CLINICIAN CONSULTATION CENTER
Translating science into care

Care of the Infant Exposed to HIV

SEATEC Conference

Peter L. Havens MS, MD
Medical College of Wisconsin

January, 2018

I have no conflicts to declare

I am on the Pediatric guidelines committee—not the perinatal…

www.aidsinfo.nih.gov

I am a consultant to the Clinician Consultation Center

http://nccc.ucsf.edu/

(888) 448-8765

AIDSinfo

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TREATMENT, PREVENTION, AND RESEARCH

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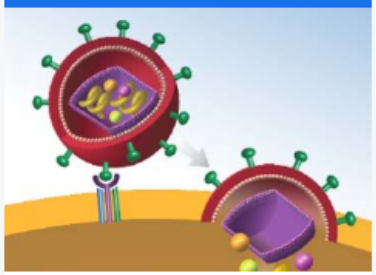
Federally approved HIV/AIDS medical practice guidelines

- View and Download the Guidelines
- Adult ARV Guidelines
- Pediatric ARV Guidelines
- Perinatal Guidelines

Understanding HIV/AIDS



Links to HIV/AIDS-related resources

- Fact Sheets
- Infographics
- Glossary
- HIV/AIDS Awareness Days

Drugs

Information on FDA-approved HIV/AIDS and opportunistic infection drugs and investigational HIV/AIDS drugs

- HIV/AIDS-Related Drugs

Clinical Trials

Search tool to find HIV/AIDS-related clinical trials

- HIV/AIDS-Related Clinical Trials
- HIV Preventive Vaccine Clinical Trials
- HIV Therapeutic Vaccine Clinical Trials

Talk Today

- **Identification of HIV exposure in infants**

  ≈ Identification of HIV infection in pregnancy
- **Perinatal HIV Transmission: Overview**
- **Testing for HIV infection in infants**
- **Treatment of Exposed Infants**

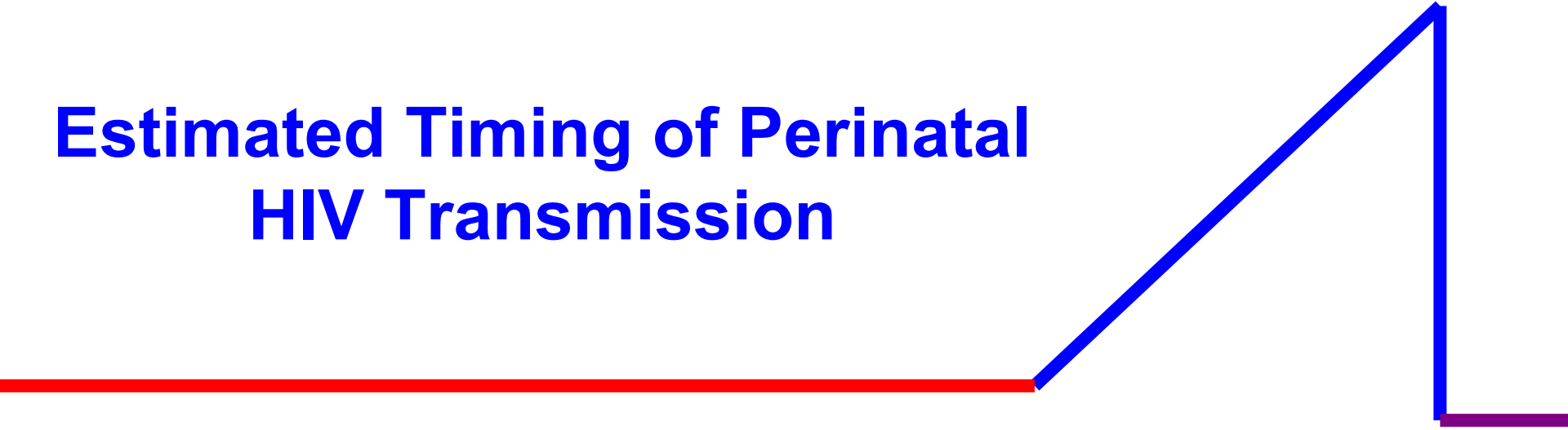
Abbreviations
cART=combination antiretroviral therapy
BLQ=viral load below the limit of quantitation
BLD=viral load below the limit of detection
ZDV=zidovudine
3TC=lamivudine
NVP=nevirapine

Identification of HIV Infection in Pregnancy

Test all pregnant women for HIV in each pregnancy

- Early in pregnancy
- Again if indicated by STI, other identified risk in pregnancy, high prevalence hospital
- At presentation in labor if status not known
- Test the infant if mother's status is unknown
  - Antibody test identifies infant exposure
  - NAT is for diagnosis of infection
- Many states: Consent is "opt out"
  - Explain that you are doing HIV testing and give the patient the right of refusal
- IL, NY, CT- mandatory testing of newborns

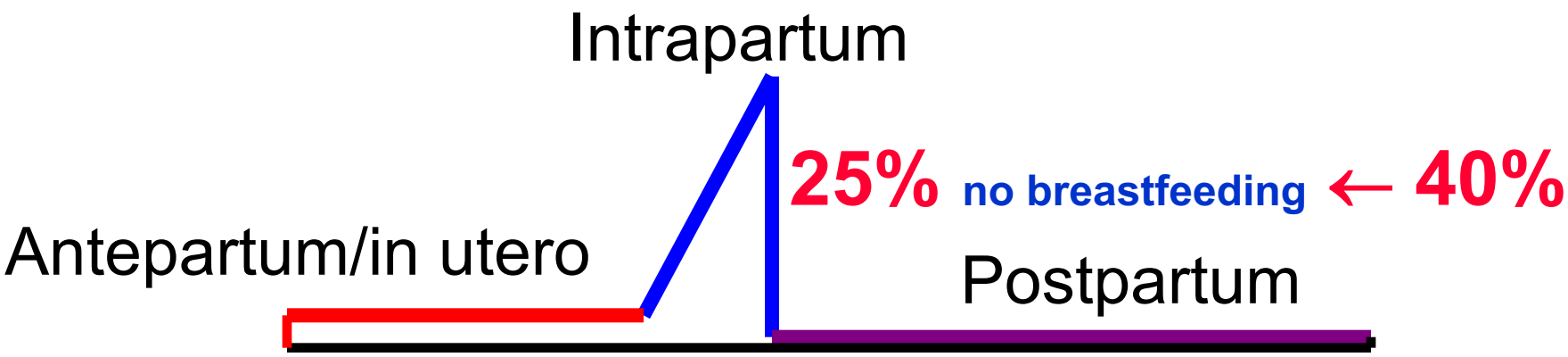
Estimated Timing of Perinatal HIV Transmission



Timing	<14wks	14-36wks	36wk→labor	Intrapartum
% of total infected	4%	16%	50%	30%
N infected that time period	1	4	12	8
N total infected	1	5	17	25
N total uninfected	99	95	83	75

Kourtis AP, Bulterys, Nesheim, Lee. JAMA 2001;285:709

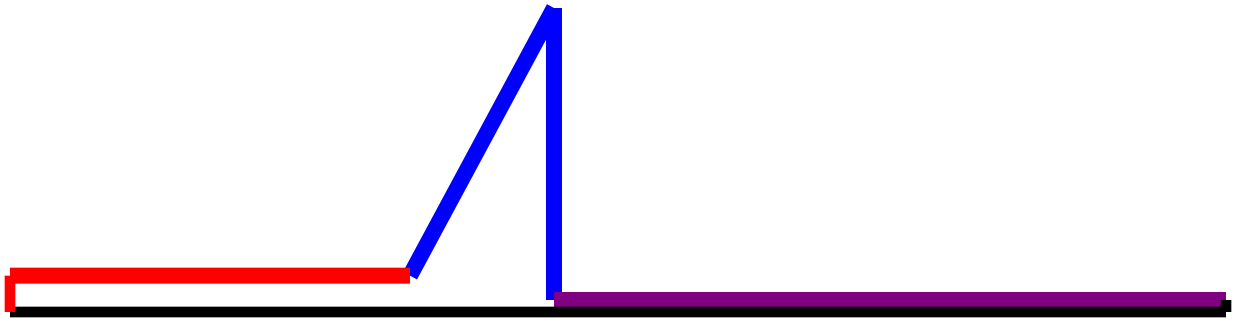
Preventing Mother-to-Child HIV Transmission: Summary



AP/IP/PP	IP/PP	PP only [5.7% in utero][1]
≤1%	7-10%	4.8% ZDV
cART + ZDV	ZDV[2]	2.2% (2 or 3 drugs)
	ZDV+NVP[3]	*ZDV + NVP + 3TC*←??? (No breastfeeding)

1--Nielsen-Saines K. HPTN 040 NEJM 2012;366:2368
2--Wade NEJM 1999;339:1409
3--Taha TE. Lancet 2003;362:1171

Diagnosis of HIV Infection in Infants age <18m



HIV DNA or RNA PCR (NAT) Result*

HIV Infection Category	Day of Birth	2-4 wk	4 mo	>6 mo	18 mo
In Utero	+	+	+	+	+
Peripartum	-	+/-	+	+	+
Via Breast Milk	-	-/+	-/+	+	+
Seroreverter	-	-	-	-	-

* all will be antibody positive initially

Testing the Infant with *in utero* HIV Exposure

- HIV NAT (DNA or RNA)
  - Birth (to identify *in utero* transmission)
  - 2 weeks
  - 4 weeks
  - 4 months
- Antibody test
  - 18 months (to prove seroreversion)
- Points of discussion:
  - Birth NAT perhaps not needed in low risk
  - Add 6-8 week NAT if infant 3-drug Rx
  - Some don't do the 18 month antibody test

Testing the infant with breastfeeding HIV exposure

- **Not clearly defined**
- ***One approach:***
- **Same sequence of NAT testing as *in utero***
- **Based on the time breast feeding stops**
- **NAT at time 0, 2 weeks, 4 weeks, 4 months**
- **Antibody at 18 months (?)**

Low Risk and Higher Risk Situations Identified in the US Perinatal Guidelines

- ***Low Risk:***
- **Infants born to mothers who received standard ART during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence.**
- ***Higher Risk:***
- **Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, mothers who initiated ART late in pregnancy (late second or third trimester), were diagnosed with acute HIV infection during pregnancy, who had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression.**

Mother Taking cART UK/Ireland 2007-2011:HIV Perinatal transmission increases with increasing maternal viral load

Undetectable maternal viral load is best
Detectable (50-399) is *>10x worse* than <50
(Cutoff for concern may depend on the intervention)

		Infant Infections	
Maternal viral load (copies/mL)	N	Total	
		N	%
<50[1]	3859	2	0.05%
50-399	655	7	1.1%
400-999	104	2	1.9%
1000-9999	100	3	3.0%
>10,000	65	6	9.2%

1 <50 = “undetectable” measured closest to delivery

Townsend CL. AIDS 2014;28:1049

Perinatal transmission increases with maternal viral load

Undetectable maternal viral load is best
Detectable (50-399 or 50-999) is *5 to >20x worse*

	Myer 2017			Mandelbrot 2015			Townsend 2014		
		Infant Infections			Infant Infections			Infant Infections	
Maternal viral load (copies/mL)	N	N	%	N	N	%	N	N	%
<50[1]	406	1	0.25%	5345	14	0.3%	3859	2	0.05%
50-399	102	2	2.0%	1174	18	1.5%	655	7	1.1%
400-999				818	23	2.8%	104	2	1.9%
1000-9999	47	4	8.5%				100	3	3.0%
>10,000							65	6	9.2%

1 <50 = “undetectable” measured closest to delivery

Myer L. HIV Med 2017;18:8
Mandelbrot L. Clin Infect Dis 2015;61:1715
Townsend CL. AIDS 2014;28:1049

Low Risk and Higher Risk Situations

- ***Low Risk***
- **Mother on cART with good adherence and viral load BLQ or BLD during pregnancy**
- ***Higher risk***
- **Mother with viral load detectable close to delivery**
  - **Higher is worse**
    - **Infant at risk for peripartum transmission**
- ***Even if viral load BLQ at delivery:***
  - **Mother started cART late in pregnancy**
    - **Risk for *in utero* or peripartum infection**
  - **Mother with acute HIV during pregnancy**
    - **Risk for *in utero* infection**

Table 7: Newborn Antiretroviral Management– USA Nov 2017

HIV Transmission Risk Category	Description	Newborn ARVs
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Presumed Newborn Exposure	Mother with *unknown HIV status who tests positive at delivery* or postpartum or newborn with positive HIV antibody test	ARVs as for higher risk
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Issues with Assessment of Transmission Risk

- Low level viremia in a mother on cART
  - A "blip" is detectable viral load surrounded by many viral loads BLQ/BLD
  - If you don't have all the data, you may not be able to differentiate a "blip" from a rising virus load due to lack of adherence or presence of resistance
- Mother with no HIV testing during pregnancy, now with positive rapid HIV 1-2 antigen/antibody screen at delivery
  - Do you believe the screen, or not?
    - Ask for RNA PCR on mother right away

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HPTN 040 study ZDV + NVP regimen

The "040 regimen"

Zidovudine ≈4 mg/kg twice daily for 6 weeks
Plus
Nevirapine ≈4 mg/kg 3 doses.

- **Dose #1: ASAP day 1;**
- **Dose #2: 48 hours after dose 1;**
- **Dose #3: 96 hours after dose 2**

[nevirapine clearance is slow in this age group, so plasma concentration is high enough for prophylaxis for 2 weeks]

Intrapartum HIV Transmission *reduced more with 2 or 3 drugs than with zidovudine alone* (HPTN 040)[1]

Infant Treatment Regimen		Infant Infections[2]					
	N	Total		In utero		Intrapartum	
		N	%	N	%	N	%
overall	1684	140	8.5%	93	5.7%	47	3.2%
ZDV alone[3]	566	61	11%	37	6.8%	24	4.8%
ZDV+NVP[4]	562	39	7.1%	28	5.1%	11	2.2%
ZDV+NFV+3TC[5]	556	40	7.4%	28	5.2%	12	2.4%
P value		0.03		0.24		0.046	

1 Most from Brazil and South Africa; Breast feeding <1% at 2 weeks; *mean maternal viral load 15,000 copies/mL*; >100,000=13.6%; <10,000=42.5%

2 Intrapartum infection measured at 3 months; rate by Kaplan-Meier

3 Zidovudine ≈4 mg/kg twice daily for 6 weeks

4 ZDV + nevirapine ≈4 mg/kg 3 doses. Dose #1: ASAP day 1; Dose #2: 48 hours after dose 1; Dose #3: 96 hours after dose 2

5 ZDV plus lamivudine ≈2 mg/kg and nelfinavir ≈60 mg/kg both twice daily for 2 weeks

Nielsen-Saines K. HPTN 040 NEJM 2012;366:2368

Problems with the 040 ZDV-NVP regimen

- Only gets transmission rates down to 2.2%
- Increased NNRTI resistance in those with *in utero* infection
  - ZDV alone: 5.7% NNRTI resistance
  - ZDV+NVP: 18.2% NNRTI resistance
- Third drug in the 3-drug arm was nelfinavir
  - No longer readily available
  - Variable kinetics
  - 46% did not reach kinetics target

Nielsen-Saines K. HPTN 040 NEJM 2012;366:2368
Mirochnick M. PIDJ 2011;769

If you are concerned about the 040 ZDV-NVP regimen for infants with in utero infection…

What makes you think of in utero infection?

The “040 ZDV-NVP regimen”
Zidovudine ≈4 mg/kg twice daily for 6 weeks
Nevirapine ≈4 mg/kg 3 doses.

Dose #1: ASAP day 1;
Dose #2: 48 hours after dose 1;
Dose #3: 96 hours after dose 2

Primary infection during pregnancy increases the risk of in utero infection

- Primary infection during pregnancy
  - Increases perinatal transmission risk
    - 15-fold
      - (Birkhead, GS. OB-GYN 2010:1247)
    - 18-fold
      - (Drake AL. PLOSMedicine 2014)

Late start of cART in pregnancy increases the risk of in utero infection

- cART start before 30 weeks has lower risk of transmission to infant
  - Each additional week of treatment reduces transmission risk by 10%
- Often difficult to get the history

	No MTCT	MTCT occurred (N=34)
Gestational age at HAART initiation	25.9 weeks (IQR 22.4-28.7)	30.1 weeks (IQR 27.4-32.6)

Townsend CL. AIDS 2008;22:973

Same trend in the French cohort
Warszawski J. AIDS 2008;22:289

So when mother had

Primary/acute HIV infection during pregnancy,
or
Late start of cART

[so infant has higher risk of *in utero* infection]

You might consider something other than the 040 ZDV-NVP regimen

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One approach to treatment of the high risk infant

- Consider 3 drugs
  - Prophylaxis of transmission
  - Early treatment if in utero infection

Maternal viral Load and Infant Infection Risk: Implications for Infant treatment

		Infant Infections						
Maternal viral load (copies/mL)	**N**	**Total**		**In utero**		**Intrapartum**		**Possible Infant Treatment**
		N	**%**	**N**	**%**	**N**	**%**	
<50[1]	**6347**	**6**	**0.09%**	**2**	**0.03%**	**4**	**0.06%**	**ZDV (IV+PO)**
50-399[1]	**1349**	**14**	**1.0%**	**5**	**0.4%**	**9**	**0.7%**	**?**
400-999[1]	**233**	**6**	**2.6%**	*		*		**?**
≈15,000 (No ART)[2]	**1684**	**140**	**8.5%**	**93**	**5.7%**	**47**	**3.2%**	**?**

1 Townsend CL. AIDS 2014;28:1049

2 Nielsen-Saines K. HPTN 040 NEJM 2012;366:2368

Probability of acquiring HIV from an HIV-infected Source

Perinatal HIV Transmission Risk is higher than risk in many situations where "Full Dose cART" is used

	Risk per Act	
	per 10,000	percent
Blood transfusion	**9250**	**92.5%**
No maternal ART *(maternal viral load ≈15,000 copies/mL)*		***8.5%***
Maternal cART: viral load 400-999 copies/mL		***2.6%***
Receptive anal intercourse	**138**	**1.38%**
Maternal cART: viral load 50-399 copies/mL		***1.0%***
Needle sharing: injection drug use	**63**	**0.63%**
Percutaneous needlestick	**23**	**0.23%**
Insertive anal intercourse	**11**	**0.11%**
Maternal cART: viral load <50 copies/mL		***0.09%***
Receptive penile-vaginal intercourse	**8**	**0.08%**
Insertive penile-vaginal intercourse	**4**	**0.04%**

In BLACK: From **CDC 2016 nPEP** guidelines (www.AIDSINFO.NIH.gov),
In BLUE: Infant transmission risk: from Townsend, and Nielsen-Saines

One approach to treatment of the high risk infant

- **Consider 3 drugs**
  - **Prophylaxis of transmission**
    - ***Just like the 3-drug PEP you would use for an adult with an exposure of similar HIV transmission risk***
  - **Early treatment if in utero infection**

Health|NYT Now

Evidence of H.I.V. Found in a Child Said to Be Cured

By DONALD G. McNEIL Jr.JULY 10, 2014

ART start = 30 hours

ART stop = 18 months

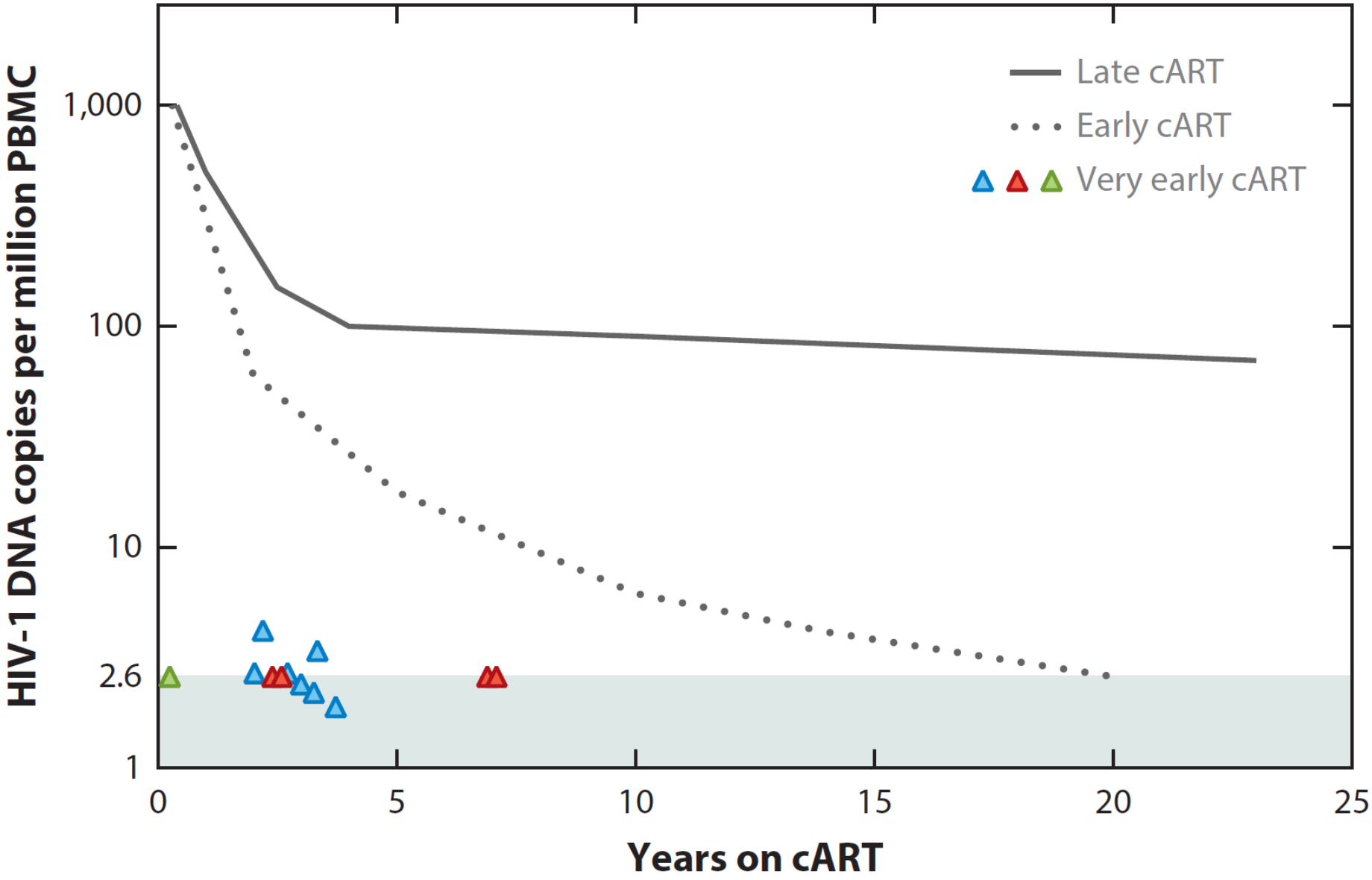
Follow-up testing negative = 30 months

Follow-up testing positive = 4 years

Studies ongoing to see if early infant treatment is beneficial

Cure?
Not yet.

Early Infant Treatment Limits Later Viral Reservoir size



Luzuriaga, K. Ann Rev Med 2016; 67:201

One approach to treatment of the high risk infant

- **Consider 3 drugs**
  - **Prophylaxis of transmission**
    - ***Just like the 3-drug PEP you would for an adult with an exposure of similar HIV transmission risk***
  - **Early treatment if in utero infection**
    - ***May limit the viral reservoir and improve immunologic outcome***
      - ***Studies in progress***

Antiretroviral Dosing in Premature Infants

- **Prematurity increases risk of HIV transmission**
- **Prematurity complicates antiretroviral dosing**
- **Extreme prematures may have increased risk of NEC with oral medications**
- **Have to balance these competing risks**

Treatment of the premature infant with higher HIV transmission risk

- Gestational age for which dosing information exists
  - Zidovudine: <30 weeks
  - Nevirapine: <27 weeks, <750 grams
  - Lamivudine: 32 weeks
- Options for the infant <32 weeks
  - ZDV:↓effectiveness compared ZDV/NVP
  - ZDV/NVP: ↑resistance compared to ZDV
  - Premature infant with in utero infection and NVP resistance: limited options (Raltegravir)

Table 8. Newborn ARV Doses by Gestational Age

Antiretroviral	Gestational Age (weeks)	Birth Weight (kg)	Oral Dose (mg/kg)	Dosing frequency	Comment
Zidovudine	<30		2	Every 12 hours	At age 28 days ↑ to 3 mg/kg/dose every 12 hours for 6 week prophylaxis. If HIV infected ↑ to 12 mg/kg/dose every 12 hours at age 8-10 weeks
	≥30 to <35		2	Every 12 hours	At age 14 days ↑ to 3 mg/kg/dose every 12 hours for 6 week prophylaxis. If HIV infected ↑ to 12 mg/kg/dose every 12 hours at age 6-8 weeks
	≥35		4	Every 12 hours	If HIV infected ↑ to 12 mg/kg/dose every 12 hours at age 4 weeks
Nevirapine – "040 dose"	<27	<0.75	2	Dose #1-ASAP day 1 Dose #2-7 days after dose 1	
	>27	0.75 to 1.5	4		
	>27	1.5 to 2.0	≈ 4	Dose #1-ASAP day 1; Dose #2-48 hr after dose 1 Dose #3-96 hr after dose 2	Weight band dose = 8 mg
	>27	>2	≈ 4		Weight band dose = 12 mg
Nevirapine-"treatment dose"	34 to 36		4	Every 12 hours	At age 7 days ↑ to 6 mg/kg/dose every 12 hours
	≥37		6	Every 12 hours	If HIV infected ↑ to 200 mg/M^2/dose every 12 hours at age 4 weeks
Lamivudine	≥32	≥1.5	2	Every 12 hours	If HIV infected ↑ to 4 mg/kg/dose every 12 hours at age 4 weeks
Raltegravir	≥37	≥2	1.5	Birth to 1 week: once daily 1 to 4 weeks: twice daily	If mother took raltegravir 2-24 hours prior to delivery, delay infant dose to age 24 hours. At 4 weeks ↑ to 6 mg/kg/dose twice daily

Intravenous zidovudine dose is (oral dose) X 0.75, with same dosing frequency

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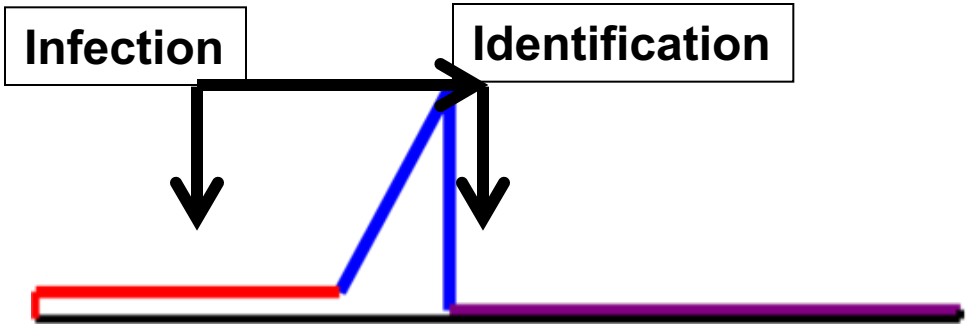
Footnote d to Table 7: Duration of empiric therapy in newborns at higher infection risk = Unknown

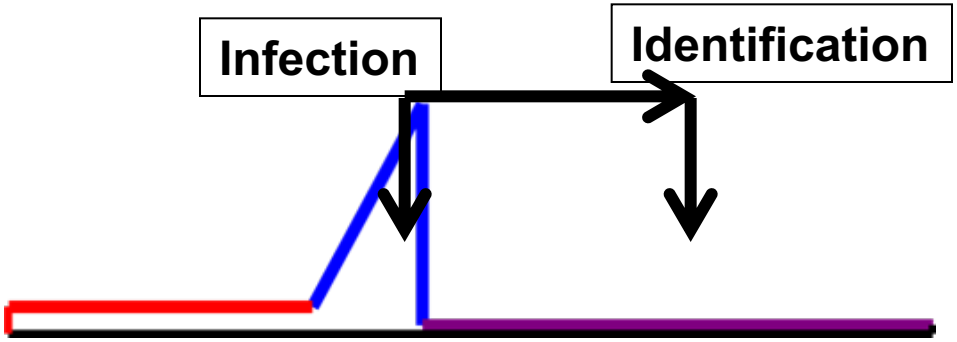
- **Optimal duration** of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is **unknown**. Many experts **administer 6 weeks** of combination therapy; others opt to **discontinue NVP and/or 3TC after return of negative newborn testing**. **ZDV** should be continued for **6 weeks**.

- **Birth PCR is important for decision making**
- **If positive, repeat. Continue 3 drugs.**
- **If negative, stop 3 drugs?**
  - **Give enough NVP to mimic 040 kinetics (last dose day 7) then finish 6 wks ZDV**
  - **4 weeks like adult PEP?**
    - **Then 2 more weeks of ZDV**
- **6 weeks of 3 drugs?**

Lack of data. Guidelines panel→ no clear recommendation.

Uncertainty about timing of infection leads to Diagnostic Uncertainty leads to Treatment Uncertainty





Maternal viral Load and Infant Infection Risk: Implications for Infant treatment

		Infant Infections						
Maternal viral load (copies/mL) closest to delivery	**N**	**Total**		**In utero**		**Intrapartum**		**Possible Infant Treatment**
		N	**%**	**N**	**%**	**N**	**%**	
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50-399[1]	**1349**	**14**	**1.0%**	**5**	**0.4%**	**9**	**0.7%**	**?**
400-999[1]	**233**	**6**	**2.6%**	*		*		**?**
≈15,000 (No ART)[2]	**1684**	**140**	**8.5%**	**93**	**5.7%**	**47**	**3.2%**	**ZDV-3TC-NVP**

Test infant NAAT soon after delivery to identify in utero infection (not cord blood)

1 Townsend CL. AIDS 2014;28:1049

2 Nielsen-Saines K. HPTN 040 NEJM 2012;366:2368

Cases

Case 1

- **You are in clinic seeing an infant aged 2 weeks. This is the first visit since the baby was placed in foster care because mother was put in jail for selling sex for drugs. It is reported that mother had no prenatal care, and none of mother's labs are available to you.**
- **Is HIV testing indicated?**
- **If so, what tests would you send**

Case 1 Choices

- Appropriate to test?
  - Yes
  - No
- Test to use?
  - HIV DNA PCR
  - HIV RNA NAT
  - Antibody test or antigen/antibody test

Case 1 Response

- Appropriate to test?
  - Yes
  - No
- Test to use?
  - HIV DNA PCR
  - HIV RNA NAT
  - Antibody test or antigen/antibody test
    - Sent to identify infant exposure.
      - If positive, then send NAT
      - If negative, further testing not needed
- Also send Hepatitis C antibody if not done

Case 2

- **You are asked to recommend testing and treatment for a term newborn infant, now aged 1 hour, whose G2P2 mother, aged 20 years, had HIV diagnosed during her first pregnancy 3 years ago. Mother has had viral load BLQ on cART since one month after her diagnosis.**
- **What infant testing is recommended?**
- **What infant treatment is recommended?**

Case 2 Choices: Testing

a. Antibody test at birth to prove HIV exposure
b. NAT at Birth, 2 weeks, 4 weeks, 4 months
c. NAT at 2 weeks, 4 weeks, 4 months
d. Antibody test at 18 months

Case 2 Response: Testing

- **Antibody test at birth to prove HIV exposure**
  - ***Not needed: you know mother's status***
- **NAT at Birth, 2 weeks, 4 weeks, 4 months**
  - ***Very low risk of in utero infection so likely do not need the birth NAT***
- **NAT at 2 weeks, 4 weeks, 4 months**
- **Antibody test at 18 months in addition to the NAT at 2 weeks, 4 weeks, and 4 months**
  - ***"some practitioners" continue to do this to make sure there was sero-reversion***

Case 2 Choices: Treatment

- ZDV 4 weeks
- ZDV 6 weeks
- ZDV and 3 doses of infant nevirapine (040)
- ZDV-3TC-NVP 4 weeks
- ZDV-3TC-NVP 4 weeks then ZDV 2 weeks
- ZDV-3TC-NVP 6 weeks
- ZDV-3TC-NVP to start, then ZDV alone when birth NAT returns as negative

Case 2 Response: Treatment

- **ZDV 4 weeks**
  - **This is a low risk setting**
- **ZDV 6 weeks**
- **ZDV and 3 doses of infant nevirapine (040)**
- **ZDV-3TC-NVP 4 weeks**
- **ZDV-3TC-NVP 4 weeks then ZDV 2 weeks**
- **ZDV-3TC-NVP 6 weeks**
- **ZDV-3TC-NVP to start, then ZDV alone when birth NAT returns as negative**

Case 3

- **25 year old G1 mother just delivered a term infant. You are called because she had an HIV 1-2 Antigen / antibody screen done when she came in labor, and it just came back positive. Further history: she had a negative HIV screen in the first trimester. Gonorrhea was treated at 30 weeks, and she had a "mono-like illness" at weeks 30-32, but EBV serology was negative.**
- **What infant testing is recommended?**
- **What infant treatment is recommended?**

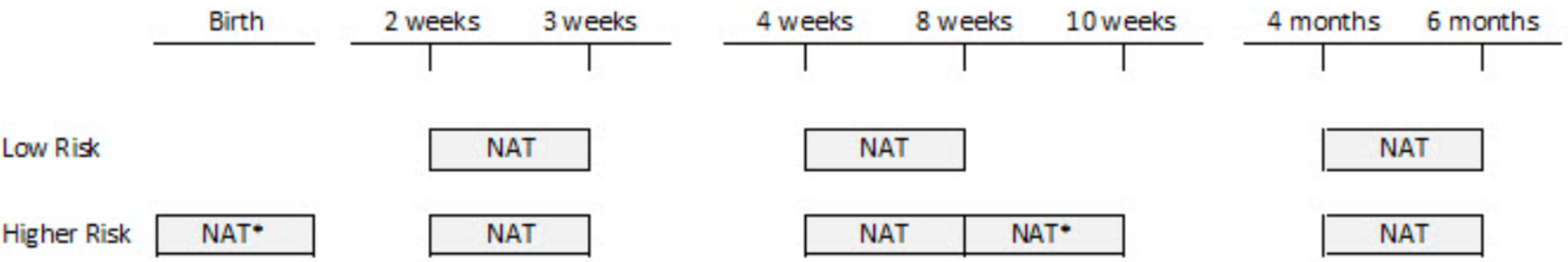
Case 3 Choices: Testing

a. Antibody test at birth to prove HIV exposure
b. NAT at Birth, 2 weeks, 4 weeks, 4 months
c. NAT at 2 weeks, 4 weeks, 4 months
d. Antibody test at 18 months

Case 3 Responses: Testing

- Antibody test at birth to prove HIV exposure
  - Perhaps negative if mother doesn't yet have IgG antibody. Interpret carefully.
- NAT at Birth, 2 weeks, 4 weeks, 4 months
  - The birth test is needed here because of the high risk of in utero transmission with acute HIV in mother. Might do DNA not RNA NAT while patient on 3-drug therapy
  - Add a NAT at 2-4 weeks after stopping 3-drug empiric therapy
- NAT at 2 weeks, 4 weeks, 4 months
- Antibody test at 18 months

Timing of Diagnostic Testing in Infants with HIV Exposure



Low Risk:
Infants born to mothers who received standard ART during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence.

Higher Risk:
Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, mothers who initiated ART late in pregnancy (late second or third trimester), were diagnosed with acute HIV infection during pregnancy, who had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression.

Case 3 Choices: Treatment

- ZDV 4 weeks
- ZDV 6 weeks
- ZDV and 3 doses of infant nevirapine (040)
- ZDV-3TC-NVP 4 weeks
- ZDV-3TC-NVP 4 weeks then ZDV 2 weeks
- ZDV-3TC-NVP 6 weeks
- ZDV-3TC-NVP to start, then ZDV alone when birth NAT returns as negative

Case 3 Response: Treatment

- ZDV 4 weeks
- ZDV 6 weeks
- ZDV and 3 doses of infant nevirapine (040)
- ZDV-3TC-NVP 4 weeks
- ZDV-3TC-NVP 4 weeks then ZDV 2 weeks
- ZDV-3TC-NVP 6 weeks
- ZDV-3TC-NVP to start, then ZDV alone when birth NAT returns as negative (as long as initial NVP enough to = 040 exposure)
- No breastfeeding until you are sure mother not infected (pump and freeze until mother's status known)

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Thank you!

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