IAS 2019

10TH IAS CONFERENCE ON HIV SCIENCE

Mexico City, Mexico 21-24 July 2019

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occurrences of neural tube defects among 382 wom on Dolutegravir at pregnancy conception in Brazil

IAS 2019 Co-chairs' choice, 22 July 2019

MOAX0104LB

G. Pereira, A. Kim, E. Jalil, F. Fernandes Fonseca, B. Shepherd, V. Veloso, R. Rick, R. Ribeiro, A. Bebe Jayathilake, R. Girade, R. Lima, F. Maruri, A. Caruso, C. McGowan, A. Benzaken, J. Castilho, B. Grinsztej

The National Cohort Study of Dolutegravir and Pregnancy Outcomes in Brazil

FIOCRUZ Fundação Oswaldo Cruz

CCASAnet

NIH National Institute of Allergy and Infectious Diseases

SUS

MINISTÉRIO DA SAÚDE

Conflict of Interest Disclosure

I have no conflict of interest.

w was it possible?

iversal HIV care & ART free of charge (1996)

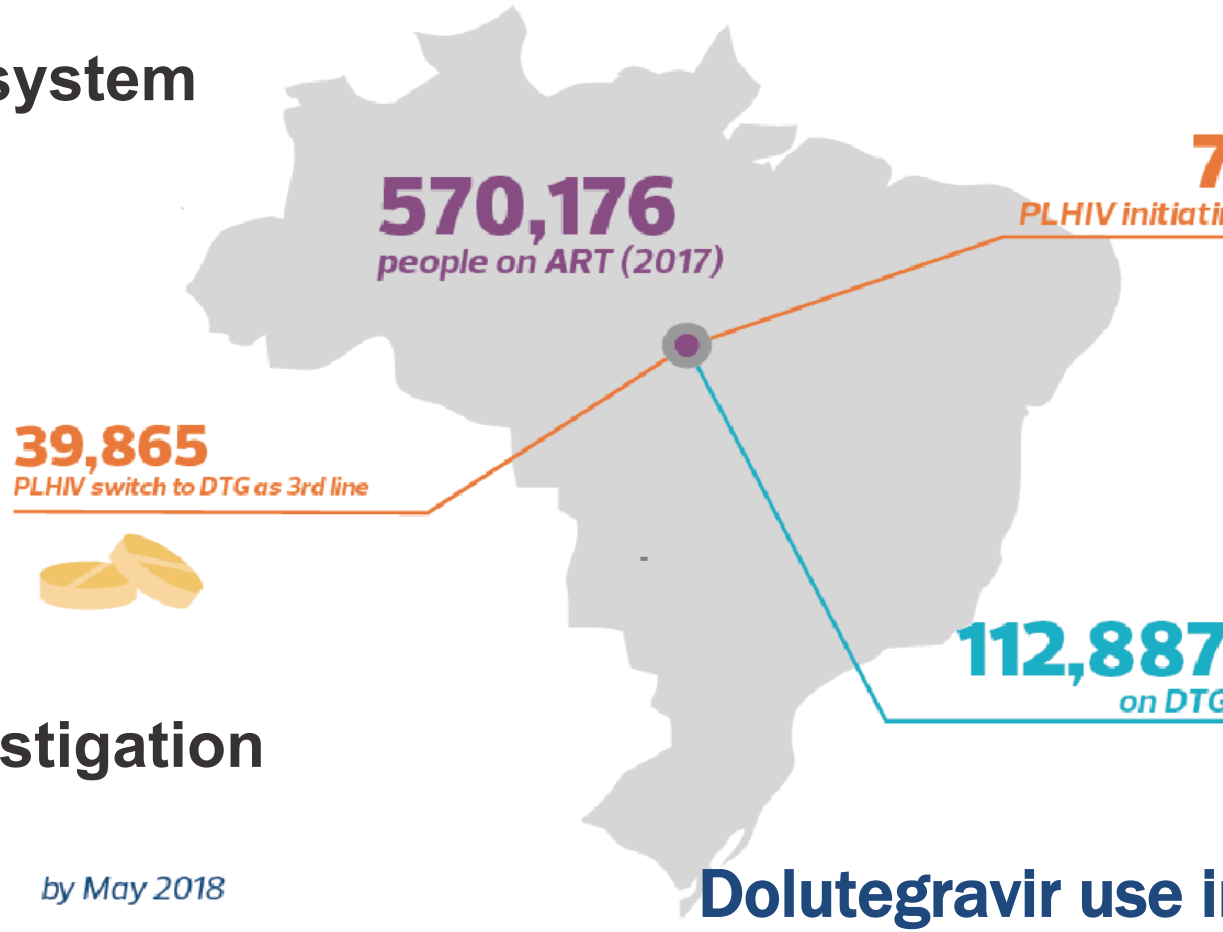
mputerized ART distribution system CLOM)

- Every person on ART
- Rules based on national guidelines

G for 1st line (2017)

- Use in pregnancy systematically restricted
- As of May 2018> **22,624 women between 49 years were on DTG in Brazil**

D signal led to a national investigation



by May 2018

Dolutegravir use i

Aim

o estimate the risk of NTD in infants born to women eceiving DTG and non-DTG ART regimens at time of conception in Brazil

rimary outcomes of interest:

- All NTD
- Stillbirths
- Abortions*

Composite outcome
for multivariable analyses

ve abortions are illegal in Brazil. All abortions presumed to be spontaneous.

thodology

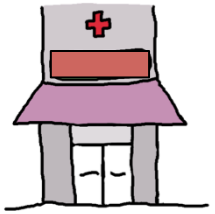
ospective cohort of **every women** identified in SICLOM
ossible exposure to DTG or RAL during pregnancy
7-2018)

xposed group: pool of women with **exposure to EFV**
ng pregnancy (2015-2018)
FV 3: DTG 1

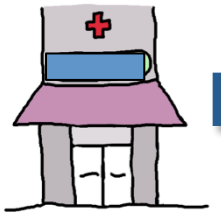
tematic data collection by trained public health
essionals:

Chart review of all health services

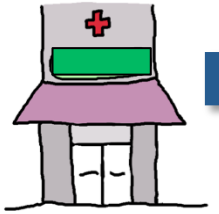
Maternal demographic, behavioral, HIV history, comorbidities, obstetrical history, prenatal care, and birth outcomes



HIV clinic



Antenatal clinic



Maternity

thodology

posure: **periconception window** (16-week period)

+/- 8 weeks of estimated date of conception (EDC)

- (1) 1st or 2nd trimester ultrasound (preferred method),
- (2) last recorded menstrual period (LMP), and
- (3) gestational age at delivery or 3rd trimester ultrasound

atistical approach:

Calculation of NTD incidence with Wilson 95% CI among women with and without DTG exposure

Matched propensity score weighted logistic regression for composite pregnancy outcome for

- Any DTG vs. EFV only
- Sensitivity analyses: Only DTG vs. Only EFV / Only DTG or RAL vs. Only EFV

Used multiple imputation for missing data

sults

ion Criteria

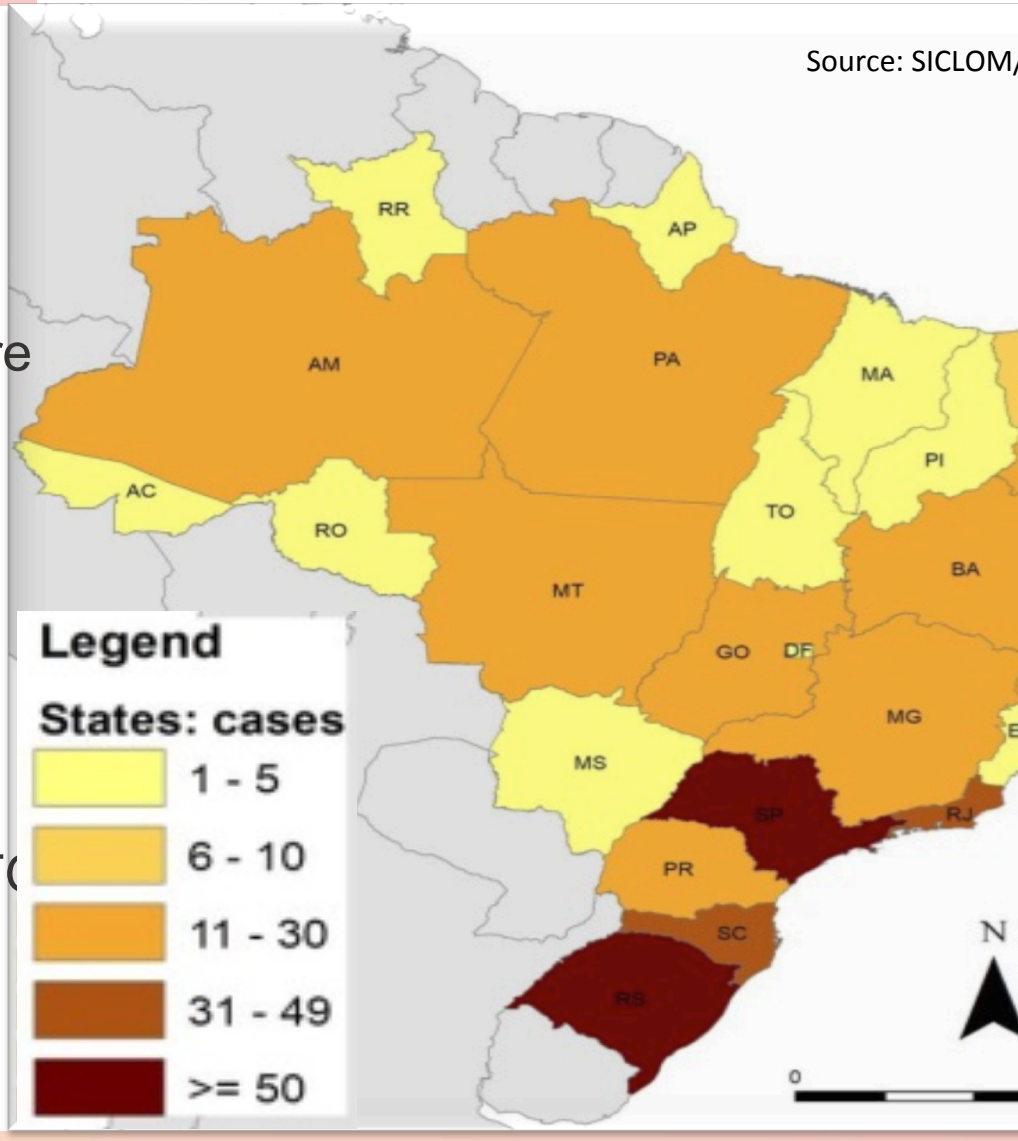
omen with possible DTG or RAL exposure
ng pregnancy:

- ndication of pregnancy in SICLOM,
- Women of childbearing age on DTG whom were switched to an approved ART regimen for pregnancy,
- Women who received IV AZT one time.

sion Criteria

- onfirmed pregnancy
- periconception ART exposure
- exposure including medications other than DT , EFV
- ing/unknown periconception ART or birth omes

Women with possible prenatal exposure



hort Creation

Total pool of **presumed pregnancies**
(SICLOM: 1/2015-5/2018)
N=3390 women

Pregnancies with **complete investigation**
N=2507

Women with **exclusion criteria**
N=1039

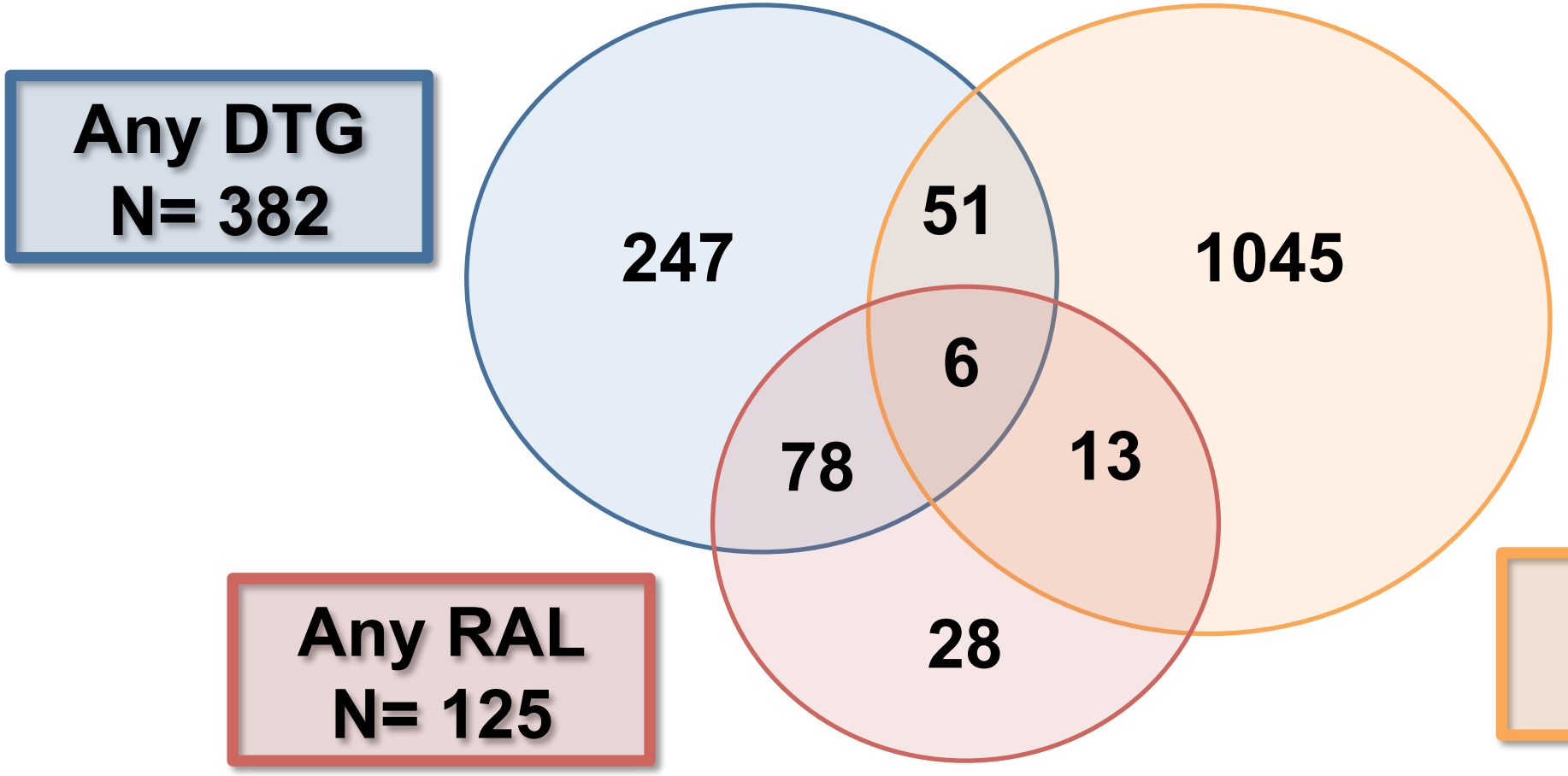
2 NTD cases:

- **Started RAL at week 9** of pregnancy: myelomeningocele and spi
- **Started EFV at week 10** of pregnancy: myelomeningocele

NEITHER WOMEN HAD ANY EXPOSURE TO DTG BEFO
DURING PREGNANCY!

Periconception final cohort
N=1468

(women with EFV, DTG, or RAL within 8 weeks of EDC)



ble 1. Maternal characteristics at EDC

	No DTG (N=1086)	Any DTG (N=382)	P
years, median (IQR)	28.4 (23.2-33.3)	26.6 (21.9-31.9)	
f HIV diagnosis	2014 (2011-2016)	2017 (2014-2017)	
since HIV diagnosis	2.9 (1.4-6.1)	0.7 (0.3-2.7)	
ll count (cells/μL)	605 (420-838)	530 (375-751)	
A below limit of detection	483 (74)	139 (58)	
dverse pregnancy outcome	376 (35)	128 (34)	
co use	209 (19)	78 (20)	
l use	177 (16)	77 (20)	
nce use	117 (11)	54 (14)	

ble 2. Prenatal characteristics

	No DTG (N=1086)	Any DTG (N=382)
r of ART regimens, median (IQR)	1.0 (1.0-2.0)	2.0 (2.0-2.0)
cid supplementation, n (%)		
y before pregnancy	18 (2)	11 (3)
y during pregnancy	488 (45)	183 (48)
ore and during pregnancy	26 (2)	10 (3)
nown	554 (51)	178 (47)
than 6 total prenatal visits	410 (38)	175 (46)
s	63 (6)	40 (11)
	3 (0)	0 (0)
onal hypertension	35 (3)	25 (7)

Outcomes

the total 1452 birth outcomes, **there were no NTD observed**

DTG-exposed women incidence = 0 [95% CI: 0, 0.0099]

DTG-unexposed women incidence = 0 [95% CI: 0, 0.003]

	No DTG (N=1068)	Any DTG (N=384)	P value
NTD	0 (0)	0 (0)	-
Live birth	1025 (96.0)	359 (93.5)	<0.01
Stillbirth	15 (1.4)	2 (0.5)	
Abortion	28 (2.6)	23 (6.0)	

posite Outcome Regression Models

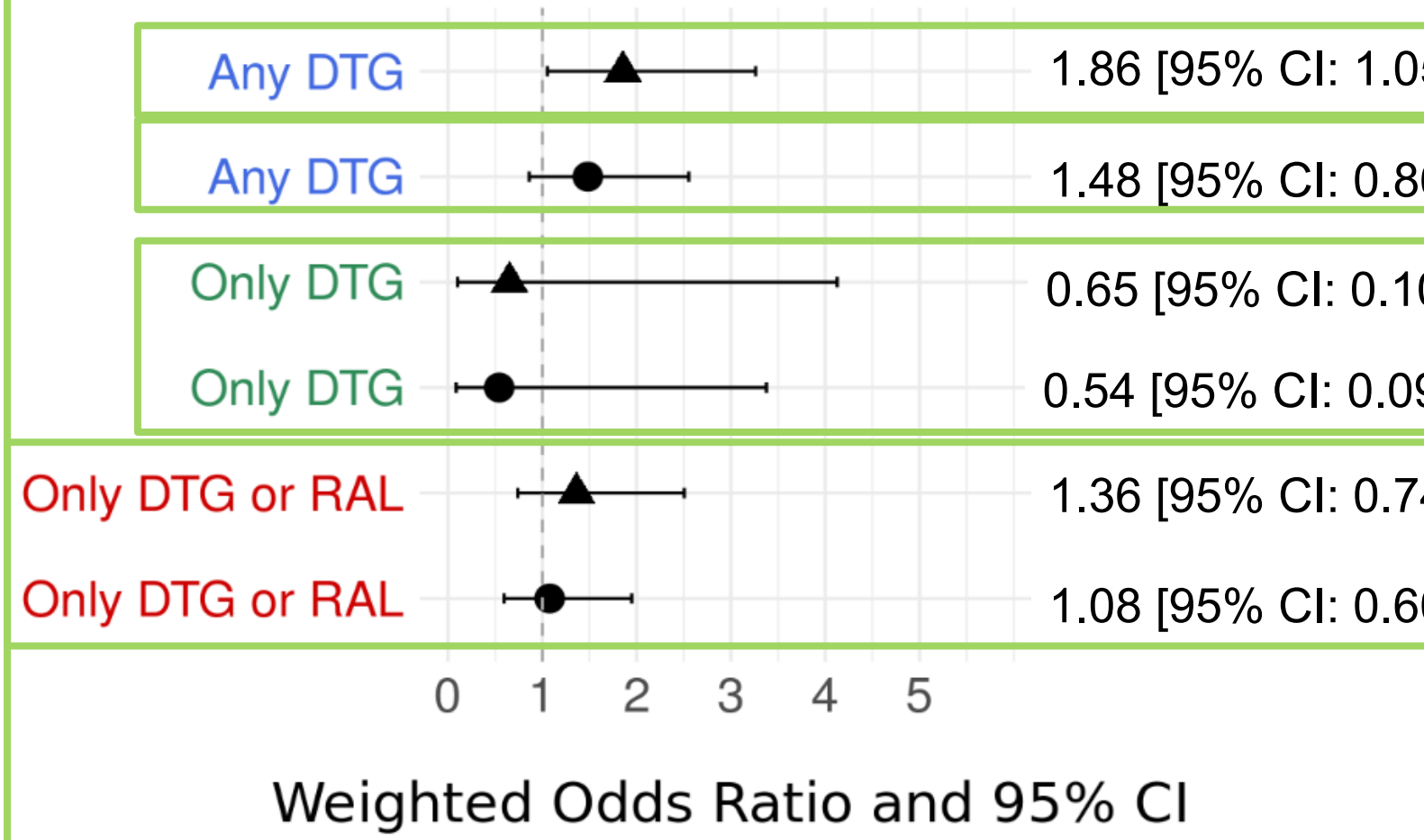
eighted PS Models

EDC Covariates

EDC + Prenatal Covariates

ariates: age, education, race,
ars since ART initiation,
e HIV diagnosis, CD4 cell
RNA below limit of
epilepsy or antiepileptic
n use, tobacco, alcohol,
aine, number of previous
es, prior adverse pregnancy
any folic acid use, BMI

Covariates: number of
sits, syphilis, diabetes,
l hypertension, average
n per week



imitations

etrospective study

ssing data

ericonception ART exposure

hile we observed no NTD events in our analysis cohort, it is possible that ou
udy remained underpowered to detect a difference in exposure groups

onclusions

o occurrences of NTD in this national cohort study.

lic acid supplementation in Brazil: Enriched flour and high

evalence of prenatal supplementation in this study

armacovigilance is a priority for the Ministry of Health in Brazil

esults of this study do not conclusively indicate increased or

creased risk of stillbirth and/or abortion associated with

riconception DTG exposure.

knowledgements

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Thank you!
Gracias!
Obrigada!

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clusion Criteria

The identification of potential DTG exposures during pregnancy included:

- Indication of pregnancy in SICLOM,
- Women of childbearing age on DTG that underwent ART change to an ART regimen recommended during pregnancy,
- Women who received a single dose of IV AZT.

Selection of unexposed group included women with possible exposure to EFZ during pregnancy from 2015 to 2018, on a 3:1 ratio.

- Unexposed women were balanced by geographic location with women possible exposed to DTG/ RAL

xclusion Criteria

245 women who were not pregnant on chart review
52 women with unknown or missing birth outcomes

- Included 5 women with DTG exposure

713 were not on ART of interest during EDC window (either started after the window, were on other ART, or stopped before window)
29 had missing ART data from window EDC

imated Date of Conception

or each woman confirmed to have a pregnancy, we alculated the estimated date of conception by: 1st or 2nd mester USG (preferred method), LMP, or EGA at elivery

- **USG:** subtracting the estimated gestational age reported from the first prenatal ultrasound occurring in the first or second trimester (preferred method), or
- **LMP:** as the first day of the woman's last recorded menstrual period (if no ultrasound was obtained in the first or second trimester), or
- **EGA at delivery:** by subtracting an estimated gestational age obtained from a third trimester ultrasound or at the time of delivery if no other data were available.

N=146
1108 (76
255 (17
105 (7%

Next Steps

aluation of other adverse pregnancy outcomes using this cohort

aluation of birth outcomes and DTG exposure later in pregnancy

se-control study based on national surveillance data to complete the estigation regarding neural tube defects, abortions and stillbirths among dren perinatally exposed to HIV