Local Experience with High-Risk & Low-Risk Perinatal HIV Exposure in Infants

Roberto P. Santos, MD, MSCS, FAAP, AAHIVS, FIDSA

Pediatric Infectious Diseases, Children's of Mississippi MS-AIDS Education Training Program Center, April 27, 2022 (12:00 - 1:00 PM), UMMC, Jackson, MS



Disclosures

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)
American Board of Pediatrics – SubBoard ID	Х							
JNJ			X (Site PI)					Contract with UMMC
MSD			X (Site PI)					Contract with UMMC
Eli Lilly			X (Site PI)					Contract with UMMC
HRSA								COVID-19 Response

- I will not be discussing any off label use of medications related to this talk
- Cases may not be diagnostic & therapeutic in nature, management should be individualized

Objectives

- Review the epidemiology of perinatal HV infection
- Discuss the various clinical scenarios (high risk versus low risk) associated with perinatal HV exposure in infants
- Recognize the appropriate antiretroviral regimen and the initial postnatal management of the newborn exposed to HV
- Determine the long-term follow up of infants exposed to ART



Epidemiology of perinatal HIV

 We don't know exactly how many women with HV give birth annually in the US

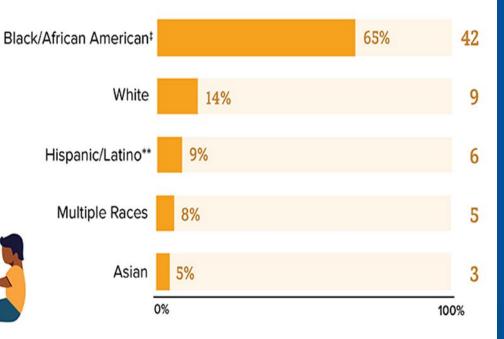
More recent evidence suggests that the number is less than 5,000
 Our local experience at the Children's of Mississippi: no perinatal transmission in the last decade

Of the **37,968 NEW HIV DIAGNOSES** in the US and dependent areas in 2018, <1% (65) were due to perinatal transmission.



Diagnoses of Perinatal HIV Infections in the US and Dependent Areas by Race/Ethnicity, 2018*

Most perinatal HIV diagnoses were among Black/African American children.⁺



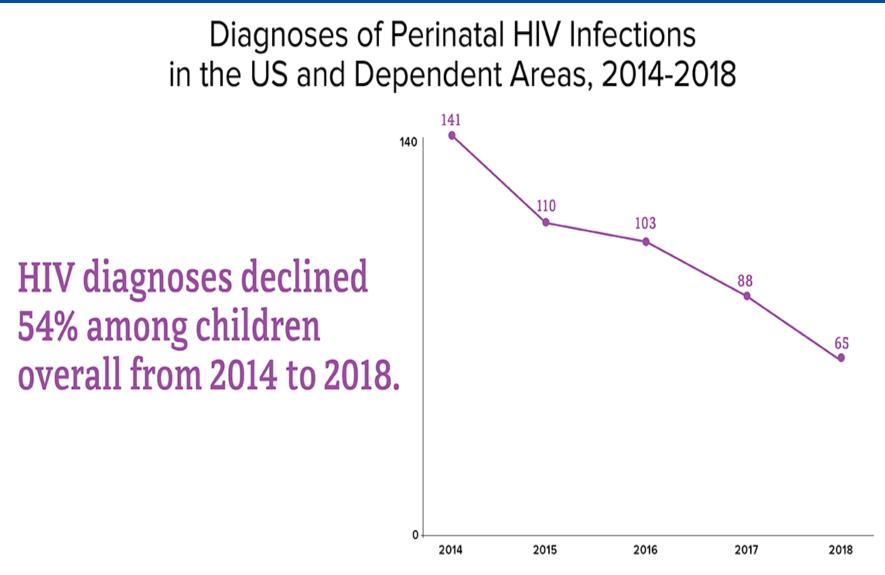
*In 2018, there were no cases of perinatal HIV among Native Hawaiians/Other Pacific Islanders and American Indians/Alaska Natives. [†] Children under the age of 13.

[†] Black refers to people having origins in any of the Black racial groups of Africa. African American is a term often used for Americans of African descent with ancestry in North America.

** Hispanics/Latinos can be of any race.

Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2018 (updated). HIV Surveillance Report 2020;31.

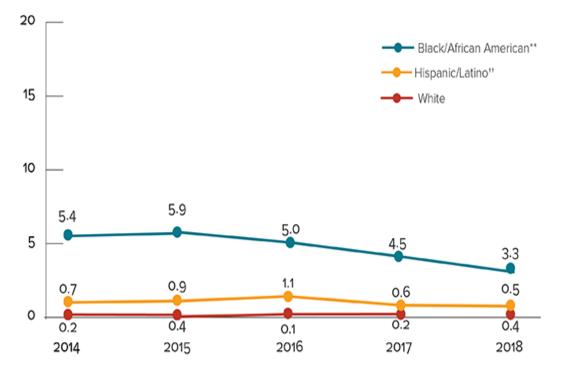




Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2018 (updated). HIV Surveillance Report 2020;31.



Rates of Perinatally-Acquired HIV Infections Among Persons Born in the United States, by Year of Birth and Mother's Race/Ethnicity, 2014-2018 ***



*Data include only persons born in the United States (50 states and District of Columbia). Data accounted for delays between birth and diagnosis, as well as between diagnosis and reporting. *Rates are per 100,000 live births. *Live-birth data reflect race/ethnicity of the infant's mother. **Black refers to people having origins in any of the Black racial groups of Africa. African American is a term often used for Americans of African descent with ancestry in North America. **Hispanics/Latinos can be of any race.

Source: Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2018. *HIV Surveillance Supplemental Report* 2020;25(2).



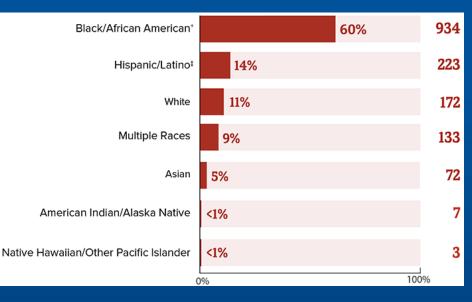
Living with HIV from Perinatal Exposure



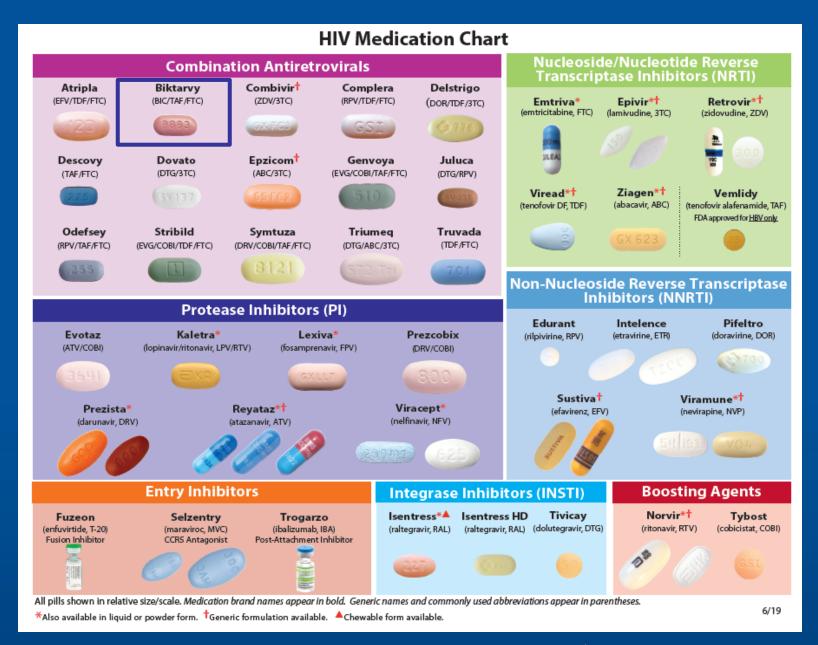
Of the **1,042,270 people with diagnosed HIV** at the end of 2018, <1% (1,544) were among children with diagnosed perinatal HIV.

Most children with diagnosed perinatal HIV are Black/African American.







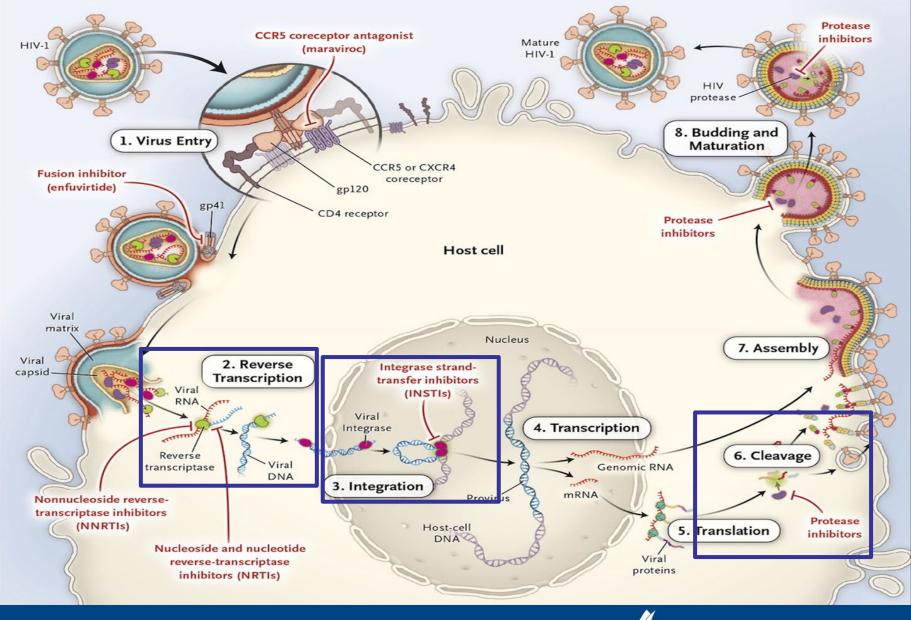




ARV in the NB with Perinatal HIV Exposure

- Nucleoside reverse transcriptase inhibitors (NRTI) ZDV, 3TC
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
 NVP
- Integrase inhibitors (INSTI)
 RAL (at birth), DTG (at 4 weeks)
- Protease inhibitors (PI)
 LPV/r (at 2 weeks)
- Available ARV in local hospital pharmacy





Gandhi RT. Single-pill combination regimens for treatment of HIV-1 infection. N Engl J Med. 2014;371:248-59

THE UNIVERSITY OF MISSISSIPPI MEDICAL CENTER

1st scenario

- Mother (G2PI) with HV infections (behaviorally), on cART, CD4 >500 cells/cmm HVVL <50 copies/mL (<4 weeks ago)
- Infected before her 1st pregnancy & her 2 yo is HV negative
- She is very adherent on her daily cART
- Delivered via SVD to healthy baby boy at 38 weeks gestation
- Plans for the NB



Management of Infants Born to People with HIV Infection

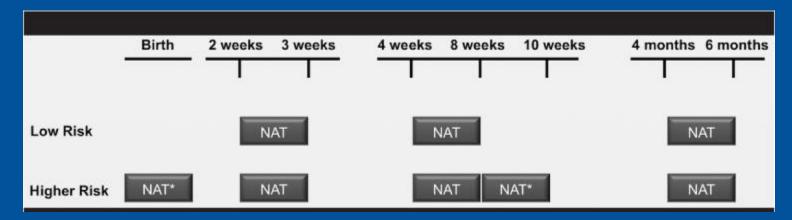
- All newborns who were exposed perinatally to HV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HV
- Newborn ARV regimens administered at doses that are appropriate for the infant's gestational age should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery
- A 4-week zidovudine (ZDV) ARV prophylaxis regimen can be used in newborns whose mothers received ART during pregnancy and had viral suppression within 4 weeks prior to delivery (defined as a confirmed HV RNA level <50 copies/mL) and for whom maternal

https://clinicalitio.hiv.gov/en/guitlelines/perinatal/antiretroviral-management-newbornsperinatal-hickgostra-childicecto?/iiOfuOf CONCENN



Level of Perinatal HIV Transmission Risk		Description		Neonatal ARV Management		
Low Risk of Perinatal HIV Transmission	pregn as a c <50 c	ers who received ART durin ancy with viral suppression confirmed HIV RNA level opies/mL) within 4 weeks p ry and no concerns related ence	(defined rior to	ZDV for 4 weeks ^a		
Drug	Drug Doses by Gestational Age at Birth					
ZDV		≥35 Weeks' Gestation at Birth				
Note: For newborns who are unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.		 Birth to Age 4 Weeks: ZDV 4 mg/kg per dose orally twice daily Age >4 Weeks: ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection. 				
		Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks' Gestation from Birth to 4 Weeks				
		Weight Band	Volume	me of ZDV 10 mg/mL Oral Syrup Twice Daily		
		2 to <3 kg	1 mL			
		3 to <4 kg	1.5 mL			
		4 to <5 kg	2 mL			
		 ≥30 to <35 Weeks' Gestation at Birth Birth to Age 2 Weeks ZDV 2 mg/kg per dose orally twice daily 				
					2000 C	





- Fig 3.8. Recommended Virologic Testing Schedules for Infants Exposed to HV by Perinatal HV Transmission Risk
- NAAT or NAT nucleic acid amplification test
- Low Risk: Infants born to mothers who received standard antiretroviral therapy (ART) during pregnancy with sustained viral suppression (usually defined as confirmed HV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence.
- Hgher Risk * For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2 to 4 weeks after cessation of ARV prophylaxis (ie, at 8-10 weeks of life).

2021-24 Red Book, 32nd AAP - Report of the Committee on Infectious Diseases, pp. 432



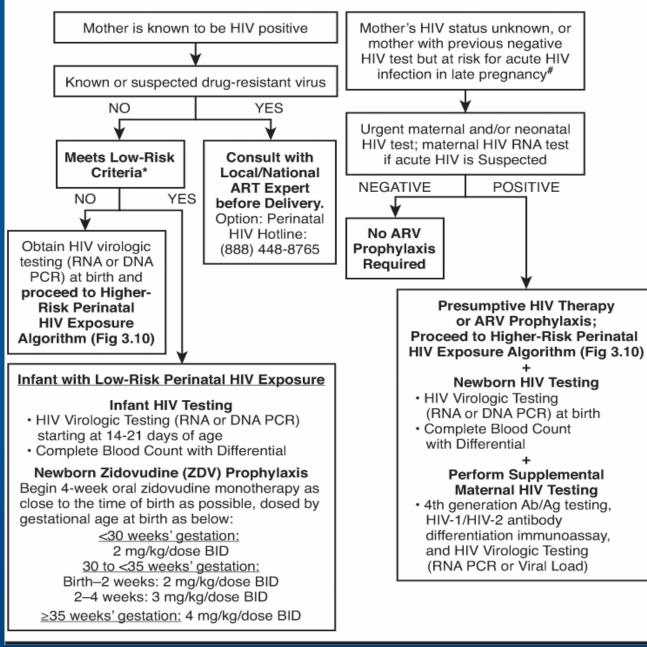


Fig 3.9. Newborn testing and prophylaxis recommendations following low-risk* perinatal HV exposure

> THE UNIVERSITY OF MISSISSIPPI MEDICAL CENTER

2021-24 Red Book, 32nd AAP - Report of the Committee on Infectious Diseases, pp. 436

Fig 3.9. Newborn testing and prophylaxis recommendations following low-risk* perinatal HV exposure

- *Low-risk criteria:
- (1) mother with HV who received ART throughout pregnancy or from the early 1st/2nd trimester; AND
- (2) confirmed maternal HV RNA <50 copies/mL near delivery (within 4-6 weeks); AND
- (3) no concerns regarding ART adherence; AND
- (4) mother did not have primary or acute HV infection during pregnancy.
- #Mothers with previous negative HV test at risk for seroconversion in late pregnancy are those with: documented STI, unprotected sex, partner with HV, multiple partners, or IV drug

2021-24 Red Book, 32nd AAP - Report of the Committee on Infectious Diseases, pp. 436

ISO

1st scenario (Low Risk)

- Mother (G2PI) with HV infections (behaviorally), on cART (DTG-TDF-FTC), CD4 >500 cells/cmm HV VL <50 copies/mL (<4 weeks ago)
- Infected before her 1st pregnancy & her 2 yo is HV negative
- She is very adherent on her daily cART
- Delivered via SVD to healthy baby boy at 38 weeks gestation
- Plans for the NB

CEC, HV DNA at 2 weeks (follow up at 2 weeks, 4 weeks, 4 months) ZDV within 6 hours of life for 4 weeks Peds ID (NP, RN, SW), no breastfeeding, no pre-chewed food

2nd scenario

- Mother (G2PI) with HV infections (behaviorally), prescribed cART but did not fill her Rx, CD4 >500 cells/cmm HV VL >15,000 copies/mL (<4 weeks ago)
- Infected for the first time during this pregnancy
- She is not on her daily cART
- Delivered via CS to healthy baby boy at 38 weeks gestation
- Plans for the NB?



Management of Infants Born to People with HIV Infection

- Newborns at high risk of perinatal acquisition of HV should begin presumptive HV therapy.
- Newborns at high risk of HV acquisition include those born to people with HV who—

Have not received antepartum ARV drugs, or

Have received only intrapartum ARV drugs, or

Have received antepartum ARV drugs but who did not achieve viral suppression (defined as a confirmed HV RNA level <50 copies/mL) within 4 weeks of delivery, or

Have primary or acute HV infection during pregnancy



Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery and no concerns related to adherence	ZDV for 4 weeks ^a
High Risk of Perinatal HIV Transmission ^{a,b}	Mothers who did not receive antepartum ARV drugs Mothers who received only intrapartum ARV drugs Mothers who received antepartum ARV drugs but did not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother should immediately discontinue breastfeeding)°	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL administered from birth up to 6 weeks ^d





≥37 Weeks' Gestation at Birth

Birth to Age 4 Weeks

NVP 6 mg/kg per dose orally twice daily

Age >4 Weeks

 NVP 200 mg/m² BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.

≥34 to <37 Weeks' Gestation at Birth

Birth to Age 1 Week

NVP 4 mg/kg per dose orally twice daily

Age 1 to 4 Weeks

• NVP 6 mg/kg per dose orally twice daily

Age >4 Weeks

 NVP 200 mg/m² BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.

≥32 to <34 Weeks' Gestation at Birth

Birth to Age 2 Weeks

NVP 2 mg/kg per dose orally twice daily

Age 2 to 4 Weeks

NVP 4 mg/kg per dose orally twice daily

Age 4 to 6 Weeks

NVP 6 mg/kg per dose orally twice daily

<mark>Aae >4 Weeks</mark>



RAL

Note: If the mother has taken RAL 2 to 24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24 to 48 hours after birth; additional ARV drugs should be started as soon as possible.7

≥37 Weeks'	Gestation	at Birth a	nd Weighing ≥2 kg⁰

Birth to Age 6 Weeks			
Body Weight	Volume (Dose) of RAL 10 mg/mL Suspension		
Birth to 1 Week: Once-Daily Dosing	Approximately 1.5 mg/kg per dose		
2 to <3 kg	0.4 mL (4 mg) once daily		
3 to <4 kg	0.5 mL (5 mg) once daily		
4 to <5 kg	0.7 mL (7 mg) once daily		
1 to 4 Weeks: Twice-Daily Dosing	Approximately 3 mg/kg per dose		
2 to <3 kg	0.8 mL (8 mg) twice daily		
3 to <4 kg	1 mL (10 mg) twice daily		
4 to <5 kg	1.5 mL (15 mg) twice daily		
4 to 6 Weeks: Twice-Daily Dosing	Approximately 6 mg/kg per dose		
3 to <4 kg	2.5 mL (25 mg) twice daily		
4 to <6 kg	3 mL (30 mg) twice daily		
6 to <8 kg	4 mL (40 mg) twice daily		



ZDV

Note: For newborns who are unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.

≥35 Weeks' Gestation at Birth

Birth to Age 4 Weeks:

ZDV 4 mg/kg per dose orally twice daily

Age >4 Weeks:

ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.

Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks' Gestation from Birth to 4 Weeks

Weight Band	Volume of ZDV 10 mg/mL Oral Syrup Twice Daily
2 to <3 kg	1 mL
3 to <4 kg	1.5 mL
4 to <5 kg	2 mL

≥30 to <35 Weeks' Gestation at Birth

Birth to Age 2 Weeks

ZDV 2 mg/kg per dose orally twice daily

Age 2 Weeks to 6 to 8 Weeks

ZDV 3 mg/kg per dose orally twice daily

Age >6 to 8 Weeks

ZDV 12 mg/kg per dose orally twice daily; make this dose increase only for infants with confirmed HIV infection.

<30 Weeks' Gestation at Birth

Birth to Age 4 Weeks

ZDV 2 mg/kg per dose orally twice daily

Age 4 to 8 to 10 Weeks

ZDV 3 mg/kg per dose orally twice daily

Age >8 to 10 Weeks

ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection



Management of Infants Born to People with HIV Infection

3TC	≥32 Weeks' Gestation at Birth
	 Birth to Age 4 Weeks 3TC 2 mg/kg per dose orally twice daily
	Age >4 Weeks 3TC 4 mg/kg per dose orally twice daily



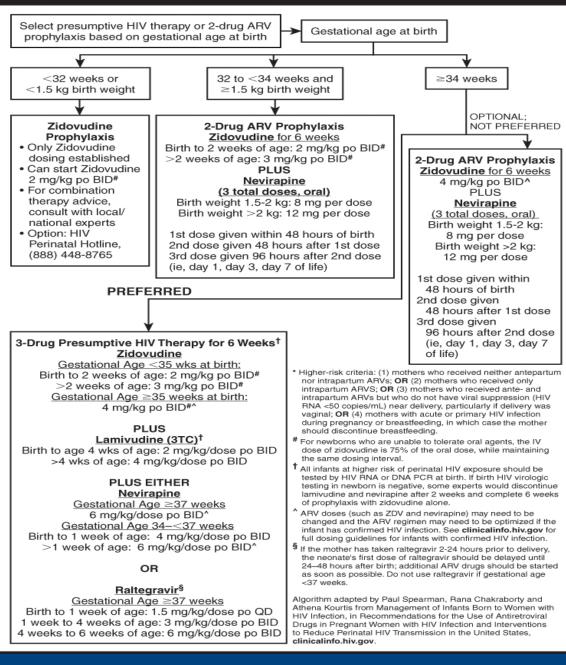


Fig 3.10. Newborn Testing and Prophylaxis Recommendations Following Hgher-Risk Perinatal HV Exposure*

ses, dd. 437

2021-24 Red Book, 32nd AAP - Report of the Committee on Infectious Diseases, pp. 437

2nd scenario (High Risk)

- Mother (G2PI) with HV infections (behaviorally), prescribed cART but did not fill her Rx, CD4 >500 cells/cmm HV VL >15,000 copies/mL (<4 weeks ago)
- Infected for the first time during this pregnancy
- She is not on her daily cART
- Delivered via CS to healthy baby boy at 38 weeks gestation
- Plans for the NB?

CBC, HV DNA & HV RNA VL at birth (follow up at 2 weeks, 4 weeks, 4 months) ZDV within 6 hours of life for 6 weeks, 3TC, RAL or N/P Peds ID (NP, RN, SW), no breastfeeding, counseling regarding pre-chewed food

3rd scenario

- Mother (G2PI) with HV infections (behaviorally), on cART, CD4 >500 cells/cmm HVVL200 copies/mL (<4 weeks ago)
- Infected before her 1st pregnancy & her 2 yo is HV negative
- She is adherent on her daily cART
- Delivered via SVD to healthy baby boy at 38 weeks gestation
- Plans for the NB?



Management of Infants Born to People with HIV Infection

- Newborns at high risk of perinatal acquisition of HV should begin presumptive HV therapy.
- Most Panel members would recommend initiating presumptive HV therapy with any detectable level of viremia within 4 weeks prior to delivery, others may opt for a two-drug prophylaxis regimen if meternal viral load was less than 200 to 400 copies/mL.



Two-Drug Antiretroviral Prophylaxis

- Two-drug regimen consists of 6 weeks of ZDV plus three doses of the prophylactic dose of NVP, with the NVP doses given within 48 hours of birth, 48 hours after the first dose, and 96 hours after the second dose.
- The prophylactic doses are NP12 mg per dose orally for infants weighing >2 kg and NP 8 mg per dose orally for infants weighing 1.5 kg to 2 kg. These are the actual doses, not the milligram per kilogram doses.



3rd scenario

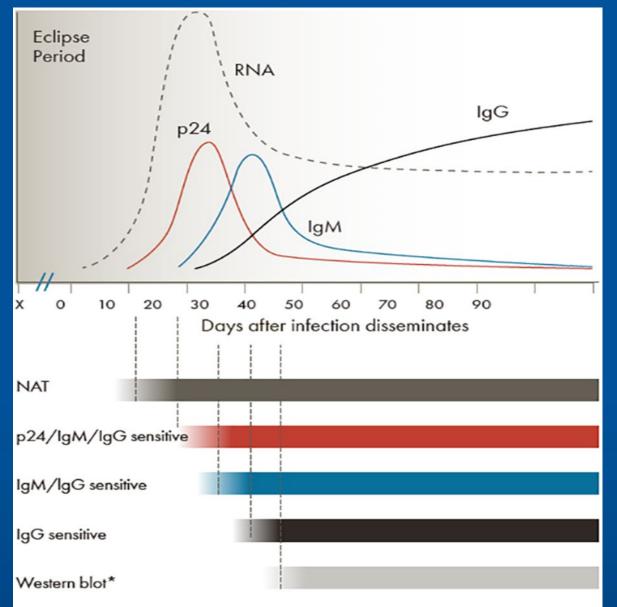
- Mother (G2PI) with HV infections (behaviorally), on cART (DTG-TDF-FTC), CD4 >500 cells/cmm HV VL 200 copies/mL (<4 weeks ago)
- Infected before her 1st pregnancy & her 2 yo is HV negative
- She is adherent on her daily cART
- Delivered via SVD to healthy baby boy at 38 weeks gestation
- Plans for the NB?

CBC, HV DNA & HV RNA VL at birth (follow up at 2 weeks, 4 weeks, 4 months) ZDV within 6 hours of life for 6 weeks, N/P versus 3 cART (RAL/N/P, ZDV, 3TC) Peds ID (NP, RN SW), no breastfeeding, counseling regarding pre-cheved food

4th scenario

- Mother (G2PI) without prenatal care, HV screening test positive at delivery
- Delivered via SVD to healthy baby boy at 38 weeks gestation
- Plans?





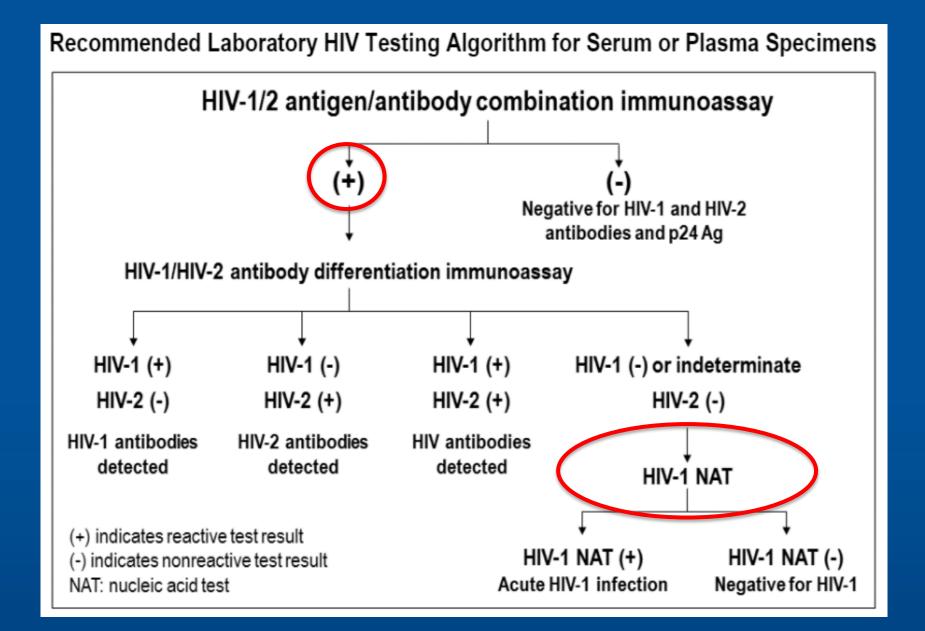
Western blot is no longer used for HIV.

https:www.cdc.gov/hiv/clinicians/screening/diagnostic-tests.html

TRUE POSTIVE

- Eclipse period the amount of time during which no existing diagnostic test is capable of detecting HV
- Window period the time between potential HV exposure and an accurate test result
- HV screening (+), HV NAT (+)







False Positive HIV Test

- HV Screening is (+), HV Ab differentiation (-), HV NAT (-)
- The HVRNA assay can detect the presence of HV as early as 10 days post-infection, so this test should be used when acute HV infection is suspected.
- The combination of a positive antigen-antibody screen with a negative antibody differentiation assay and a negative HVRNA assay is seen in people without HV who have a false-positive antigen-antibody screen.
- False positive results occur during pregnancy may be associated
 with cross-reactivity with alloantibodies & autoantibodies

https://clinicalinfo.hiv.gov/en/guidelines/perinatal/maternal-hiv-testing-and-identification-perinatal-hiv-exposure J Infect Dis. 2021 Jan 15; 223(2): 234-237. Published online 2020 Jun 19. doi: 10.1093/infdis/jiaa343



4th scenario

- Mother (G2PI) without prenatal care, HV screening test positive (at delivery)
- Delivered via SVD to healthy baby boy at 38 weeks gestation
- Plans?

Check HV RNA VL in the mother CBC, HV DNA & HV RNA VL at birth (follow up at 2 weeks, 4 weeks, 4 months) ZDV within 6 hours of life for 6 weeks, 3TC, RAL or NVP Peds ID (NP, RN, SW), no breastfeeding, counseling regarding pre-chewed food



Initial Postnatal Management

- ARV (one-, two-, three-drug regimen)
- HVDNA or HVRNAVL
- CBC diff
- 4 weeks check for neutropenia & anemia (s/p ZDV & 3TC)
- 4-6 weeks PCP prophylaxis if cannot presumptively exclude HV infection
- Inquire regarding breastfeeding & the use of pre-masticated food
 In the US, it is recommended that women with HV refrain from breastfeeding their infants as safe infant feeding alternatives are available
 - Counseling against the use of premasticated (prechewed or prewarmed) food should be provided as safe infant options are available.

https://clinicalinfo.hiv.gov/en/guidelines/perinatal/initial-postnatal-management-neonate-exposed-hiv?view=full

Diagnosis of HIV infection

- Presumptively excluded in non-breastfed infants with two or more negative virologic tests (one at age \geq 2 weeks & one at age \geq 4 weeks)
- Definitively excluded in non-breastfed infant is based on two or more negative virologic tests (i.e., negative NATs [RNA or DNA]), one at age ≥1 month and one at age ≥4 months, or two negative HV antibody tests from separate specimens obtained at age ≥6 months.



Practice of Feeding Premasticated Food to Infants: A Potential Risk Factor for HIV Transmission

- 3 cases of HV infections diagnosed in children ages 9, 15, & 39 months; clinical symptomatology prompted HV testing.
- In 2 cases, the mothers were known to be infected with HV, had not breastfed their children, and perinatal HV transmission had previously been ruled out following US HV testing guidelines.
 In the 3rd case, a great aunt who helped care for the child was infected with HV, but the child's mother was not.



Practice of Feeding Premasticated Food to Infants: A Potential Risk Factor for HIV Transmission

All 3 children were fed food on multiple occasions that had been premasticated by a care provider infected with HV; in 2 cases concurrent oral bleeding in the premasticating adult was described
Phylogenetic analyses supported the epidemiologic conclusion

that the children were infected through exposure to premasticated food from a caregiver infected with HV in 2 of the 3 cases.



Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs

 Children with in utero or neonatal exposure to antiretroviral (ARV) drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential metabolic dysfunction (mitochondrial dysfunction).

 It is important that the long-term medical record of a child without HV includes information about in utero and neonatal ARV exposure



Initial Consult

Preventive:

Continue ZDV or ZDV + NVP or NVP/RAL + ZDV + 3TC Peds HV nurse case manager will deliver the medication supply to the caregiver in person with a syringe color tapemarked at the dosage to be administered, before discharge.

In the US, it is recommended that women with HV refrain from breastfeeding their infants as safe infant feeding alternatives are available



Initial Consult

Preventive:

Counseling against the use of premasticated (prechewed or prewarmed) food should be provided as safe infant options should are available

It is important that the long-term medical record of a child without HV includes information about in utero and neonatal ARV exposure

Follow up:

F/u with HV clinic at 2 weeks of age



Take Home Message

- Reviewed the epidemiology of perinatal HV infection <1%
- Discussed the various clinical scenarios & the ART for newborns with perinatal HV exposure ZDV or ZDV-NVP or ZDV-3TC-NVP or ZDV-3TC-RAL
- Identified the initial postnatal management of NB exposed to HV ART, HV DNA (HV RNA), CBC diff (CMP) No breastfeeding, no pre-masticated food
- Determined the long-term follow-up of infants exposed to ART Document in-utero & neonatal ARV exposure



Further Reading & Resources

 DH-5 - Management of Infants Born to People with HV Infection Updated & reviewed, Dec. 30, 2021 Antiretroviral Management of Newborns with Perinatal HV Exposure or HV Infection

National Perinatal HV Hotline (1-888-448-8765) Free clinical consultation on all aspects of perinatal HV 2021-24 Red Book, 32nd AAP – Report of the Committee on Infectious Diseases, pp. 427-440



Local Resources

- Pediatric HV Clinic Children's of Mississippi (HRSA, Part D)
- Spencer F. Brooks FNP, April Palmer MD, Roberto P. Santos MD Daphne Sigler RN, Cindy Stubblefield LMSW, Patricia Powers
 601-984-5206, 601-815-1117, 601-815-1119 UM/C MEDCOM 601 984 4367



