



Antiretroviral Considerations in Conception and Pregnancy

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Conflict of Interest Disclosure Statement

- The presenter has no conflicts to declare.

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Learning Objectives

1. Discuss antiretroviral agents considered preferred in pregnancy.
2. Review recommendations for the use of antiretroviral therapy during pregnancy.
3. Assess the data related to neural tube defects with dolutegravir and efavirenz.

Stopping Perinatal HIV Transmission

- August 1994 – zidovudine to reduce perinatal HIV transmission
- Universal counseling and testing
- Antiretroviral therapy (ART) for all pregnant people with HIV
- Delivery recommendations (c-section with plasma HIV RNA >1000 c/mL near delivery)
- Infant antiretroviral (ARV) management
- Avoidance of breastfeeding (recent changes related to breast feeding)
- In 2019 and 2020 <45 infants were born with perinatal HIV annually in the US (estimated 5,000 people with HIV give birth yearly)

Resources

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV



Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States



Developed by the HHS Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

THE ANTIRETROVIRAL PREGNANCY REGISTRY INTERIM REPORT

1 JANUARY 1989 THROUGH 31 JULY 2022

(Issued: December 2022)

(Expiration: 6 months after issue)



Antiretroviral Safety and Efficacy

- Utilize both animal and human data when considering efficacy and toxicity
 - Limited human clinical data as pregnant women are commonly excluded from clinical trials
 - Pharmacokinetic (PK) studies to evaluate changes in pregnancy
- Antiretroviral Pregnancy Registry
- Continually evolving based on continued data collection
- Guideline recommendations
 - Based on assessment of evidence and professional opinion
 - Clinical efficacy, acceptable toxicity and ease of use, PK data to guide dosing, data supporting favorable risk-benefit balance for woman, fetus, and newborn

Panel on Treatment of Women Living with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs during pregnancy. Jan 21, 2023. <https://hivinfo.nih.gov>
National HIV Curriculum. <https://www.hivinfo.nih.gov>

Antiretroviral Pregnancy Registry

- Voluntary registry
- Detect any major teratogenic effects
- 25,600 women enrolled
- Enrolls 1300 women annually of estimated 5000 births to women with HIV
- No increase in total birth defects noted
 - 2.9 birth defects per 100 live births (MACDP 2.72/100 and TBDR 4.17/100)
 - No difference between first-trimester exposure and later exposures

Antiretroviral Pregnancy Registry Interim Report. 1 January 1989 to 31 July 2022

Antiretroviral Pregnancy Registry Interim Report. 1
January 1989 to 31 July 2022

Graded Recommendations

- Preferred
 - Pregnancy-specific PK data
 - Favorable risk-benefit including pregnant people, fetuses, and/or newborns
- Alternative
 - Data in pregnancy generally favorable but limited
- Insufficient Data
- Only in Special Circumstances
 - May be circumstances that warrant use
- Not Recommended
 - Inferior efficacy and/or serious safety concerns

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs during pregnancy. Jan 31, 2023.

<https://hivinfo.nih.gov>

National HIV Curriculum (<https://www.hivinfo.nih.gov>)

Antiretroviral Therapy (ART) in Pregnancy

- Combination ART (3-drug) for all pregnant women to decrease the risk of perinatal HIV transmission and to benefit the mother's health
 - Regardless of CD4 count and HIV RNA (viral load)
 - Two-drug therapy is not recommended for initiation
- Perinatal transmission risk increases with increasing maternal HIV RNA but transmission can occur even at low HIV RNA levels
- ART decreases HIV transmission independently of HIV RNA effects

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs during pregnancy

Timing of ART in Pregnancy

- A French study reported that transmission was inversely related to duration of antenatal ART
 - Higher rates of transmission in patients with shorter duration of therapy and preterm delivery <33 weeks
- Approximately 80% of perinatal transmissions occur after 36 weeks (including labor and delivery)
 - Goal to lower HIV RNA as much as possible by 36 weeks
- All women with HIV who become pregnant should start ART without delay
 - Prior to ART start, genotypic drug-resistance testing should be completed. This should not, however, delay therapy.

Preferred Agents

NRTI Backbone

Preferred

1. Abacavir + Lamivudine
2. Tenofovir AF + Emtricitabine
3. Tenofovir AF + Lamivudine
4. Tenofovir DF + Emtricitabine
5. Tenofovir DF + Lamivudine

Alternative

1. Zidovudine + Lamivudine

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs during pregnancy. Jan 31, 2023.

<https://hivinfo.nih.gov>

also available at <https://www.hiv.uw.edu>

Anchor

Preferred

1. Dolutegravir
2. Darunavir/ritonavir

Alternative

1. Raltegravir
2. Atazanavir/ritonavir
3. Efavirenz
4. Rilpivirine

Backbone Specifics

Abacavir

- HLA-B*5701 negative
- Caution with HIV RNA >100,000 (ATV/r, EFV)
- Not active against hepatitis B
- Good PK data
- Fixed dose combination of ABC/3TC/DTG

Emtricitabine(FTC) / Lamivudine(3TC)

- Excellent tolerability
- Active against hepatitis B (must use with tenofovir)
- Available in multiple fixed dose combinations
- Good PK data

Tenofovir

- Active against hepatitis B
- Good PK data
- DF – renal and bone toxicity
- AF – fewer adverse birth outcomes when used with DTG (compared to DF)
- AF – associated with weight gain (combined with DTG in nonpregnant)

Specifics Anchor

Dolutegravir

- Good PK data
- High rates of viral suppression
- Limited drug interactions
- Rapid viral load decrease
- Weight gain?
- Divalent cation interactions
- Early association with neural tube defects

■ Darunavir/ritonavir

- Twice daily administration
- Administration with food
- Drug interactions

Alternative Specifics

Zidovudine

- Experience during pregnancy
- BID dosing
- ↑ adverse effects

Efavirenz

- Experience during pregnancy
- Fixed dose combinations
- CNS adverse effects

Raltegravir

- Good safety and PK data
- BID dosing
- Rapid viral load decrease
- Divalent cation interaction

Atazanavir/ritonavir

- Experience during pregnancy
- Increased dosing in 2nd/3rd trimester
- ↑ maternal indirect bilirubin
- Drug interaction

Rilpivirine

- Fixed dose combination
- Not for baseline HIV RNA >100,000 or CD4 <200
- Decreased drug levels in 2nd/3rd trimester, increase monitoring
- Acid suppressor interactions

And What About the Others?

- Insufficient data
 - Bictegravir
 - Limited data on PK, toxicity, and efficacy
 - Limited data on clinical outcomes with pregnancy
 - Doravirine
 - Limited data on PK, toxicity, and efficacy
 - Limited data on clinical outcomes with pregnancy

And What About the Others?

- Not recommended
 - Cobicistat containing regimens (atazanavir, darunavir, elvitegravir)
 - Decreased drug concentrations in the 2nd and 3rd trimester that could lead to virologic breakthrough
 - Adequate numbers to detect a two-fold increase in birth defects have been monitored with no increase detected
 - Injectable cabotegravir/rilpivirine
 - Limited data
 - Not recommended as initial treatment

Treatment Considerations

1. A person who is pregnant and needs ART

2. A person of childbearing potential with HIV

A person who is pregnant and needs ART

- Select therapy as appropriate given guideline recommendations
- Start ART as early as possible

Childbearing Potential

- Consider in all persons with HIV regardless of reported pregnancy plans and/or contraceptive use
 - Reproductive and sexual health counseling
 - Half of all pregnancies in the US are unplanned
- Therapy selection – shared decision making
 - Include consideration of pregnancy
- Pregnancy testing prior to ART initiation

Best Case Scenario

- On ART with maximal viral suppression prior to conception
 - Maternal health
 - Transmission prevention (partner)
 - In utero transmission prevention (infant)
- ART started before pregnancy, maintained throughout, and nondetectable viral load at delivery holds essentially no risk of transmission to the newborn
- Discuss ART safety prior to pregnancy

ART at Time of Pregnancy

- In most circumstances, if a woman with HIV infection is taking a fully suppressive combination antiretroviral regimen and becomes pregnant, she should continue the current antiretroviral regimen
- Considerations for changing therapy should include shared decision making and a discussion of what is and is not known
- Clinicians may want to consider increased viral load monitoring

Neural Tube Defects

- Neural tube development
 - Closes approximately 4 weeks post conception (6 weeks following last menstrual period)
- Neural tube: spinal cord, spine, brain, and skull
- Neural tube defect (NTD) occurs when the neural tube does not close properly
 - Anencephaly and spina bifida
- Safety at conception (early pregnancy) and safety during pregnancy may be different

Efavirenz

- Indication from animal studies of neural tube defects (NTD)
- Recommended to avoid in pregnancy
- Meta-analysis – 2014
 - Treatment early in pregnancy did not increase risk of birth abnormalities (RR 0.78)
 - Overall incidence of birth abnormalities was comparable to the general population
- Alternative therapy in U.S. guidelines, still used first line in some developing countries

Dolutegravir

- May 2018 - interim analysis of a study in Botswana (Tsepamo Study) reported 4 cases of NTDs out of 426 infants born (rate of 0.9% compared to 0.1% with non-DTG regimens)

	DTG pre- conception	Antiretroviral therapy not including DTG	Non-HIV- infected women
2018 interim analysis (95% CI)	4 of 426 0.94% (0.37-2.4)	14 of 11,300 0.12% (0.07-0.21)	61 of 66,057 0.09% (0.07-0.12)
2019 updated analysis (95% CI)	5 of 1,683 0.3% (0.13-0.69)	15 of 14,792 0.1% (0.06-0.17)	70 of 89,372 0.08% (0.06-0.1)
2020 updated analysis (95% CI)	7 of 3,591 0.19% (0.09-0.40)	21 of 19,361 0.11% (0.07-0.17)	87 of 119,630 0.07% (0.06-0.09)
2022 updated analysis	10 of 5,860 0.11% (0.06-0.19)	25 of 23,664 0.11% (0.07-0.16)	108 of 170,723 0.07% (0.05-0.08)

Zash R., et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana. Presented at: AIDS 2022; 2022. Montreal, Canada. Available at: <https://programme.aids2022.org/Abstract/Abstract/?abstractid=>



Dolutegravir

- Guidelines place DTG as a Preferred drug for use throughout pregnancy and a Recommended Initial Agent for Most People with HIV
 - This includes women of childbearing age
 - High rates of virologic suppression
 - Faster rates of viral load decline
 - Excellent tolerability
 - High genetic barrier to resistance

Resources

- National Clinician Consultation Center <http://nccc.ucsf.edu/>
 - HIV Management
 - Perinatal HIV
 - HIV PrEP
 - HIV PEP line
 - HCV Management
 - Substance Use Management
- AETC National HIV Curriculum <https://aidsetc.org/nhc>
- AETC National Coordinating Resource Center <https://targethiv.org/library/aetc-national-coordinating-resource-center-0>
- Target HIV – Health Resources and Services Administration
 - <https://www.targethiv.org>
- Additional trainings
 - AETC@arcare.net
 - www.scaetc.org