BEYOND THE DIAGNOSIS: A CASE-BASED APPROACH TO CARING FOR THE HIV-EXPOSED NEONATE

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DISCLOSURES

- I, Jennifer Fitzgerald DNP, NNP-BC, have no relevant financial relationships with any commercial interests to disclose.

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OBJECTIVES

- At the conclusion of this presentation the learner will be able to:
  - Describe the impact of perinatal HIV exposure on the fetus/neonate
  - Classify HIV medications used in the treatment of neonates
  - Use knowledge of pharmacodynamics, pharmacokinetics, and exposure risk when considering neonatal HIV drug selection
  - Apply knowledge to two case studies

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REDUCING PERINATAL HIV TRANSMISSION

- WHO reports a global decline in pediatric cases by 62% since 2010 (2010-2024)
  - Of all people with HIV→87% were aware of status, 77% were receiving ART, and 73% had achieved viral load suppression
  - Of children with HIV globally 55% are on ART
  - United Nations has set target goals of 95-95-95 to be achieved by 2030

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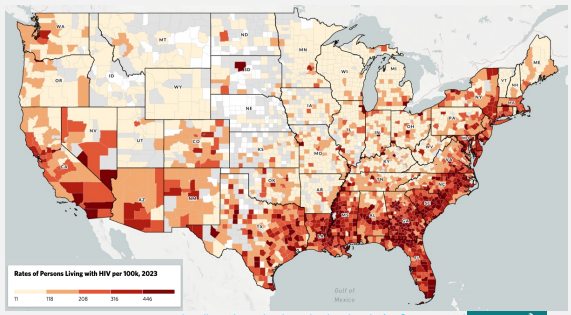

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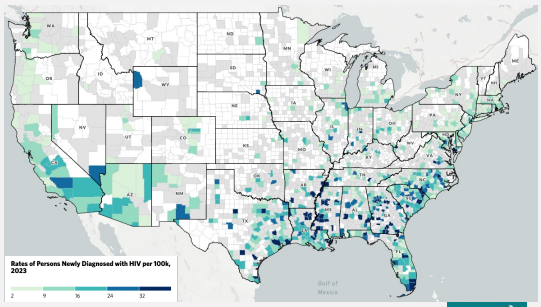

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REDUCING PERINATAL HIV TRANSMISSION

- Goal: reduce perinatal transmission to <1% and 1 case per 100,000k live births
  - CDC published framework and set goals in 2012
  - Strategies developed to reduced incidence of antenatal and intrapartum transmission included:
    - HIV screening during pregnancy
    - Initiation of ART therapy in newly diagnosed pregnant women
    - Cesarean delivery for women with elevated viral loads
    - Avoidance of breastfeeding for women living with HIV
    - ART therapy for newborns

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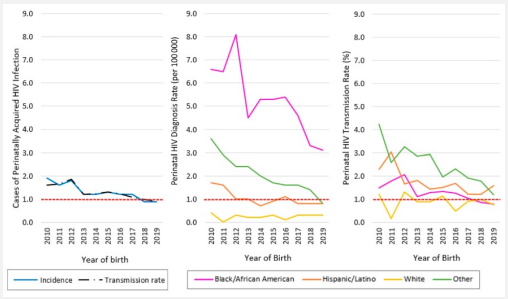

Lampe, et. al. (2023)

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CASE #1

Maternal History	Prenatal Labs	Management--Maternal
• 24 y.o. Hispanic female • G2P1001 • Prenatal care initiated at 30 weeks' gestation • Social history: Recently relocated to the area, limited social supports, no family in the area, Urine Tox + for cannabis, denies ETOH and other drug use	• Blood type: A+ • RPR: Non-reactive • GC: +(treated with TOC pending) • Chl: negative • Hep B & Hep C: Non-reactive • **HIV: Positive** with 4th generation testing confirming HIV-type 1; Viral load at time of confirmatory testing 25,430 copies/mL; CD4 count low-normal (930 cells/mm³) • GBS pending	• ART initiation at time of diagnosis but with delays on starting therapy (started 10 days prior to delivery) • Initiated IV AZT in L&D • Cesarean delivery performed at 35 3/7 weeks due to preterm labor and premature rupture of membranes (6 hrs PTD)

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HIV INFECTIONS

- Human immunodeficiency virus (HIV) infection caused by one of two viral strains: Type 1 or Type 2
  - HIV type 1 most prevalent strain in the US
  - HIV type 2 commonly found in West Africa*
- Infect peripheral blood mononuclear cells, brain, bone marrow, & GU tract with transmission noted by blood, human milk, and genital secretions (excluding urine)
- Modes of transmission: sexual contact, blood exposure via mucous membranes, sharps/needles, perinatal, & transfusion

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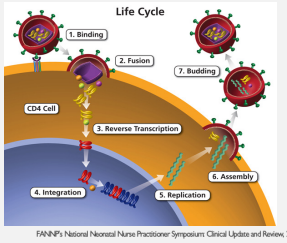
HIV REPLICATION



1. HIV virus attaches to CD4 receptor
2. Fusion of virus to cell wall
3. Injection of virus core into cytoplasm of the cell→RT enzyme translates RNA to DNA
4. DNA now in host cell nucleus and incorporated into host genome
5. Steps 5-7 replicates HIV viral DNA creating and releasing more HIV virus

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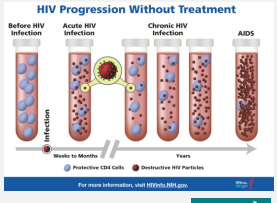
CLINICAL PRESENTATION

- Adolescents and Adults
  - Staged→specific criteria indicating timing & severity of immune suppression
  - Stage 1: First weeks following infection, 40-90% demonstrate:
    - Fever, malaise, lymphadenopathy, & skin rash (known as acute retroviral syndrome) accompanying rapid viral multiplication



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CLINICAL PRESENTATION

- Pediatric
  - Undiagnosed HIV infections present with:
    - Unexplained fevers
    - Lymphadenopathy
    - Hepato/splenomegaly
    - FTT
    - Infections: candidiasis, recurrent bacterial infections, opportunistic infections
    - Severe immune deficiencies/CBC derangements—challenging in the neonate
    - CNS involvement

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DIAGNOSTIC TESTING

- Who to test?
  - Routine care—discussion with primary care providers
    - Yearly testing for high-risk groups
    - Access to PrEP
  - Risk-based exposures
  - Clinical signs concerning for HIV
  - Prenatal testing
    - Maternal-fetal transmission as high as 24% if untreated
    - *Testing early in 1st trimester and again mid-pregnancy if increased risk
  - Postnatal/Neonatal testing

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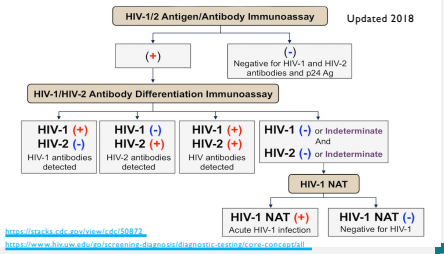
DIAGNOSTIC TESTING



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DIAGNOSTIC TESTING

4th Generation	Point of Care tests	HIV DNA PCR
• Combined immunoassay • HIV 1 & 2 Ab (IgG and IgM)* • p24 antigen (protein from core of the virus) • Ideal test for early-stage infection (after 2 weeks)	• Antibody only testing • Saliva or finger stick testing • Not helpful with early-stage infection* • Ease of access, convenient (risk of false+)	• NAT that detects specific HIV DNA in PBMCs • Qualitative result (+/-) • Good option for newborn • Not available in all institutions

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DIAGNOSTIC TESTING

HIV RNA PCR	CD4 Lymphocyte Count
• "Viral Load" • NAT that detects extracellular viral RNA in plasma • Quantitative result • Used to detect acute infection and to follow treatment response* • Recommended for use in newborn exposure testing	• Evaluates health of the immune system • Quantitative result • Helpful in staging and determining severity of illness • Helps to understand opportunistic infection risk and need for prophylaxis

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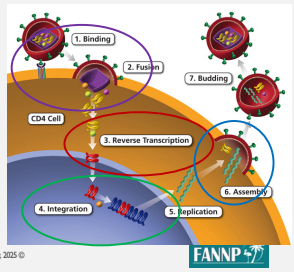
HIV DRUG CLASSES

- **Nucleoside reverse transcriptase inhibitor (NRTI)**
  - Tenofovir, Zidovudine, Emtricitabine, Lamivudine
- **Non-Nucleoside reverse transcriptase inhibitor (NNRTI)**
  - Doravirine, Efavirenz, Nevirapine
- **Protease Inhibitor (PI)**
  - Darunavir/Ritonavir
- **Integrase Inhibitor (INSTI)**
  - Bictegravir, Dolutegravir, Raltegravir
- **Fusion Inhibitors**



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HIV INFECTION—MATERNAL

- Risk for perinatal transmission as high as 22% in neonates born to women who acquired HIV during pregnancy
- Prompt initiation of ARV plus additional testing to include HIV drug resistance testing
- Maternal ARV therapy options, there are many→therapy often determined by timing of diagnosis and previous exposure to ARV therapy.
  - Preferred ARV in acute HIV*→Bictarvy or Dolutegravir PLUS dual NRTI

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HIV EXPOSURE

- New maternal diagnosis during pregnancy, non-adherence to prescribed ARV therapy or with elevated viral load >1,000 copies/mL→intrapartum
  - Scheduled cesarean is recommended*
  - Intrapartum management with IV Zidovudine→2 mg/kg loading dose over the 1st hour followed by continuous infusion of 1 mg/kg/hr for at least 2 hrs (minimum of 3 hours prior to delivery)

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CASE #1—NEONATE

Resuscitation	Initial labs	Management
• Delivered at 35 3/7 weeks • APGARs: 7/9[5] • Brought to the NICU for management of TTN and HIV exposure • Placed on CPAP +5 for RR of 80 and FiO2 requirement of 33%	• HIV PCR & CBC testing sent following delivery* • LFT's sent for baseline on DOL 1 • Blood gas • Additional ID testing to be considered if unable to wean from CPAP	• Initiate enteral nutrition via gavage tube • Initiate ARV therapy within 6-12 hours • Repeat testing at 2-3 weeks, 1-2 months, 8-10 weeks, and 4-6 months • Consideration of Bactrim prophylaxis

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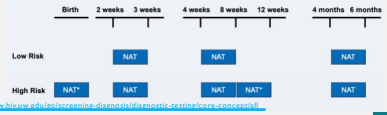
POST-NATAL NEONATAL EVALUATION

- Diagnostic testing:
  - Baseline CBC and LFT's shortly after delivery
  - HIV DNA or RNA PCR testing at the following intervals:



https://www.hiv.uw.edu/go/screening-diagnosis/diagnostic-testing/core-concept/all

https://publications.aap.org/redbook/book/755/chapter/14078400/Human-Immunodeficiency-Virus-Infection?1

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PHARMACOLOGIC MANAGEMENT

- Zidovudine (NRTI)
  - Primary drug for neonatal post-exposure prophylaxis and treatment of active infection, initiate within 1 hour of birth (high-risk)
  - MOA: Inhibits RT enzyme activity and blocks RNA→DNA replication; high first-pass metabolism
  - Dosing: Dependent on size and GA
    - <34 6/7 weeks: 2 mg/kg/dose q12 hours with dose increasing to 3mg/kg/dose q12 hrs between 2-4 weeks PNA*
    - >35 weeks: 4 mg/kg/dose q12 hours for duration of therapy 4-6 weeks
    - IV dosing is a 25% dose reduction with same dosing interval

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PHARMACOLOGIC MANAGEMENT

- Lamivudine (NRTI)
  - Adjunct therapy to be initiated for neonates at high risk of perinatal transmission, presumptive treatment, start in first 6 hours
  - MOA: Inhibits RT enzyme activity and blocks RNA→DNA replication. Synergistic effect with other retrovirals
    - Good oral bioavailability; Clearance improves with PNA
    - Used as part of combination therapy as monotherapy associated with resistance.
  - Dosing: 2 mg/kg/dose enteral BID

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PHARMACOLOGIC MANAGEMENT

- Nevirapine (NNRTI)
  - Adjunct therapy for neonates at high risk of perinatal transmissions; start within first 6 hours
  - MOA: Inhibits RT enzyme activity and blocks RNA→DNA replication without requiring intracellular metabolism. Synergistic effect with Zidovudine.
    - Rapid absorption and quickly metabolized but slow excretion in the neonate, with long ½ life
  - Dosing: needs close attention to dosing as doses for premature neonate adjust with improving renal function

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PHARMACOLOGIC MANAGEMENT

- Raltegravir (INSTI):
  - For use in neonatal presumptive therapy when concern is high for HIV-2, start within first 6 hours
  - MOA: Blocks integration of HIV DNA into the host CD4 cell. Highly protein bound
  - Dosing: available for neonates >37 weeks and is either weight based or fixed dosing based on weight*
    - Dosing increases with advancing PNA due to maturation of the glucuronidation pathway in the liver

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SIDE EFFECTS OF THERAPY

- Common, known complications of ARV therapy
  - Myelosuppression →anemia and neutropenia, may be profound
  - GI symptoms→emesis, nausea, diarrhea, elevated liver enzymes, elevated bilirubin levels
  - Skin→Rash (esp with Nevirapine)

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ADDITIONAL MANAGEMENT

- Feeding options:
  - For the neonate at *high-risk* of HIV transmission
    - Maternal breast milk discouraged in US
    - Alternatives include donor BM or standard/preterm formula
- Evaluation for opportunistic or co-infections
  - Consideration of CMV, Hepatitis infections, syphilis, toxo and TB
  - Additional imaging if concern for TORCH infections

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CASE #2

Maternal History	Prenatal Labs	Management--Maternal
• 31 y.o. Black female • G3P2002 • Prenatal care initiated at 30 • Care started in 1st trimester with consistent care throughout pregnancy and undetectable viral loads throughout pregnancy • Social history: Married and lives with partner and other 2 children, good family support system, Urine Tox negative, denies ETOH and other drug use	• Blood type: O+, neg Ab screen • RPR: Non-reactive • GC/Chl: negative • Hep B & Hep C: Non-reactive • GBS negative • **HIV: Positive,** undetectable viral load throughout pregnancy	• On combination ART with Bictarvy • PNV and Iron supplementation only other meds • Spontaneous VD following ROM x3.5 hours

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CASE #1—NEONATE

Resuscitation	Initial labs	Management
• Delivered at 39 2/7 weeks • APGARs: $8^{1}/9^{5}$ • 3.4 kg BW • Admitted to the NBN for newborn care and HIV exposure evaluation	• Initial HIV PCR RNA or DNA testing to be sent at 2-3 weeks of age • CBC at baseline	• Initiate enteral nutrition as tolerated→Mom desires breastfeeding • Initiate ARV therapy within 6 hours • Repeat testing at 1-2 months, and 4-6 months

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UPDATED FEEDING RECOMMENDATIONS

- New guidance in 2024 highlights benefits to both mom and baby for breastfeeding
  - Need regular and frequent counseling throughput pregnancy on risk of transmission with breastfeeding*
  - Counseling should include that donor milk or formula are only methods of eliminating post-natal HIV exposure
  - No known toxicity from maternal ARV therapy; Hales classifications for this case would be L3
  - Conditions with increased risk of transmission: mixed feeding, mastitis, and thrush

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MANAGEMENT RECOMMENDATIONS

- Viral load testing and breastfeeding
  - Monitored periodically throughout time breastfeeding ~ every 1-2 months
  - Plan in place if viral load becomes detectable during breastfeeding
- Ongoing ARV following initial prophylaxis—is it necessary?
  - Initial prophylaxis 2 weeks for low-risk transmission and continued VL suppression
    - debated by experts with some recommending full 6 weeks followed by transition to Nevirapine or Lamivudine for duration of time breastfeeding*

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PRIMARY CARE CONSIDERATIONS

- Ensure regular PCP appointments
  - PCP comfortable in management of HIV exposure
  - Link to pediatric HIV specialist
  - Ideally medical home model to address social, emotional, health-care access, and prescription coverage
  - Ongoing testing
- Assistance with diagnosis disclosure

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PRIMARY CARE CONSIDERATIONS

- Pneumocystis jirovecii pneumonia (PCP) prophylaxis
  - Start at 4-6 weeks unless there is adequate information to exclude HIV infection
- Ongoing testing
  - Nearly all positive infants identified by 2-4 months of age
  - Will be followed until 18 months or unless definitive testing identifies them earlier

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RULING OUT HIV TRANSMISSION

- Infection can be ***presumed*** to be excluded in non-breastfed infants
  - with 2 or more negative tests (at ≥2 and ≥ 4 weeks)
  - One negative NAT (RNA or DNA PCR) test at ≥8weeks
  - One negative antibody test at ≥6 months
- ***Definitive*** exclusion
  - 2 or more negative tests at ≥1 month and again at ≥4 months or on 2 separate specimens collected at ≥ 6 months
  - Documentation of negative antibody testing between 12-18 months

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IMMUNIZATIONS

- Immunizations
  - Give all early vaccines
  - https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-pediatric-opportunistic-infections/recommended-immunizations-schedule#ry
- Considerations
  - Increased risk for infections due to compromised immune system
  - Lower response rate to many vaccines
  - Avoid live vaccines in patients with low CD4 counts as increased risk for illness
    - Avoid MMR and Varicella if severely immuno-comprimised

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SUMMARY

- Understand Maternal testing and goal of ARV
- Early ARV can prevent transmission
- Open, collaborative relationship with family
- Understand timing of subsequent viral testing and any ongoing monitoring necessary due to ARV therapies

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KNOWLEDGE QUESTIONS

Which of the following strategies is most effective in reducing perinatal HIV transmission according to CDC guidelines?

a. Routine prenatal HIV screening and timely initiation of ART
b. Scheduled cesarean delivery for all HIV-positive women
c. Breastfeeding exclusively for 6 months with maternal ART

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KNOWLEDGE QUESTIONS

HIV replication begins with which of the following steps?

a. Integration of viral DNA into the host genome
b. Attachment of HIV to the CD4 receptor on host cells
c. Translation of viral RNA into proteins in the cytoplasm

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KNOWLEDGE QUESTIONS

Which antiretroviral drug class includes Zidovudine and Lamivudine?

a. Nucleoside reverse transcriptase inhibitors (NRTIs)
b. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
c. Integrase inhibitors (INSTIs)

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KNOWLEDGE QUESTIONS

According to updated 2024 feeding recommendations, what is the only method to eliminate postnatal HIV transmission risk?

a. Exclusive breastfeeding with maternal viral load suppression
b. Use of donor breast milk or infant formula
c. Mixed feeding with maternal ART

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KNOWLEDGE QUESTIONS

A neonate, born to an HIV-positive mother with a viral load >1,000 copies/mL, is started on Zidovudine, Lamivudine, and Nevirapine within 1 hour of birth. What is the physiologic rationale for initiating triple therapy so early?

a. To decrease gastrointestinal side effects by combining drugs from different classes
b. To delay the need for further diagnostic testing in the first 6 months of life
c. To reduce the risk of perinatal HIV transmission in high-risk infants through synergistic antiviral activity

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