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Perinatal HIV Management

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Disclosures

No conflicts of interest to disclose

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Objectives

- To discuss barriers to prevention of mother-to-child transmission of HIV and measures to address these
- To review current national guidelines for the management of the HIV-exposed infant
- To describe the epidemiology of perinatal HIV infection in the US and locally

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Resources

- https://www.cdc.gov/hiv/
  surveillance data
- https://aidsinfo.nih.gov/
  guidelines

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MOTHER-TO-CHILD TRANSMISSION OF HIV

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Mother-to-Child Transmission (MTCT) of HIV

- Perinatal transmission
  - *in utero*
  - Intrapartum
    - Accounts for majority of MTCT
- Breast milk
- Premastication

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Historical Perspective

- 1981 – AIDS first reported
- 1982 – pediatric cases reported
- 1987 – FDA approval of first drug for treatment of HIV: **AZT**(3'-**az**ido-3'-deoxy**t**hymidine) = **zidovudine**
  - 1989 – syrup formulation
  - 1990 – IV formulation

Observational Data – Zidovudine Use During Pregnancy, Late 1980s

- AIDS Clinical Trials Group (ACTG, established 1987) sites surveyed re: women taking zidovudine who became pregnant and intended to maintain pregnancy
- Data reported for 43 women from 17 sites
- Doses ranged from 300 – 1200 mg per day, 56% took for at least 2 trimesters, 29% of infants exposed during 1st trimester
- Zidovudine was well-tolerated, no associations with congenital anomalies, premature birth, fetal distress

Sperling et al. N Engl J Med. 1992;326:857-861

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(P*)ACTG Protocol 076

- Began enrollment in April 1991
- Double-blind, placebo-controlled trial
- Pregnant women between 14 and 34 weeks gestation
- CD4 count >200 cells/mm^3
- "Had no indication for antiretroviral therapy in the judgment of their health care providers"
- 59 centers in US and France (including St. Jude)

**Pediatric ACTG split off 1995*

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076 Regimen

- Antepartum: 100 mg by mouth FIVE TIMES a day
  - Standard adult dose at the time (now 300 mg twice daily)
- Intrapartum: 2 mg/kg IV over 1 hour, then 1 mg/kg/hour until delivery
  - Based on PK modeling of data obtained during pregnancy (ACTG 082)
- Newborn: 2 mg/kg by mouth every 6 hours for 6 weeks
  - Dose established in studies of zidovudine in newborns (ACTG 049)
  - Now dose for TNBs is 4 mg/kg/dose twice daily

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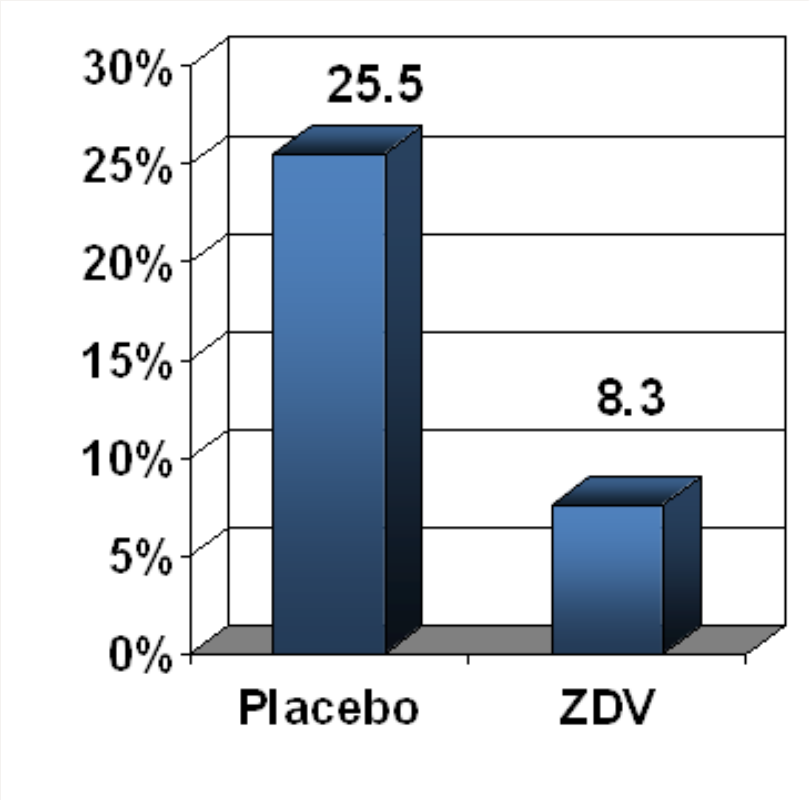
076 Results

- Transmission rate decreased by 2/3 in zidovudine group
- Stopped at planned first interim analysis in December 1993 and all participants offered zidovudine
- Landmark study demonstrating medication could prevent mother-to-child transmission of HIV



Connor et al. N Engl J Med. 1994;331:1173-80

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Post-076

- 076 regimen quickly adopted in the US and other resource-abundant countries → significant declines in MTCT
- Further studies with combination antiretroviral therapy showed even greater effects (<2%)

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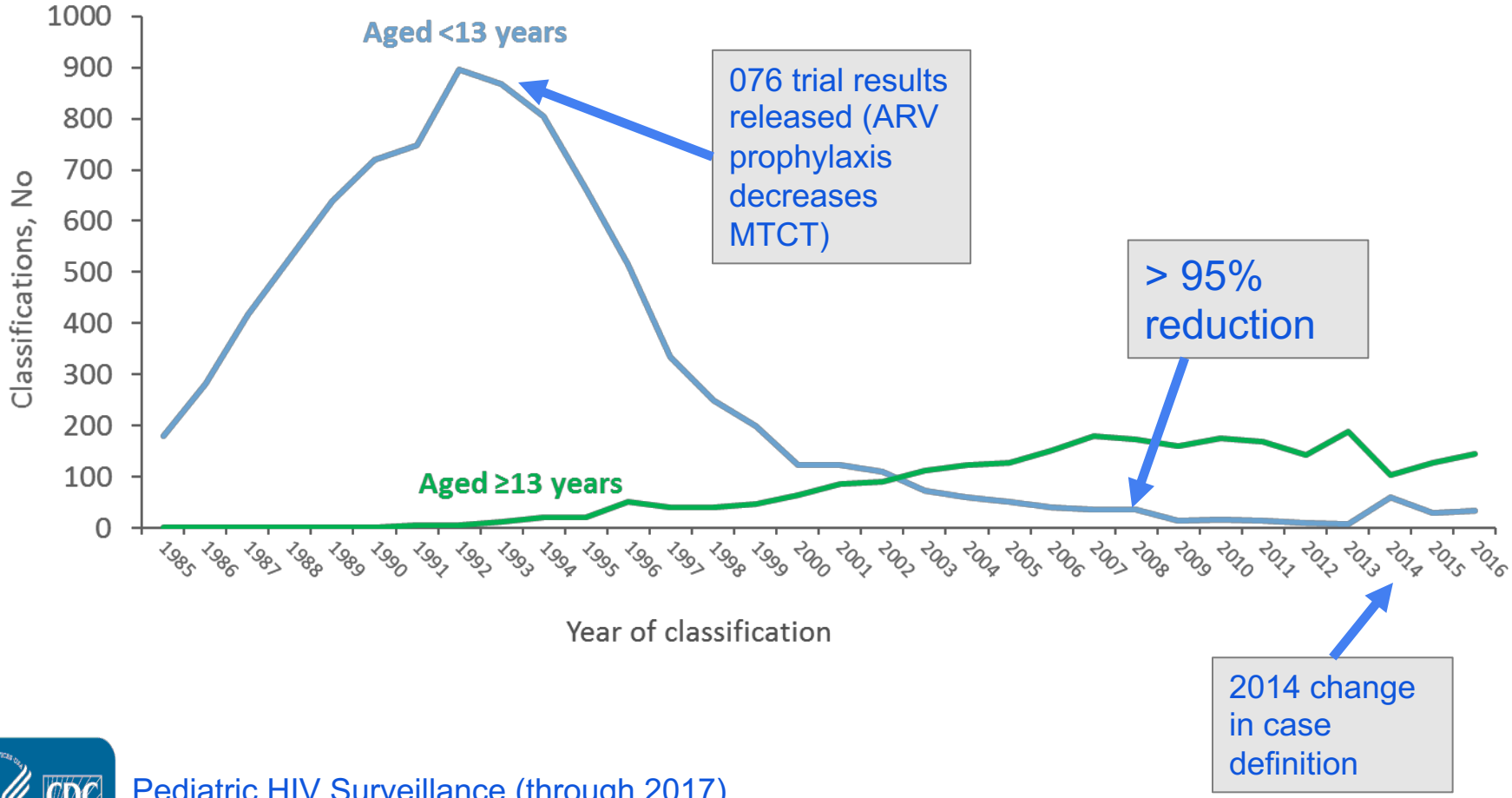
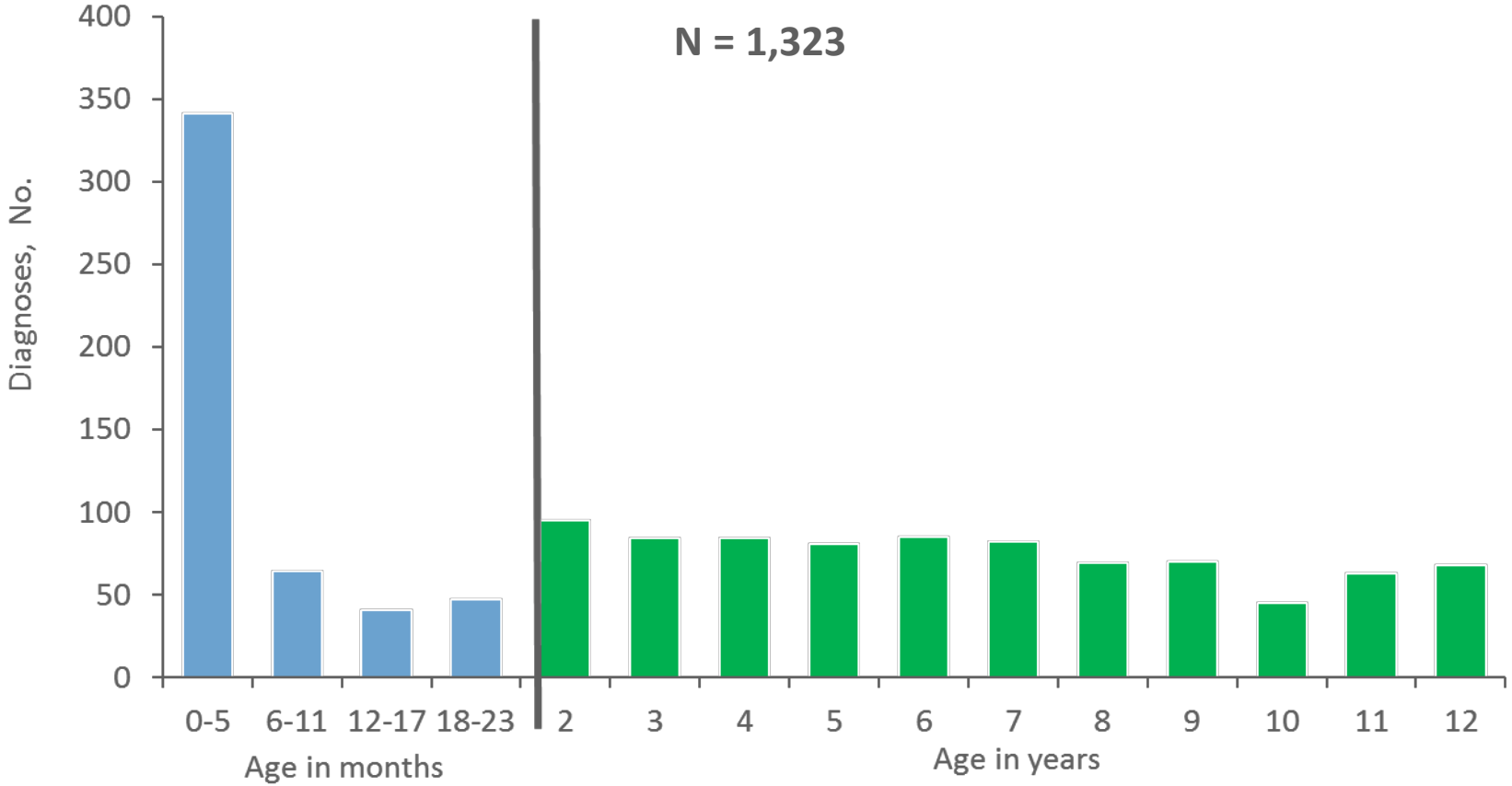
PEDIATRIC HIV EPIDEMIOLOGY

Stage 3 (AIDS) Classifications among Persons with Perinatally Acquired HIV Infection, 1985–2016—United States and 6 Dependent Areas



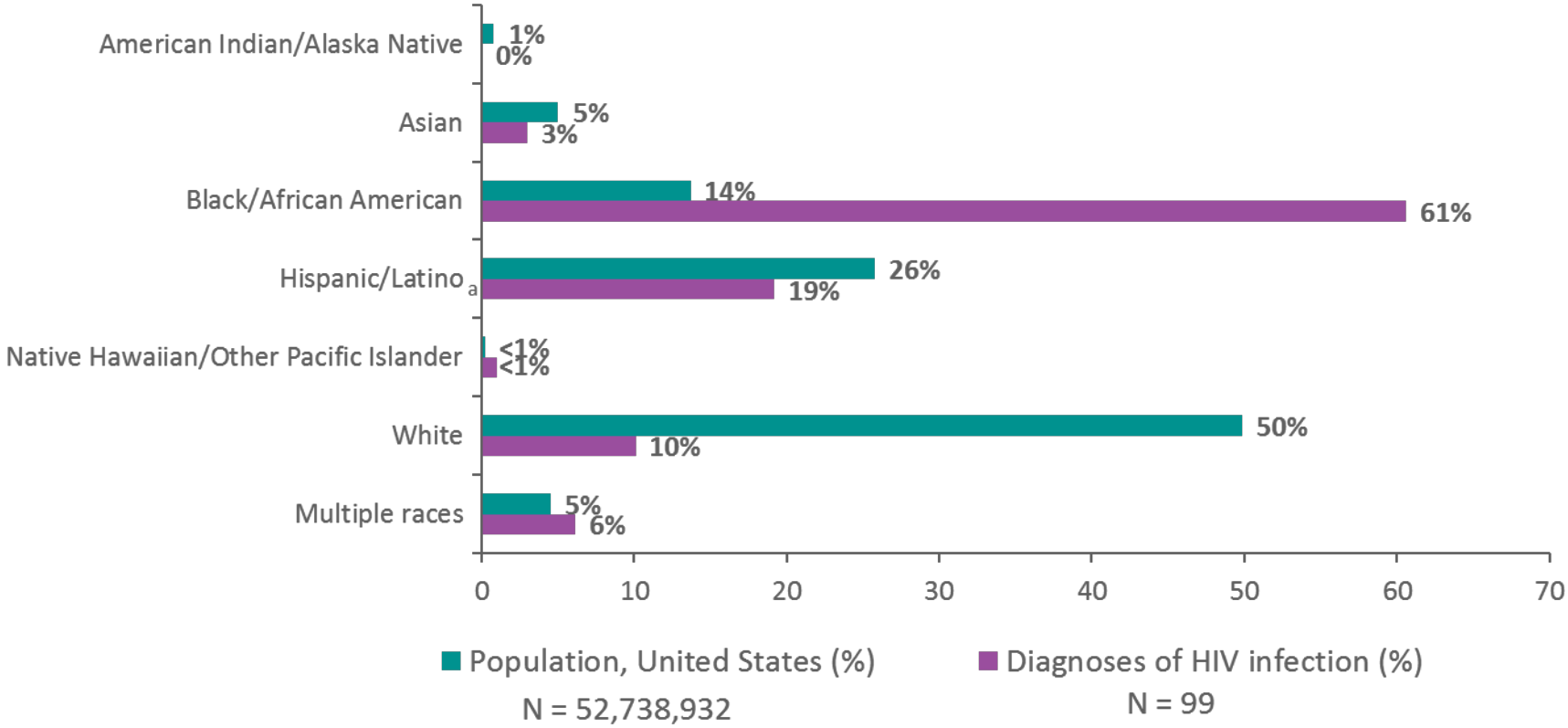
Pediatric HIV Surveillance (through 2017)

Diagnoses of HIV Infection among Children Aged <13 Years, by Age at Diagnosis, 2010–2016—United States and 6 Dependent Areas



Pediatric HIV Surveillance (through 2017)

Diagnoses of HIV Infection and Population in Children Aged <13 Years by Race/Ethnicity, 2017—United States

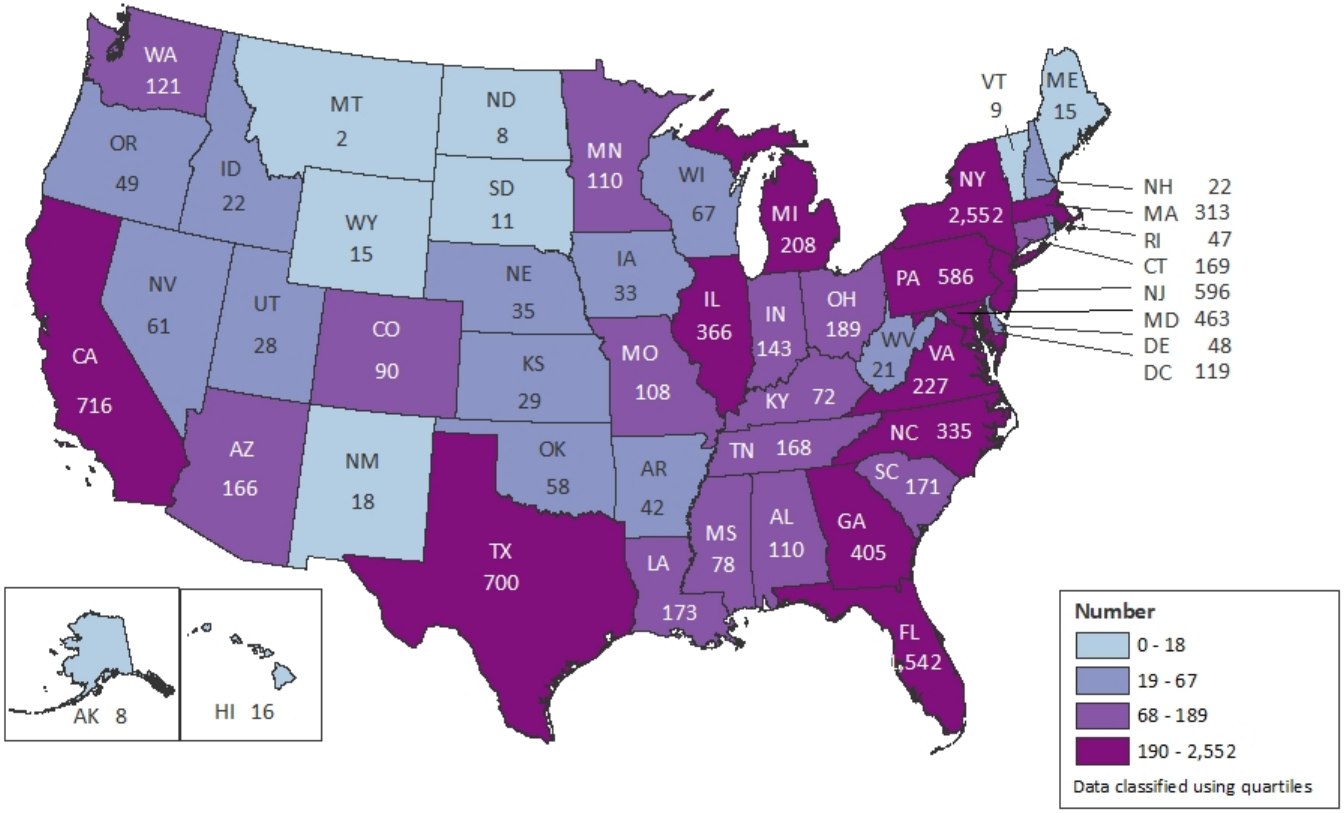


Note. Data for the year 2017 are preliminary and based on 6 months reporting delay.
[a] Hispanics/Latinos can be of any race.

Persons Living with Diagnosed Perinatally Acquired HIV Infection, Year-end 2016—United States and 6 Dependent Areas

N = 11,915

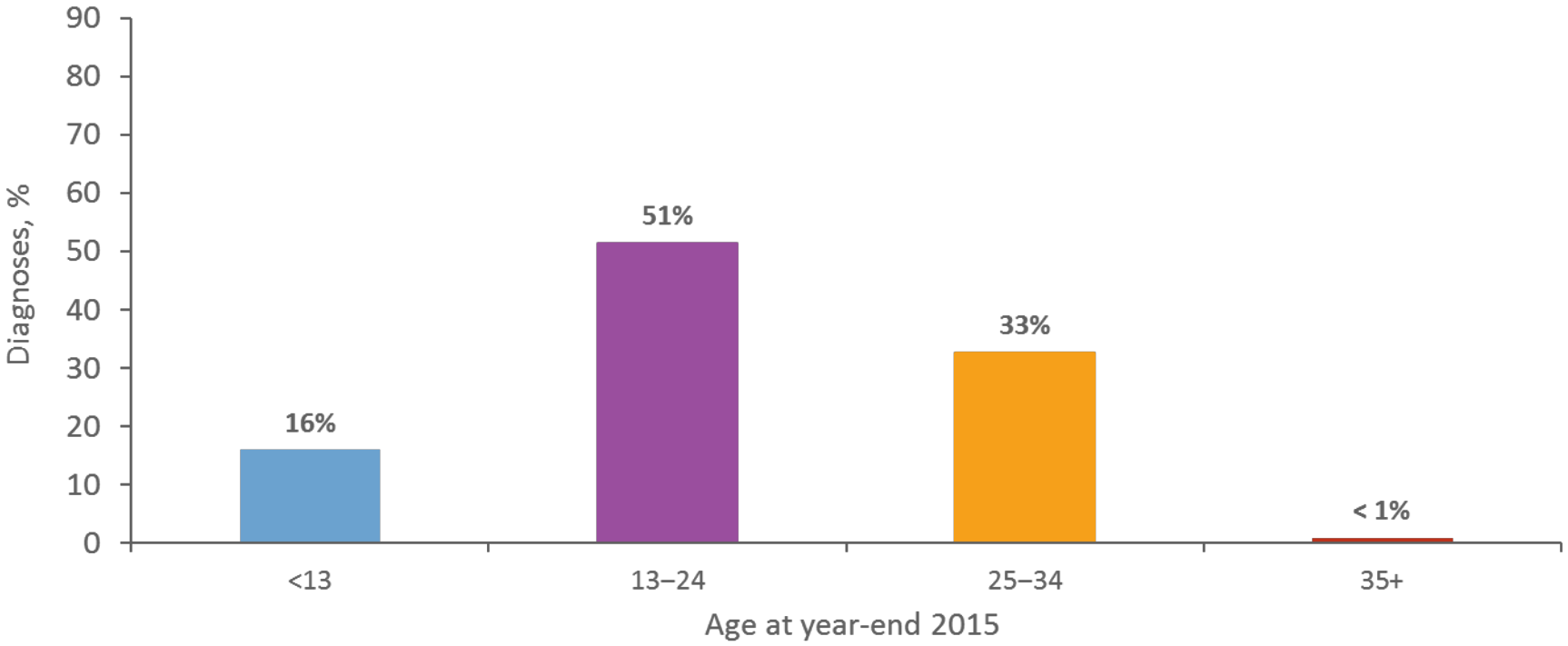
American Samoa	0
Guam	2
Northern Mariana Islands	0
Puerto Rico	244
Republic of Palau	0
U.S. Virgin Islands	9



Note. Data are based on address of residence as of December 31, 2015 (i.e., most recent known address).

Age Distribution of Persons Living with Diagnosed Perinatally Acquired HIV Infection, Year-end 2016—United States and 6 Dependent Areas

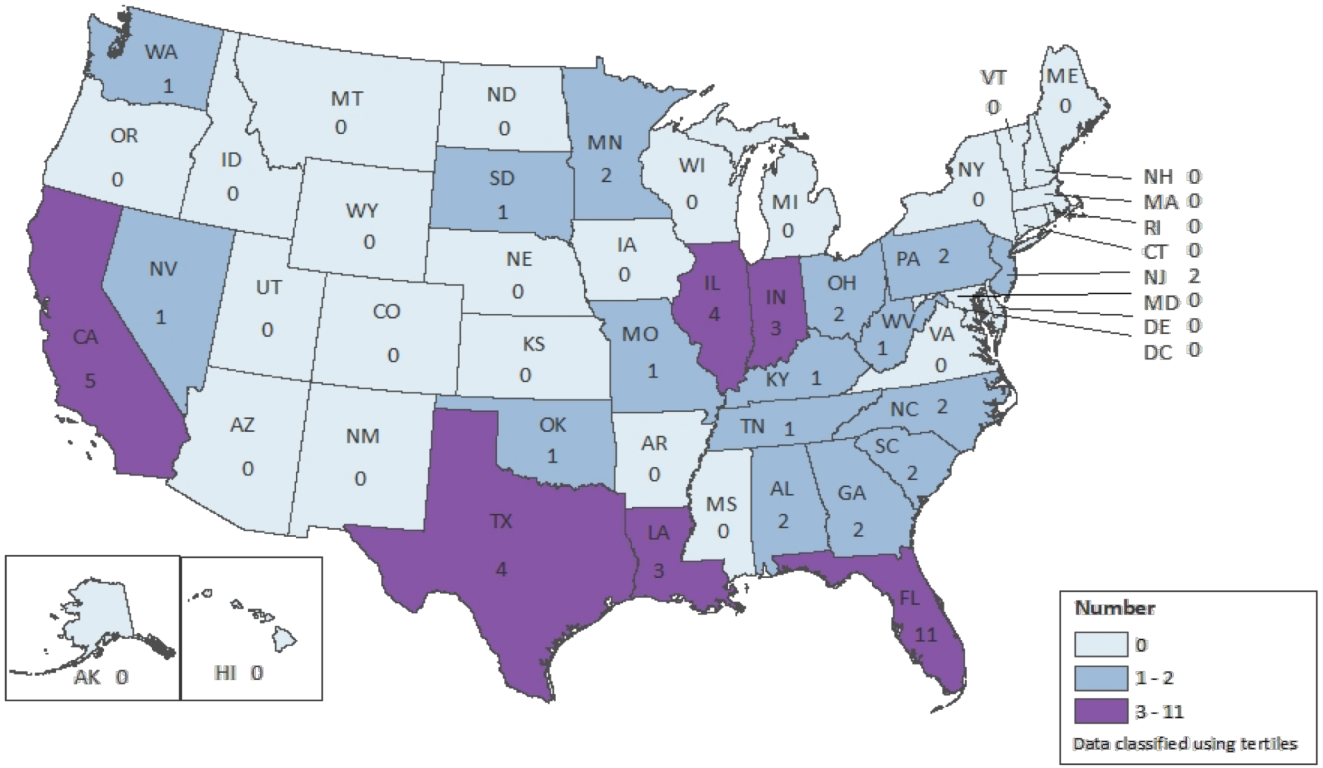
N = 11,915



Diagnoses of Perinatally Acquired HIV Infection among Children Born During 2015, by Area of Residence—United States and Puerto Rico

N = 54

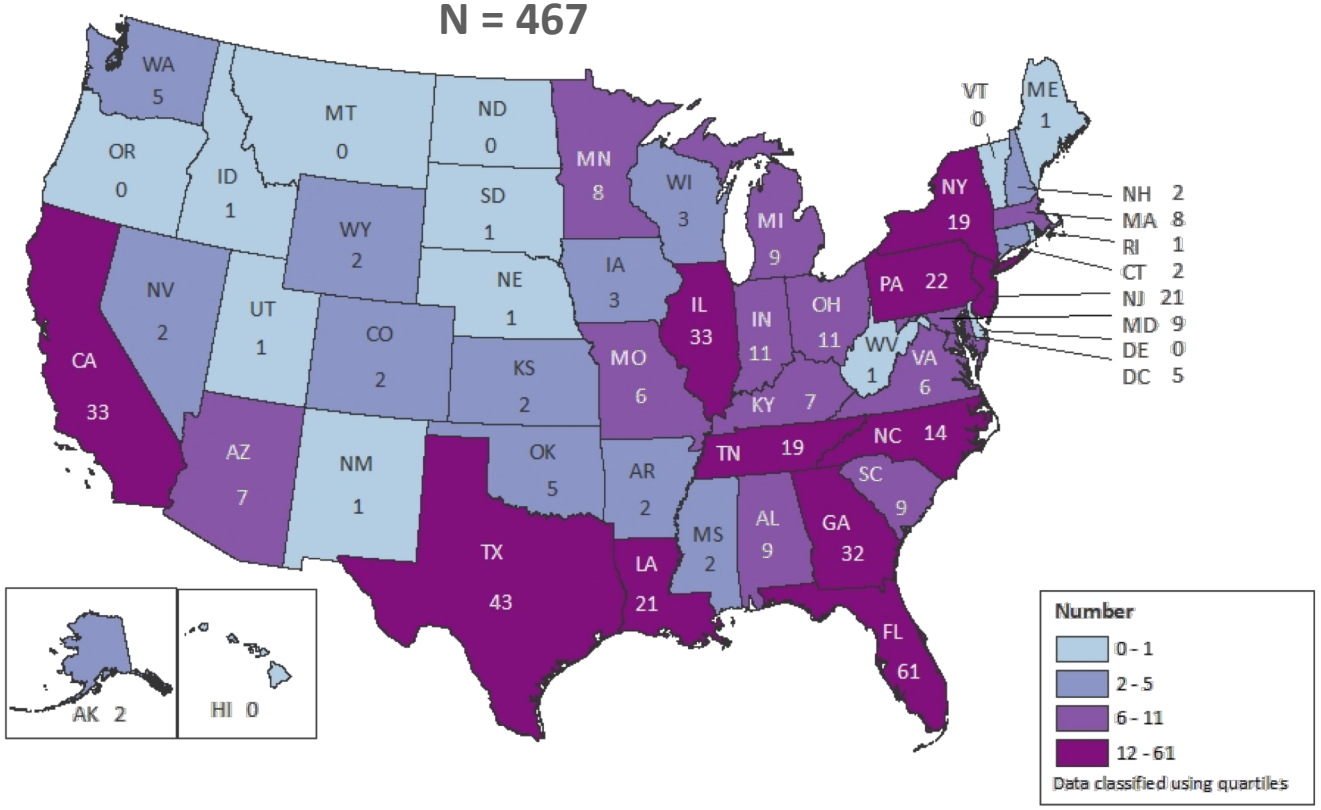
Puerto Rico 0



Diagnoses of Perinatally Acquired HIV Infection among Children, Birth Years 2010–2015, by Area of Residence—United States and Puerto Rico

N = 467

Puerto Rico 2



Note. Data for children residing in, but born outside of, the United States and Puerto Rico are included.

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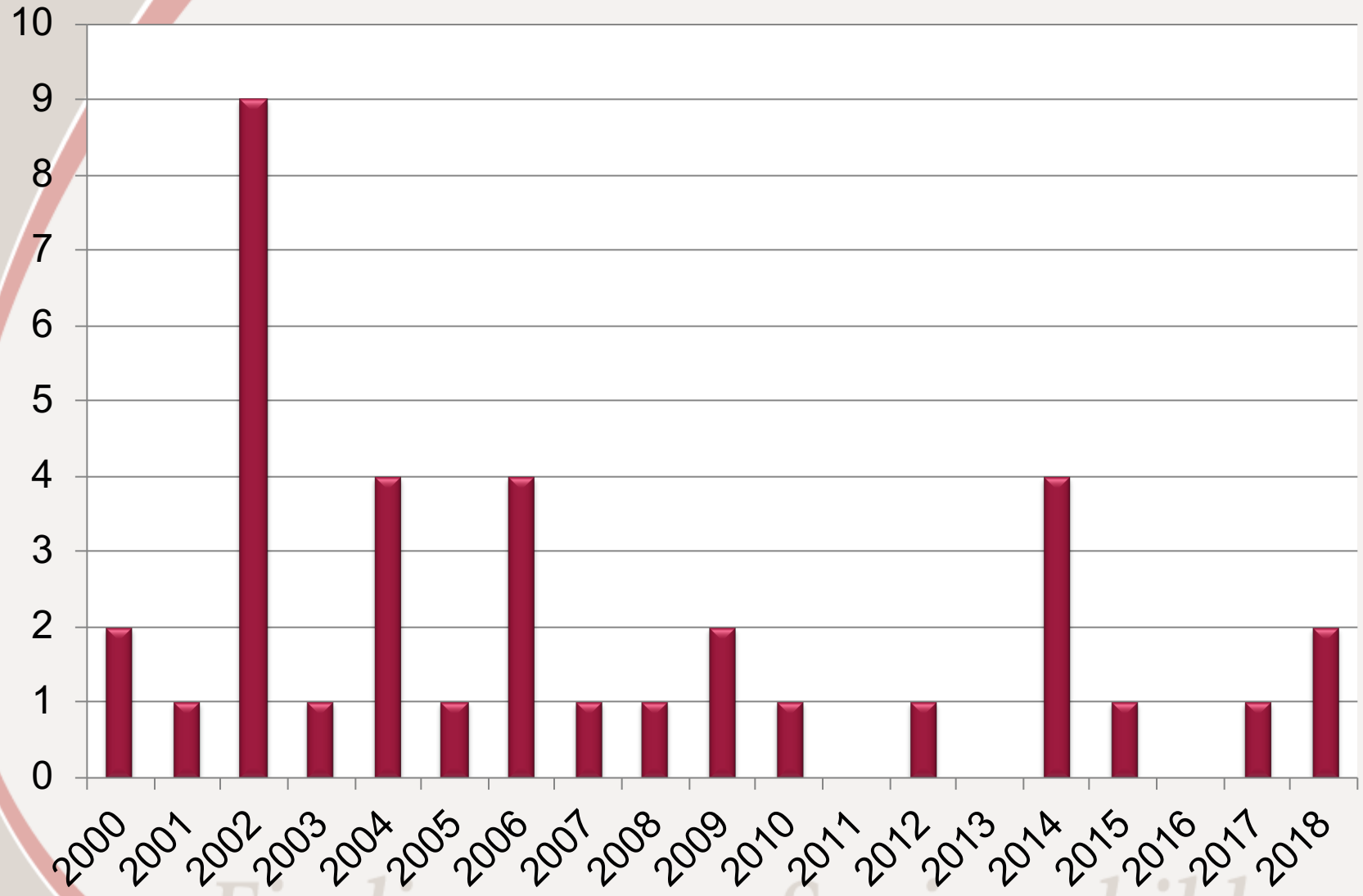
Infected Infants Born in Memphis Area



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Perinatal Transmission Today

- Approximately 8500 women living with HIV give birth each year
- Transmission risk <1%
- Between 1994 and 2010 an estimated 21,956 cases of perinatal HIV infection were prevented
- 99 children under the age of 13 received a diagnosis of perinatal HIV infection in 2017

https://www.cdc.gov/hiv/group/gender/pregnantwomen/index.html

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So why can't we prevent ALL cases of perinatal HIV infection?

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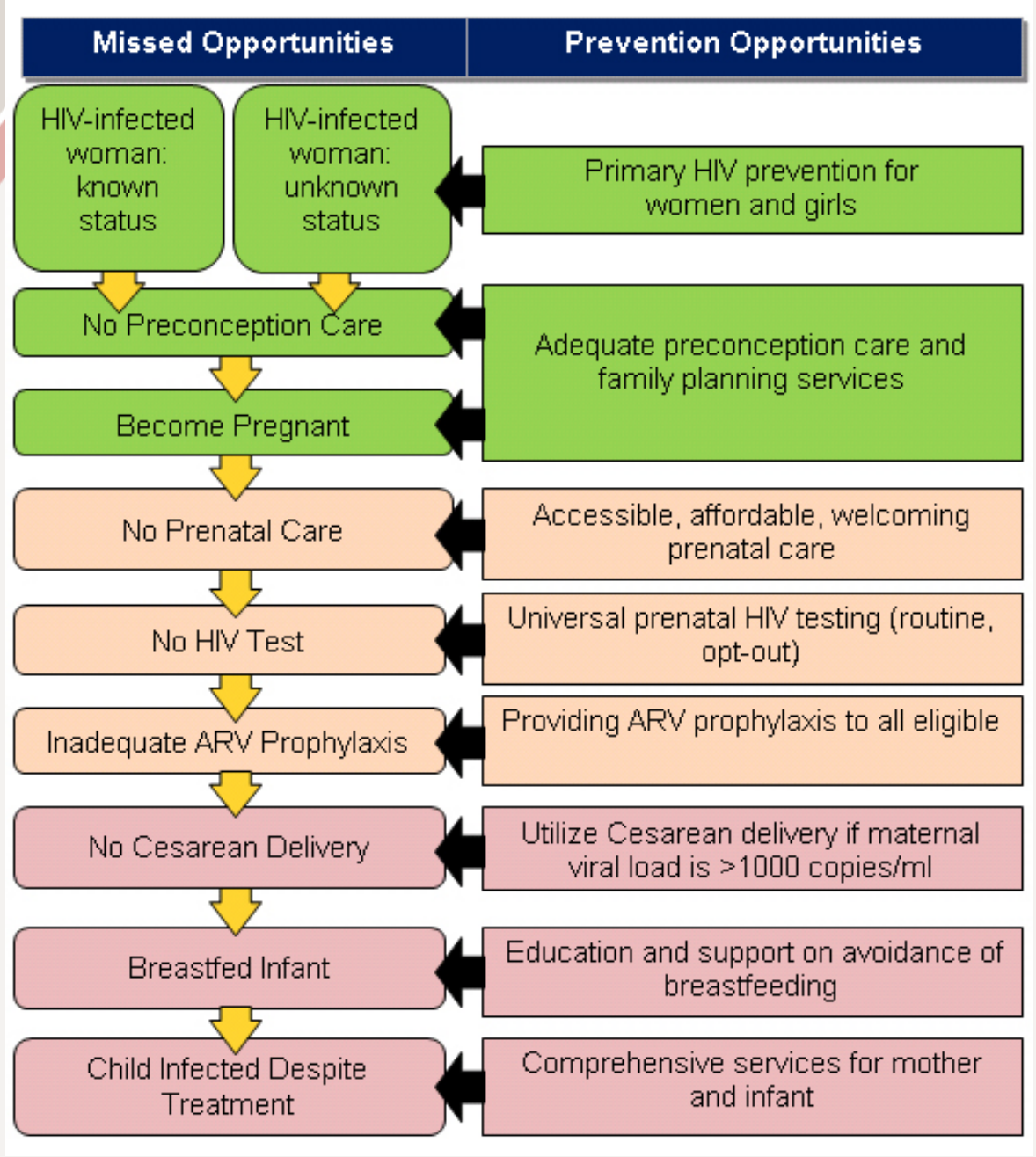

Perinatal HIV Prevention Cascade
Source Report: Institute of Medicine, 1998

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Missed Opportunities for Prevention

IDENTIFICATION OF HIV INFECTION

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HIV Testing in Pregnant Women

- Recommended by CDC since 1995
- Opt-out approach (used in TN):
  - Told that HIV test included in routine prenatal tests, but they may decline
  - Unless they decline, test performed
  - 85% acceptance rate in TN (2002)
- Opt-in approach
  - Receive pre-test counseling
  - Must agree to testing, usually in writing

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Repeat Testing in Third Trimester (Before 36 Weeks' Gestation)

- 2006 CDC: should be considered for all women, may be cost-effective even in areas of low prevalence
- Recommended:
  - Women known to be at high risk
  - High-prevalence areas
  - Signs/symptoms of acute HIV

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Third Trimester HIV Testing – Women at High Risk

- IVDU (self or partner)
- Exchange sex for money or drugs
- Partner with HIV
- New partner or ≥1 partner during pregnancy
- Diagnosis of other STI during pregnancy
- Recently incarcerated (higher prevalence of risk-related behaviors)

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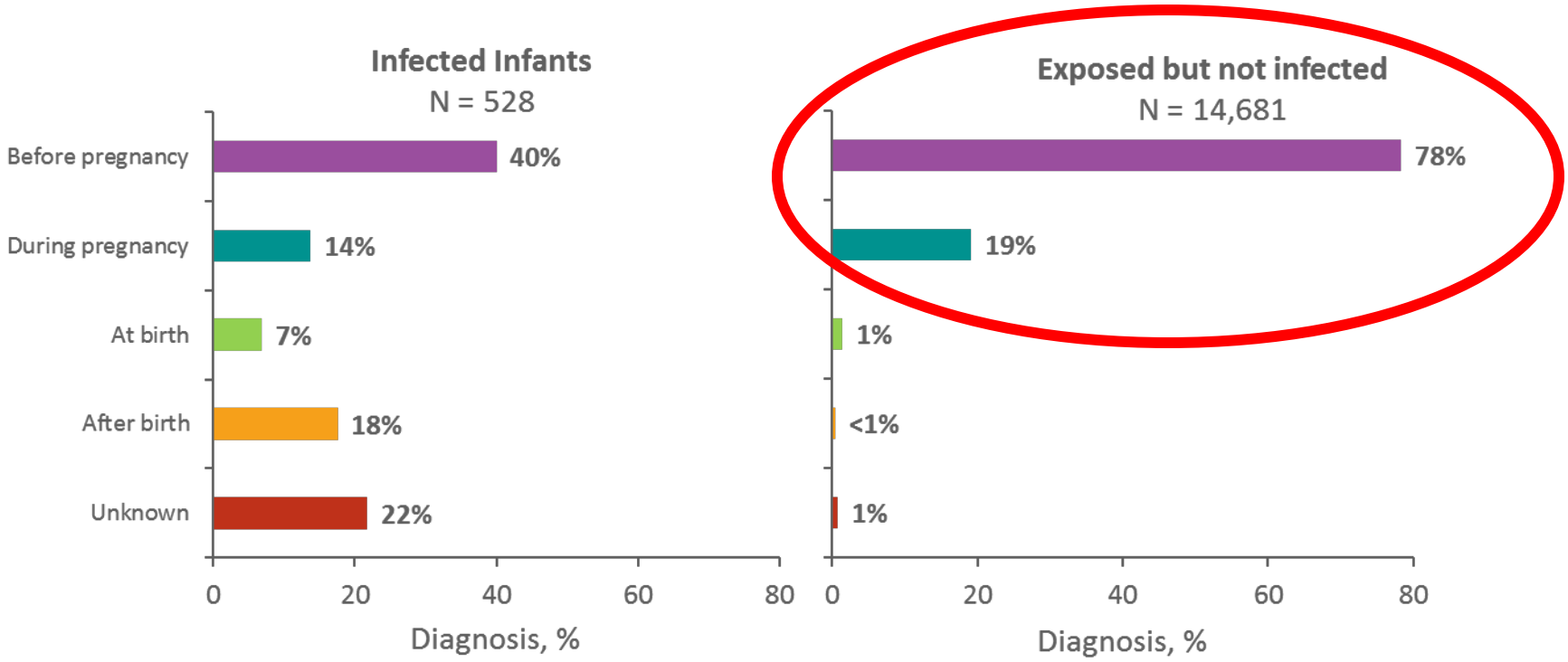
Third Trimester HIV Testing – High-Prevalence Areas

- Receiving health care at facility with ≥1 pregnant woman with HIV per 1000 screened
- Reside in jurisdiction (like Tennessee) with high incidence* of HIV in women between 15-45 years of age (testing required in some states)

* ≥17 cases per 100,000 person-years
List not updated since 2006 guidelines

Time of Maternal HIV Testing among Children with Diagnosed Perinatally Acquired HIV Infection and Children Exposed to HIV, Birth Years 2010–2015—United States and Puerto Rico



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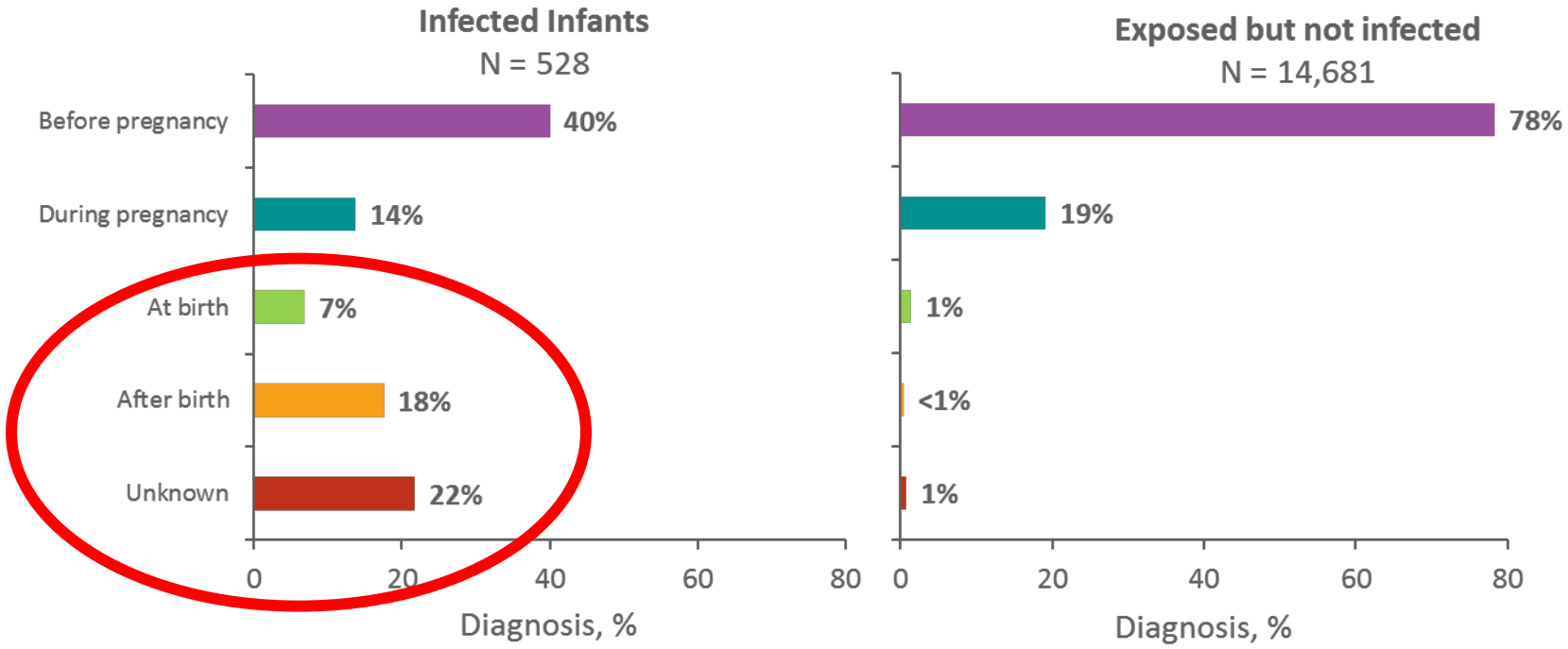

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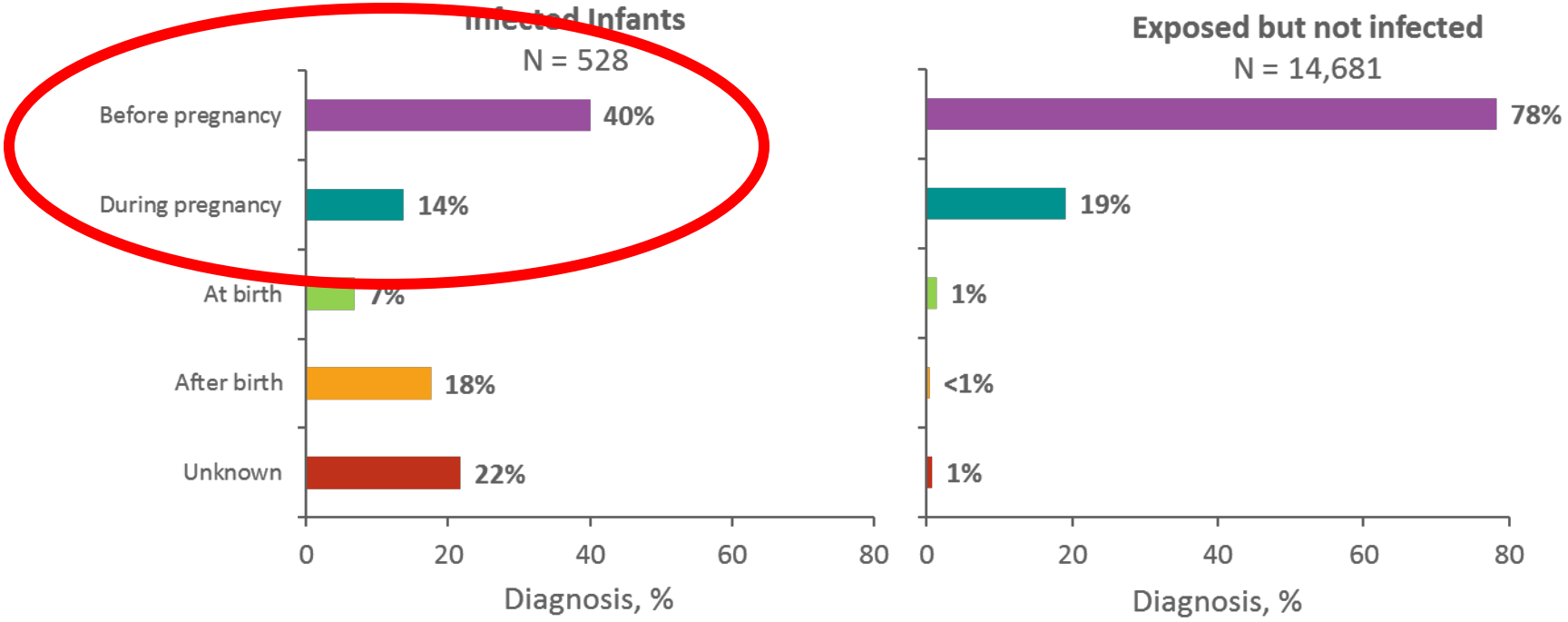

Pediatric HIV Surveillance (through 2017)

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Acute HIV Infection During Pregnancy – Higher Risk of MTCT

- 22% (9/41) transmission in New York 2002-2006 (Obstet Gynecol. 2010;115(6):1247-1255)
- 17% (12/70) transmission in Florida 2007-2014 (South Med J. 2017;110(2)L116-128)
- Enhanced Perinatal Surveillance, 15 sites in US 2005-2010 (Singh et al. CROI 2013)
  - 124 of 10,308 pregnant women seroconverted during pregnancy (1.2%)
  - 12.9% transmission (8x higher) among this group

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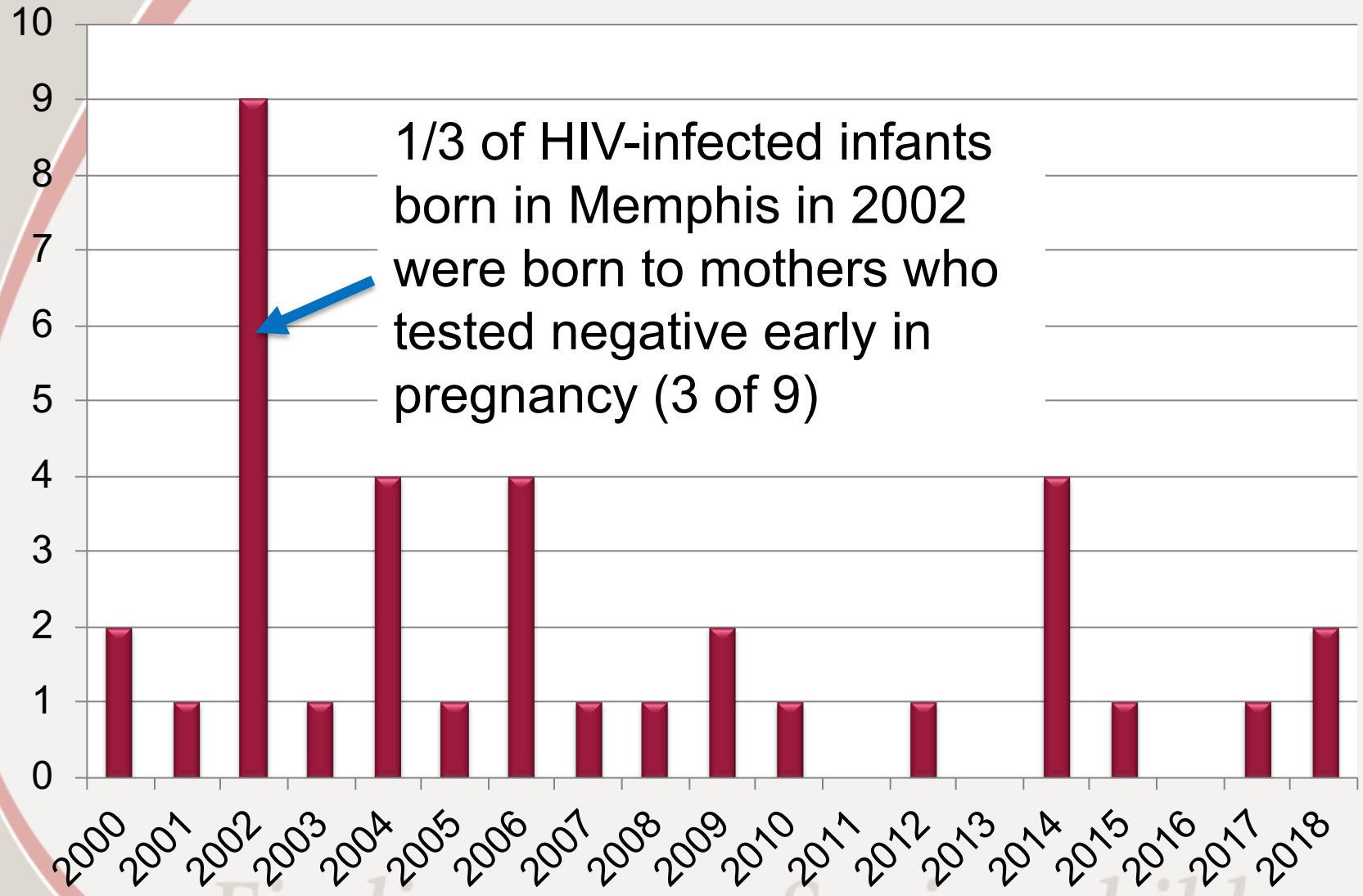
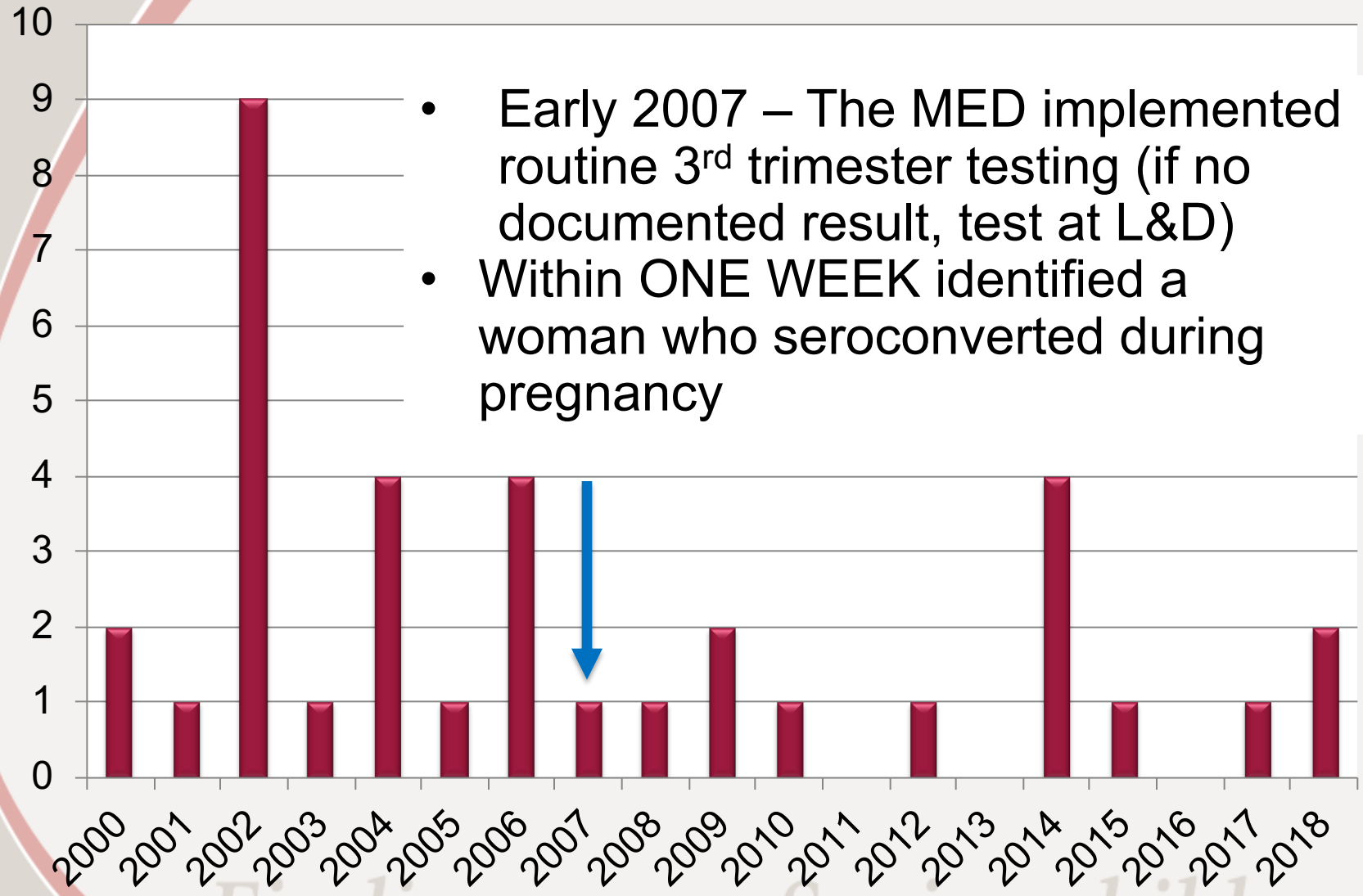
Infected Infants Born in Memphis Area



Infected Infants Born in Memphis Area



- Early 2007 – The MED implemented routine 3rd trimester testing (if no documented result, test at L&D)
- Within ONE WEEK identified a woman who seroconverted during pregnancy

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Must Have DOCUMENTATION

- HIV-infected women may not self-identify at L&D
  - Disclosure issues (family may not know)
  - May assume you know
- Testing at L&D has identified women who were known HIV+ but did not disclose diagnosis
  - One of the infants born in 2002 wasn't diagnosed until 2009 – but her mother was known + in 2002

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HIV Testing at Delivery

- Pending confirmatory testing of positive result:
  - Administer IV zidovudine intrapartum
  - Neonatal prophylaxis should be initiated ASAP, preferably within 6 hours of birth
  - Counsel against breastfeeding (may pump and discard)

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Testing Infants for HIV Exposure

- Mandated in several states
- Laws vary from state to state
- Recent example:
  - No HIV test result documented for mother, so infant tested (positive Ab, started on ART)
  - Mother reported needle phobia – no labs during pregnancy
  - Later learned mother diagnosed with HIV two years previously in another state

HIV Diagnostic Outcomes among Infants, by Time of Antiretroviral (ARV) Administration Birth Years 2009–2013—United States and Puerto Rico

Time of ARV Administration	Infected		Exposed but not infected		Total
	No.	% of Row Total	No.	% of Row Total	No.
During Pregnancy (DP) only	3	2.6	112	97.4	115
During Labor and Delivery Only (L&D) only	3	4.3	66	95.7	69
Infant received ARV after birth (Infant ARV) only	71	8.3	781	91.7	852
DP and L&D	8	2.5	314	97.5	322
DP and Infant ARV	21	2.2	950	97.8	971
L&D and Infant ARV	45	5.1	837	94.9	882
DP and L&D and Infant ARV	113	1.3	8,896	98.7	9,009
No known ARVs	233	20.4	908	79.6	1,141
Total	**497**	**3.7**	**12,864**	**96.3**	**13,361**

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis

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Prevention Opportunities once Maternal Infection Identified

GUIDELINES FOR PMTCT

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Perinatal Guidelines

- Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States
- Developed by the Department of Health & Human Services (HHS) Panel on Treatment of Pregnant Women with HIV Infection and Prevention
- Last updated December 7, 2018
- http://aidsinfo.nih.gov/

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Preconception Care

- Discuss reproductive desires on an ongoing basis
- Contraception
  - Potential decreased effectiveness of pills, patches, rings (decreased hormone levels) with some RTV-boosted Pis (DRV, FPV, LPV)
  - Potential decreased efficacy of implants with EFV
- Women contemplating pregnancy should be receiving ART and have undetectable VL

Antepartum Care

- Additional screening: HAV, HCV, GC/CT
- If not on ART already, start ASAP (before genotype results available)
- Antiretroviral Pregnancy Registry
- Potential teratogenicity
  - Limited data, especially for newer drugs
  - Dolutegravir is NOT RECOMMENDED for women of childbearing potential or in 1st trimester (potential for increased risk of NTDs)

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ART in Pregnancy

- In general, continue current regimen if virologically suppressed
  - Discuss potential risks for DTG
- Initial ART recommendations generally same as for any adult
  - NOT RECOMMENDED
    - Potential teratogenicity
      - DTG in 1st trimester
    - Low levels in late pregnancy
      - Cobicistat-boosted ARVs (ATV, DRV, EVG)
      - Once-daily DRV

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ART in Pregnancy

- Monitor VL more frequently (every 1-2 months) if continuing ART that may be less effective during pregnancy
  - Cobicistat-boosted ARVs
- Dose increases in 2nd-3rd trimesters
  - LPV/r
  - Consider for ATV/r
  - Not recommended for DRV/r

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Monitoring During Pregnancy

- Viral load
  - Monthly until undectectable, then every 3 months
  - More frequently (every 1-2 months) if continue cobicistat-containing therapy
  - VL at 34-36 weeks' gestation to inform delivery decisions
- CD4
  - If on ART ≥2 years, virologically suppressed, and CD4 >300 consistently: obtain CD4 at baseline only
  - If not, assess every 3-6 months

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Intrapartum

- Continue antepartum ART
- IV zidovudine
  - VL known or suspected to be >1000 copies/mL (or VL unknown) near delivery
  - Consider if VL 50-999, consider recent adherence
- Scheduled c-section at 38 weeks' gestation
  - VL known or suspected to be >1000 copies/mL (or VL unknown)

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Other Intrapartum Considerations

- Artificial rupture of membranes
  - may be performed if virologically suppressed and on ART
- Avoid these procedures:
  - Artificial ROM in setting of viremia
  - Routine use of fetal scalp electrodes
  - Operative delivery with forceps or vacuum extractor

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Missed Opportunities for Prevention

MEASURES TO PREVENT MOTHER-TO-CHILD TRANSMISSION

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Breastfeeding not Recommended in the US

- ART does not eliminate risk of transmission via breast milk (may not correlate with serum VL)
- Safe and affordable feeding alternatives available
- Lack of safety data on most ART regimens

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Counseling about Breastfeeding

- Discuss with women prior to/during pregnancy
- Stigma for many who don't breastfeed – concern about disclosure
- First addressed in guidelines March 2018 - still not recommended, but provide recommendations re: harm reduction counseling

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Breastfeeding Management Plan

- Maintain viral suppression – VL every 1-2 months while breastfeeding
- Breastfeed exclusively for up to 6 months, then wean slowly as foods introduced
- Prompt treatment of maternal mastitis and infant thrush
- Additional testing, prophylaxis for infants

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Premastication

- 2008 – 3 cases of HIV transmission linked to premastication
  - Miami (2), Memphis (1)
  - Diagnosed at 9, 15 and 39 months
  - HIV-infected caregiver: mother (2), great-aunt (1)
  - 2 cases associated with oral bleeding
  - Phylogenetic analyses supported conclusion in 2 of 3 cases

Gaur et al, Pediatrics, August 2009

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Prevalence of Premastication

- 14% among the general US population
- CDC survey of HIV-infected caregivers Dec 2009-Feb 2010
  - 9 sites (GA, TX, TN, FL, LA, NJ, PR, DC)
  - 31% HIV-exposed children received premasticated food

MMWR March 11, 2011

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MANAGEMENT OF THE HIV-EXPOSED NEWBORN

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For All HIV-Exposed Newborns

- Obtain baseline CBCD
- Begin antiretroviral prophylaxis ASAP, preferably within 6 hours of birth
- All infants receive zidovudine prophylaxis at a minimum

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Infant Zidovudine Dosing

- ≥35 weeks gestation at birth
  - 4 mg/kg/dose every 12 hours
- <35 weeks gestation at birth
  - 2 mg/kg/dose every 12 hours
  - Increase to 3 mg/kg/dose every 12 hours:
    - At 2 weeks of age if ≥30 to <35 weeks gestation at birth
    - At 4 weeks of age if <30 weeks gestation at birth
- IV dose is 75% of oral dose

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Infants at Low Risk of Perinatal HIV Acquisition

- Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence
- ARV prophylaxis: 4 weeks of zidovudine (ZDV)

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Infants at Higher Risk of Perinatal HIV Acquisition

- Mothers who did not receive ARVs during pregnancy (regardless of whether they received intrapartum prophylaxis)
- Mothers with detectable VL near delivery, particularly if delivery was vaginal
- Mothers with acute HIV infection during pregnancy or breastfeeding
- Breastfed infants

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Additional ARVs for Exposed Infants

- Now recommended for infants at increased risk of HIV acquisition
- Additional prophylaxis v. empiric therapy
- Limited treatment options available

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Combination Prophylaxis for Infants

- NICHD-HPTN 040/PACTG 1043 enrolled 1746 infants born to mothers who did not receive antepartum ARVs
- Compared 3 regimens:
  - ZDV for 6 weeks
  - ZDV + 3 doses nevirapine
  - ZDV + 2 weeks of lamivudine/nelfinavir
- Transmission significantly lower in combination arms
  - 2.2% and 2.5% v. 4.9%
- Neutropenia significantly higher in 3-drug arm
- Nelfinavir powder no longer commercially available in the US

Nielsen-Saines et al. N Engl J Med. 2012;366(25):2368-2379.

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Additional Combination Therapy for Infants – "Mississippi Baby"

- HIV-exposed infant began receiving ART 30 hours after birth
- Infection confirmed by PCR testing
- Treatment discontinued at 18 months of age
- At 30 months, in absence of treatment, VL remained undetectable, HIV antibody negative
- Viral rebound at 27 months after stopping ART

Persaud et al, NEJM, November 7, 2013

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ARVs for Neonates at Higher Risk of Perinatal Infection

- ARV Prophylaxis (Combination):
  - 6 weeks ZDV, plus
  - 3-dose course of nevirapine (NVP) (prophylactic dose)

OR:

- Empiric HIV Therapy
  - ZDV + lamivudine (3TC) backbone, plus: NVP (treatment dose) or raltegravir (RAL)

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1, 2, or 3 Drugs?

- Level of viremia that would trigger combination therapy is unknown
- Some would use combination therapy for any detectable VL
- Transmission possible at low-level viremia*
  - 0.05 – 0.3% with VL <50 at delivery
  - 1.1 – 1.5% with VL 50 – 399
  - 2.8 – 4.1% with VL >400

Mandelbort et al, Clin Infect Dis. 2015. Townsend et al. AIDS. 2014;28(7)

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Duration of Empiric Therapy?

- Optimal duration unknown
- Some give 3 drugs for 6 weeks
- Some stop 3TC/NVP or RAL after newborn testing negative (continue zidovudine for 6 weeks)

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Lamivudine (3TC) Dosing

- ≥32 weeks gestation at birth
  - Birth – Age 4 Weeks:
    - 2 mg/kg/dose orally twice daily
  - Age 4 – 6 Weeks:
    - 4 mg/kg/dose orally twice daily

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Raltegravir (RAL)

- Added to guidelines as part of recommended regimen for empiric therapy for high-risk newborns in December 2018
- Integrase inhibitor
- Well-tolerated
- Drawback: solution must be mixed immediately prior to dosing

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Raltegravir (RAL) Dosing

- If mother received RAL 2-24 hours prior to delivery, delay baby's dose until 24-48 hours after birth (give other ARVs)
- Birth – 1 week of age: once daily
- ≥ 1 week of age: twice daily
- Initial dosing (~1.5 mg/kg/dose):
  - 2 to < 3 kg: 0.4 mL (4 mg)
  - 3 to <4 kg: 0.5 mL (4 mg)
  - 4 to <5 kg: 0.7 mL (7 mg)
- Subsequent dosing also by weight range:
  - 1 – 4 weeks: ~ 3 mg/kg/dose BID
  - 4 – 6 weeks: ~ 6 mg/kg/dose BID

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Nevirapine: Treatment Dosing

- ≥37 weeks gestation at birth
  - 6 mg/kg/dose orally twice daily

- 34 to <37 weeks gestation at birth
  - Birth – Age 1 Week:
    4 mg/kg/dose orally twice daily
  - Age 1 – 6 Weeks:
    6 mg/kg/dose orally twice daily

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Nevirapine: Prophylaxis Dosing

- ***NOTE: no calculation is required for prophylaxis dosing***
- Birth weigh >2 kg: 12 mg dose
- Birth weight 1.5 – 2 kg: 8 mg dose
- Dosing schedule
  - 1st dose: at birth – 48 hours of life
  - 2nd dose: 48 hours after 1st dose
  - 3rd dose: 96 hours after 2nd dose

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Considerations for ARVs in Infants

- Community pharmacies may not stock liquid formulations of ARVs
- DO NOT administer in bottle of formula – use syringes
- Provide marked syringes

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Newborns with Presumed HIV Exposure

- Mothers with positive test at L&D or postpartum
- Infants with positive HIV Ag/Ab test
- Treat as for infants at higher risk of acquisition
- ARV should be discontinued immediately if supplemental testing is negative for HIV

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Breastfed Infants - Treatment

- At least 6 weeks of ARV treatment
  - Standard zidovudine prophylaxis, and/or
  - Nevirapine
- PROMISE study
  - Maternal ART v. infant nevirapine
  - Infants continued NVP for 6 weeks after cessation of breast milk feeds

Flynn et al. J Acquir Immune Defic Syndr. April 1, 2018

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Breastfed Infants - Monitoring

- Additional virologic testing every 3 months during breastfeeding, then at 4-6 weeks, 3 months, and 6 months after cessation of breast milk feeds
- Treat infant thrush and maternal mastitis
- Women should maintain virologic control

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Additional Labs for Infants Receiving Combination Therapy

- CBCD
  - Repeat at 4 weeks if receiving ZDV/3TC
- LFTs
  - Monitor if receiving NVP
    - Baseline, at 2 and 4 weeks

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HIV TESTING IN INFANTS

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HIV Testing

- HIV antibody testing
  - Not useful for diagnosing infants due to transplacental transfer of maternal antibody
  - Infants who are uninfected should "serorevert" by 18 months of age
- HIV DNA PCR
  - Preferred test in infants
- HIV RNA PCR ("viral load")
  - Acceptable, concerns about sensitivity in infants exposed to antiretrovirals

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PCR Testing – All Infants

- At 1-3 weeks of age
- At ≥ 1month of age
- At ≥ 4 months of age

Birth PCR not routinely recommended – detects *in utero* transmission, and most perinatal infection occurs intrapartum

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Additional PCR Testing for Certain Infants

- For infants at higher risk of perinatal infection
  - PCR after birth (within 48 hours)
  - Consider at 2-4 weeks after cessation of ARVs (i.e., at 8-10 weeks of age)
- For breastfed infants
  - Every 3 months while breastfed
  - After cessation of breastfeeding:
    - 4-6 weeks later
    - 3 months later
    - 6 months later

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Excluding HIV Infection in Infants

- HIV infection may be *presumptively* excluded
  - PCRs not detected ≥ 14 days and ≥ 4 weeks of age (or one ≥ 8 weeks or one negative antibody test ≥ 6 months)
  - It is not necessary to prescribe TMP-SMX prophylaxis if HIV infection presumptively excluded
- HIV infection may be *definitively* excluded
  - PCRs not detected ≥ 1 and ≥ 4 months of age (or two negative antibody tests ≥ 6 months)

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Antibody Testing in Perinatally Exposed Children

- Many clinicians obtain antibody testing after 1 year of age to document seroreversion with loss of maternal antibody
- Seroreversion may take up to 18 months or more

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4th Generation HIV Antigen/Antibody Testing

- If (+) → HIV-1/-2 antibody differentiation
- If HIV-1/-2 antibody differentiation (-):
  - Consistent with seroreversion in perinatally-exposed child
  - Lab normally proceeds to nucleic acid testing to assess for recent infection
- If HIV-1/-2 antibody differentiation (+):
  - Confirms infection in adolescents/adults (lab does not proceed to NAT)
  - May reflect maternal antibody in perinatally-exposed (can request lab to add NAT)

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LONG-TERM OUTCOMES

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Potential Long-Term Effects

- Mitochondrial toxicity
  - Neurologic, cardiac, increased lactate
- Cancer risk with exposure to nucleoside analogues
- Immunologic dysfunction
- Increased morbidity & mortality

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Pediatric HIV/AIDS Cohort Study

- PHACS was established in 2005 to address two critical pediatric HIV research questions:
- the long-term safety of fetal and infant exposure to prophylactic antiretroviral (ART) chemotherapy; and
- the effects of perinatally acquired HIV infection in adolescents and young adults

Pediatric HIV/AIDS Cohort Study

https://phacsstudy.org

pHACS
A Study of the National Institutes of Health

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PHACS SMARTT Study

- Surveillance Monitoring for ART Toxicities
- Enrolls up to 400 perinatally-exposed infants a year

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PHACS Key Findings To Date re: Children Perinatally Exposed to HIV

- Hearing loss more common
- High risk of language impairment not related to ARV exposure
- High rates of mental health problems
- Data presented at IDSA 2018 showing trend toward increased adverse neurologic outcomes in children exposed to efavirenz and dolutegravir *in utero*

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Thank You for Your Attention!

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