROMISE study was a multinational, clinical trial aimed to determine the optimal antiretroviral regimen for reducing MTCT. The 1077BF component was conducted in countries that recommend that HIV-infected women breastfeed their infants.

This Study: Nested case-control study (1:3 ratio) of mother-infant pairs from the PROMISE 1077BF study (Figure 1).

- Cases:** 85 transmitting mothers and their infants
 - 48 *in utero*/peripartum (IU) infections
 - 37 breastfeeding (BF) infections
- Controls:** 254 non-transmitting mothers, matched by delivery date and clinical site

Figure 1. PROMISE 1077 BF Antepartum and Postpartum Schema



METHODS & ANALYSES

- Plasma RNA from the following timepoints were tested for HIV DR:
 - Mothers:**
 - Time-point nearest infant diagnosis (or matching case's time of MTCT for controls)
 - Infants:**
 - Diagnosis and last study visit
 - If DR emerged by last study visit, the ART-start specimen (collected prior to infant initiating an ART regimen) was also genotyped, if available
- Genotyped HIV *pol* by consensus sequencing (CS) and categorized as wild-type (WT) or DR based on major DRM defined by Stanford HIV Drug Resistance Database
- Phylogenetic and bioinformatic analyses used for quality assurance
- Maternal DR rates and viral loads (VL) at infant diagnosis were compared using Fisher's Exact and Mann-Whitney tests, respectively; adjusted analyses were performed using logistic regression

Results

Figure 2. Frequency of Maternal HIV Drug Resistance at Infant Diagnosis

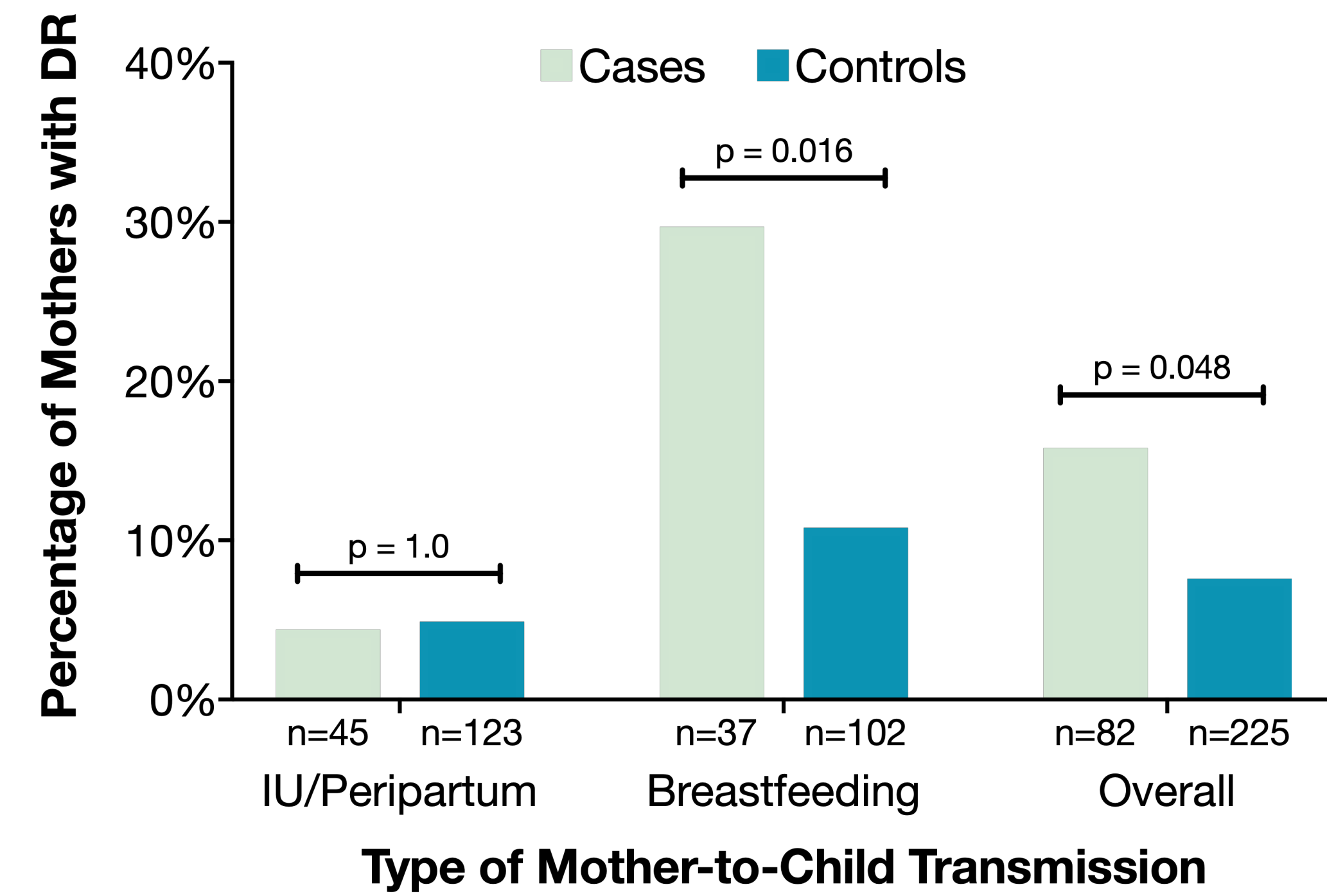


Figure 3. Comparison of Maternal HIV Plasma Viral Load at Infant Diagnosis

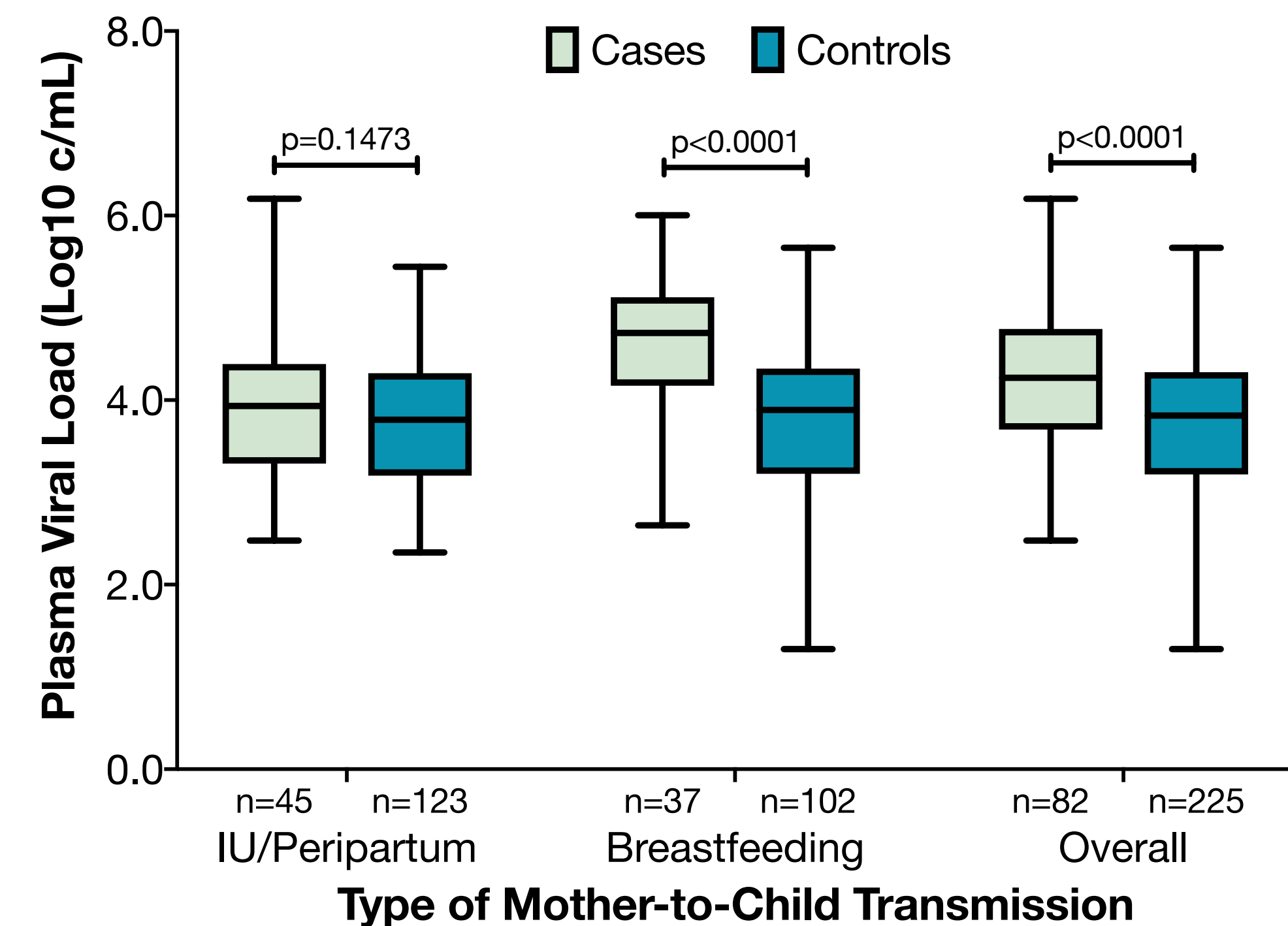
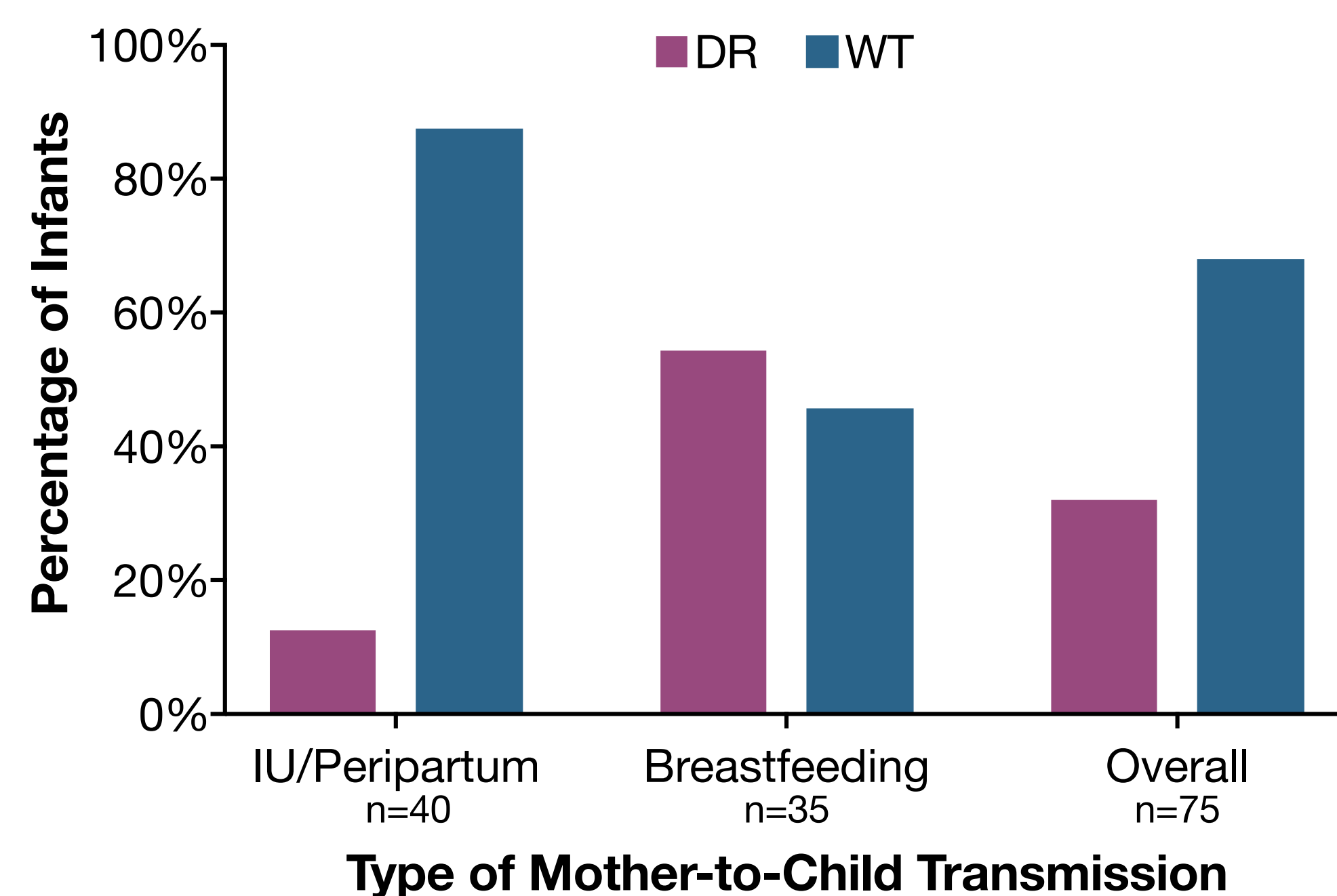


Table 1. Multivariate Analysis of MTCT Risk by Logistic Regression

Covariate (Reference)	OR (95% CI)	p-value
≥4 Log c/mL Plasma Viral Load (<4 Log c/mL)	2.40 (1.38-4.22)	0.002
DR Genotype (WT Genotype)	2.35 (1.01-5.37)	0.043
Antepartum Triple ARV (None, Late Presenter)	0.24 (0.09-0.67)	0.006
Antepartum ZDV-monotherapy (None, Late Presenter)	0.48 (0.17-1.31)	0.148

Complete antepartum treatment comparison for PROMISE trial: Fowler et al. N Engl J Med 2016;375:1726-37.

Figure 4. Infants' HIV Genotype at Diagnosis



Results

Figure 2. HIV Genotype Concordance of Mother-Infant Pairs (N=72) at Infant Diagnosis

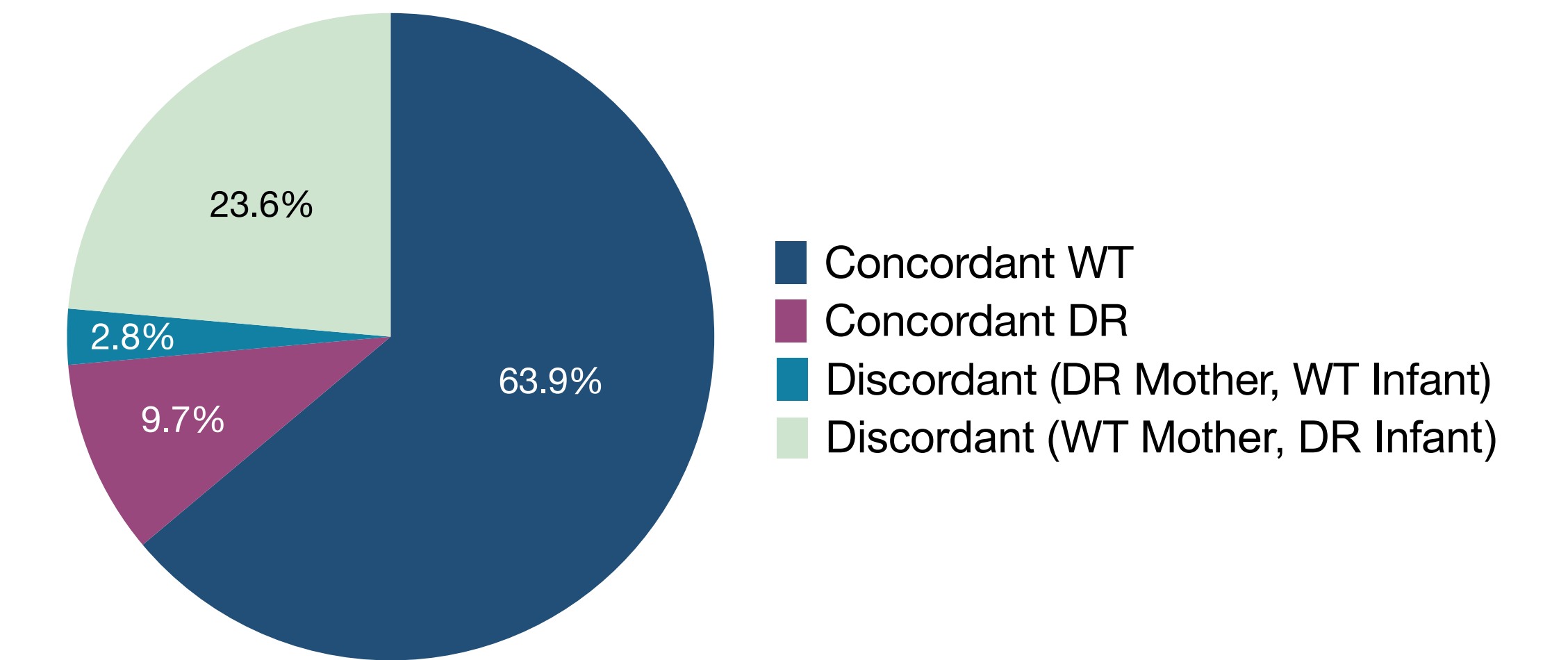
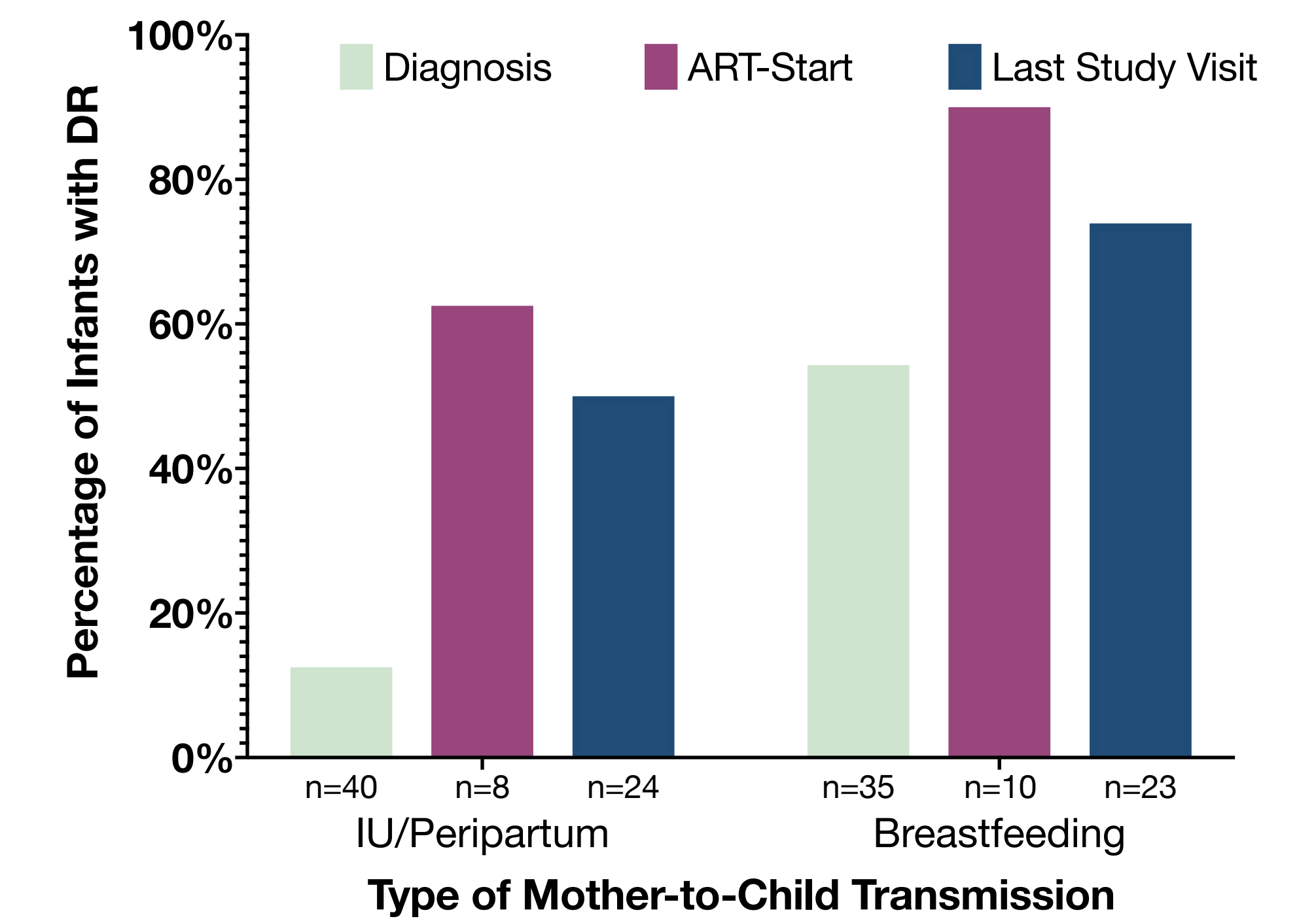


Figure 6. Emergence of HIV Drug Resistance in Infants During Breastfeeding



- Median time in weeks between Diagnosis and ART-Start:
 - IU/Peripartum: 6 weeks (range: 5-23)
 - Breastfeeding: 10 weeks (range: 1-24)
- Median time in weeks between Diagnosis and Last Study Visit:
 - IU/Peripartum: 14 weeks (range: 1-204)
 - Breastfeeding: 48 weeks (range: 1-92)

Summary/Conclusions

- Maternal DR at infant diagnosis was associated with MTCT during breastfeeding but not with *in utero*/peripartum transmission
 - After adjusting for HIV RNA load, DR was significantly associated with increased risk of perinatal transmission
- DR was less prevalent in infants diagnosed with IU vs BF transmission; but DR emerged over time – possibly due to prolonged exposure to maternal ARV or NVP prophylaxis or due to ART failure in the infant
 - This increase in DR in infants during early infancy provides a rationale for trials examining alternative regimens with a greater barrier to resistance for infant prophylaxis and ART

Acknowledgements

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