**HIV and Pregnancy**

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**Learning Objectives**

1. Develop a framework for addressing preconception planning among women of childbearing potential who are living with HIV/AIDS.
2. Understand the risk of perinatal transmission of HIV and transmission during breastfeeding
3. Identify treatment guidelines for a woman of childbearing potential living with HIV
4. Review guidelines for post-exposure prophylaxis for infants born to mothers living with HIV

**Case 1:**

JH is a 28-year-old woman with well-controlled HIV who presents to clinic with her male partner, who is HIV negative, for preconception counseling. She states that she has been overall feeling well, and is taking her Odefsey (TAF/3TC/RPV) daily without any missed doses.

She has been virally suppressed for over 2 years on routine lab testing, and her CD4 has consistently been > 500. She and her partner are sexually active, monogamous for the past two years, and always use condoms.

They are ready to have children but JH is concerned about HIV transmission to her partner, and to her child.

1. **Outline an approach for addressing preconception planning among women of childbearing age who are living with HIV.**

Preconception counseling should be a component of comprehensive health care for all women of childbearing potential (WOCBP), and particularly among women living with HIV to ensure a healthy pregnancy and mitigate risk of vertical transmission. This discussion should be integrated into routine health visits, even if your patient does not express a desire for pregnancy at initial evaluation because approximately half (45%) of the 6.1 million pregnancies in the United States are unintended (either mistimes or unwanted) which translates to nearly 5% of reproductive-age women having an unintended pregnancy each year.

If a WOCBP who is living with HIV expresses a desire for pregnancy, establish a pregnancy plan:

1. Ask if she is planning to get pregnant in the next year – women living with HIV can have safe pregnancies, and deliveries.
2. Counsel women about risk factors for perinatal transmission of HIV, including cART medication adherence, the importance of viral suppression, mode of delivery, and potential risks of breast feeding.
3. Discuss U=U\* (Undetectable =Un-transmittable), and the almost negligible risk of HIV transmission if the partner living with HIV has an undetectable viral load. Encourage partners to receive HIV counseling and testing, and review indications for pre-exposure prophylaxis (PrEP)
4. Review all of her medications for teratogenic medications, including her cART regimen and ensure it is safe and appropriate for her to continue (this will be discussed in detail below)
5. Start folic acid 400-800 mcg/day (35-50% reduction in neural tube defects) – all woman between 15 – 45yo should consume at least 0.4mg of folic acid per day. Counsel that birth defects can occur within 3-4 weeks after conception, before most women know they are pregnant.
6. Ensure immunity of all reproductive age women
7. Address active tobacco use, alcohol use, and other substance use
8. Address mental health disorders and their current treatment plan, including active medications that have teratogenic effects

1. **What is the risk of maternal to child HIV transmission? What factors are involved in risk?**

The risk of perinatal HIV transmission for women NOT on cART has ranged between 14-45% across studies, with significant variability depending on maternal risk factors and breastfeeding practices. The most important factors that determine risk of transmission are viral load, and CD4 count. A high viral load, and a low CD4 count increase the risk of transmission to the fetus, and also increase maternal morbidity/ mortality.

There are three main time periods during which maternal to child transmission of HIV can occur:

1) Intrapartum: HIV can pass through the placenta and infect the fetus.

2) Labor and Delivery: This is often the highest risk of transmission at a single time point, particularly after the amniotic sac breaks and during exposure to the mother’s blood, and other body fluids. Most perinatal transmission of HIV occurs at or near the time delivery.

3) Post-partum (while breastfeeding): This confers high risk of transmission due to the presence of high HIV VL within colostrum and breast milk.

The risk of HIV acquisition among newborns born to women who received standard ARV treatment regimens during pregnancy and labor, and had an undetectable VL at delivery, is estimated to be less than 1%. The current rate of perinatal HIV transmission rate in the US is <1%; with a combination of universal prenatal HIV counseling and testing, maternal ARV initiation for all pregnant women living with HIV, scheduled C-section for women with higher VL near delivery, infant ARV prophylaxis, and avoidance of breastfeeding.

1. **What is the risk of transmission of HIV from a HIV-positive partner to a HIV-negative partner?**

Among sero-different heterosexual and MSM couples in which the partner living with HIV is virologically suppressed on cART, there is an almost negligible risk of transmission through condomless sex for both anal and vaginal penetrative sex.

The landmark PARTNERS study evaluated 1166 sero-different heterosexual and MSM couples who had condomless sex, with the partner living with HIV on suppressive cART, and found that there was no documented within-couple HIV transmission. This led to the U=U\* (Undetectable = Untransmissible) campaign, which reflects the evidence that people living with HIV who take cART daily as prescribed and maintain an undetectable viral load have effectively NO risk of sexually transmitting the virus to an HIV-negative partner.

Some guidelines suggest that for sero-different couples, when the female partner is living with HIV, assisted insemination at home or in-office can further eliminate risk of HIV transmission to the partner without HIV. If the male partner is living with HIV, the use of donor sperm from a male who is not HIV infected is a potential conception strategy to eliminate HIV transmission risk. For sero-different couples attempting to conceive in which the partner living with HIV is not virally suppressed, administration of pre-exposure prophylaxis to the partner without HIV can reduce risk of HIV transmission. If both partners are living with HIV, they should both be on cART with maximum viral suppression before attempting conception,

Male-to-female transmission is more efficient than female-to-male transmission, though at higher viral loads, and during menses, there is increased risk of female-to-male transmission.

**CASE 2:**

AT is a 24 year-old G1P0 woman who is referred to you from Maternal-Fetal Medicine for newly diagnosed HIV. She has a VL 45,000 and CD4 450. Her GA is 10w3d, and this is a desired pregnancy.

She presents to your clinic with her partner who is also HIV positive. She has not seen a medical provider since she was 20-years old and no longer received medical care with her pediatrician. She has never had any STI testing. Her partner recently established HIV care at another local clinic and is on active cART.

1. **Should all pregnant women be screened for HIV?**

All pregnant women should be screened for HIV infection. If a woman tests negative for HIV in her first trimester of pregnancy, she should undergo repeat testing in the third trimester if she is at risk of acquiring HIV, is receiving care at a facility with a HIV incidence in pregnant women >= 1/1,000 per year, or is incarcerated. Any pregnant or breastfeeding woman who has symptoms suggestive of acute retroviral syndrome should be evaluated for acute HIV infection.

For women who present in labor and have unknown HIV status, expedited fourth generation HIV Ab/Ag testing should be done with HIV VL.

1. **How do you approach initiating antiretroviral treatment in a pregnant patient with HIV?**

ART is recommended for all pregnant women living with HIV, regardless of viral load, to optimally reduce the risk of perinatal transmission. This is to target two goals of cART: 1) reduce perinatal transmission, and 2) treat maternal HIV disease. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, there is no threshold below which no risk transmission can be definitively ensured.

The mechanism by which ARV drugs reduce perinatal transmission of HIV is multifactorial. While lowering maternal antenatal viral load is an important component of prevention in women with higher viral load, ARV therapy is also important in preventing vertical transmission among women with low viral load. Earlier initiation of cART is associated with increased likelihood of viral suppression by time of delivery and decreased risk of transmission. For pregnant women who are not on cART at time of pregnancy, the rate of virologic suppression after cART initiation is comparable to that of non-pregnant women with HIV. In the setting of acute maternal HIV infection, a pregnant woman should immediately begin ARV therapy while genotype is pending.

ARV selection is similar to that of selection for a non-pregnant patient, with the exception that certain agents preferred in the general population of patients infected with HIV are not preferred in women that are pregnant due to lack of safety data and/or data suggesting harm to the fetus. Resistance testing should be done to inform optimal cART regimen selection, as with a non-pregnant HIV patient, but testing should not preclude initiation of cART. The regimen can be adjusted based on resistance profile if necessary.

Guidelines for ART selection are to include a dual-NRTI backbone with a protease inhibitor or integrase inhibitor.

Whenever possible, cART regimens initiated during pregnancy should include an NRTI with high transplacental passage, such as lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF), or abacavir (ABC). Generally, TDF-3TC is selected as the dual NRTI backbone, or ABC-3TC if there is significant renal impairment. TAF is not used in pregnancy due to limited safety data during pregnancy.

PI’s have the most clinical safety data in pregnancy, with Atazanavir-ritonavir most often selected due to extensive clinical experience and data during pregnancy. PI’s can also be boosted with cobicistat, but the combination has not been as well studied in pregnancy and there is a theoretical concern of decreased cobicistat levels during pregnancy. If ATZ/r is selected, this should not be used with 3TC/ABC for women with VL> 100K due to higher risk of virologic failure.

The preferred integrase inhibitor (INSTI) for use in pregnancy is raltegravir (RAL), which has limited data during pregnancy, but is generally reassuring. It can also rapidly reduce viral load, which makes it an attractive option for women who present late to care in pregnancy with high VL (estimated 2-log decline in VL within two weeks). HIV experts often add RAL to cART regimen of women later in pregnancy who have not yet achieved virologic suppression, though this has not been adopted as a guideline due to insufficient data.

Dolutegravir has been associated with neural tubular defect in pregnancy and should not be used in the first 8 weeks of pregnancy. There is limited data on elvitegravir/ cobicistat in pregnancy, with data strongly suggesting that levels in the third trimester are significantly lower than in the postpartum period (below that which is expected to result in virologic suppression), and evidence of viral breakthrough. As such, this is not recommended as first line treatment, but if there is no other option, viral load should be monitored more frequently.

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| Dual NRTI backbone   * ABC + 3TC * TDF + FTC * TDF + 3TC | **PLUS** | Protease Inhibitor   * ATZ/r * DRV/r   Second line:   * lopinavir/r   or  Integrase Inhibitor   * RAL |

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| ***Preferred two NRTI backbone*** | |
| **ABC + 3TC** | Available as FDC, once daily. ABC should not be used in patients who test positive for HLA-B\*5701 due to concern for hypersensitivity reaction. ABC+3TC with ATV/r or EFV is not recommended if HIV VL > 100K. |
| **TDF + FTC** | Available as FDC. Potential renal toxicity.  *Concerns about bone and growth abnormalities in infants exposed to TDF in utero; clinical significance requires further evaluation.* |
| **TDF + 3TC** | Potential renal toxicity. |
| ***Preferred PI Regimens*** | |
| **ATV/r + two-NRTI** | Once daily administration; most extensive data and experience in pregnancy.   * Can cause maternal hyperbilirubinemia, though with no clinically significant neonatal hyperbilirubinemia or kernicterus (neonatal bilirubin monitoring is still recommended). * Cannot use with PPIs, and must be timed separately from h2-blockers |
| **DRV/r + two-NRTI** | Less experience in pregnancy than with ATV/r, but increasing. Must be used twice daily in pregnancy. Better tolerated than lopinavir-ritonavir. |
| ***Preferred INSTI Regimens*** | |
| **RAL + two-NRTI** | Rapid viral load reduction, ideal for women who present late in pregnancy or with high viral loads. Twice daily dosing. Less risk of drug interactions than with PI regimens. |

1. **Does maternal ARV treatment confer risk to the fetus?**

There are many studies over the years to assess risks to the fetus of mothers living with HIV who are on cART, with conflicting data. In general, ARVs used in pregnancy are safe with the most data for possible risk of pre-term delivery with the use of ART. Studies show that the benefit for maternal health and reduction in perinatal transmission outweigh any potential risk, and until more information is available, all pregnant women should continue to receive recommended ART regimens with close monitoring for complications.

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| **CASE 2 continued:**  AT was started on Atazanavir boosted with ritonavir (ATV/r), Tenofovir (TDF), and emtricitabine (FTC). She is adherent to her medications, and has not missed any doses. Within one month of cART initiation, her VL is UD, and CD4 is stable at 500. Genotype revealed WT virus. Her partner is also on stable treatment with UD viral load.  She is seen for routine follow up at GA 20w, and has several concerns about the risks of transmission to her fetus both during pregnancy and at the time of delivery. She prefers to deliver vaginally, but has heard that this can increase transmission risk. |

1. **What are the guidelines on carrying a pregnancy to term in patients living with HIV? How should you counsel your patient about the risks of a vaginal delivery versus caesarean section?**

In general, women with HIV VL <1000 on cART have a low incidence of HIV transmission regardless of mode of delivery. These women are not typically scheduled for cesarean delivery, unless it is for other obstetric complications. Scheduled cesarean delivery at 38 weeks’ gestation to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1,000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral therapy (ART).

The threshold of 1,000 copies/mL was based largely on data from the Women and Infants Transmission Study, a large prospective cohort study that reported no HIV transmission among 57 women with HIV RNA levels < 1000 copies/mL. Studies reported since then have demonstrated that HIV transmission can still occur in infants born to women with low viral loads.

The data shows that maternal transmission can occur even at very low plasma HIV RNA levels, likely due to presence of detectable HIV in the genital secretions (studies have shown discordance between plasma and genital viral loads). However, given the low rate of transmission in this low to UD VL group, it is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission. Furthermore, there is evidence that complication rates for cesarean deliveries are higher in women with HIV compared with women without HIV.

Therefore, **decisions about mode of delivery for women receiving ART with HIV RNA levels ≤1,000 copies/mL should be individualized** based on discussion between an obstetrician and a pregnant woman. Women should be informed that there is no evidence of benefit for scheduled cesarean delivery performed solely for prevention of perinatal transmission in women receiving ART with HIV RNA ≤1,000 copies/mL and that it is not routinely recommended in this group

When delivery method is selected as scheduled C-section and VL > 1000 copies/ mL, a 1-hour loading dose followed by continuous IV zidovudine infusion for 2 hours before the C-section should be administered. If the mode of delivery is unscheduled cesarean delivery, and maternal VL > 1000 copies/mL, loading dose of zidovudine is still given. It is thought that 3 hours of infusion is what provides adequate equilibrium across placenta. For women who are delivering vaginally, they receive at 2mg/kg loading dose and then a continuous infusion of 1mg/kg/hour until delivery.

IV Zidovudine should be administered to all women with VL > 1000 near time of delivery, though many providers will administer this regardless of VL to provide additional protection against perinatal transmission. Zidovudine crosses the placenta rapidly and provide pre-exposure prophylaxis to the fetus (PACTG 076 trial). Guidelines suggest that IV zidovudine is NOT required for women with HIV VL =<50, if there are no concerns about cART adherence. There is inadequate data about IV zidovudine for women with HIV VL between 50-1000, though most providers will administer it.

*[Supplement: In an analysis of 957 women with plasma viral loads ≤1,000 copies/mL, cesarean delivery (scheduled or urgent) reduced the risk of HIV transmission when adjusting for potential confounders including receipt of maternal ARV medications (AOR 0.30; P = 0.022); however, zidovudine alone was the regimen primarily used as prophylaxis. Among infants born to 834 women with HIV RNA ≤1,000 copies/mL receiving ARV medications, 8 (1%) were born with HIV. In a report from a comprehensive national surveillance system in the United Kingdom and Ireland, 3 (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA levels.]*

1. **What are the guidelines for post-exposure prophylaxis for the infant?**

It is recommended that all infants born to women infected with HIV receive post-exposure prophylaxis after birth to decrease risk of HIV acquisition, regardless of mother’s VL. All newborns with perinatal HIV exposure should receive ARV medications within 6-12 hours following delivery.

For infants born to women with HIV on cART with VL <1000, four to six weeks of zidovudine prophylaxis is generally appropriate (at YNHH four-weeks of AZT prophylaxis is administered to the infant). CBC should be checked at 4-weeks to monitor for anemia, which is the most common complication of zidovudine prophylaxis. For infants born to mothers without viral suppression, it is recommended they receive two drug (zidovudine plus 3-doses prophylactic dose nevirapine within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose) or triple drug regimen (zidovudine, lamivudine, and nevirapine) for 6 weeks.

HIV testing for viral load should be performed at at least 3 time points:

* + 14-21 days of life,
  + 1-2 months, and
  + 4-6 months of age.
  + *If high risk (detectable VL in mother):* HIV PCR at time of birth

If infants are not breastfed, presumptive HIV negative testing includes:

1. When two or more HIV VL PCR tests are negative (14d and 1mo), or
2. One negative HIV VL PCR at >= 8 weeks, or
3. One negative HIV 4th gen Ab test at >= 6mo.

Definitive HIV negative testing is when:

1. Two negative HIV VL PCR at >=1mo, and >=4 mo; or,
2. Two negative HIV 4th gen Ab/Ag at >= 6mo.

All infants born to mothers with HIV should also receive prophylaxis for PJP with TMP/SMX at 4-6 weeks of age, unless HIV has been presumptively excluded. This can be stopped once HIV is either presumptively or definitively excluded.

1. **How often should you follow her in clinic?**

HIV viral load and CD4 count should be monitored at initial visit, 2-4 weeks after initiating or changing an ARV regimen, monthly until VL is undetectable, and then at least every 3 months during pregnancy. Viral load should also be checked at approx. 34-36 GA to inform decisions about mode of delivery and optimal treatment of the newborn.

Viral suppression should be achieved in 12-24 weeks. Most patients with adequate viral response have at least a 1-log viral load decrease within 1-4 weeks after starting therapy.

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| **Case 2 continued:**  AT carries her pregnancy to term and has an uncomplicated vaginal delivery. Her daughter is evaluated by a pediatric HIV provider, with a plan for HIV testing at 14d and 4 weeks of ZDV treatment.  On her follow up appointment with you, she tells you she has received mixed messages about safety of breastfeeding from friends, family, and various providers, and asks you today about guidelines on breastfeeding. |

1. **What are the recommendations for breastfeeding in the United States for women who are living with HIV?**

Breastfeeding is **NOT recommended** for women living with HIV in the United States, including women who are on cART and have an undetectable viral load.

In the United States, where access to clean water and affordable or subsidized formula is easily available, the Centers for Disease Control (CDC) and American Academy of Pediatrics (AAP) recommendation for mothers living with HIV is that they should not breastfeed, due to 1-5% risk of transmitting HIV to their newborn infant, even when on adequate cART with undetectable viral load. Breast milk is known to contain high levels of HIV, particularly in colostrum.

New data from Tanzania shows that risk of perinatal transmission was essentially zero among a group of mothers infected with HIV. The study included mothers who initiated cART before delivery with infants who tested negative for HIV DNA-PCR at 4-12 weeks and were exclusively breastfed for >= 6months. During breastfeeding 91% of mothers in the study had a VL <1000 copies/ mL and 75% had a VL < 100 copies/mL. At the conclusion of study at 11-mo post-delivery, there was no maternal to child transmission from mothers retained in care and had suppressed viral load. While this newer data on “undetectable = untransmissible” is changing expert opinion about transmission risk, there remains debate amongst medical providers, and cases of HIV transmission via breastfeeding have been known to occur despite UD maternal plasma VLs. There is unfortunately limited research on women on treatment who are breastfeeding that includes good data on viral loads and adherence to cART. Many providers believe any risk is too high risk, while others believe the benefits of breastfeeding outweigh the very small risk of HIV transmission. Counseling a woman living with HIV should be patient centered and focused on harm reduction if women decide to breastfeed.

In resource limited areas, without safe drinking water and access to formula, this recommendation varies; in this case, the WHO recommends mothers infected with HIV should exclusively breastfeed for the first 6 months of life.

**CASE 3:**

MT is a 30-year-old woman with well-controlled HIV and undetectable VL who presents to clinic with her male partner, who is also HIV positive with a VL that is undetectable.

She has a regular menstrual cycle, but missed her period last month. She is on Odefsey (TAF/3TC/RPV) daily without any missed doses. She has been virally suppressed for 5 years, and her CD4 has consistently been >200. She and her partner are sexually active, monogamous, and this is a desired pregnancy.

1. **What are the guidelines for adjusting treatment of pregnant women living with HIV who are already on cART?**

It is recommended that women who become pregnant while on a stable ART regimen with viral suppression remain on that same regimen, even if it is not the preferred regimen for pregnant women, provided they are virally suppressed and doing well. Discontinuing or changing therapy could result in viral rebound, thereby increasing risk of perinatal transmission. There are exceptions to this approach:

1. High risk of toxicity during pregnancy: Women on a regimen containing didanosine, stavudine, or treatment-dose ritonavir should not continue them due to toxicity risks. These are generally not in any recommended regimens for persons living with HIV anymore. In May 2018 the FDA issued a safety alert warning of potential serious neural tube birth defects in infants born to mothers with HIV who were taking dolutegravir at the time of conception or early in the first trimester.
2. High risk of virologic failure: Elvitegravir/cobicistat has been shown to have lower levels in pregnancy and potentially high risk of virologic failure. Preliminary data from the IMPAACT protocol P1026 suggests that women on this regimen have significantly lower levels of elvitegravir and cobicistat during the third trimester of pregnancy, raising concern for virologic failure later in pregnancy. Guidelines suggest changing cART regimen of these women to a recommended regimen. If elvitegravir/cobicistat is continued, more frequent HIV VL monitoring should be performed.

**Recommended Reading:**

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. AIDSinfo. <https://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf>

Panel on Antiretroviral Therapy and Medical Management of HIV-infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Diagnosis of HIV infection in Infants and Children. Nov 2017. <https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv-guidelines/55/diagnosis-of-hiv-infection-in-infants-and-children>

National Perinatal HIV Hotline (1-888-448-8765) – federally funded service providing free clinical consultation

***Additional Resources:***

Ioannidis et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. J Infect Dis. 2001; 183(4):539. https://www.ncbi.nlm.nih.gov/pubmed?term=11170978

Lugga et al. No HIV transmission from virally suppressed mothers during breastfeeding in rural Tanzania. J Acquir Immune Defic Syndr. 2018 May 16. https://www.ncbi.nlm.nih.gov/pubmed/29781882

Mandelbrot et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin Infect Dis. 2015; 61(11):1715. https://www.ncbi.nlm.nih.gov/pubmed?term=26197844

Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 2016; 316: 171-181.

Siegfried et al. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev. 2011. https://www.ncbi.nlm.nih.gov/pubmed?term=21735394

Shetty A, and Maldonado Y. HIV transmission Prevention of Perinatal HIV-1 Transmission in the United States. NeoReview from American Academy of Pediatrics.

Warszawksi et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS. 2008; 22:289-99. <https://www.ncbi.nlm.nih.gov/pubmed/18097232>

Rahangdale L et al. Integrase Inhibitors in late pregnancy and rapid HIV viral load reduction. Am J Obstet Gynecol. 2016; 214: 385. https://www.ncbi.nlm.nih.gov/pubmed/26928154

**Resources for patients**

HIV and Pregnancy. ACOG. <https://www.acog.org/Patients/FAQs/HIV-and-Pregnancy>

HIV and Pregnancy. https://www.avert.org/sites/default/files/fact-sheet-hiv-pregnancy-2016.pdf