ART in Women and Contraception: InSTIs, Comorbid Conditions, and Other Current Issues

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe data on ARVs when used during pregnancy
  - Dosing, toxicity, efficacy
- Monitor DTG use during pregnancy
  - Neural tube defects: what do we know
- Discuss other current issues in HIV+ pregnant women
  - What does the community say about their choices?

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Data on ARV use in pregnancy

- No prelicensure studies for ARVs
- Of 32 approved ARVs mean lag between approval and data in pregnancy is about 6 years
  - NOT GOOD!
- What do we need to know?
  - Dosing by trimester
  - Dosing at delivery
  - Washout in babies
  - Lactation
  - ..and the list goes on
- Importantly women metabolize ARVs different than men…so the playing ground was never equal

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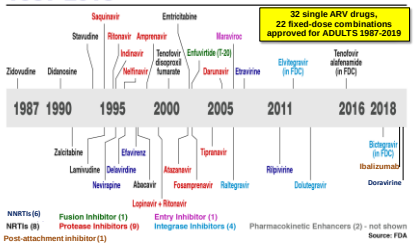
ADULT
Antiretroviral Drugs Approved by FDA, 1987-2018



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Antiretroviral Drug Approvals in Adults and Children

- 25 of the 32 ARVs approved in adults are approved in children

→8 simultaneous approval adults/children;17 significant delay

Year approved adults		Year 1st approved pediatrics	
NRTI/NkRTI (9 counting TDF and TAF separately) 4/9 delayed, 1 not approved			
ABC	1998	1998	
AZT	1987	1990	+3 YEARS
ddI	1991	1991	
FTC	2003	2005	+2 YEARS
3TC	1995	1995	
ddC	1992	Not approved	
d4T	1995	1995	
TAF	2015 (≥12 yr & ≥35 kg)	2017	+2 YEARS
TDF	2001	2010	+9 YEARS
NNRTI (6) 3/6 delayed, 2 not approved			
EFV	1998	1998	
DLV	1997	Not approved	
ETV	2008	2012	+4 YEARS
NVP	1996	1998	+2 YEARS
RPV	2011	2015	+4 YEARS
DRV	2018	Not approved	

Year approved adults		Year 1st approved pediatrics	
Protease inhibitors (9) 5/9 delayed, 2 not approved			
ATV	2003	2008	+5 YEARS
DRV	2006	2008	+2 YEARS
F-APV	2003	2007	+4 YEARS
IDV	2004	Not approved	
LPV/r	2000	2000	
NFV	1997	1997	
RTV	1996	1997	+1 YEAR
SQV	1995	Not approved	
TPV	2005	2008	+3 YEARS
Entry & Fusion Inhibitors (3) 2/3 delayed			
T20	2003	2003	
MVC	2007	2016	+9 YEARS
Ibalizumab	2018	Not approved	
Integrase Inhibitors (4) 4/4 delayed			
BIC	Feb 7 2018	Not approved	
DTG	2013 (≥12 yr & ≥40 kg)	2016	+3 YEARS
EVG	2012 (≥12 yr & ≥35 kg)	2017	+5 YEARS
RAL	2007	2011	+4 YEARS
Pharmacologic Boosters (2 counting RTV) 1/1 delayed			
COBI	2015 (≥12 yr & ≥35 kg)	2017	+2 YEARS

→Delay adult-pediatric approval was 1-9 yrs (mean 3.8 yrs)

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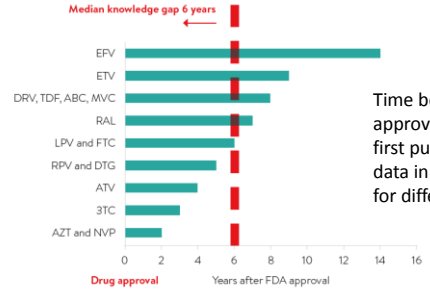

Time between approval and the first published PK data in pregnancy for different ARVs

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Label approval in pregnancy

- Only ZDV is approved for prevention of mother to child transmission
- Pregnant women excluded from ARV drug development programs
- No pregnancy data when initial labels come out:

  'Use during pregnancy only if the potential benefit justifies the potential risk'
  - Complera changed in 2018 to Pregnancy: Monitor viral load closely during pregnancy as rilpivirine exposures were generally lower during pregnancy
  - But still no approval for use in pregnancy

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So, what do we know about dosing ARVS? -NRTIs

Abacavir	No change in dose
Emtricitabine	No change in dose
Lamivudine	No change in dose
TAF	No change in dose
TDF	No change in dose: AUC is lower in third trimester than postpartum, but trough levels are adequate.
Zidovudine	No change in dose

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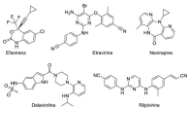
NNRTIs

Efavirenz	No dosage adjustments; AUC is decreased during the third trimester compared with postpartum, but nearly all 3rd trimester participants exceeded target exposure.
Nevirapine	No dosage adjustments
Etravirine	No dosage adjustments
Doravirine	*Insufficient data*
Rilpivirine	*Insufficient data*



- While RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied
- 2-drug regimens (e.g., RPV/DTG FDC) are not recommended in pregnancy

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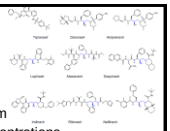
Protease inhibitors



- Atazanavir
  - Only ritonavir-enhanced atazanavir should be used
  - AUC reduced in 2nd and 3rd trimesters compared with postpartum
  - Co-administration with tenofovir may further reduce trough concentrations
  - ATV/COBI is **not recommended for use in pregnancy**. For women who become pregnant while taking ATV/COBI, consider switching to a more effective, recommended regimen.
- Darunavir
  - Once daily use not recommended. Also not recommended is DRV/c
  - Can use twice daily DRV(600)/r(100), but **not daily** DRV (800)/r(100)
- Fosamprenavir
  - Only twice daily ritonavir (100) enhanced fosamprenavir (700) should be used during pregnancy
  - Take with food

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Integrase inhibitors

- Raltegravir
  - No dosage adjustments required
- Elvitegravir/cobicistat
  - EVG/*COBI* is not recommended for use in pregnancy.
  - PK studies in women who received EVG/COBI demonstrated significant reduction in EVG plasma exposure during pregnancy.
  - As an extra precaution: doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.
- Bictegravir
  - *No data!!*
- Dolutegravir
  - No dosage adjustments during pregnancy

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Other ARVs…

- Use of *COBI-boosted* ATV, DRV, or EVG is **not recommended** in pregnancy
  - Subtheraputic Cobicistat levels
- Maraviroc
  - A PK study in human pregnancy demonstrated a 20% to 30% overall decrease in AUC, but Ctrough exceeded the recommended minimal concentration of 50 ng/mL.
  - Standard adult dosing adjusted for concomitant ARV use appears appropriate.
- Enfuvirtide
  - *Insufficient data* to make dosing recommendation

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ART Regimen Component Note: ARV drugs and ARV regimens are listed alphabetically within drug classes and recommendation categories	ART for Pregnant Women Who Have Never Received ARV Drugs and Who Are Initiating ART for the First Time	Continuing ART for Women Who Become Pregnant on an ART Regimen that has been Well Tolerated and Virologically Suppressive[a]	ART for Pregnant Women Who Have Received ARV Drugs in the Past and Who Are Restarting ART[b]	New ART Regimen for Pregnant Women Whose Current ART is not Well Tolerated and/or is not Resulting in Virologic Suppression[a]	ART for Nonpregnant Women Who Are Trying to Conceive[c,d]
NRTIs[e]					
ABC	Preferred	Continue	Preferred	Preferred	Preferred
FTC	Preferred	Continue	Preferred	Preferred	Preferred
3TC	Preferred	Continue	Preferred	Preferred	Preferred
TDF	Preferred	Continue	Preferred	Preferred	Preferred
ZDV	Alternative	Continue	Alternative	Alternative	Alternative
TAF	Insufficient data[f]	Continue	Insufficient data	Insufficient data	Insufficient data
INSTIs					
Used in combination with a dual-NRTI backbone[e]					
DTG These are interim recommendations, pending the availability of additional data.[g]	Not recommended during the first trimester[h] Preferred after the first trimester	Consider continuation with counseling or switch during the first trimester[h] Continue if patient is in the second or third trimester	Not recommended during the first trimester[h] Preferred after the first trimester	Not recommended during the first trimester[h] Preferred after the first trimester	Not recommended[h]
RAL	Preferred	Continue	Preferred	Preferred	Preferred
BIC	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
EVG/COBI	Not recommended[i]	Consider switch, or continue with frequent viral load monitoring[j]	Not recommended[i]	Not recommended[i]	Not recommended[i]
PIs					
Used in combination with a dual-NRTI backbone[e]					
ATVr	Preferred	Continue	Preferred	Preferred	Preferred
DRVr	Preferred	Continue	Preferred	Preferred	Preferred
LPVr	Alternative	Continue	Alternative	Alternative	Alternative
ATV/COBI	Not recommended[i]	Consider altering the regimen, or continuing the same regimen with frequent viral load monitoring[j]	Not recommended[i]	Not recommended[i]	Not recommended[i]
DRV/COBI	Not recommended[i]	Consider altering the regimen, or continuing the same regimen with frequent viral load monitoring[j]	Not recommended[i]	Not recommended[i]	Not recommended[i]

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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What happens during pregnancy?

- Pregnant women experience unique physiological changes that may result in clinically significant alterations in drug PK and PD
- These changes begin early in gestation and include:
  - (a) ⇑GI transit time that can *alter the rate and extent* of drug absorption
  - (b) large changes in total body water and fat, increasing drug distribution volume
  - (c) ⇓albumin and increased alpha-1 acid glycoprotein (AAG) concentrations that may cause changes in drug protein binding
  - (d) ⇑cardiac output, ventilation, and hepatic and renal blood flow which may impact drug metabolism and elimination
  - (e) ⇑concentrations of endogenous glucocorticoids that may affect the activity of hepatic enzyme systems that regulate drug metabolism

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How do we find out about toxicity/teratogenic effects?

- Preclincial; animal studies
  - Need 2 sets of animal data to get FDA approval
- Not all animal models mimic human pregnancy models
  - Outcomes from thalidomide, valproate, DES only noted when pregnant women were given drug
  - Different animal models available and only one was used…
- Even when a toxicity is noted in an animal model, it does not predict a human teratogenic effect
  - Efavirenz had CNS toxicity in monkeys, but not humans
- So a negative animal tox test is somewhat reassuring, but gaps exist…

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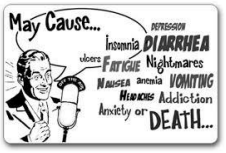
Questions we need to ask ourselves

- Its not just:
  - Which ARV
  - What dose
- What do we consider a toxicity
- Synergistic toxicity
- Uncommon toxicity events



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So, lets think about toxicities

- Toxicities to mom
  - Heme and chemistry abnormalities
  - Other toxicities:
    - Preeclampsia
    - Gestational diabetes
    - Others?
- Premature/Preterm delivery
  - <37 weeks is considered preterm!
    - <28 week is extremely preterm, 28-32 very preterm, 32-37 late preterm
  - 15 million babies born preterm every year
  - 1 in 9 babies born in US is preterm

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Data from PROMISE

- 3 treatment arms:
- Zidovudine plus single-dose nevirapine with 6 to 14 days of tenofovir and emtricitabine post partum (zidovudine alone)
- Zidovudine, lamivudine, and lopinavir–ritonavir (zidovudine-based ART)
- Tenofovir, emtricitabine, and lopinavir–ritonavir (tenofovir-based ART)
  - preterm delivery before 37 weeks was more frequent with zidovudine-based ART than with zidovudine alone (20.5% vs. 13.1%, P<0.001)
  - Tenofovir-based ART was associated with higher rates than zidovudine-based ART of very preterm delivery before 34 weeks (6.0% vs. 2.6%, P=0.04) and early infant death (4.4% vs. 0.6%, P=0.001)
  - The rate of HIV-free survival was highest among infants whose mothers received zidovudine-based ART

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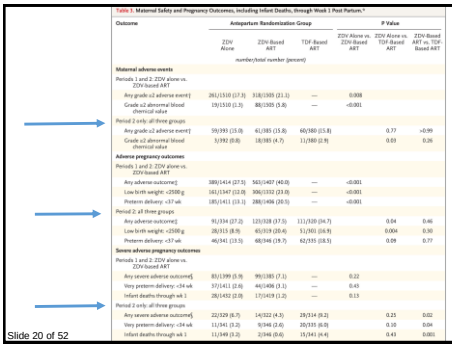

Table 3. Maternal Safety and Pregnancy Outcomes, Including Infant Deaths, through Week 1 Post Partum.*

Outcome	Antepartum Randomization Group			P Value		
	ZDV Alone	ZDV-Based ART	TDF-Based ART	ZDV Alone vs. ZDV-Based ART	ZDV Alone vs. TDF-Based ART	ZDV-Based ART vs. TDF-Based ART
	number/total number (percent)					
Maternal adverse events						
Periods 1 and 2: ZDV alone vs. ZDV-based ART						
Any grade ≥2 adverse event†	261/1510 (17.3)	318/1505 (21.1)	—	0.008		
Grade ≥2 abnormal blood chemical value	19/1510 (1.3)	88/1505 (5.8)	—	<0.001		
Period 2 only: all three groups						
Any grade ≥2 adverse event†	59/393 (15.0)	61/385 (15.8)	60/380 (15.8)		0.77	>0.99
Grade ≥2 abnormal blood chemical value	3/392 (0.8)	18/385 (4.7)	11/380 (2.9)		0.03	0.26
Adverse pregnancy outcomes						
Periods 1 and 2: ZDV alone vs. ZDV-based ART						
Any adverse outcome‡	389/1414 (27.5)	563/1407 (40.0)	—	<0.001		
Low birth weight: <2500 g	161/1347 (12.0)	306/1332 (23.0)	—	<0.001		
Preterm delivery: <37 wk	185/1411 (13.1)	288/1406 (20.5)	—	<0.001		
Period 2: all three groups						
Any adverse outcome‡	91/334 (27.2)	123/328 (37.5)	111/320 (34.7)		0.04	0.46
Low birth weight: <2500 g	28/315 (8.9)	65/319 (20.4)	51/301 (16.9)		0.004	0.30
Preterm delivery: <37 wk	46/341 (13.5)	68/346 (19.7)	62/335 (18.5)		0.09	0.77
Severe adverse pregnancy outcomes						
Periods 1 and 2: ZDV alone vs. ZDV-based ART						
Any severe adverse outcome§	83/1399 (5.9)	99/1385 (7.1)	—	0.22		
Very preterm delivery: <34 wk	37/1411 (2.6)	44/1406 (3.1)	—	0.43		
Infant deaths through wk 1	28/1452 (2.0)	17/1419 (1.2)	—	0.13		
Period 2 only: all three groups						
Any severe adverse outcome§	22/329 (6.7)	14/322 (4.3)	20/314 (6.2)		0.25	0.02
Very preterm delivery: <34 wk	11/341 (3.2)	9/346 (2.6)	20/335 (6.0)		0.10	0.04
Infant deaths through wk 1	11/349 (3.2)	2/346 (0.6)	15/341 (4.4)		0.43	0.003

November 3, 2016
N Engl J Med 2016; 375:1726-1737

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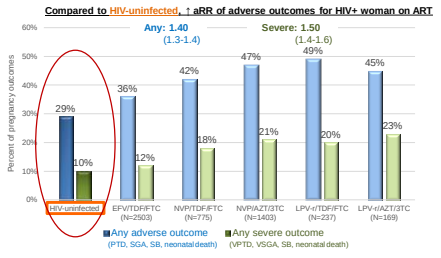
Regardless of ART Regimen, Pregnancy Outcomes Were Worse in HIV+ Women On ART than HIV-Uninfected Women

Zash R et al. JAMA Pediatr. 2017;171:e172222



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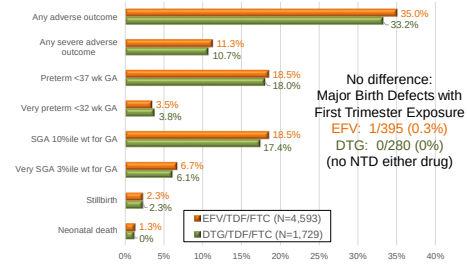
When Started During Pregnancy, No Difference Pregnancy Outcomes EFV vs DTG-Based ART

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



No difference:
Major Birth Defects with First Trimester Exposure
EFV: 1/395 (0.3%)
DTG: 0/280 (0%)
(no NTD either drug)

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Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Dolutegravir (DTG) Tivicay **DTG/RPV Juluca** (DTG/ABC/3TC) Triumeq	DTG (Tivicay) Tablet • DTG 50 mg tablet DTG/RPV (Juluca) • DTG 50 mg plus RPV 25 mg tablet DTG/ABC/3TC (Triumeq) • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet	Standard Adult Dose: *In ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) Patients* DTG (Tivicay) • 1 tablet once daily, without regard to food DTG/RPV (Juluca) • 1 tablet once daily with food DTG/ABC/3TC (Triumeq) • 1 tablet once daily, without regard to food *ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) If Given with EFV, FPV/r, TPV/r, or Rifampin, or Integrase Inhibitor-Experienced* DTG (Tivicay) • 1 tablet twice daily, without regard to food PK in Pregnancy: • AUC may be decreased during the third trimester compared with postpartum, but good viral suppression observed in third-trimester recipients. Dosing in Pregnancy: • No change in dose indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC, RPV)	High placental transfer to fetus.† No evidence of teratogenicity in mice, rats, or rabbits. Preliminary data suggest a possible increased risk of NTDs in infants born to women who initiated DTG prior to pregnancy and were receiving it at the time of conception. DolutegravirDTG **should not be initiated** during the first trimester of pregnancy (less than 14 weeks [up to 13 6/7 weeks] gestational age by LMP).† For more information see Interim Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy To maximize DTG absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins	December 7, 2018
Biktarvy (EVG/COBI/FTC/TAF) Genvoya **Vitekta** **Note:** As of October 2017 Vitekta (i.e., EVG as a single-entity formulation) is no longer available (EVG/COBI/FTC/TAF) Genvoya (EVG/COBI/FTC/TDF) Stribild	EVG/COBI/FTC/TAF (Genvoya) • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet EVG/COBI/FTC/TDF (Stribild) • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg tablet	Standard Adult Dose (Genvoya and Stribild): • 1 tablet once daily with food Dosing in Pregnancy: • Insufficient data to make dosing recommendation PK in Pregnancy: • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy.	Evidence of high placental transfer of EVG and low transfer of COBI.† Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. EVG/COBI **is not recommended** for use in pregnancy. For women who become pregnant while taking EVG/c, consider switching to a more effective, recommended regimen. If an EVG/ COBI regimen is continued, doses should not be administered within 2	December 7, 2018

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce

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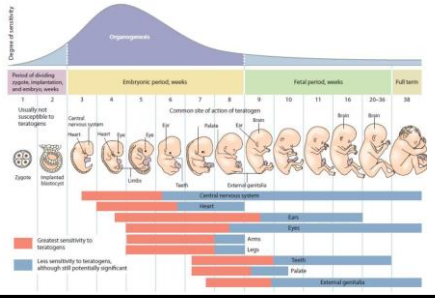
Timing of *In Utero* Medication Exposure and Fetal Risk



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Timing is everything

- Prenatal exposure
- 1st trimester
  - Toxoplasma infection in first trimester is severe, subclinical in 3rd trimester
  - Rubella in first trimester triad of congenital rubella
    - cardiac, cochlear, cataracts
- Week 20: smoking and IUGR
- Week 24: Alcohol and fetal alcohol syndrome
- 3rd trimester
  - Herpes; worse outcomes in late infection of fetus

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What are the events leading up to NTD?

- NTD is a spectrum of maldevelopment affecting the neural tube, associated meninges and axial skeleton
- Depending onset time, can affect different regions of neural tube and non-neural organs

Two types: Open and Closed

- Open: arise during process of primary neurulation, primary failure of neural tube closure (~17-20 post-fertilization days); tissues of unclosed neural tube (brain, spinal cord) are exposed.
- Most frequent open NTD are anencephaly and open spina bifida.
- Closed: post-neurulation defect which is covered by skin.
  - Encephaloceles and other skin covered lesions are examples of closed NTD

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Multifactorial Pathogenesis of Neural Tube Defects

- Development of the neural tube is a multi-step process strictly controlled by genes but modulated by a host of environmental factors (including drugs)
- Exact etiology remains poorly understood
- It is generally agreed that most NTD cases are multifactorial
  - genetic sensitivity to their etiology
  - environmental risk factors
- Occurrence NTD in abortuses and stillbirths is many-fold higher than that in live births

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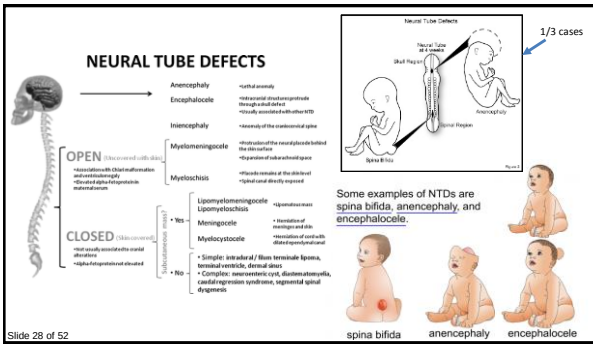

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Background on NTD

- The incidence of myelomeningocele is 1 case in 1200–1400 live births
- NTDs are among the most common birth defects globally
  - marked geographical variation
- A study of long-term trends in prevalence of NTDs in Europe found the pooled total prevalence of NTD during the study period was 9.1 per 10,000 births
- Prevalence of NTD fluctuated slightly but without an obvious downward trend
- Currently, the highest reported incidence is in Northern China
  - 3.7 cases per 1000 live births

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Genetic factors?

- Multifactorial genetic and environmental factors have been implicated in the pathogenesis of neural tube defects (NTDs)
- The most common historical cause of NTDs globally is folate deficiency in the maternal diet
- A slight female predominance, and the higher incidence in certain ethnic groups and in the offspring of consanguineous marriages, have suggested a genetic basis for NTDs.
- Chromosomal abnormalities (trisomy 13, 18, 21) are also associated with NTDs
- Interestingly, concordance between monozygotic twins is higher than dizygotic twins

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Environment?

- Possible environmental factors include geographic location, season of conception, socioeconomic class, maternal diabetes, maternal age, zinc and folate deficiencies, maternal alcohol abuse, maternal use of valproate, and intrauterine hyperthermia
- Seasonal trends in the birth incidence of NTDs have historically been reported
- Anencephaly and spina bifida tend to occur more frequently in spring conceptions
- This is especially true in areas where the risk is high; however, most US studies failed to demonstrate such variations

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Folate?

- The recommended intakes are **0.4 mg/d**
  - **4 mg/d** for those at high risk (prior NTD)
  - The addition of nutrients (notably folic acid, vitamin C, and riboflavin) to common foods, such as cereals and grain products, has significantly decreased the incidence of NTDs globally
  - Now it is about .5/1000 births
- Several research gaps remain:
  - identification of the mechanism by which the defect occurs and how folate ameliorates it;
  - characterization of the relative efficacy of food folate,
  - folic acid added to foods, and folic acid by itself;
  - delineation of the dose-response relations of folate and NTD prevention;
  - and more precise quantification of the dose needed to prevent recurrences.

- Whole methylation metabolism

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What if it's not just folate?

- Autoantibodies binding folate receptors and blocking the uptake of folates have been described more frequently in women with affected fetuses
- NTD mouse models unresponsive to folate:
  - Impaired thymidylate biosynthesis
  - adequate functioning of the methylation cycle is essential for cranial neural tube closure
  - high doses of methionine given during embryogenesis reduced NTD incidence
- Homocysteine, Vitamin B12 and Choline Pathways have also been implicated…

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Int J Environ Res Public Health. 2013 Sep; 10(9): 4352–4389.

Botswana HIV Birth Cohort

- Birth outcome surveillance at 8 government hospitals
- As of May 1, 2018, a total of 89,064 births had been included in surveillance;
  - 88,755 births (99.7%) had an infant surface examination that could be evaluated
  - 86 neural-tube defects identified (0.10% of births; 95% confidence interval [CI], 0.08 to 0.12)
  - 57% identified with a photograph, 43% identified by description
- Among the 426 infants born to HIV-positive women who had been taking **DTG** based antiretroviral therapy from the time of conception
  - **4/426 (0.94%) had a neural-tube defect.**
- The 4 mothers delivered in three geographically separated hospitals over a 6-month period; none had epilepsy or diabetes
- None received folate supplementation at conception

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What about the other ARV-treated cohorts in Botswana?

- In comparison, neural-tube defects occurred in 14 (**0.12%**) of 11,300 infants born to women who had been exposed to any non-dolutegravir antiretroviral therapy from the time of conception
  - 0 (0.00%) of 2812 infants born to women who had been exposed to dolutegravir treatment that was started in pregnancy
  - 61 (0.09%) of 66,057 infants born to HIV-uninfected women

Zash, R. September 6, 2018 N Engl J Med 2018; 379:979-981

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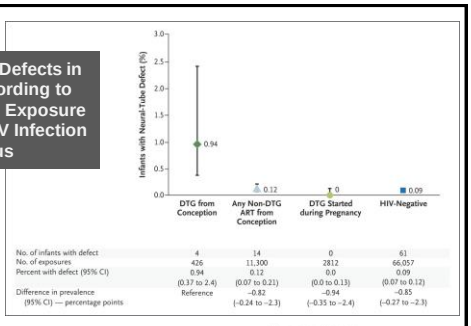
Neural-Tube Defects in Infants According to Maternal ART Exposure Group and HIV Infection Status



	DTG from Conception	Any Non-DTG ART from Conception	DTG Started during Pregnancy	HIV-Negative
No. of infants with defect	4	14	0	61
No. of exposures	426	11,300	2812	66,057
Percent with defect (95% CI)	0.94 (0.37 to 2.4)	0.12 (0.07 to 0.21)	0.0 (0.0 to 0.13)	0.09 (0.07 to 0.12)
Difference in prevalence (95% CI) — percentage points	Reference	−0.82 (−0.24 to −2.3)	−0.94 (−0.35 to −2.4)	−0.85 (−0.27 to −2.3)

R Zash et al. N Engl J Med 2018;379:979-981.

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- There were 7 additional infants with neural-tube defects in the full cohort:
  - 3 born to women who started non–dolutegravir (DTG) antiretroviral therapy (ART) during pregnancy
  - 3 to human immunodeficiency virus (HIV)–infected women who did not receive ART during pregnancy
  - 1 to a woman of unknown HIV infection status who did not receive ART.
- Among the women who had been receiving any non-DTG ART at conception:
  - 5675 were receiving tenofovir–emtricitabine–efavirenz,
  - 1446 tenofovir–emtricitabine–nevirapine,
  - 2439 zidovudine–lamivudine–nevirapine,
  - 452 tenofovir–emtricitabine–lopinavir–ritonavir,
  - 312 zidovudine–lamivudine–lopinavir–ritonavir,
  - 242 other specified ART regimens, and
  - 734 unspecified non-DTG regimens.
- Among the women receiving DTG treatment that was *started during pregnancy*
  - the median gestational age at the initiation of ART was 19 weeks
  - 75 women who started ART at a gestational age of less than 6 weeks

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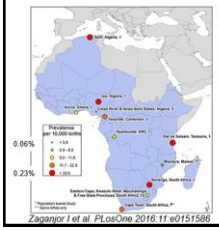
Any other country wide data?

- 43,293 births (4,634 HIV+ women, 77% on EFV ART) in Uganda
- Prevalence NTD: HIV-uninfected 0.09%, HIV+ 0.04%

P Musoke CROI 2018, abstract 829

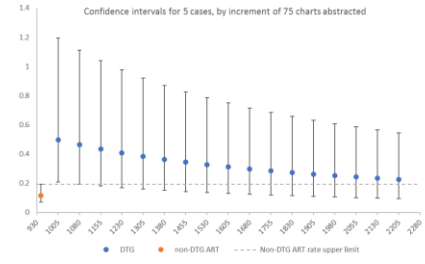


Zaganjor I et al. PLosOne 2016;11:e0151586

- African Region: Data from 11 studies from 8 countries analyzed
- Median prevalence of NTD in Africa was 0.12% (range 0.06% to 0.23%)

Estimated prevalence of NTD in 2015 globally was 0.19%
15–23/10,000 birth outcomes

NTD Cases with DTG Exposures



Estimations of neural tube defect frequencies and 95% confidence intervals by month with varying numbers of defects

Laurence Brunet, Edward Vonesh, Jennifer Fusco, Vani Vannappagari, Kimberly Smith, and Gregory Fusco

ViiV Healthcare, Research Triangle Park, NC

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Where do we go from here?

- ..We Wait…many groups are also looking at their data sets
- The ability to rule out an increase in a rare birth defect with an incidence of **.1%** would need about 2000 exposures to prove relatedness…
- More moms delivering at the 8 sites
  - No additional NTD among a further 170 preconception DTG exposures in Botswana (July 2018)
- Will need to add more sites
  - Next analysis occurring after March 2019
  - Coverage will increase to 72% of all births in Botswana
- Think about other possibilities…

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Population	First line	Second line	Third line
Women of child bearing potential	2 NRTIs + DTG* 2 NRTIs + EFV	2 NRTIs + ATV/r 2 NRTIs + LPV/r	DRV/r + DTG + 1-2 NRTIs Consider genotyping
Children	2 NRTIs + DTG 2 NRTIs + LPV/r 2 NRTIs + NNRTIs	2 NRTIs + ATV/r or LPV/r 2 NRTIs + DTG 2 NRTIs + DTG	

*= only if on contraceptives

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What about countries with high EFV resistance?

- Countries with pre-treatment resistance to EFV or nevirapine (NVP) at 10% or above should urgently consider using an alternative regimen that does not contain non-nucleoside reverse- transcriptase inhibitors (NNRTIs).
- Choices:
  - DTG with consistent and reliable contraception for women and adolescent girls
  - Atazanavir/ritonavir (ATV/r)

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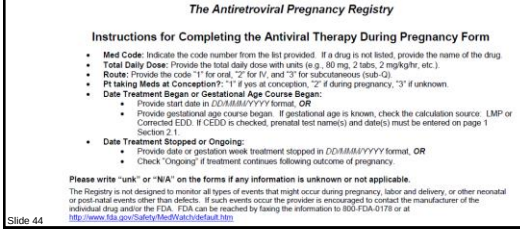
What about passive reporting of adverse events?

- ARV pregnancy registry: http://www.apregistry.com/
- Started in 1990



The Antiretroviral Pregnancy Registry

Instructions for Completing the Antiviral Therapy During Pregnancy Form

- **Med Code:** Indicate the code number from the list provided. If a drug is not listed, provide the name of the drug.
- **Total Daily Dose:** Provide the total daily dose with units (e.g., 80 mg, 2 tabs, 2 mg/kg/hr, etc.).
- **Route:** Provide the code "1" for oral, "2" for IV, and "3" for subcutaneous (sub-Q).
- **Pt taking Meds at Conception?:** "1" if yes at conception, "2" if during pregnancy, "3" if unknown.
- **Date Treatment Began or Gestational Age Course Began:**
  - Provide start date in *DD/MMM/YYYY* format, ***OR***
  - Provide gestational age course began. If gestational age is known, check the calculation source: LMP or Corrected EDD. If CEDD is checked, prenatal test name(s) and date(s) must be entered on page 1 Section 2.1.
- **Date Treatment Stopped or Ongoing:**
  - Provide date or gestation week treatment stopped in *DD/MMM/YYYY* format, ***OR***
  - Check "Ongoing" if treatment continues following outcome of pregnancy.

Please write "unk" or "N/A" on the forms if any information is unknown or not applicable.

The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post-natal events other than defects. If such events occur the provider is encouraged to contact the manufacturer of the individual drug and/or the FDA. FDA can be reached by faxing the information to 800-FDA-0178 or at http://www.fda.gov/Safety/MedWatch/default.htm

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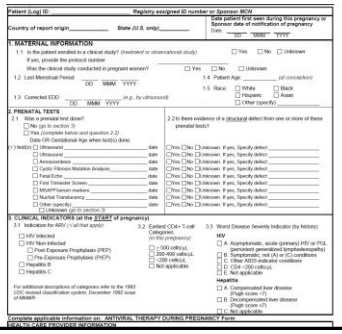

Telephone:
1-800-258-4263 (US and Canada)
+32-2-714-5028 (Europe)

FAX:
1-800-800-1052 (US, Canada)
+32-2-714-5024 (Europe)

Email:
SM_APR@INCResearch.com

Have we seen any NTD in registry?

- Due to the narrow exposure window of interest for neural tube defects (the neural tube closes by 28 days postconception), the APR is providing the below supplemental data regarding exposure to InSTIs (dolutegravir, elvitegravir, raltegravir)
- Neural tube defects have not been observed among the 688 periconception InSTI exposures reported to date:
  - 201 dolutegravir
  - 207 elvitegravir
  - 280 raltegravir periconception exposures.

Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2018. Wilmington, NC: Registry Coordinating Center; 2018. www.APRegistry.com

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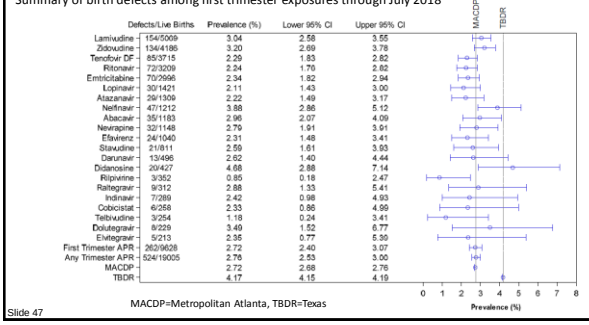
Summary of birth defects among first trimester exposures through July 2018



MACDP=Metropolitan Atlanta, TBDR=Texas

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What has the IMPAACT network done?

- IMPAACT 1026:
  - licensed therapies used in HIV+ pregnant women
  - Version 10
- Intensive PKs
  - Over 25 ARV studied
- Over 1000 pregnant women evaluated
- 27 manuscripts

Class	P1026s Citations/Total # of PK Studies in Pregnancy* Citations	Percent of Data from P1026s
NRTI	3/19	16%
NNRTI	4/9	44%
PI	12/40	30%
INSTI	2/4	50%
Entry/Fusion	1/1	100%
PK Enhancers	2/3	67%

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What is IMPAACT's next study: 2026

- Component 1:Pregnant women living with HIV receiving oral ARVs and no TB treatment, and their infants:
  - Arm 1.1: Bictegravir (BIC) 50 mg q.d.
  - Arm 1.2: Doravirine (DOR) 100 mg q.d.
  - Arm 1.3: TAF 10 mg q.d. boosted with cobicistat
  - Arm 1.4: TAF 25 mg q.d. without boosting
  - Arm 1.5: TAF 25 mg q.d. boosted with cobicistat or ritonavir
- Component 2: Long-acting injectable formulation of cabotegravir (CAB LA)
- Component 3: Pregnant women living with HIV receiving ARVs and first-line TB treatment, and their infants
- Component 4: Pregnant women, including women living with HIV and HIV-uninfected women, receiving second-line TB treatment, and their infants

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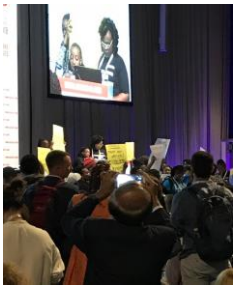
What does the community want?

- Use DTG across all ages, including women who want to become pregnant
  - Allow use of DTG once they become pregnant
- Increase availability of contraception
- Remember rape is never a choice
- Zimbabwe Women Living with HIV/Aids Forum

'DTG NOW for all women'
IAS 2018



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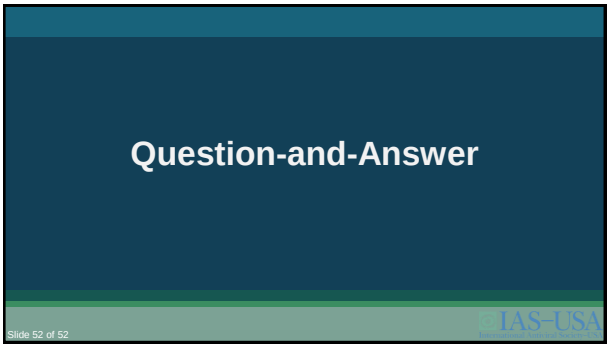
Question-and-Answer
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IAS–USA