Revised November 2021

HIV PRACTICE GUIDELINE

Introduction:

Since 10/2010 Ohio has adopted "opt-out" testing, supported by ODH, CDC, IOM, and ACOG, in which HIV-1 testing with patient notification is a routine component of prenatal care. One in 139 women will be diagnosed with HIV in her lifetime with African Americans and Latinos having the highest risk. Nearly all cases of childhood HIV are attributable to perinatal transmission. Early intervention and treatment is the key to decreased neonatal transmission, and Ohio is still far below national testing average for universal testing. Prevention challenges include the fact that women may not know her partner is infected with HIV, lack of personal awareness of HIV serostatus, limited access to resources, presence of other STDs increasing infectivity, sexual abuse, unprotected anal and vaginal intercourse, and engaging in high-risk behaviors including drug injection, which pose barriers to healthcare providers.

HIV is in the family of retroviruses and uses reverse transcriptase to convert viral RNA to DNA in a rapidly evolving process, creating further mutations and combination strains. HIV-2 infection is endemic in West African countries and not distinguished in most commercially available screening tests. From the PACTG 076 landmark trial, AZT therapy alone can decrease risk of HIV-1 transmission by 68% with a transmission rate of 8%. Scheduled cesarean sections prior to onset of labor can decrease transmission risk by 50%.

Historically, the bundle of AZT and planned c-section either before labor or early in labor was applied to all patients with HIV, as these interventions are effective at preventing transmission. However, with ART, very low or undetectable viral loads are able to be achieved by most patients, and we now know that with very low or undetectable viral load the risk of transmission is extremely low, regardless of delivery mode, timing, or membrane status.

National perinatal HIV consultation and Referral Service – 1-888-448-8765. This service is available to providers that allows 24/7 access to perinatal HIV experts. It is available for urgent/ emergent concerns regarding delivery and intrapartum management, as well as non-emergent issues. It is based at University of California, San Francisco.

Preconception:

- Educate patient on risk of transmission to partner and safe practice for prevention
- Discuss that partner disclosure of HIV status is mandated by law in Ohio and non-disclosure may be prosecuted as a felony (felonious assault: Ohio Revised Code 2903.11).
- Ensure all immunizations are up-to-date (TDaP, Hepatitis B, Flu, COVID, and meningococcal)
- Maximal viral suppression prior to conception optimal
- Refer to IDX to ensure safest and most effective anti-retroviral (ARV) regimen prior to conception
- Sero-discordant couples should consider IDX and REI consultation for expert approach with regards to pre-exposure prophylaxis, transmission, safety and conception based in individual couples' needs.

Diagnosis:

Laboratory Criteria

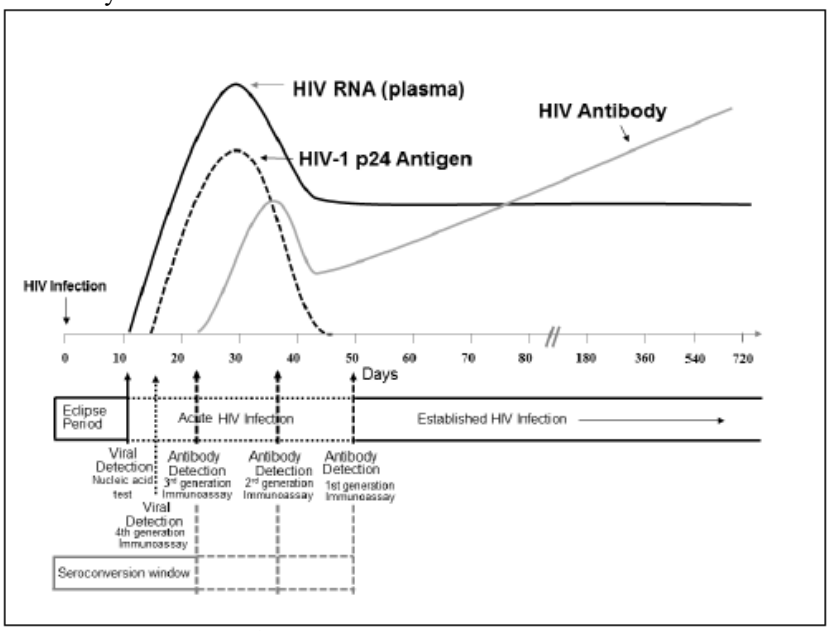
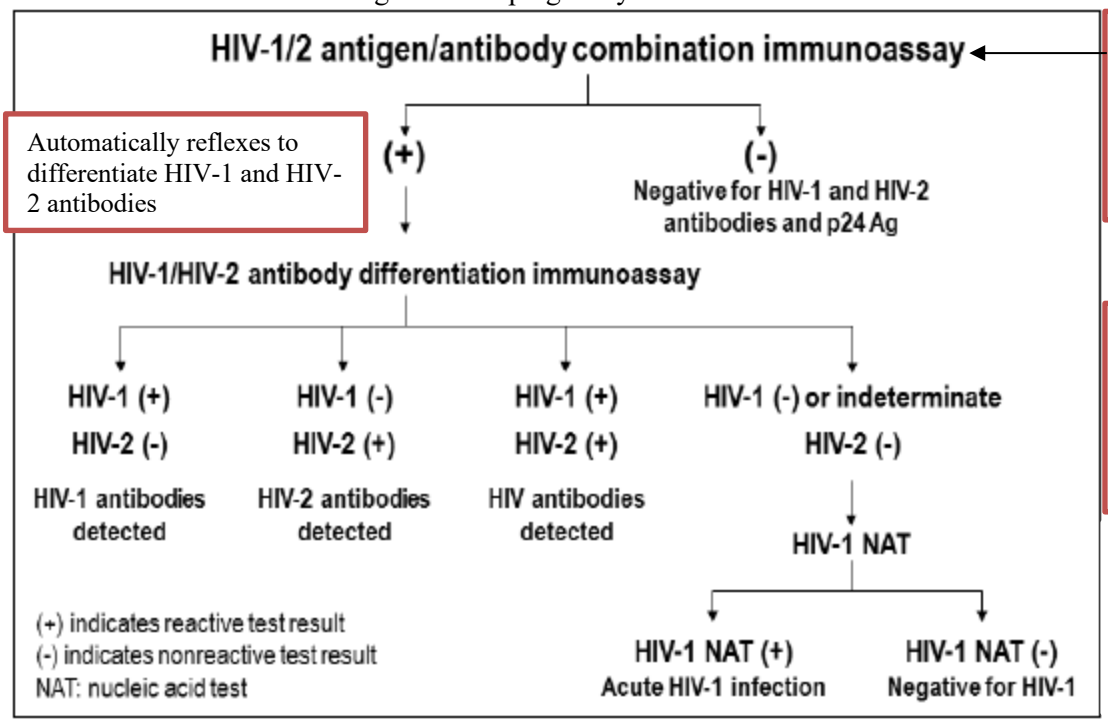


Figure 1. Sequence of appearance of laboratory markers for HIV-1 infection. (CDC AidsInfo)

1. Check HIV 4th generation testing with general initial prenatal panel. *Must document if patient declines testing*.
2. Recheck screening test in high risk populations in the 3rd trimester. Criteria includes but not limited to following:

a. Lives in high HIV prevalent area
b. Diagnosed other STD within last year
c. Injection drug use or other high risk sexual behavior
d. New or more than one sexual partner
e. Declined testing earlier in pregnancy



(1) 4th Generation – checks for p24 antigen and HIV-1/HIV-2 antibody; advantage to detect more acute HIV-1 infections than prior assays

(2) HIV-1/HIV-2 antibody differentiation assay detects HIV-1 Ab earlier than Western blot, identifies HIV-2, & less indeterminant results

Figure 2. Recommended laboratory HIV testing algorithm for serum or plasma specimens. (CDC AidsInfo)

Causes of false (+) screen results include but not limited to specimen mix-up, mislabeling, and autoimmune disorders.

Antepartum: *Individualized* care

- Confirmation of pregnancy dating recommended
- Assess patient's history, prior therapies & toxicities, previous ARV drug resistance testing, immunizations, barriers to care, social challenges, and obstacles for compliance. Explain importance of compliance, risks for drug resistance, and risk for perinatal transmission.
- Suggested initial labs: CBC, CMP, CD4 count, plasma HIV RNA level (VL), hepatitis C, toxoplasmosis IgG, TB screening (Quantiferon Gold), pap smear, early diabetes screen, and HIV resistance testing if it has not been previously performed (*in addition* to general prenatal labs).
    - Patients with non-suppressed viral load should have HIV genotypic resistance testing (Genosure), this should not delay starting ART.
- ***All women regardless of VL and CD4 count should be started on combination ARV drug regimen*. This should be started as early in pregnancy as possible, and should continue at all points including antepartum and intrapartum**
    - Do NOT discontinue therapy. If patient is not compliant with medications, discuss with the patient importance of compliance and notify IDX
- Check monthly VL until undetectable followed by VL & CD4 counts every 3 months; final labs at 34-36 weeks gestation to determine optimal delivery method
- Serial biometry ultrasound assessments
- ANFS is not indicated except for accepted obstetrical indications
- Mode of delivery discussion based on ARV drug compliance and regimen, VL, prior obstetrical history, and risks/benefits of procedures and transmission.

Anti-Retroviral Medications:

General concepts:

1. Three-part strategy:
    a. Antepartum – start ART as early as possible. Each additional week of treatment reduces risk
    b. Intrapartum – continue combined ART along with IV AZT
    c. Infant prophylaxis – depends on viral load at time of delivery, for infants of well controlled disease, 4 weeks of AZT is generally sufficient.
2. Treatment experienced women can usually continue their current regimen, even if not a preferred regimen in pregnancy, unless regimen contains stavuding, didanosine, or full-dose ritonavir.
3. Pharmacokinetic changes in pregnancy may require increased dosing, more frequent dosing, or boosting.
4. Preferred regimens in pregnancy generally include a NRTI 'backbone' with a third drug that may be an integrase inhibitor or boosed protease inhibitor.

Specific Medications –

1. Nevirapine - Increases of hepatic transaminase levels associated with rash or systemic symptoms (hepatotoxicity) may be observed during the first 18 weeks of treatment with nevirapine.
    - Nevirapine-based regimens should be only initiated in women with CD4 T-lymphocyte (CD4-cell) counts >250 cells/mm^3 if the benefits clearly outweigh the risks because of the drug's potential for causing hepatic toxicity/hypersensitivity reaction
2. Tenovir based regimens – preferred in chronic HBV infections but alternative treatment in combination in pregnancy is advised due to high placental transfer to the fetus.
3. Corbicistat containing regimens are not generally recommended to start in pregnancy, and precaution is given with continuing medication during advancing gestation due to decreasing drug levels and loss of viral suppression.
4. Protease inhibitors (PI) – ***associated with hyperglycemia***. Patients need to be screened early in pregnancy and followed closely.
    - **When methergine (ergot alkaloid drug) is co-administered with protease inhibitors (potent CYP3A4), this can lead to severe vasospasms with risk for cerebral and extremity ischemia**.
5. Stavudine and didanosine (NRTIs) should not be prescribed during pregnancy with reports of lactic acidosis and maternal/neonatal mortality with prolonged use in pregnancy.
6. Dolutegravir and risk of neural tube defects – although an observational study in 2018 reported a possible association with neural tube defects, an updated analysis from 2020, along with further observational studies have not found increased risk of birth defects, stillbirth, neonatal death, SGA, or preterm birth. Dolutegravir is now considered a preferred medication in all trimesters.

Intrapartum:

- **Continue oral ART throughout admission including during labor. Patients scheduled for c-section should not miss dose on day of delivery.**
- Inform pediatric team upon admission, inform ID service
- **Our general practice guidelines are to use IV AZT for all patients with HIV infection during labor, although CDC recommendations depend on viral load** (CDC 2017 guidelines):
    - > 1000 copies/ ml – should be administered for 3 hours prior to planned c-section
    - 50-1000 copies/ ml – intrapartum prophylaxis can be considered
    - < 50 copies/ ml – intrapartum prophylaxis is not required
    - With or without IV AZT, perinatal transmission can occur with viral load < 1000, with current risk estimates of < 2% for viral load 50-1000 copies/ ml, and < 1% for viral load < 50 copies/ ml. IV AZT may, theoretically, decrease transmission risk at low viral levels, although this has not been shown in large cohort studies.
- Risk of IV AZT is low. UCMC perinatal HIV taskforce currently recommends AZT in labor for all patients as compliance can be difficult to ascertain, and viral load on admission doesn't come back till after delivery.
- If consideration for no IV AZT is given, recommend all of the following be true:

  - Viral suppression throughout pregnancy - < 50
  - Repeat c-section at normal obstetric timing
  - Confirmed compliance – viral load within 1-2 weeks and confirmation with patients pharmacy regarding appropriate refilling practices
- Mode and timing of delivery
  - Viral load > 1000 copies/ml or unknown viral load near the time of delivery – c-section at 38 weeks prior to the onset of labor is recommended. Women who present in labor or with spontaneous rupture of membranes, there is insufficient evidence to determine if c-section reduces the risk of transmission, and individual delivery plan should be made in consultation with an expert in perinatal HIV transmission. Telephone consultation with the National Perinatal HIV/AIDS Clinical Consultation Center at (888)448-8765 may be helpful in rapidly making a delivery plan.
  - Viral load < 1000 copies/ml - if scheduled c-section or induction is indicated, it should be performed at the standard time for obstetric intervention.
  - In women on ART with viral load < 1000 copies/ml, duration of ruptured membranes is not associated with increased risk of perinatal transmission
  - While very low risk (VL < 50) and high risk (VL > 1000) decisions regarding delivery route and timing are relatively easy, decisions regarding optimal route and timing of delivery in between 50 and 1000 copies/ ml should be a shared decision between medical providers and patient

Pre-operative/Pre-induction/Immediate Zidovudine (AZT) 2mg/kg IV infusion over 1 hour followed by 1mg/kg continuous infusion for at least 3 total hours (including 1 hour loading dose) prior to cesarean section and continued throughout labor course for ALL patient with viral load > 1000 copies/ ml, consider for viral load 50-1000 copies/ ml, not required with viral load < 50 copies/ ml with no concern for ART compliance.

Unknown HIV status

Rapid HIV positive (send confirmatory test & presume positive)

1. HIV RNA level >1000 copies/mL
2. Unknown HIV RNA level
3. Late entry to care (3rd Trimester)
4. No prenatal ARV therapy/regimen

Premature *rupture of membranes* >37 weeks gestational age

Mode/timing of delivery to be individualized based on duration of rupture, obstetrical history, HIV RNA levels, and current ARV drug regimen.

Cesarean Section at 38 weeks gestational age

HIV RNA level <1000
Compliant with prenatal ARV therapy/regimen

Continue Prenatal ARV therapy/regimen

Routine delivery timing.
Vaginal delivery acceptable.

1. AVOID INVASIVE MONITORING AND OPERATIVE-ASSISTED DELIVERIES unless emergently obstetrically indicated (Episiotomy, IUPC, FSE, AROM, vaginal instruments)
2. AVOID methergine as first line uterotonic
3. Notify Pediatrics/NICU for delivery
4. Notify & involve Infectious Disease as necessary

Special Considerations:

- *Amniocentesis* –Optimally, women should have compliant ARV therapy and undetectable or low (<1000 copies/mL) viral load prior to receiving an amniocentesis. A theoretical risk exists for vertical transmission. Individualized counseling should be offered, with choice of plan for testing and risk/benefit discussion reviewed if amniocentesis for prenatal diagnosis is desired by an HIV infected gravida. Benefit of lung maturity amniocentesis usually outweighed by risk of infection.
- *Preterm premature rupture of membranes* – risks of vertical transmission must be weighed with risks of prematurity. Expectant management up to 32-34 weeks gestation is preferred in women with well controlled disease.
- *Betamethasone* – no contraindications in this population. Women receiving ARV therapy are at increased risk for glucose intolerance (see below). Follow post-corticosteroids glycemic monitoring per diabetes protocol.
- *Chemoprophylaxis* for women with $CD4^+$ count of <200 cells/μL or a history of oropharyngeal candidiasis**,** $CD4^+$ cell percentage of <14% or a history of an AIDS-defining illness, but do not otherwise qualify.
- *Gestational Diabetes Screening* – ARV therapy is an indication for screening early AND standard screening periods throughout gestation.

Postpartum:

- Breastfeeding is **NOT** recommended, including women receiving ART
- Discuss with IDX to establish management plans after delivery and to determine if prenatal ARV regimen requires dose adjustments postpartum.
- Contraceptive care should be thoroughly discussed and assess if current ART therapy will require hormonal adjustments
- Encourage compliance with ART and follow up with IDX to decrease risk for drug resistance and improve disease control

Disclosure: These care clinical guidelines follow ACOG and evidence of available literature. Clinical evaluation of each, individual patient to determine optimal management is recommended and MFM consultation is available for further assistance.

References:

1. ACOG Committee Opinion. Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome and Women of Color. Number 536, September 2012
2. ACOG Committee Opinion. Prenatal and Perinatal Human Immunodeficiency Virus Testing: Expanded Recommendations. Number 418. Reaffirmed 2011
3. AIDSInfo. 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. http://aidsinfo.nih.gov/guidelines.
4. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994 Nov 3;331(18):1173-80.
5. Cooper, ER; et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr. 2002 Apr 15;29(5):484-94.
6. Prevention of Perinatal HIV Transmission and Ohio's HIV Testing Laws, Issue Brief July 2011. Ohio Department of Health.
7. Sperling RS, Shapiro DE, Coombs RW, Todd JA, Herman SA, McSherry GD, O'Sullivan MJ, Van Dyke RB, Jimenez E, Rouzioux C, Flynn PM, Sullivan JL. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1996 Nov 28;335(22):1621-9.

HIV Classification

CDC Stage*	CDC T-lymphocyte (%)	WHO Stage	WHO T-lymphocyte (%)
Stage Unknown	Lab confirmation & no CD4+ count available	Stage 1	CD4+ count ≥500 cells/μL
Stage 1	CD4+ count ≥500 cells/μL or (≥29%)	Stage 2	CD4+ count 350-499 cells/μL
Stage 2	CD4+ count 200-499 cells/μL or (14-28%)	Stage 3 (advanced)	CD4+ count 200-349 cells/μL
Stage 3 (AIDS)	CD4+ count <200 cells/μL or (<14%) or presence of AIDS-defining condition	Stage 4 (AIDS)	CD4+ count <200 or (<15%)

*CDC requires laboratory confirmation of HIV infection at all stages

CDC (2008). Retrieved August 22, 2012 from http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a1.htm?s_cid=rr5710a1_e

AIDS Defining Conditions

- Bacterial infections, multiple or recurrent (<13y/o)
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive (≥13y/o)
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex (<13y/o)
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary (≥13y/o), disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent (≥13y/o)
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

CDC (2008). Retrieved August 22, 2012 from http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a1.htm?s_cid=rr5710a1_e