AETC AIDS Education & Training Center Program Southeast

Update on the Perinatal Guidelines

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Disclosures

- The activity planners and speakers do not have any financial relationships with commercial entities to disclose.
- The speakers will not discuss any off-label use or investigational product during the program.
- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation

Objectives

- 1. Describe the current guideline recommendations for management of ARV therapy during pregnancy and at birth
- 2. Describe the recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential
- 3. List alternative ARV options for women of childbearing potential prescribed dolutegravir.

INTRODUCTION

Epidemiology

- At the end of 2013, ~1.2 million persons 13+ were living with HIV infection in the US
  - including ~161,200 (13%) persons whose infections had not been diagnosed
- In 2016: There were **39,782** new HIV diagnoses in the United States
  - 32,131 adult and adolescent **males** (13+)
  - 7,529 adult and adolescent **females**
  - 122 **children** < 13 years

Centers for Disease Control and Prevention. HIV Surveillance Report, 2016; vol. 28.
http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2017. Accessed 12-8-17.

Modes of Transmission

- **Blood**
- Semen
- **Vaginal and cervical secretions**
- **Breast milk**
- Outside of the body, HIV is very fragile and dies very quickly
  - Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered infectious unless they are visibly bloody

Epidemiology Continued

- There were 99 children diagnosed with HIV from the perinatal route in the US in 2016

Race	American Indian/ Alaskan	Asian	Black/ African American	Hispanic/ Latino	White	Multiple Races
Number of perinatal infections	0	3	64	15	13	4

Centers for Disease Control and Prevention. HIV Surveillance Report, 2016; vol. 28. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2017. Accessed 12-8-17.

Vertical Transmission

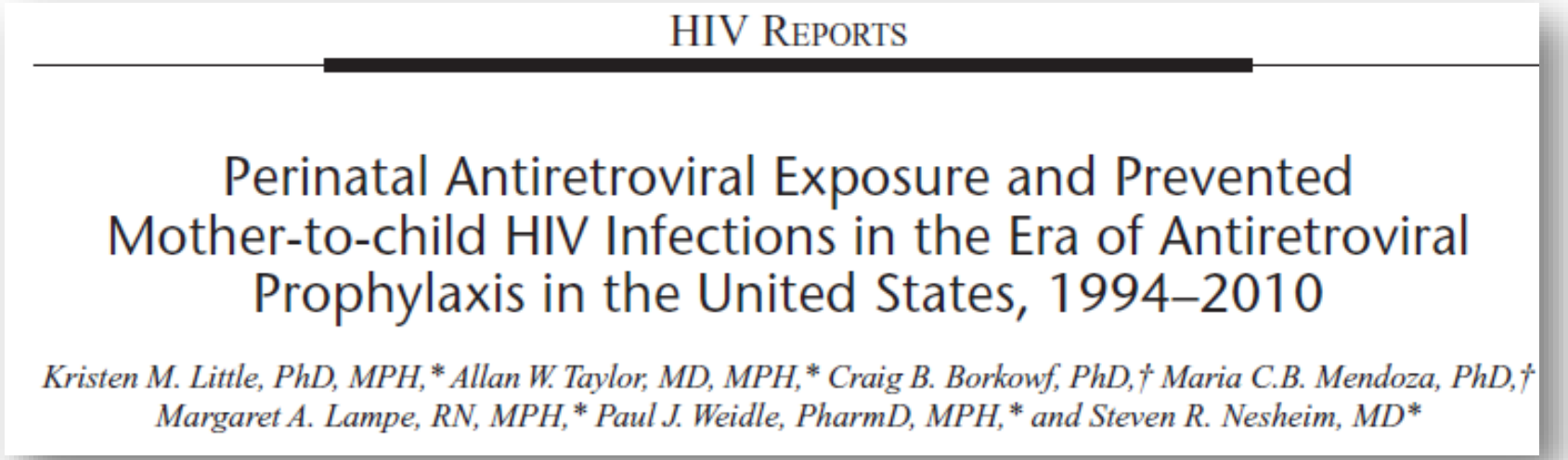
- Mother-to-child transmission of HIV (MTCT) is the transmission of HIV from an infected mother to her baby during pregnancy, labor/delivery and breastfeeding
- Also known as “vertical transmission” or “perinatal transmission”
- Most children with HIV acquired the virus through MTCT

Brief Historical Milestones MTCT

- In 1994 the USPHS recommend the use of zidovudine to reduce perinatal transmission (after “076” trial results)
- In 1997, combination ARV and elective C-section* recommended

  *Although no longer required if virally suppressed
- In 1999, opt-OUT HIV testing for pregnant women

Pediatr Infect Dis J. 2017;36:66-17



HIV REPORTS

Perinatal Antiretroviral Exposure and Prevented Mother-to-child HIV Infections in the Era of Antiretroviral Prophylaxis in the United States, 1994–2010

Kristen M. Little, PhD, MPH, Allan W. Taylor, MD, MPH,* Craig B. Borkowf, PhD,† Maria C.B. Mendoza, PhD,† Margaret A. Lampe, RN, MPH,* Paul J. Weidle, PharmD, MPH,* and Steven R. Nesheim, MD**

- Approx 187,157 women with HIV gave birth
- Approx 21,003 infants were perinatally infected
  - Peaked in 1991, declined steadily after 1993
- In the United States, there are approximately 8500 women living with HIV who give birth annually

Pediatr Infect Dis J. 2017;36:66-17

Rate of HIV Infection Among Children is Declining in the US

Table 11a. Diagnoses of HIV infection among children aged <13 years, by race/ethnicity, 2011–2016—United States

	2011		2012		2013		2014		2015		2016	
Race/ethnicity	**No.**	**Rate[a]**	**No.**	**Rate[a]**	**No.**	**Rate[a]**	**No.**	**Rate[a]**	**No.**	**Rate[a]**	**No.**	**Rate[a]**
American Indian/Alaska Native	0	0.0	0	0.0	0	0.0	3	0.7	2	0.4	0	0.0
Asian	8	0.3	13	0.5	16	0.6	12	0.5	9	0.4	8	0.3
Black/African American	118	1.6	168	2.3	122	1.7	112	1.6	87	1.2	78	1.1
Hispanic/Latino[b]	24	0.2	16	0.1	11	0.1	18	0.1	13	0.1	16	0.1
Native Hawaiian/Other Pacific Islander	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0	0	0.0
White	35	0.1	32	0.1	24	0.1	29	0.1	18	0.1	16	0.1
Multiple races	13	0.6	11	0.5	13	0.6	5	0.2	6	0.3	4	0.2
Total	**198**	**0.4**	**240**	**0.5**	**186**	**0.4**	**180**	**0.3**	**135**	**0.3**	**122**	**0.2**

Note. Data for the year 2016 are preliminary (subject to change) because they are based on only a 6-month reporting delay. Data for the year 2016 should not be used when assessing trends. Numbers less than 12, and rates and trends based on these numbers, should be interpreted with caution.

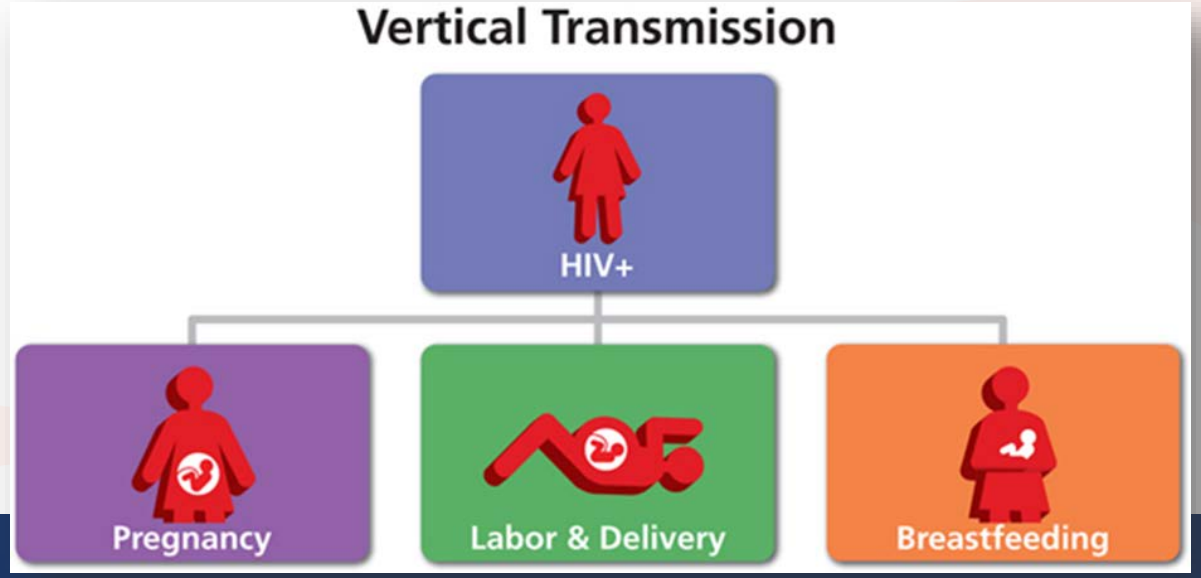
[a] Rates are per 100,000 population.

[b] Hispanics/Latinos can be of any race.

Centers for Disease Control and Prevention. HIV Surveillance Report, 2016; vol. 28. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2017. Accessed 12-8-17.

How Does Transmission Occur?

- For an HIV-positive woman not taking HIV medications, chance of passing the virus to her child
  - Range of 15 to 45% during pregnancy, labor and delivery
  - Breastfeeding carries an additional 35 to 40% chance of transmission



Current Strategies in the US

Pregnancy

- Treatment with ART to control the virus and make it undetectable

Labor and delivery

- Cesarean delivery

Neonatal/ infant

- Newborn ARV prophylaxis and avoidance of breastfeeding

CURRENT GUIDELINE RECOMMENDATIONS FOR MANAGEMENT OF ARV THERAPY DURING PREGNANCY AND AT BIRTH

Guideline Recommendations ABCs

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	**III:** Expert opinion

Preconception Counseling and Care for HIV-Infected Women of Childbearing Age

Discuss childbearing on an ongoing basis, *if age appropriate* (**AIII**)

Provide info about contraceptive methods (**AI**)

- Including info on drug-interactions with hormonal contraceptives (table 3 from guidelines)

All HIV-infected women contemplating pregnancy should be receiving antiretroviral therapy

- Viral load below the limit of detection prior to conception (**AII**)

PrEP for Serodiscordant Partner?

- In patients not able to achieve viral suppression (or unknown status) and attempting conception, PrEP for partner is recommended to reduce the risk of sexual transmission of HIV **(AI)**.
- Administration of PrEP for 30 days before and 30 days after conception for HIV-uninfected partners may offer additional protection (**CIII**)
  - Listed as optional when the partner is virally suppressed

General Principles Regarding Use of ARV Drugs During Pregnancy

All pregnant HIV-infected women should receive ART ASAP(**AI**)

Maternal antepartum and intrapartum (ARV) treatment/prophylaxis is needed as well as newborn ARV prophylaxis (**AI**)

Adherence to ARV should be emphasized (**AII**)

Antiretroviral Pregnancy Registry

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see http:// www.APRegistry.com) (**AIII**).

- For additional guidance, please contact the Perinatal HIV/AIDS Hotline at (888) 448-8765.

Patients on ART Prior to Pregnancy

- If virally suppressed ➡ continue regimen (**AII**)
  - **UNLESS** it contains didanosine, stavudine, or treatment-dose ritonavir
    - These regimens should initiate a change in therapy
    - Consider replacing drugs that have low drug exposure in pregnancy associated with potential increase in virologic failure (elvitegravir/cobicistat).
    - *Dolutegravir- updated guidance discussed later in presentation*
  - Although FDA recommends efavirenz to be avoided, studies in humans have not reproduced the neuro-tube defects seen in animal studies

ART Prior to Pregnancy Requiring Switches

More frequent virologic monitoring is warranted when an antiretroviral (ARV) regimen is altered during pregnancy **(CIII**)

The switch should be made to one of the preferred ARVs recommended in pregnancy (**BIII**)

Antiretroviral Drug Regimen for a Pregnant Woman

Multiple factors must be considered when choosing regimen including:

- Potential teratogenic effects and other short-and long-term adverse effects on fetuses or newborns including preterm birth, mutagenicity, and carcinogenicity.
- Experience with use in pregnancy
- Drug-drug interactions
- Genotypic resistance testing and prior ART use
- PK changes in pregnancy
- Potential maternal adverse effects
- Comorbidities
- Convenience

Considerations When Designing a Regimen

- Transplacental passage of ARV drugs is an important mechanism of infant pre-exposure prophylaxis
  - At least one NRTI agent with high placental transfer should be included as a component of the ART regimen
    - TDF, 3TC, FTC, ABC (all preferred with high placental transfer)
    - Zidovudine(AZT) has high placental transfer

Preferred Regimens

- 2 NRTI Backbone Plus
  - Raltegravir (twice daily is preferred) → Integrase inhibitor based regimen
    - Or
  - Darunavir/r (**must** be BID due to PK changes)
    - Or
  - Atazanavir/r (once daily option)

PI based regimens

Preferred NRTIs for Backbone

- Abacavir, emtricitabine, lamivudine and tenofovir disoproxil fumarate (TDF)
  - No changes to dosing recommended
  - Choose backbone similar to non-pregnant patients

- Tenofovir alafenamide has no PK studies in pregnancy and thus dosing recommendations do not exist

Atazanavir

Caution in pregnant patients with GERD due to DDIs

- *Must be boosted* 300 mg dose, ritonavir is *preferred*
  - Cobicistat has limited data in pregnancy
  - Once daily with food
- Not recommended in tx-experienced taking TDF and **H2 blockers**
- **Can not be given with proton pump inhibitors**
- Dosing *may* need to be increased in 2nd/3rd trimester if patient is ARV-experienced and taking either TDF or H2
  - Increase to the 400 mg dose, w/ 100 mg RTV

Darunavir

- *Must* be boosted with ritonavir
  - Cobicistat has limited data in pregnancy, so not recommended
  - Must be bid and with food
- **Twice daily dosing** with 600 mg DRV plus 100 mg RTV
  - Further increase of dose of 800 mg qd or bid is **not recommended**

Raltegravir

- Dosing does not change throughout pregnancy
  - **Twice daily dosing with 400 mg**
  - Without regard to food

Elvitegravir/c is Not Recommended

- PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy
  - *Switch* should be considered if woman becomes pregnant on this regimen
  - If an EVG/c regimen is continued, viral load should be monitored frequently, and TDM (if available) may be useful

In the Case of Lack of Viral Suppression

- Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible
- If an ultrasensitive HIV RNA assay indicates failure of viral suppression (after an adequate period of treatment):
  - **Assess adherence** and resistance
  - Consult an HIV treatment expert and consider possible antiretroviral regimen modification
- Scheduled cesarean delivery at 38 wks is recommended for women who have HIV RNA levels >1,000 copies/mL near the time of delivery (**AI**)

Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

Drug-resistance studies ordered before starting or modifying ARV in all pregnant women with HIV RNA >500 to 1,000 copies/mL

- Unless they have already been tested for ARV resistance

ART should be initiated in pregnant women *prior to* receiving results of ARV-resistance studies. (Don't wait!) (**BIII**)

Zidovudine resistance **does not** affect the indications for use of intrapartum zidovudine (**BIII**)

Consultation with a pediatric HIV specialist is needed if virus is resistant

- Preferably before delivery

Monitoring of the HIV/CD4 Counts During Pregnancy

Plasma HIV RNA levels should be monitored:

- Initial visit
- 2 to 4 weeks after initiating (or changing) ART
- Monthly until RNA levels are undetectable
- At least every 3 months during pregnancy
- Approx 34 to 36 weeks' gestation

CD4 count should be monitored

- At initial antenatal visit (**AI**)
- Every 3-6 months during pregnancy

Question

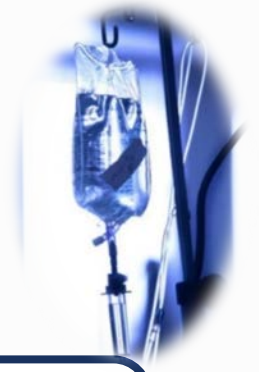
- A pregnant woman living with HIV has been attending your clinic and today is her first perinatal visit. She is asking how often she will need to get her viral load checked. She is currently undetectable based on labs 1 week prior. Which of the following statements is correct?
- A. She will need to get her VL checked in 2-4 weeks, and monthly after that
- B. She will need to get her VL checked every 3 months, and at 34-36 weeks gestation
- C. She will need to get her VL checked monthly, and at 34-36 weeks gestation
- D. She will need to get her VL checked every 6 months, and at 34-36 weeks gestation

Intrapartum Antiretroviral Therapy/ Prophylaxis

- Women should continue (ART) drug regimen on schedule as much as possible during labor and before scheduled cesarean delivery (**AIII**)
  - Oral medications can be continued preoperatively with sips of water
  - Consult anesthesiologist about meds requiring food for absorption (since pt will be NPO)

- Women who present in labor with unknown HIV status should undergo expedited antigen/antibody HIV testing (**AII**)

Zidovudine Intrapartum



Should be administered to women living with HIV with HIV RNA >1,000 copies/mL (or unknown HIV RNA) near delivery **(AI)**

- May be considered in women with HIV RNA btw 50-999 copies/mL (**CII**)

Not required for women on ART with HIV RNA <50 copies/mL in late pregnancy and/or near delivery (**BII**)

- As long as no concern about adherence

IV zidovudine administration should begin 3 hrs before the scheduled operative delivery

- Loading dose: 2 mg/kg followed by a continuous IV infusion of 1 mg/kg/hour until delivery

Postpartum Care

ART should be continued

- Prior to hospital discharge, the woman should be given ARV medications for herself and her newborn to take at home **(AIII**)

Immediate postpartum period poses unique challenges to adherence, arrangements for new or continued supportive services should be made *before hospital discharge* (**AII**)

Contraceptive counseling/plan should be developed prior to discharge (**AIII**)

Breastfeeding is **not recommended** for HIV-infected women in the United States (**AI**)

- Address possible barriers to formula feeding during the antenatal period.
- Also discuss of the risks of HIV transmission via premastication (prechewing or prewarming) of infant food

Infant Antiretroviral Prophylaxis

- All HIV-exposed infants should receive ART (**AI**) pref. w/in 6-12 hrs of delivery (**AII**)

- The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of HIV transmission **(AIII)**.

- The uses of ARV regimens in newborns include:
  - ARV prophylaxis: 1 or more ARVs to newborn without confirmed HIV infection
  - Empiric HIV therapy: 3 drug combo regimen to infants at highest risk of HIV acquisition
  - HIV therapy: 3 drug combo in infants with confirmed HIV infection

Infant Antiretroviral Prophylaxis

- A 4-wk neonatal zidovudine prophylaxis regimen can be used for full-term infants
  - 4 mg/kg/dose orally twice daily
  - If mother has received ART throughout pregnancy w/ sustained viral suppression and no maternal adherence concerns (**BII**)
- Combination infant prophylaxis regimen is recommended in infants at higher risk
  - (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk)
- Risks to consider include infants born to women with HIV who:
  - Have not received antepartum or intrapartum ARV drugs (**AI**)
  - Have received only intrapartum ARV drugs (**AI**)
  - Have received antepartum ARV drugs but lack viral suppression near delivery (**AII**)
  - Have acute HIV infection during pregnancy (**AII**) or during breastfeeding (**AII**)
- Use of ARV drugs other than zidovudine, lamivudine and nevirapine cannot be recommended in premature infants as prophylaxis bc of lack of dosing and safety data (**BIII**)

Infant Antiretroviral Prophylaxis for High Risk

- Combination therapy for 6 weeks is recommended

- For ARV prophylaxis
  - 6 weeks of zidovudine
  - With 3 doses of nevirapine (48 hrs after birth, then at 4 days old, followed by at 8 days old) *birth weight 1.5-2kg: dose is 8 mg, if >2 kg: dose is 16 mg

- For empiric HIV therapy (3 drug combo)
  - Zidovidine
  - Lamivudine
  - Nevirapine (treatment dosage, if >37 wks dosed 6 mg/kg/dose orally twice daily)

What is the Optimal Postnatal-Infant Prophylaxis (PnP) for “High Risk” Infants?

- Recent systematic review
- Multi-drug regimens significantly reduce transmission rates vs. single-drug regimens
  - No significant difference between 2 vs 3 drug regimens
- Two large studies (PHPT-5 and HPTN-040) provide the evidence that multi-drug regimens have superior protection

Optimal Anti-Retroviral Prophylaxis in Infants At High-Risk of Acquiring Human Immunodeficiency Virus: A Systematic Review. Pediatr Infect Dis J. 2017 Jul 18.

Describe the Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents With HIV Who Are Pregnant or of Child-bearing Potential

Dolutegravir (DTG) Safety

An independent NIH-funded observational surveillance study of birth outcomes identified a potential safety issue

- Concern stems from preliminary unscheduled analysis
- Study population is pregnant women on ART in Botswana

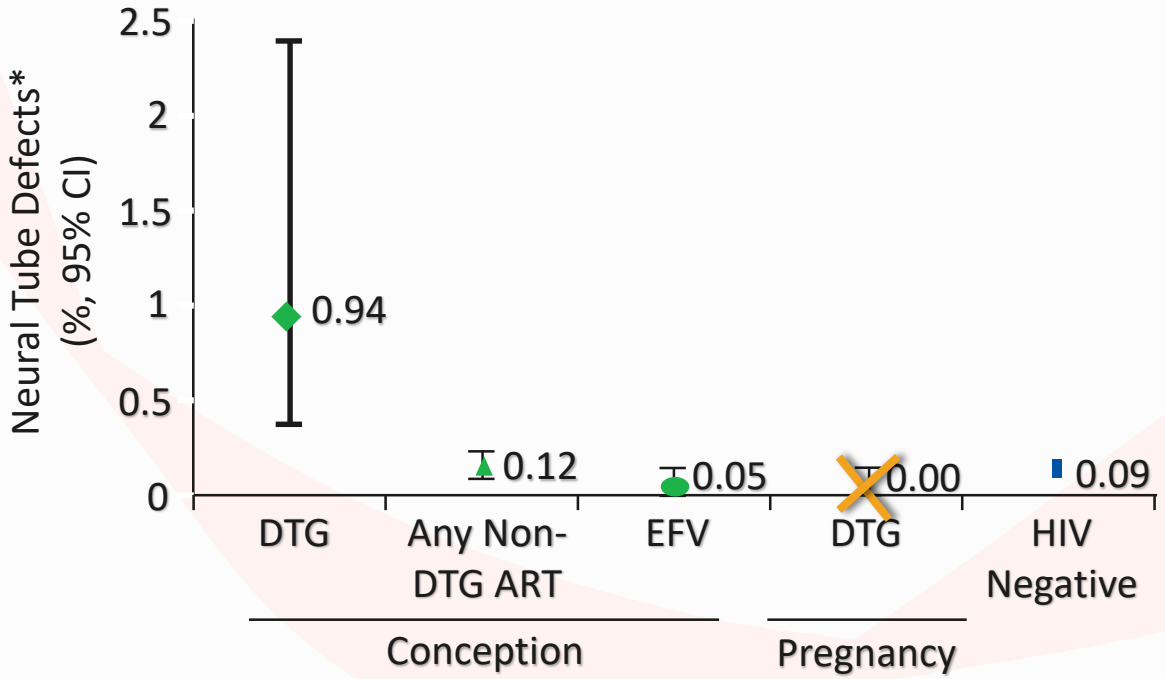
Potential safety issue was seen in women living with HIV using dolutegravir **at the time** of conception

- At the time of the warning, 4/426 infants born to women who were on a DTG regimen at conception experienced neural tube defects (NTDs)

DHHS. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.

Tsepamo: Neural Tube Defects and DTG Exposure

- Unplanned analysis of ongoing birth outcomes surveillance study among Botswanan women ± HIV infection[1,2]



*In 89,064 births as of May 1, 2018.

- At latest analysis on **July 15, 2018**[2]
  - NTD prevalence with DTG exposure **at conception**: 4/596 (0.67%; 95% CI: 0.26% to 1.7%)
  - NTD prevalence with DTG started **during pregnancy**: 1/3104 (0.03%; 95% CI: 0.01% to 0.18%)
- Next formal analysis to occur after **March 31, 2019,** which will include 72% of national births

1. Zash R, et al. N Engl J Med. 2018;[Epub ahead of print]. 2. Zash R, et al. AIDS 2018. Session TUSY15.

Dolutegravir in Women Who Are Pregnant

Pregnant, taking DTG, and within 8 weeks from last menstrual period should discuss the risks/benefits of their current regimens with their health care providers. If there are other good options to replace DTG, then switching to a non-DTG ART regimen is recommended

Pregnant and 8 weeks+ from last menstrual period may initiate or continue DTG-based regimens. Discontinuing DTG-based regimens is unlikely to confer any benefits after the neural tube has formed, and medication changes during pregnancy could increase the risk of viremia and transmission of HIV to the infant.

DHHS. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.

Dolutegravir in Women Who Are of Child-bearing Potential

For individuals not known to be pregnant, documentation of a negative pregnancy test is recommended *prior to initiating DTG*. Discuss effective use of contraception.

Those who are receiving DTG or who wish to be started on DTG should be counseled about the potential risk of NTDs when DTG is taken near the time of conception

DHHS. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.

Dolutegravir in Women Who Desire Pregnancy OR Are Not Using Effective Contraception:

1. Have other effective treatment options

- Switch to an alternative to DTG
- Do not stop ART without replacement regimen
- Discuss the potential risk of DTG to the fetus

2. Have drug resistance, using DTG as part of salvage regimen with no other effective ART options

- Continue DTG
- Discuss potential risks of DTG to the fetus AND the risks of viremia rebound if DTG is stopped (including transmission)

DHHS. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.

Data Are Preliminary

The panels are emphasizing that these recommendations are **interim** recommendations

Additional data will provide a more complete understanding of the risk/benefit

These recommendations will be updated once more data is available (April 2019 is next scheduled analysis)

Alternatives to Dolutegravir: Pregnant or of Child-Bearing Potential

INSTI:

- Raltegravir 400 mg bid
- Uncertainty of potential class effect should be acknowledged and discussed with the patient
- Do not initiate DTG-based regimen in those who desire pregnancy or are not using effective contraception

Protease inhibitor (PI):

- Atazanavir/r 300 mg/100 mg once daily with food
  - Careful with GERD due to DDI
- Darunavir/r 600 mg/100 mg BID with food

ALTERNATIVE: NNRTI:

- Efavirenz: Primate studies raised concern, however it is considered safe, monitor for depression
- Rilpivirine: not recommended if HIV RNA >100,000 copies/mL or CD4 count <200 cells/mm^3
  - Careful with GERD due to DDI

DHHS. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.

Question

- A 24 year old woman living with HIV is here for a follow-up visit related to the management of ART. Her current regimen includes dolutegravir and TDF/emtricitabine as she needs a once daily option for adherence. She mentions her desire to stop birth control soon and interest in preconception counseling. Which of the following would be the most appropriate alternative to DTG?
- A. Raltegravir
- B. Darunavir/r
- C. Atazanavir/r
- D. Elvitegravir/c

Question

- RY is a 34 year old woman who was recently diagnosed with HIV. She is ARV naïve and is here for initiation of ART. RY had an initial viral load of 23,000 copies/mL, and has a CD4 count of 460 cells/mm^3. She states she is sexually active and is not on contraceptives.
- Which of the following statement is correct regarding the DTG recommendations in RY?
- A. Do not initiate a DTG-based regimen
- B. Pregnancy test, if negative DTG can be considered
- C. DTG can be started and if RY gets pregnant it can be switched
- D. Pregnancy test, if negative DTG can be considered along with discussing the potential risks to the fetus

Summary

- Viral suppression is a major factor in preventing MTCT
- ART selection will be similar to non-pregnant (with a few exceptions)
- Newborn ART prophylaxis and avoidance of breastfeeding are important strategies
- Use of dolutegravir in ARV-naïve patients should be avoided in women who may become pregnant
- Use of dolutegravir can be continued in pregnant women already taking it who are past 8 weeks from LMP

References

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