Safety of Antiretroviral Therapy in Pregnancy

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Elizabeth Glaser Pediatric AIDS Foundation
Learning Objectives
Upon completion of this presentation, learners should be better able to:

1. Analyze the implications of timing of antiretroviral (ARV) exposure on birth defect risk

2. Describe the results of the Botswana Tsepamo birth surveillance study related to preconception dolutegravir (DTG) use and neural tube defects (NTD) and what they mean for practice in the U.S.

3. Appraise the importance of prospective reporting of antiretroviral drug exposure in pregnancy to the Antiretroviral Pregnancy Registry

Question
Which one of the following is correct regarding the mean time between FDA drug approval and availability of data in human pregnancy:

A. None, because drug data in human pregnancy are required before a drug can be approved by FDA

B. 1 year

C. 6 years

D. 12 years
Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects

Unfortunately there are often only minimal data to make recommendations

Limited Data on Pregnancy for Approved Antiretroviral Drugs

- Of the 32 drugs approved in adults, only one (AZT) has indication in pregnancy (for prevention of perinatal transmission)
- Generally, drug label language is “use in pregnancy only if potential benefit exceeds potential risk” and prohibition of use during breastfeeding
- Of the 32 approved drugs:
  - 26 had significant delay between FDA approval and data in pregnancy, and the rest have no data
Time from FDA Antiretroviral Drug Approval to First Published Pharmacokinetic Data in Pregnancy

Mean knowledge gap 6 years

Drug approval

0 1 2 3 4 5 6 7 8 10 12

Years After Initial Drug Approval

AZT NVP TDF DRV EFV

F-APV COBI

Bornovirine Tenofovir alafenamide

No published data

Bictegravir Doravirine Ibalizumab

Question

Which one of the following is true regarding preclinical reproductive toxicology studies in animals:

A. The pathogenesis of most birth defects with drug exposure is not known

B. Preclinical studies in one animal species are sufficient

C. Positive results of animal studies reliably predict the risk of birth defects in humans

D. Negative results of animal studies are definitive proof of no risk of birth defects in humans
What Can We Learn About Safety (In Specific, Teratogenicity) From Pre-Clinical Reproductive Toxicology Studies

What is Predictive Value of Pre-Clinical Animal Studies?

- Molecular basis of birth defects with drug exposure is known for only a few drugs
- Most human teratogens were first identified by clinical/epidemiologic studies (e.g., thalidomide, diethylstilbestrol, valproate)
- Animals can be *differentially sensitive* to drugs:
  - Thalidomide was negative in mice/rat embryo-fetal studies, only positive for limb malformation in rabbits
  - FDA now requires studies in ≥2 animal species
What is Predictive Value of Pre-Clinical Animal Studies?

- Drugs known to be teratogenic in humans have shown teratogenic activity in mouse, rat or rabbit studies (often retrospectively) (van der Laan JW et al. Reg Toxicol Pharmacol 2012;63:115-23).

- While negative tests are reassuring, no absolute assurance that negative results obtained by testing drugs in these species can definitively predict that an agent will lack teratogenic effects in humans (Ujhazy E et al. Developmental Toxicology: Safety Evaluation of New Drugs 2005).

- Similarly, it cannot be said that agents teratogenic in animals will necessarily produce teratogenic effects in humans at therapeutic dose levels (e.g., EFV and CNS defects in monkeys but not in humans).

Question

Which one of the following is true regarding pregnancy outcome and antiretroviral therapy (ART) use in pregnancy:

A. Pregnancy outcomes among pregnant women with HIV on treatment are the same as in women without HIV

B. Pregnancy outcomes are similar regardless of the drugs in the treatment regimen

C. Pregnancy outcomes are similar regardless of when treatment is started

D. Preterm delivery may be associated with preconception ART
Do Pregnancy Outcomes Vary by ART Regimen?

Comparing to EFV ART, ↑aRR of adverse outcomes with other ART regimens

- EFV/TDF/FTC (N=2503) 36% (12%) Any adverse outcome
  - Early (N=1403) 1.44 (1.2-1.7)
  - Late (N=237) 1.68 (1.4-2.0)
  - LPV/r/TDF/FTC (N=169) 1.93 (1.4-2.6)
- NVP/TDF/FTC (N=775) 42% (18%) Any adverse outcome
  - Early (N=1403) 1.30 (1.2-1.4)
  - Late (N=237) 1.31 (1.1-1.5)
  - LPV/r/AZT/3TC (N=169) 1.21 (1.0-1.5)
- NVP/AZT/3TC (N=1403) 47% (21%) Any adverse outcome
  - Early (N=1403) 1.30 (1.1-1.5)
  - Late (N=237) 1.31 (1.1-1.5)
  - LPV/r/AZT/3TC (N=169) 1.58 (1.2-2.1)
- LPV/r/TDF/FTC (N=237) 48% (20%) Any severe outcome
  - Early (N=1403) 1.68 (1.4-2.0)
  - Late (N=237) 1.58 (1.2-2.1)
  - LPV/r/AZT/3TC (N=169) 1.93 (1.4-2.6)

*Any severe outcome

(Premature [PTD], small for gestational age [SGA], stillbirth [SB], neonatal death)
Regardless of Regimen, Pregnancy Outcomes Were Worse in Women with HIV on ART than Women Without HIV

Zash R et al. JAMA Pediatr. 2017;171:e172222aa

Compared to women without HIV, ↑ ARR of adverse outcomes for woman with HIV on ART

- Any: 1.40 (1.3-1.4)
- Severe: 1.50 (1.4-1.6)

Regardless of ART Regimen, Pregnancy Outcomes Were

- EFV-based treatment appears safer than NVP or LPV-r-based treatment
- However, regardless of regimen, treatment does not make pregnancy outcomes among women with HIV the same as in women without HIV
Do Birth Outcomes (Other than Birth Defects) Differ if Starting ART Before or During Pregnancy?

Preterm Delivery (PTD) and Preconception ART


- 10 studies: 9443 start ART preconception, 7773 during pregnancy
- Preconception ART associated with increased risk PTD: RR 1.20 (1.01-1.44); highest association in low income countries
- Since 2016, 10 new publications; 6 (including 73% of 7424 additional preconception exposures) also find ↑ risk PTD with preconception ART

<table>
<thead>
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<th>Start Before (N=7424)</th>
<th>Start During (N=9324)</th>
<th>Start before vs during pregnancy</th>
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<td>780</td>
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<td>Sebitloane Niger J Clin Prac 2018</td>
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<td>Yes: 1.38 (1.02,1.85)</td>
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<tr>
<td>Zash JPIDS 2018</td>
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<td>550</td>
<td>Yes: 1.33 (1.04, 1.7) vs 2/3rd trim</td>
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<td>Stringer PlosOne 2018</td>
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<td>-</td>
<td>Elevated rates (33%)</td>
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<td>Malaba Ann Epidemiol 2018</td>
<td>366</td>
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<td>Dadabjao JAIDS 2019</td>
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Preterm Delivery and Preconception ART


- Preconception ART associated with increased risk of PTD: RR 1.20 (1.01-1.44); highest association in low income countries

Since 2016, 10 new publications address this; 6 of 10 also report association of preconception ART with PTD.

Start Before vs During pregnancy

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616 780
Yes: AOR, 1.7 (1.1–2.5)

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No (trend): OR 1.24 (0.9, 1.8)

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Stringer PLosOne 2018
253-377
Elevated rates (33%)

Malaba Ann Epidemiol 2018
366 353
No

Dadabjao JAIDS 2019
299 315
No

→While most outcomes appear similar regardless of time of treatment initiation, preterm delivery may be increased with preconception treatment compared with starting during pregnancy

When Started During Pregnancy, Do Pregnancy Outcomes Differ Between Women on DTG vs EFV-Based Treatment Regimens?
When Started During Pregnancy, No Difference Pregnancy Outcomes EFV vs DTG-Based ART

Zash R et al. Lancet Global Health 2018;6:e804-10

- Any adverse outcome: EFV/TDF/FTC (N=4,593) 35.0% vs DTG/TDF/FTC (N=1,729) 33.2%
- Any severe adverse outcome: EFV/TDF/FTC (N=4,593) 11.3% vs DTG/TDF/FTC (N=1,729) 10.7%
- Preterm <37 wk GA: EFV/TDF/FTC (N=4,593) 18.5% vs DTG/TDF/FTC (N=1,729) 18.0%
- Very preterm <32 wk GA: EFV/TDF/FTC (N=4,593) 3.5% vs DTG/TDF/FTC (N=1,729) 3.8%
- SGA 10%ile wt for GA: EFV/TDF/FTC (N=4,593) 18.5% vs DTG/TDF/FTC (N=1,729) 17.4%
- Very SGA 3%ile wt for GA: EFV/TDF/FTC (N=4,593) 6.7% vs DTG/TDF/FTC (N=1,729) 6.1%
- Stillbirth: EFV/TDF/FTC (N=4,593) 2.3% vs DTG/TDF/FTC (N=1,729) 2.3%
- Neonatal death: EFV/TDF/FTC (N=4,593) 1.3% vs DTG/TDF/FTC (N=1,729) 0%

However, Women With HIV on EFV or DTG ART Still Have Worse Outcomes than Women Without HIV

Zash R et al. Lancet Global Health 2018;6:e804-10

- Any adverse outcome: HIV-UNINFECTED (N=51,156) 28.9% vs EFV/TDF/FTC (N=4,593) 9.9%
- Any severe adverse outcome: HIV-UNINFECTED (N=51,156) 15.6% vs EFV/TDF/FTC (N=4,593) 11.3%
- Preterm <37 wk GA: HIV-UNINFECTED (N=51,156) 18.5% vs EFV/TDF/FTC (N=4,593) 10.7%
- Very preterm <32 wk GA: HIV-UNINFECTED (N=51,156) 3.6% vs EFV/TDF/FTC (N=4,593) 3.5%
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- Very SGA 3%ile wt for GA: HIV-UNINFECTED (N=51,156) 5.4% vs EFV/TDF/FTC (N=4,593) 6.7%
- Stillbirth: HIV-UNINFECTED (N=51,156) 2.3% vs EFV/TDF/FTC (N=4,593) 2.3%
- Neonatal death: HIV-UNINFECTED (N=51,156) 1.4% vs EFV/TDF/FTC (N=4,593) 1.3%
However, Women with HIV on EFV or DTG ART Still

- When started during pregnancy, EFV and DTG appear equivalent in terms of pregnancy outcomes
- But adverse outcomes with EFV or DTG ART are still higher in women with HIV than in women without HIV

DTG ART Started in Late Pregnancy is Associated With More Rapid VL Decline to <50 c/mL than EFV ART

Kintu K et al. CROI, Seattle, March 2019, Abs. 40LB

DolPHIN 2

268 ART-naive pregnant women ≥28-36 wks GA (median 31 wk)

- Randomize median 3 d
- Start EFV ART
- Randomize median 3 d
- Start DTG ART

This analysis reported on delivery data (median 55 d ART before delivery)

- Delivery VL <50
  - DTG: 90/122 (73.8%)
  - EFV: 49/115 (42.6%)
  - p<0.0001

3 infant infections (thought in utero): all DTG arm

- Median time ART before delivery (55d)
Safety

Birth Defects

Question

The time of greatest risk for development of neural tube birth defects in a woman receiving antiretroviral drugs is when:

A. Using a drug any time during pregnancy
B. Starting a drug during the second or third trimester
C. Starting a drug after recognition of pregnancy during first trimester
D. Using a drug at time of conception
Timing of In Utero Drug Exposure and Fetal Risk of Birth Defect

Periods of Fetal Development

- Zygote
- Implantation blastocyst

Periods of Teratogenic Risk

- First 2.5 Weeks Post-Fertilization: Pre-Organogenic Period generally not sensitive to teratogens
Timing of *In Utero* Drug Exposure and Fetal Risk of Birth Defect

Example:

**Oral Structure Formation by Day 36**

(toxicity can result in cleft palate)

Weeks 3 to 8 Post Fertilization

Embryogenesis: Period of Major Organ Development

most sensitive period to teratogens

Preconception Exposure – Brief Review of Neural Tube Development & Defects

Neural Tube Closure Normally Occurs by 28 Days Post-Conception

Different phenotypes of neural tube defects

- Cranial neuropore closes on 25th day after conception; caudal neuropore normally closes ~ 2 days later
- Example failure of cranial neuropore closure: Anencephaly
- Example failure of caudal neuropore closure: Spina bifida

Depending on when and where toxicity occurs, location & level of the defect will differ, resulting in different NTD phenotypes
Preconception Exposure – Neural Tube Development Phenotypes

- NTD is a spectrum of maldevelopment, not a single defect; depending on time exposure during development, can affect different regions neural tube and non-neural organs.

**Two Types of NTD**

**Open NTD:** interruption of process of primary neurulation with failure of closure; neural tissue (brain, spinal cord) exposed. Most frequent: anencephaly, open spina bifida.

**Closed NTD:** defect covered by skin; are less common - examples encephalocele and iniencephaly. Some experts do not classify as traditional NTD, as may occur after (although with timing close to) primary neurulation.

**Timing of In Utero Drug Exposure and Fetal Risk of Birth Defect**

- **Examples:**
  - Alcohol after 24 weeks & fetal-alcohol syndrome
  - Smoking after 20 weeks and intrauterine growth retardation

- **After 8 Weeks Post-Fertilization**
  - Fetal Development Period
    - Fetal growth; teeth; external genitalia; continued brain development
Timing of *In Utero* Drug Exposure and Fetal Risk of Birth Defect

Greatest risk for serious defects is not in women starting a drug during pregnancy but in those who conceive while receiving the drug - but most studies do not distinguish between 1st trimester and preconception exposure.

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**Question**

The best way to get data on safety in pregnancy is:

A. Data from preclinical animal studies

B. Require a phase 3 trial in pregnant women before the FDA approves a drug

C. Evaluate spontaneous adverse outcome reports to FDA

D. Register your pregnant patient on antiretroviral therapy with the Antiretroviral Pregnancy Registry
Evaluation of Birth Defects - Important Caveats

- Studies come from different sources (trials, observational studies, registries, case reports, adverse event reporting databases), which have differing biases in reporting
- Denominator of exposures may not be provided (e.g., FDA and WHO adverse event reports)
- Some have stillbirth/abortion defect data vs only live births
- Most don’t differentiate preconception vs 1st trimester exposure
- For NTD, cofactors such as folate food fortification makes a difference in background rate in the general population
- Thus, data not always comparable between studies

Folate Food Fortification and NTD

Fortification begun 1998

Prevalence of NTD before and after folic acid fortification by maternal race/ethnicity 19 population-based birth defects surveillance programs, U.S. 1995-2011

Rate of NTDs varies by race/ethnicity - highest rates among Hispanics, lowest rates among African-Americans.

Food fortification decreased rates in all race/ethnicities.
Ability to Rule-Out An Increase in Birth Defects With Drug Exposure is Related to Defect Prevalence and Number of Observed Exposures

200 exposures can rule out a 2-fold ↑ in overall birth defects (prevalence 3%)


However, to rule-out a 3-fold increase in a relatively rare event like NTD (prevalence 0.1%), need ~ 2,000 preconception exposures

Since 1990, the Antiretroviral Pregnancy Registry has collected prospective, voluntary, anonymized reports of women on antiretroviral drugs during pregnancy, capturing data after birth on birth outcomes. Purpose is to provide an early warning signal of teratogenicity; estimates risk of major birth defects compared to general population. Currently international registry including 141 antiretroviral drugs – 52 brand, 89 generic drugs.

A registry is only as good as reporting to it! → urge that all providers caring for pregnant women with HIV participate in reporting to the registry!
Antiretroviral Pregnancy Registry Analysis

1. Prospective
   - APR Primary Analysis
     - Prevalence = number of defects / number of live births
     - Compared to:
       - MACDP* = 3/100 live births
       - TBDR* = 4/100 live births
       - 1st trimester vs. 2nd & 3rd trimester

2. Retrospective
   - Secondary Analyses
     - Secondary Review for Clusters and Patterns

3. Clinical Studies
   - Retrospective Secondary Review

Reporting during pregnancy before delivery, follow-up for outcome

Prevalence of Birth Defects (95% CI): 1 January 1989 – 31 July 2018

- 20,064 exposures, 10,072 1st trimester exposures
- MACDP: Metropolitan Atlanta Congenital Defects Program
- TBDR: Texas Birth Defects Registry

Drug-Specific Overall Birth Defect Rates*

- For drug to be included for comparison with population rates, must meet threshold of having ≥ 200 1st trimester exposed pregnancies
- No drug has 95% CI that significantly exceeds population comparisons with exception of nelfinavir and ddI, which exceed MACDP but not TBDR and have no specific defect pattern

*For drug to be included for comparison with population rates, must meet threshold of having ≥ 200 1st trimester exposed pregnancies

Prevalence of Birth Defects (95% CI): 1 January 1989 – 31 July 2018

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Botswana Tsepamo Study – Birth Surveillance

Zash R. IAS, Amsterdam July 2018 Late Breaker

- Designed to evaluate the risk of neural tube defects (NTDs) with preconception efavirenz exposure.
- Prospective birth outcomes surveillance for major surface birth defects, 8 large maternity wards, population-based (45% of Botswana births)
- Trained hospital-based midwives do surface exam of newborn
- If abnormality, research assistant consents mother for photo
- Medical geneticist reviews, blinded to exposure
- Good denominator with control; can distinguish between ART regimens
  - HIV-uninfected
  - HIV-infected ART preconception or started in pregnancy

NTD Prevalence Difference by Exposure

May 2018:
- 86 NTDs in 88,755 births, prevalence 0.1%
- Highest among stillbirths (1%) vs live birth (0.07%)
Neural Tube Defects with Preconception DTG
Zash R. IAS, Amsterdam July 2018 Late Breaker

- NTDs with preconception DTG were different phenotypes:
  - Frontal encephalocele (live birth)
  - Anencephaly (live birth, neonatal death)
  - Lumbar myelomeningocele (live birth, neonatal death)
  - Iniencephaly (stillbirth)
- No geographic clustering (3 different sites); no predisposing factors (e.g., no anti-epileptic drugs, gestational diabetes); no prenatal folate
- Botswana does not have folate food fortification

NTD Prevalence Difference by Exposure: July 2018 Update

July 2018 Update (Zash IAS 2018 Amsterdam):
2 new NTD
- 1 HIV-uninfected
- 1 DTG start during pregnancy (8 wk GA)
NTD Prevalence Difference by Exposure: July 2018 Update

July 2018 Update (Zash IAS 2018 Amsterdam):
2 new NTD
- 1 HIV-uninfected
- 1 DTG start during pregnancy (8 wk GA)

→ Sept 2018: Expanded surveillance to 18 sites, estimate >1400 births with exposure to DTG from conception by mid-2019

How Do Tsepamo Study Findings Compare to NTD Prevalence in Sub-Saharan Africa?

Birth Defect Surveillance Uganda
Barlow-Mosha et al CROI 2019 Seattle Poster 743

- 4 hospital defect surveillance: 69,766 births (6,494 to HIV+ women, 80% on TDF-3TC-EFV (no DTG used in country yet)

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<tr>
<th></th>
<th>#</th>
<th>HIV-</th>
<th>HIV+</th>
<th>NTD% births HIV- women</th>
<th>NTD% births HIV+ women</th>
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<tbody>
<tr>
<td>NTD</td>
<td>71</td>
<td>66</td>
<td>5</td>
<td>0.11% (0.08-0.13)</td>
<td>0.07% (0.03-0.17)</td>
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Tsepamo NTD prevalence:
- HIV- women: 0.09% (95% CI 0.07-0.12%)
- HIV+ EFV preconception: 0.05% (95% CI 0.02-0.15%)
Recent Data on NTD and Other Integrase Strand Transfer Inhibitor (InSTI) Drugs

Antiretroviral Pregnancy Registry
Prospective Cases of InSTI Exposure
Albano J et al. CROI, Seattle March 2019 Abs. 747

<table>
<thead>
<tr>
<th>Overall birth defects</th>
<th>Preconception</th>
<th>1st Trimester</th>
<th>2nd/3rd Trimester</th>
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<tr>
<td>Defects/live birth</td>
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| Exposure to any InSTI | 16/604 (2.6%) | 4/135 (3.0%) | 17/452 (3.8%) |

| DTG*                  | 6/174 (3.4%)  | 2/55 (3.6%)  | 4/137 (2.9%)  |
| EVG                   | 5/186 (2.7%)  | 0/27 (0%)    | 0/57 (0%)     |
| RAL**                 | 5/244 (2.0%)  | 4/68 (5.9%)  | 13/290 (4.5%) |

Can be more than one organ system for a defect
No Neural Tube Defects
2 CNS: 1 (lissencephaly – neural migration disorder) with preconception DTG; 1 (ventriculomegaly with 2nd/3rd trimester DTG exposure.
Face, ear, nose, neck: 2
Cleft lip/palate: 2
Respiratory: 1
Cardiac/circulatory: 11
Lower GI: 1
Renal: 4
Musculoskeletal: 8
Chromosome abnl: 2
Other organ systems: 1
Specified syndromes 1

Earliest Trimester of Exposure – Prospective Cases*
### Antiretroviral Pregnancy Registry

**Prospective Cases of InSTI Exposure**

Albano J et al.  CROI, Seattle March 2019 Abs. 747

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**Can be more than one organ system for a defect**

**No Neural Tube Defects**

- 2 CNS: 1 (lissencephaly – neural migration disorder) with preconception DTG; 1 (ventriculomegaly with 2nd/3rd trimester DTG exposure).
- Face, ear, face, neck: 2
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- Cardiac/circulatory: 11
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- Renal: 4
- Musculoskeletal: 8
- Chromosome abnl: 2
- Other organ systems: 1
- Specified syndromes 1

While no neural tube defects with preconception DTG as of July 2018, there are only 174 reported preconception DTG exposures in APR, most from countries with food folate fortification.

**Glasgow HIV Conf Oct 2018: Gilead review of safety database on pregnancies with EVG or BIC exposure:**
- Prospective: 155 preconception EVG, no NTD
- 18 preconception BIC, no NTD

**Poster 745: Merck review of safety database on pregnancies with RAL exposure:**
- Prospective: 456 preconception RAL, no NTD

**Poster 744: French Perinatal Study reviewed 218 preconception exposures to RAL (included in Merck report), 41 to DTG and 42 to EVG, no NTD reported**
When Will We Have More Data?

- Global effort ongoing to increase denominator of DTG preconception exposures and refute or confirm the signal.
  - Tsepamo expanded to 18 sites (>90% population births)
  - Data from other countries that have introduced DTG
  - Observational studies
  - DTG clinical trials where pregnancy occurred
  - Antiretroviral Pregnancy Registry

To Refute NTD Signal, How Many Preconception Exposures are Needed to See Lower 95% CI for NTD with Preconception DTG Overlap? NTD Prevalence Observed with Preconception Non-DTG Exposure?

Data Sources Outside of Tsepmamo

- Literature/abstract review of prospective data has not identified any further NTD with preconception DTG exposure; however, all reports come from higher income countries, most with food folate fortification, and few preconception exposures.

- Largest data bases are Antiretroviral Pregnancy Registry (N=366, **174 preconception**), UK/Ireland surveillance cohort (N=176, **92 preconception**), and Brazil case-control study (N=324 preconception) (currently ~590 at end 2018 in addition to expected 1400 in Tsepmamo).

When Will We Have More Data?

- Best data will likely be from the Botswana Tsepmamo study in mid-2019 (N>1400), hopefully combined with other good quality observational data like APR.

- In the interim, it is important to recognize
  - Neural tube defect risk is not zero in the absence of drug
  - The risk, should it be confirmed, is still relatively small: 1 in 1000 in the general population with potential increase to 7 in 1000
New Antiretroviral Drugs Continue to Be Approved with Limited to No Safety Data in Pregnancy

- Dolutegravir approved in 2013, but >200 exposures not available until 2018! Minimal to no data on many preferred drugs in non-pregnant adults (e.g. bictegravir, tenofovir alafenamide).
- For rare events which require large numbers of exposures to detect (like NTD, prevalence <0.1%), only post-marketing surveillance will be able to evaluate the safety of new drugs.
- Critically important we continue to collect prospective non-biased data on new drugs – so it doesn’t take years after the drug is first approved and widely used in non-pregnant individuals to have sufficient data on safety in pregnancy.

So How Do We Make Decisions Regarding Use of ARVs in Pregnancy?

There are no simple/easy answers…
• The Perinatal Panel is often faced with making recommendations for which there are insufficient pregnancy PK data and/or inadequate fetal safety data on exposure preconception and early in pregnancy.

• To ensure that pregnant women are not denied the best available ART regimens, the Panel uses a graded approach to making recommendations for antiretroviral regimens to use during pregnancy.

U.S. Perinatal Guidelines Panel

• Preferred drugs are those with most complete information on safety/PK during pregnancy.

• Alternative drugs are preferred for nonpregnant adults, have incomplete pregnancy data, but no specific obvious safety/PK concerns.

• Insufficient Data to Recommend are drugs with little or no pregnancy data and considered to have insufficient data for initiation in pregnancy, but for which there are no specific data to recommend discontinuing in women who become pregnant while taking them and are suppressed.
Not Recommended drugs have known inferior virologic efficacy; potentially serious maternal or fetal safety concerns; or PK data demonstrating low drug levels in the 2\textsuperscript{nd}/3\textsuperscript{rd} trimester (e.g., ATV/COBI, DRV/COBI, EVG/COBI) which could lead to viral rebound.

- For women who become pregnant on drugs not recommended because of low levels in later pregnancy but are currently suppressed, the Panel notes one could continue the regimen with more frequent viral load monitoring in later pregnancy.

Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive:

<table>
<thead>
<tr>
<th>ART Regimen Component</th>
<th>ART for Pregnant Women Who Have Never Received ARV Drugs and Who Are Initiating ART for the First Time</th>
<th>Continuing ART for Women Who Become Pregnant on an ART Regimen that has been Well Tolerated and Virologically Suppressive (^a)</th>
<th>ART for Pregnant Women Who Have Received ARV Drugs in the Past and Who Are Restarting ART (^b)</th>
<th>New ART Regimen for Pregnant Women Whose Current ART is Not Well Tolerated and/or is not Resulting in Virologic Suppression (^c)</th>
<th>ART for Nonpregnant Women Who Are Trying to Conceive (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTIs Used in combination with a dual-NRTI backbone (^e)</td>
<td>DTG</td>
<td>Not recommended during the first trimester (^f)</td>
<td>Consider continuation with counseling or switch during the first trimester (^g)</td>
<td>Not recommended during the first trimester (^h)</td>
<td>Not recommended during the first trimester (^i)</td>
</tr>
</tbody>
</table>

\(^a\) The following are interim recommendations pending additional data. DTG is a preferred INSTI for pregnant women after the first trimester, based on available PK, safety, and efficacy data. However, because of concerns about congenital anomalies that may have occurred both during and after nasal tube closure (which occurs around 4 weeks post-conception and 5 weeks after the last menstrual period), the Panel does not recommend the use of DTG in the first trimester. The first trimester is less than 14 weeks (up to 13.67 weeks) gestational age by last menstrual period.

\(^b\) This is intended to be a conservative, interim recommendation and will be revised, if indicated, as additional data become available in 2019. Although DTG is not FDA-approved for use in the first trimester, some Panel members would consider using DTG at 12 weeks gestational age by last menstrual period on an individual patient basis. For women who become pregnant while taking DTG and who present to care during the first trimester, providers should counsel patients about the risk of neural tube defects and the risk of viral rebound (with associated risk for perinatal transmission) if changes are made to the ART regimen. For more information, see Interim Panel Recommendations Regarding the Use of Dolutegravir at the Time of Conception in Preconception Counseling and Care and Interim Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs During Pregnancy.
Take-Away Messages and Resources

- When considering drug use in women of childbearing potential need to include possibility of pregnancy & preconception exposure.
- Optimally, phase I safety/PK of new drugs in pregnancy should be done before drug approval and widespread use.
- However, for rare events, post-marketing surveillance will be critical.

Reporting your pregnant patients on ART to the Antiretroviral Pregnancy Registry is critical post-marketing safety surveillance for ARV drugs. http://apregistry.com/

US Perinatal Guidelines Panel is a good source of latest information on ARV drugs in pregnancy. AIDSInfo.nih.gov

The National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free consultation to providers caring for women with HIV and their infants.

Thank you for your attention!