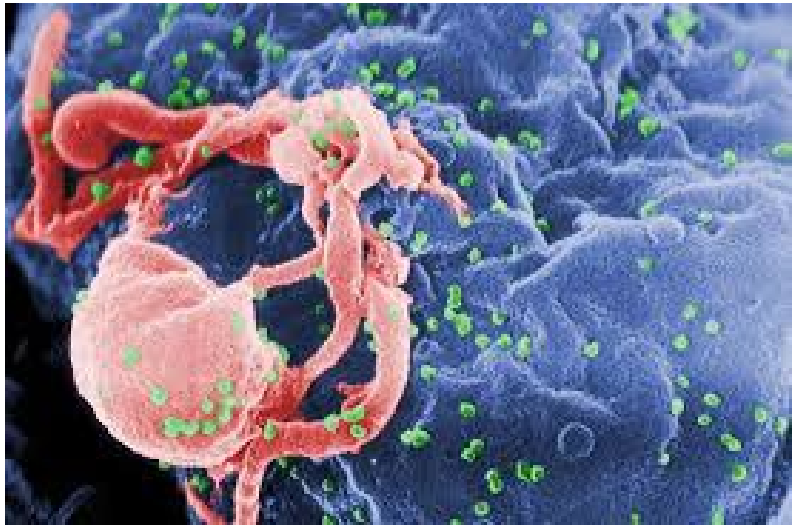
Prevention of Vertical Transmission of HIV In the United States and Globally – Successes and Challenges



Rana Chakraborty, M.D., D.Phil. (Oxon)

Faculty Disclosure Information

In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Acknowledgements: Drs. Hermione Lyall and Lynne Mofenson

Case – Expecting the Unexpected!

Newborn

- Newborn birth at 37 weeks gestation
- Transferred to the NICU for management of late preterm status, LGA, infant of a diabetic mother, & HIV exposure

Maternal History

- Type II DM (Hgb A1c 5.8 9/11)
- Transaminitis, thrombocytopenia with hepatic steatosis
- Rubella: nonimmune (first trimester lab)
  - Varicella: immune (first trimester lab)
  - RPR: NR/ Syphilis IgG/IgM NR (10/14)
  - Hepatitis B/C: neg/neg (10/14)
  - GC/Chl: neg/neg (first trimester lab)
  - HIV: positive - last viral load 13,100 on 10/15
  - GBS: unknown, GBS ppx with PCN

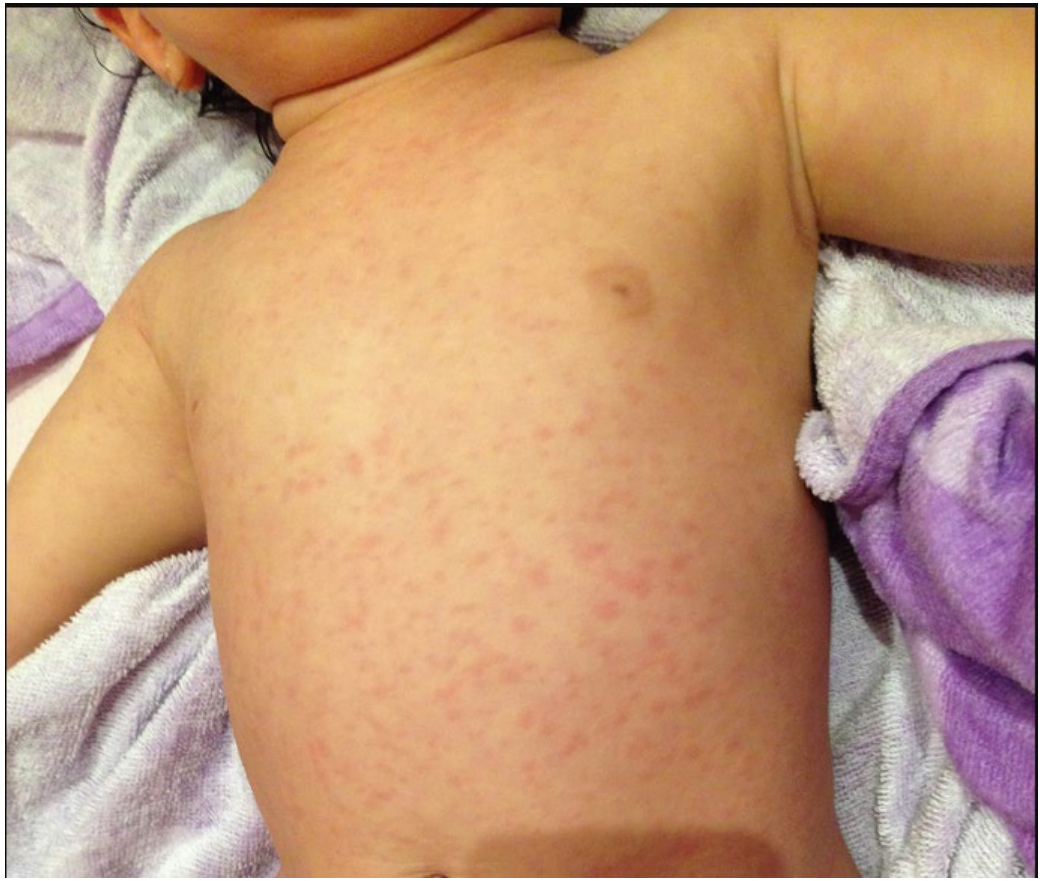
HIV Management in Pregnancy

- Mother was diagnosed with HIV on this admission and has been on dolutegravir, emtricitabine, and tenofovir alafenamide
- Her last viral load was reported to be 13,100 at GA 36/40
- HIV antibody/antigen test was previously negative on 5/6/24, with reactive antibody/antigen panel in OB/GYN triage on 10/14/24
- C- section scheduled and intravenous AZT near delivery
- Breast feeding not recommended

On Admission

- Newborn Asymptomatic
  PE: Unremarkable
- Formula feeding gradually started
- HIV DNA and HIV RNA sent at admission
- Started on 3-drug ARV prophylaxis including Zidovudine, Lamivudine and Nevirapine
- Baby admitted to NICU for observation
- On D6-7 of life, baby had recurrent desaturations with feeding and apnea. Head US noted Grade 1 germinal matrix IVH
- Evaluation for sepsis after empirically starting broad spectrum antibiotics and IV ACV.

- On day 7 the baby developed a diffuse maculopapular rash on face, chest, abdomen and lower and lower extremities (sparing the palm and soles) with high grade fevers
- RVP : Negative
- CMV PCR Negative
- HSV surface swabs : negative
- Cultures negative at 48 hrs
- HIV DNA and RNA sent on admission reported as negative
- MRI brain: Normal



Differential and Recommendations?

- Repeat HIV DNA PCR – HIV Infection in the NB acquired during labor and delivery, especially given maternal viral load of 13,100 one week prior to birth.

  OR

- Nevirapine rash

  OR

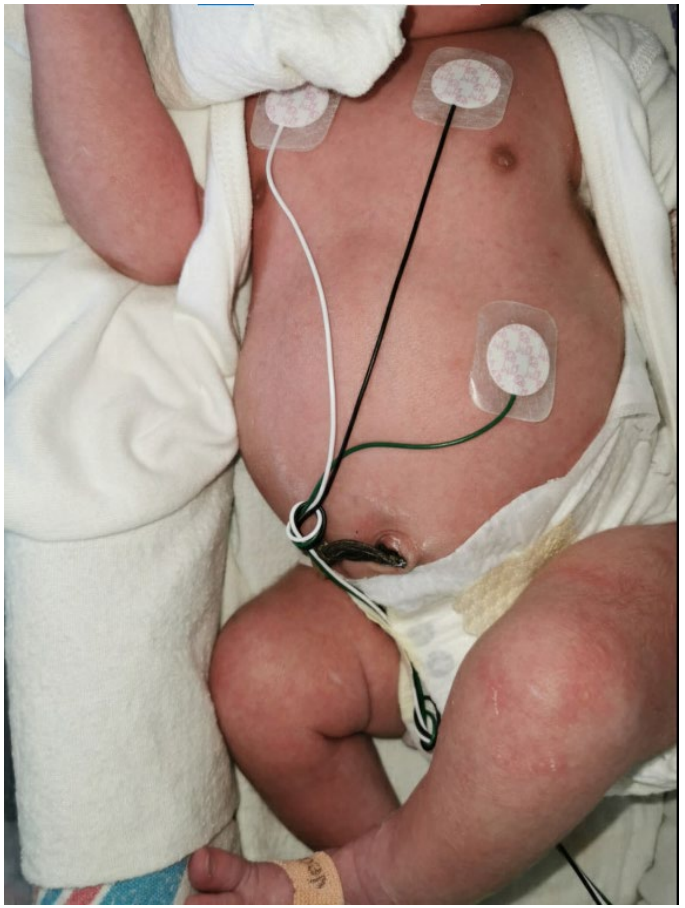
- Other viral exanthem – Rubella?

- Repeat HIV DNA PCR test

- Stop nevirapine and lamivudine and maintain prophylaxis with zidovudine.

- Rash on D9 (fading). Resolved by D10.

- D14 discharged home on Zidovudine prophylaxis



Acknowledgement: Dr. Mu'Ath Al Theibat

OBJECTIVES

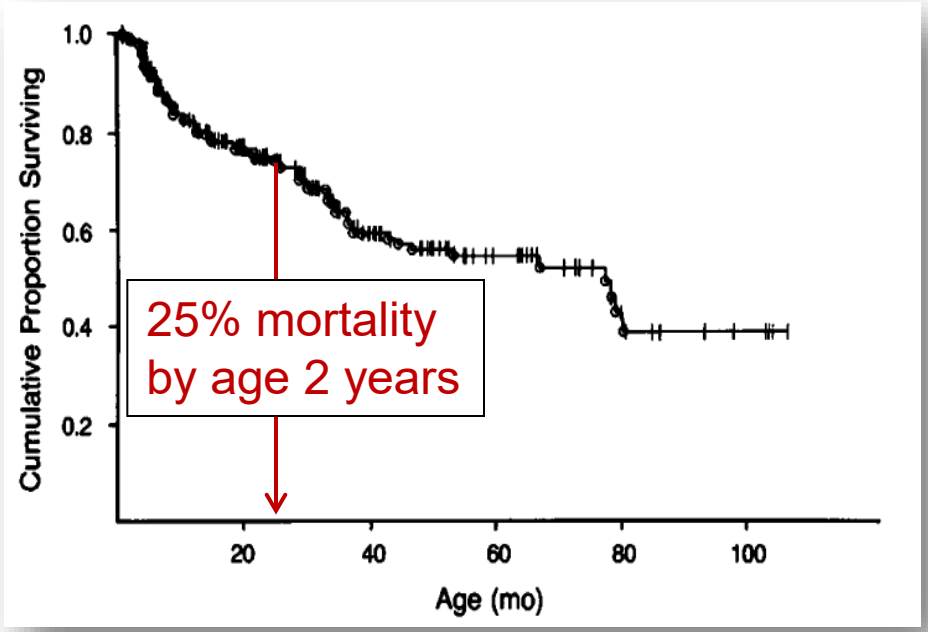
- Historical Perspective
- Important PVT Trials and their Recommendations
  Nationally
  Globally
- Current Challenges
  No Prenatal Care and/or incomplete virologic suppression
  Maternal ARVs

Late 1980's: Vertical Transmission (VT) of HIV in the U.S.

- One in four HIV-infected mothers transmitted HIV to their infant.
- Most pediatric HIV infection occurred through transmission from mother-to-child although timing of transmission unclear.
- By the early 1990s, >16,000 perinatally-infected children had been born in the U.S., with a critical need for prevention.

Acknowledgement: Dr. Lynne Mofenson

Untreated Pediatric HIV Infection Had Extremely High Mortality

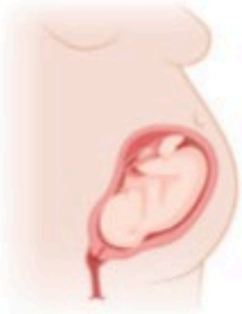


Survival from birth in 172 children with perinatal HIV infection Jackson Memorial Hospital, Miami 1981-1987

Scott G et al. NEJM1989;321:1791-6.

- In absence of treatment, pediatric HIV associated with rapid progression.
- In a Miami cohort of 172 children with perinatal HIV, 25% of children died by age 2 years.

Mechanisms of Vertical Transmission of HIV



In utero

- Fetus exposed to HIV-infected maternal blood at 10-12 weeks
- Inflammation of trophoblast cells are potentially associated with migration of HIV into fetal villi containing CD4+CCR5+ target cells such as placental macrophages
- Risk increased by higher maternal viral loads and placental inflammation
- 5-10% rate of transmission, least common

Intrapartum

- Infected maternal blood and secretions from the birth canal coming into contact with the mucosal surfaces of the fetus
- Prolonged ruptured membranes
- 15-20% rate of transmission, most common

Postpartum

- HIV RNA detected in cell-free breastmilk and colostrum
- Infected maternal CD4 cells isolated in breastmilk
- Complete elimination of HIV from breastmilk has not been achieved
- Estimated 16% rate of transmission

Created in BioRender.

Cardenas MC, Farnan S, Hamel BL, Mejia Plazas MC, Sintim-Aboagye E, Littlefield DR, Behl S, Punia S, Enninga EAL, Johnson E, Temesgen Z, Theiler R, Gray CM, Chakraborty R. Prevention of the Vertical Transmission of HIV; A Recap of the Journey so Far. Viruses. 2023 Mar 26;15(4):849. doi: 10.3390/v15040849. PMID: 37112830; PMCID: PMC10142818.

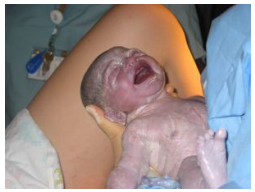
The ZDV Regimen in PACTG 076 Was Designed to Target Multiple Potential Time Points of Transmission

Pregnancy

ZDV 100 mg
5 times daily

TARGET:
In Utero
(after 1st trimester)

Labor/Delivery



ZDV IV 2 mg/kg
1 mg/kg/hr

TARGET:
Intrapartum

Pre-Exposure Prophylaxis (PrEP)

Infant

ZDV 2 mg/kg
q 6 hr x 6 weeks

TARGET:
Postpartum

Post-Exposure Prophylaxis (PEP)

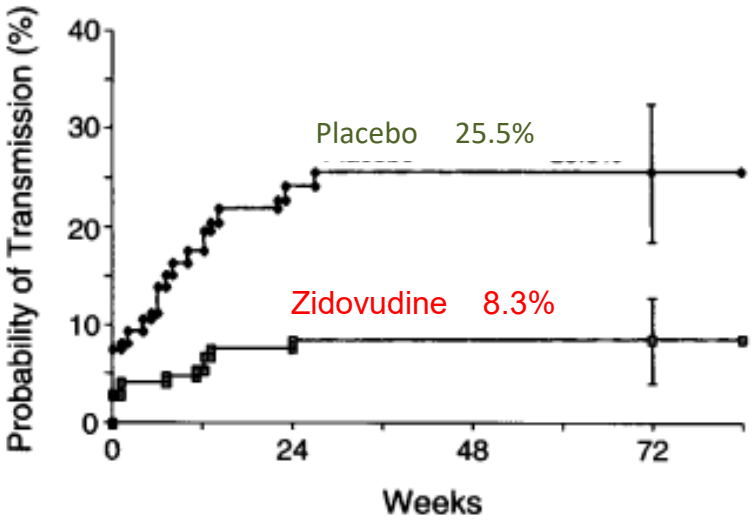
DSMB halted trial Feb 1994

The New England Journal of Medicine

Volume 331 NOVEMBER 3, 1994 Number 18

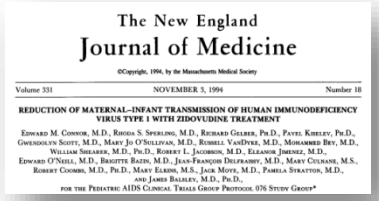
REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

Edward M. Connor, M.D., Rhoda S. Sperling, M.D., Richard Gelber, Ph.D., Pavel Kiselev, Ph.D., Gwendolyn Scott, M.D., Mary Jo O'Sullivan, M.D., Russell VanDyke, M.D., Mohammed Bey, M.D., William Shearer, M.D., Ph.D., Robert L. Jacobson, M.D., Eleanor Jimenez, M.D., Edward O'Neill, M.D., Brigitte Bazin, M.D., Jean-François Delfraissy, M.D., Mary Culnane, M.S., Robert Coombs, M.D., Ph.D., Mary Elkins, M.S., Jack Move, M.D., Pamela Stratton, M.D., and James Balsley, M.D., Ph.D., for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*



First demonstration of treatment as prevention!

Acknowledgement: Dr. Lynne Mofenson


The New England
Journal of Medicine

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REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

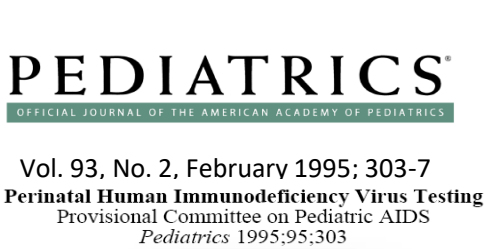
Prevention of VT – PACTG 076

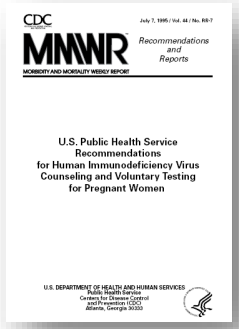
- Because knowledge of timing of VT was limited, PACTG 076 targeted multiple potential time points of transmission:
  -  Antepartum ZDV – *in utero*
  -  Intrapartum ZDV – intrapartum
  -  Infant ZDV – post-exposure prophylaxis

- 67% reduction in VT with the PACTG 076 ZDV regimen (25.5% placebo vs 8.3% ZDV).

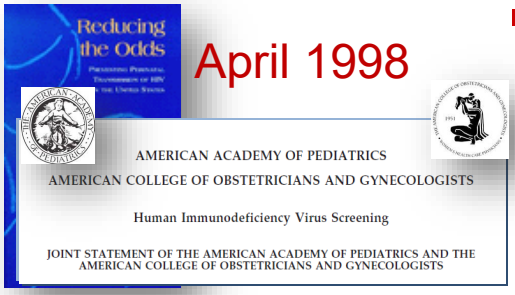
Acknowledgement: Dr. Lynne Mofenson

Move to Recommend Universal Antenatal HIV Testing





- 1995: AAP & CDC expanded recommendations from selective testing of "high risk" groups to voluntary routine testing with consent for <u>all</u> pregnant women in US

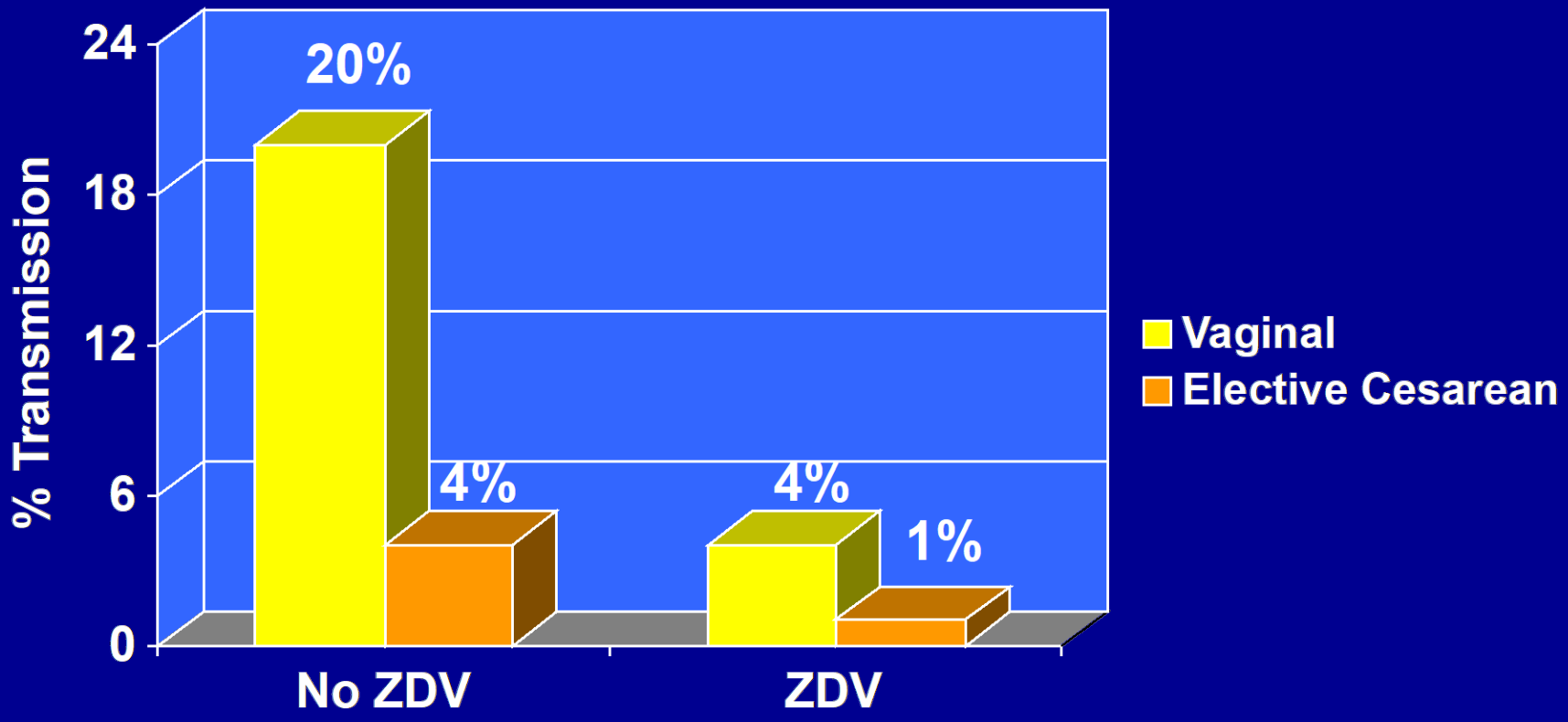


- 1998: Following Institute of Medicine Report, AAP & ACOG recommend universal routine "opt out" testing with patient notification

The evidence for recommending Caesarian-Section for all Pregnant Women Living with HIV

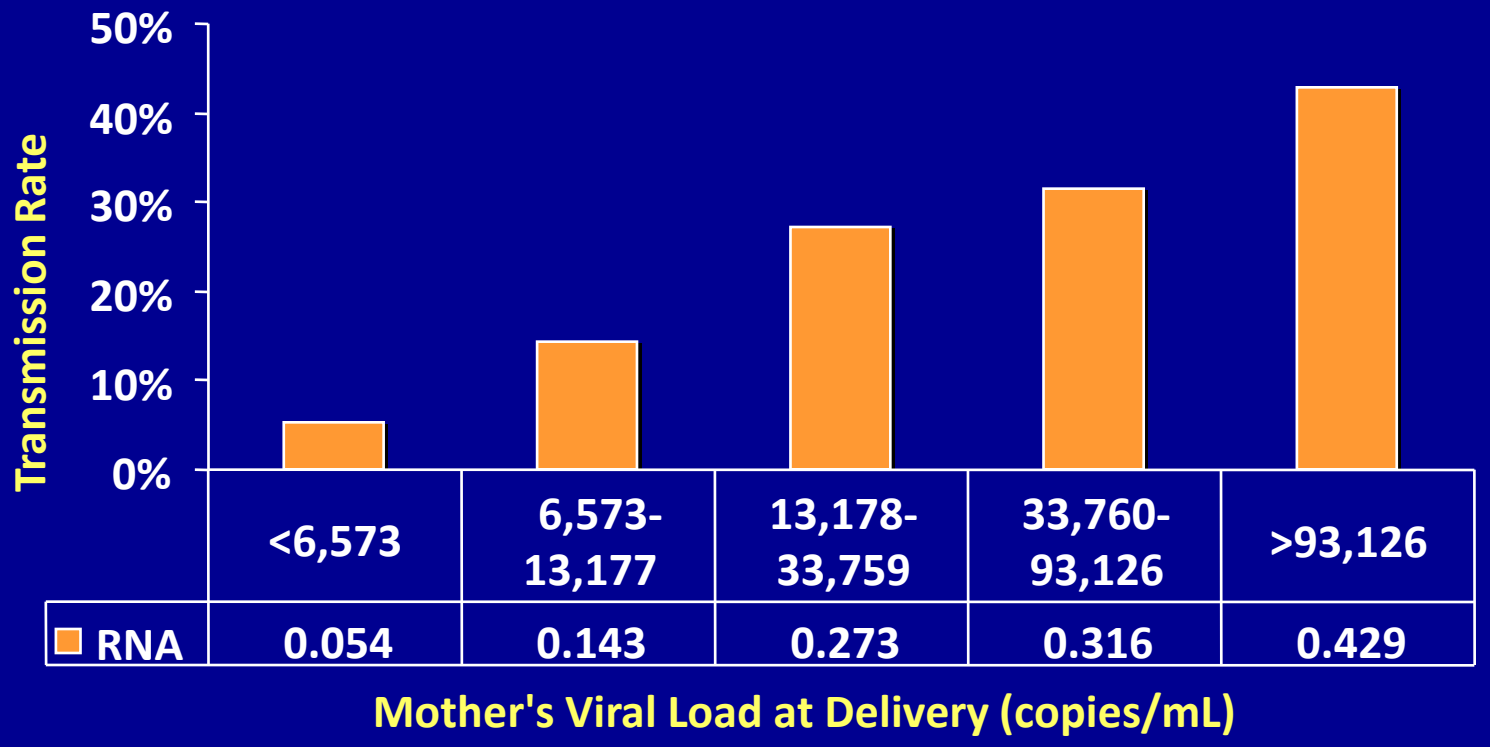
European Randomized Mode of Delivery Trial: Elective Cesarean at 38 Weeks vs Vaginal Delivery

European Mode of Delivery Collaboration. Lancet 1999;353:1035-9



What are the Primary Risk Factors for Vertical Transmission of HIV?

Bangkok: Transmission Rates by Delivery Plasma Viral Load

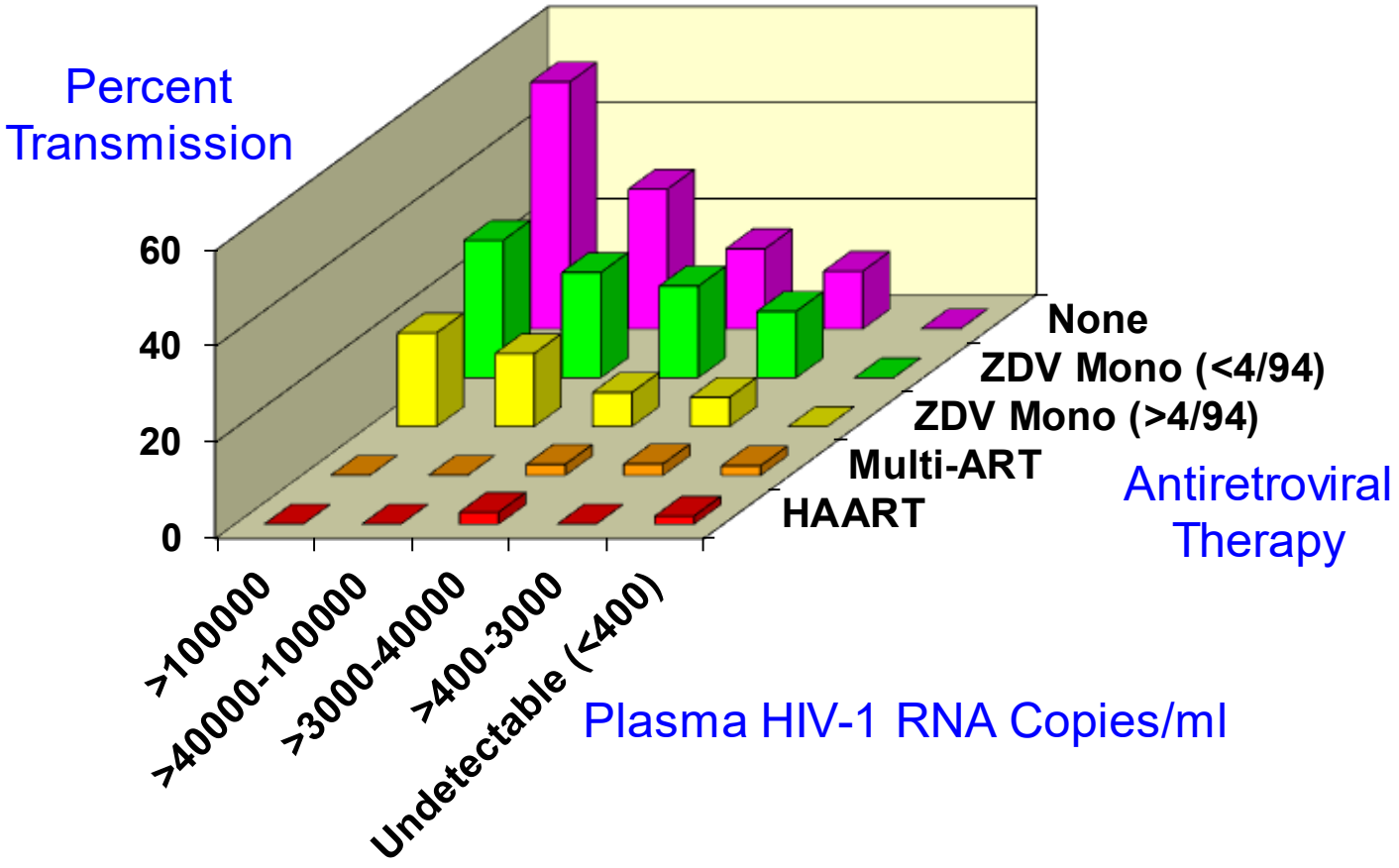


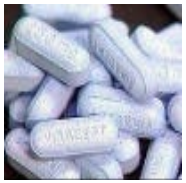
Source: Shaffer et al., J Infect Dis 1999

Maternal Delivery HIV RNA Levels and Antiretroviral Use Are Independently Associated With MTCT

Women and Infant Transmission Study, U.S. 1990-2000

Cooper E et al. JAIDS 2002;29:484-94

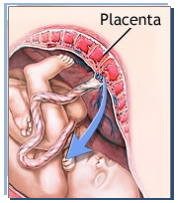




How Do Antiretroviral Drugs Reduce Vertical Transmission of HIV?

- Lowering maternal blood/genital viral load
  - This mechanism likely most important in women with high viral load.

- Two other important mechanisms through which ARVs reduce transmission:



  - Pre-exposure prophylaxis of infant (through transplacental drug passage).

  - Post-exposure prophylaxis of infant (through continued drug after birth).

Acknowledgement: Dr. Lynne Mofenson

As part of intrapartum recommendations in the US, Caesarian section and administration of intravenous zidovudine is no longer recommended for certain women living with HIV infection during labor and delivery. Where did the evidence for this change come from?

What is the Role of Elective CS in the ART Era?

Tariq S, et al. JAIDS 2011;57:326-333
Briand N et al. Am J Obstet Gynecol 2013 Jun 18 (Epub)

Study/Mode Delivery	MTCT	Adjusted Odds Ratio
Europe (ECS/NSHPC), women receiving cART 2000-2009 (*Tariq*)		
ART Elective CS (N=3515)	**0.8%**	1.0
ART Vaginal delivery (N=1051)	**0.9%**	0.8 (0.4-1.7), p=0.58
ART Emergency CS (N=1095)	1.7%	2.1 (1.1-3.8), p=0.02
France, women receiving cART 2000-2010 (*Briand*)		
VL <1000 Elective CS (N=1695)	**0.4%**	-
VL <1000 Vaginal delivery (N=1695)	**0.4%**	-
VL <1000 Emergency CS (N=893)	0.7%	-

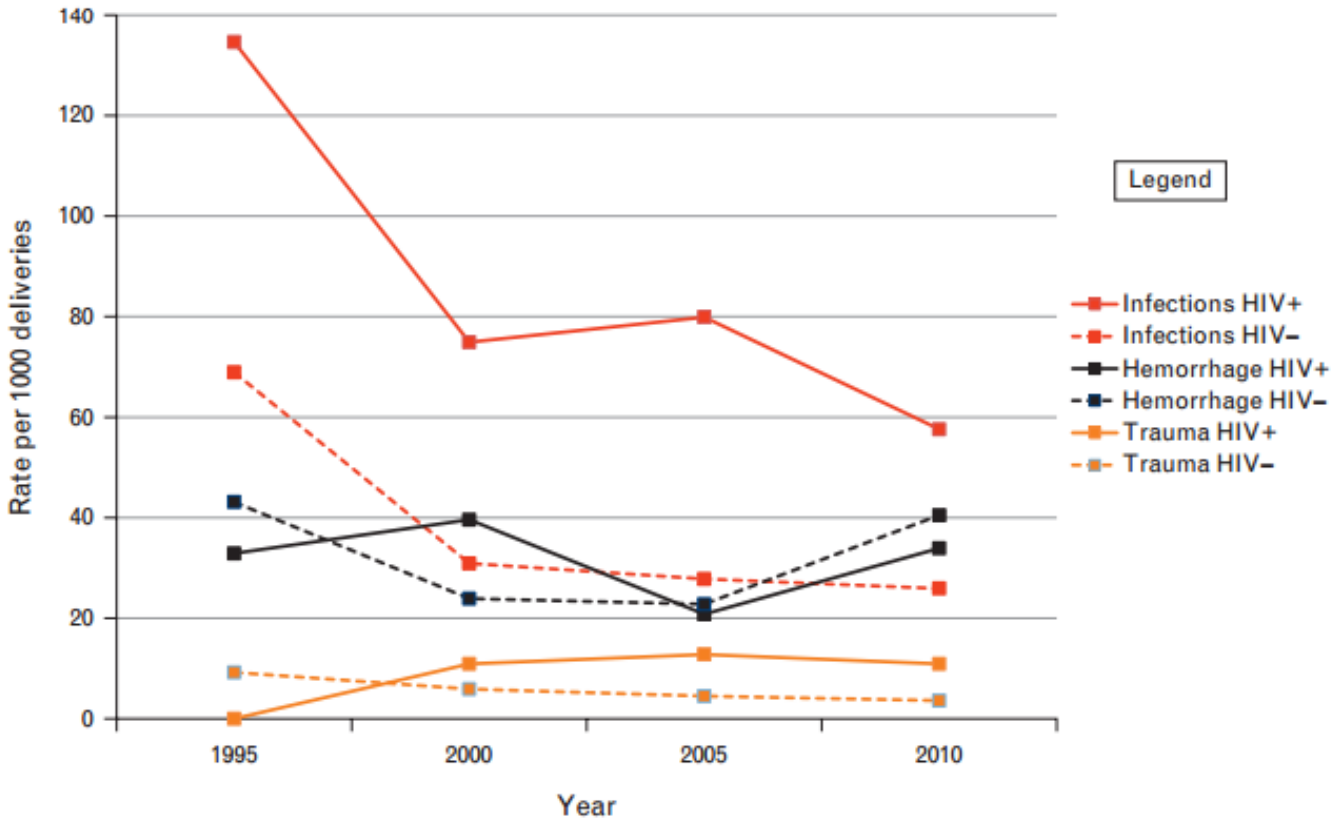
Given low VT risk, risk of CS to woman receiving ART **with viral suppression** outweighs potential benefit to the infant.

Infectious Complications of Cesarean Delivery are Higher in Women Living with HIV than in HIV-Uninfected Women

Kourtis AP et al. AIDS 2014;28:2609-18.

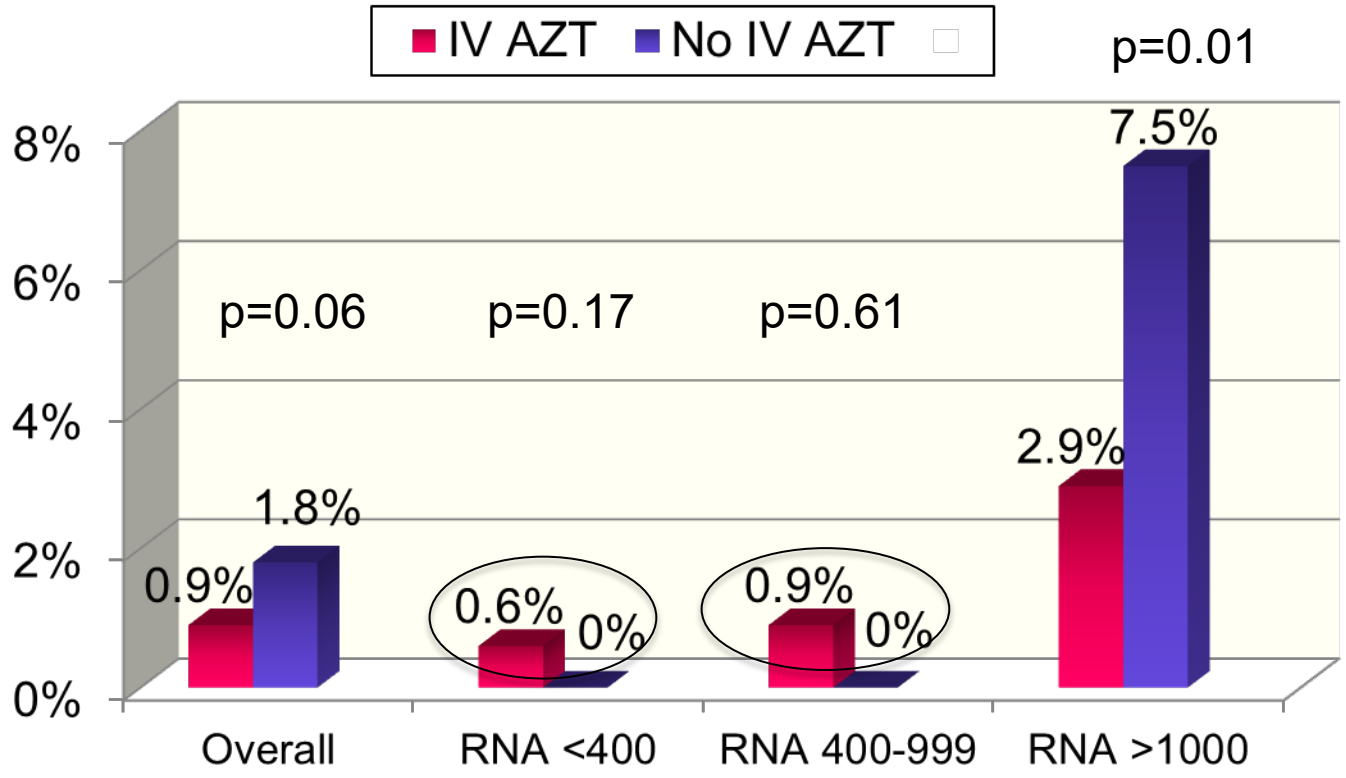
- Compared CS complication rates in HIV+/– women in US in 4 cycles: 1995-96; 2000-1; 2005-6; 2010-11.

- While CS complications decreased from 1995-2011(ART era), **infections, surgical trauma, hospital death and hospital duration were still higher in women living with HIV.**



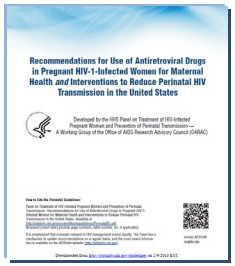
Intrapartum ZDV is no Longer Required in HIV-Infected Women During Labor with Adequate Virologic Suppression

- 11,538 HIV+ women who delivered between 1997-2010;
  - 10,984 received IV ZDV; 554 did not receive IV ZDV



2014 Guidelines: IV ZDV not required if HIV RNA <1000 c/mL

Briand N et al. Clin Infect Dis 2013;57:903-14

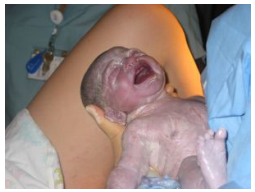


Intrapartum Recommendations for Pregnant Women Living with HIV

- Continue combination ART regimen during L&D.
- If on ART and HIV RNA is undetectable (<HIV RNA level < 50 copies/mL) near delivery, addition of IV ZDV NOT required.
- If HIV RNA is detectable (> 50 copies/mL) near delivery *or* unknown, IV ZDV recommended.
- If HIV RNA is detectable near delivery, elective cesarean delivery at 38 weeks (along with IV ZDV) is recommended.

Where did the evidence for the current U.S. HHS guidelines on postnatal prevention come from?

The ZDV Regimen in PACTG 076 Was Designed to Target Multiple Potential Time Points of Transmission

Pregnancy	Labor/Delivery	Infant
		
ZDV 100 mg 5 times daily	ZDV IV 2 mg/kg 1 mg/kg/hr	ZDV 2 mg/kg q 6 hr x 6 weeks
TARGET: *In Utero* (after 1st trimester)	TARGET: Intrapartum	TARGET: Postpartum
	Pre-Exposure Prophylaxis (PrEP)	**Post-Exposure Prophylaxis (PEP)**

DSMB halted trial Feb 1994

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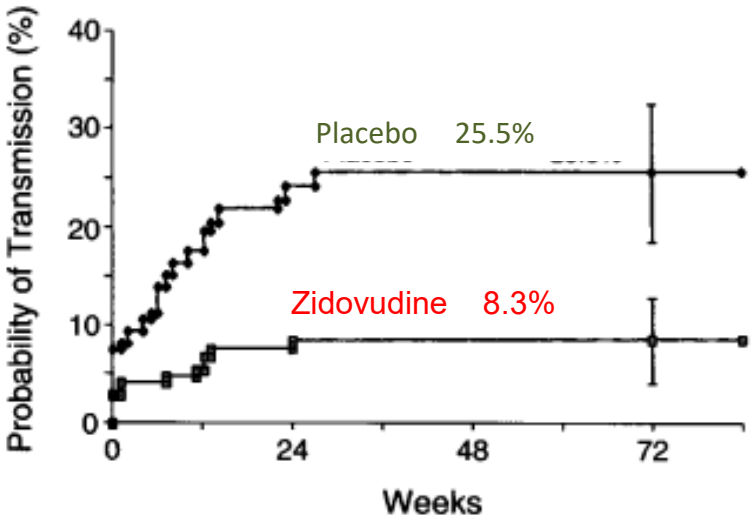
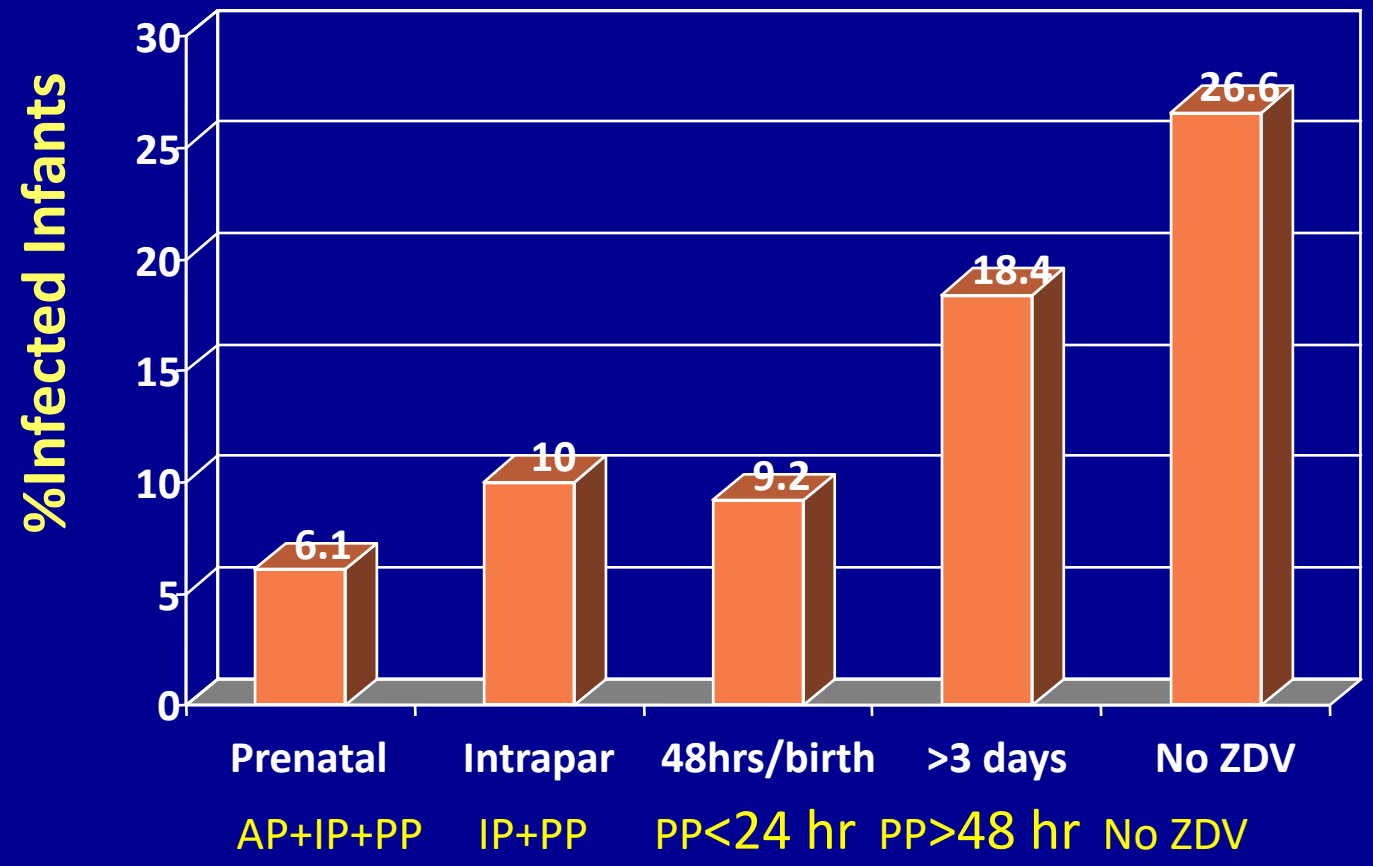


First demonstration of treatment as prevention!

Acknowledgement: Dr. Lynne Mofenson

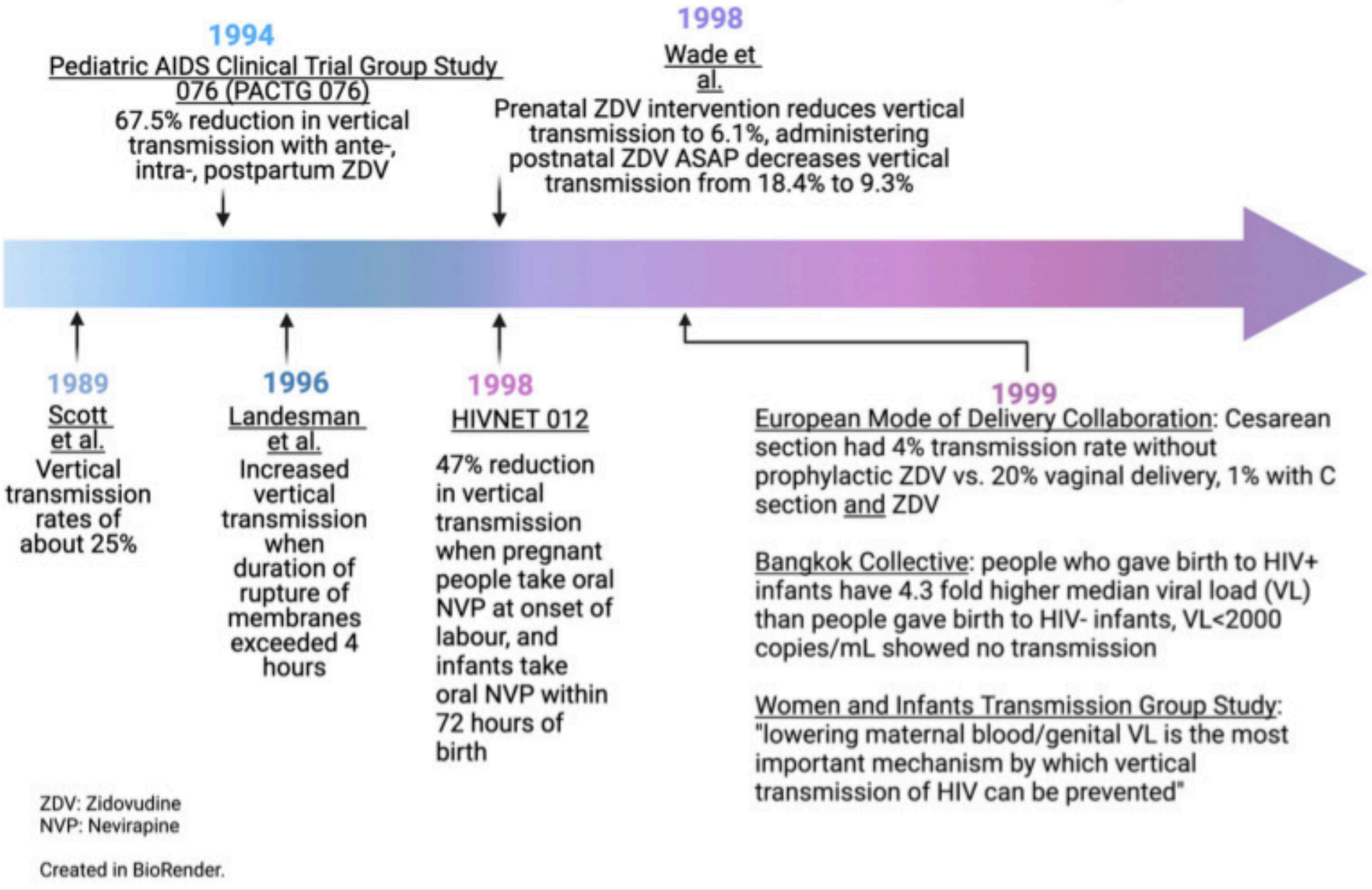
Neonatal Prophylaxis: Proportion of HIV Infected Infants by Timing of ZDV Receipt

Wade et al., NEJM, 1998



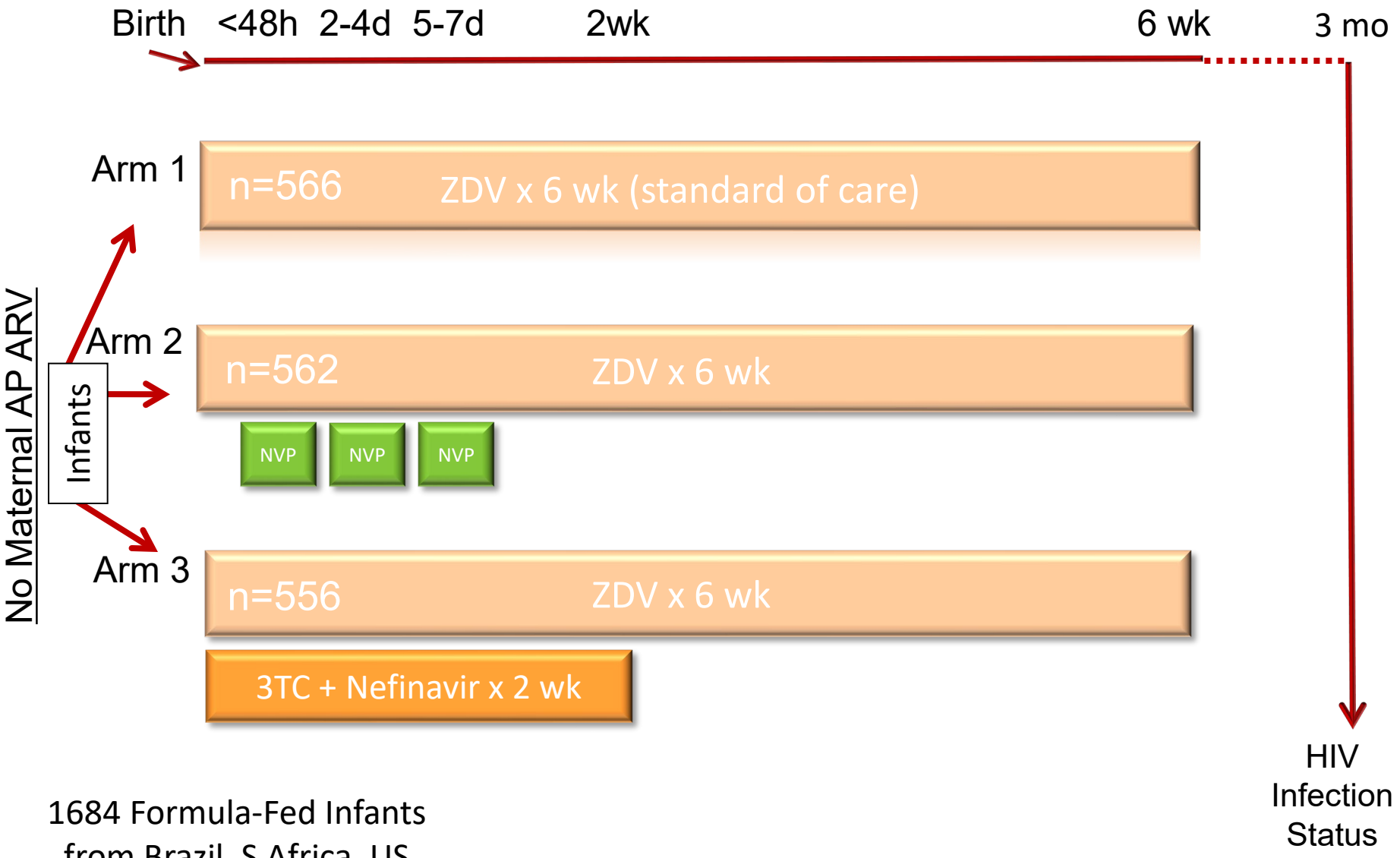
Even When No Maternal AP ZDV Given, Infant ZDV Started Within 24 Hours Reduces Transmission

Historical Studies in the Prevention of Vertical Transmission of HIV, 1989-1999



Cardenas MC, Farnan S, Hamel BL, Mejia Plazas MC, Sintim-Aboagye E, Littlefield DR, Behl S, Punia S, Enninga EAL, Johnson E, Temesgen Z, Theiler R, Gray CM, Chakraborty R. Prevention of the Vertical Transmission of HIV; A Recap of the Journey so Far. Viruses. 2023 Mar 26;15(4):849. doi: 10.3390/v15040849. PMID: 37112830; PMCID: PMC10142818.

What is Optimal Infant Prophylaxis When the Mother Has Not Received Antepartum ARV: NICHD/HPTN 040 Study

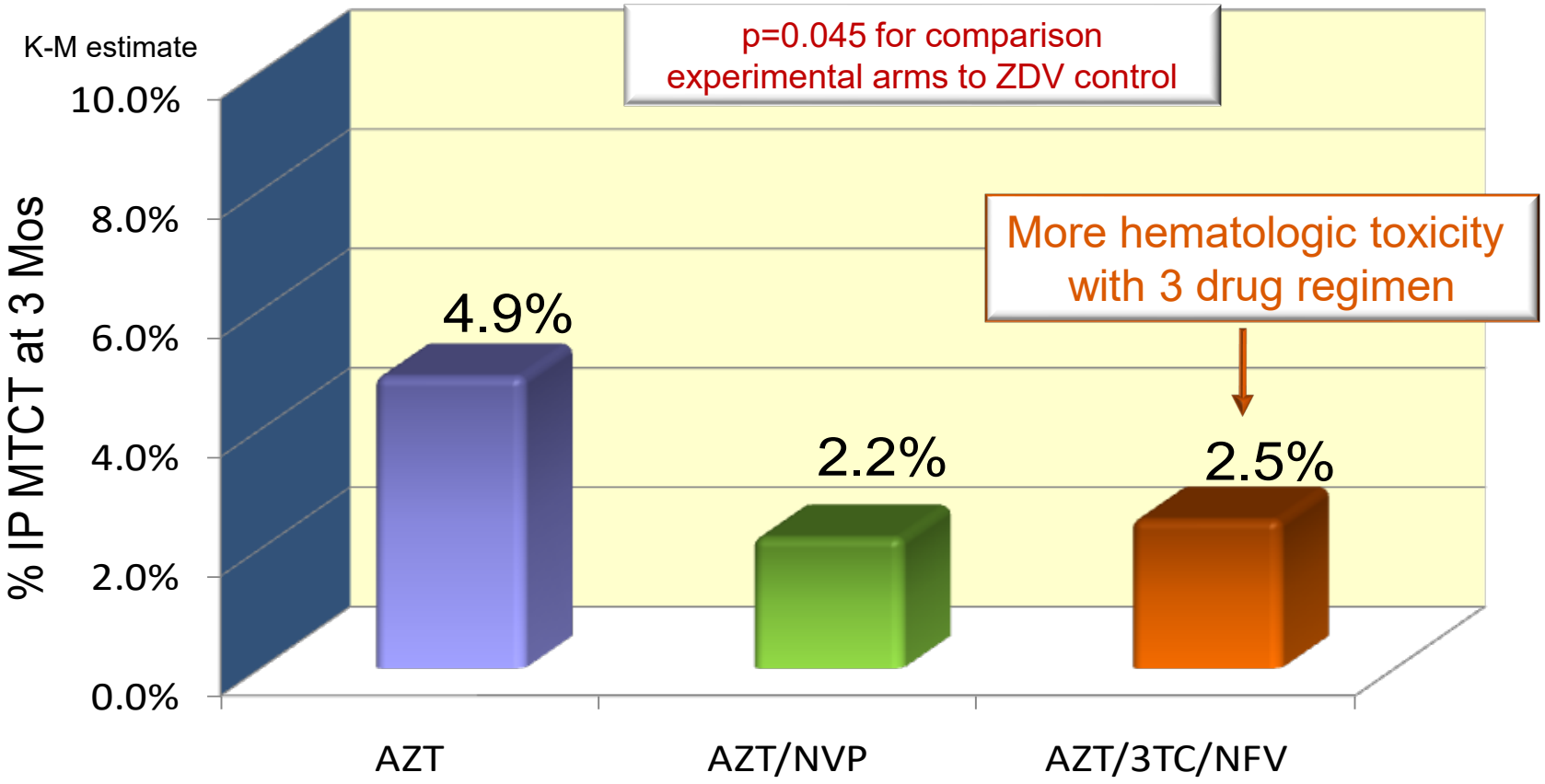


1684 Formula-Fed Infants
from Brazil, S Africa, US

NICHD/HPTN 040: Intrapartum Transmission Decreased by ~50% with Dual or Triple Infant ARV

Nielsen-Saines K et al. NEJM 2012;366:2368-79

Intrapartum Infection (HIV- at Birth, + after)



# infants infected after birth with NVP resistance:	1	2	1

Newborn Testing and Prophylaxis Recommendations following Perinatal HIV Exposure

***Low-Risk Criteria**

- Mother with HIV who received ART throughout pregnancy or from the 1st/early 2nd trimester **and**
- Confirmed maternal HIV RNA<50 copies/mL near delivery (within 4-6 weeks) **and**
- No concerns regarding ART adherence **and**
- Mother did not have primary or acute HIV infection during pregnancy

Mother is Known to Be HIV Positive

↓

Known or Suspected Drug-Resistant Virus

- **NO** → **Meets Low-Risk Criteria***
  - **NO** → Obtain HIV Virologic Testing (RNA or DNA PCR) at birth and **Proceed to Higher Risk Perinatal HIV Exposure Algorithm**
  - **YES** → **Infant with Low Risk Perinatal HIV Exposure**

    Infant HIV Testing
    - HIV Virologic Testing (RNA or DNA PCR) starting at 14-21 days of age
    - Complete Blood Count with Differential

    Newborn Zidovudine (ZDV) Prophylaxis

    Begin 4-week oral zidovudine monotherapy as close to the time of birth as possible, dosed by gestational age at birth as below:

< 30 weeks Gestation:	30 to <35 weeks Gestation:	≥35 weeks Gestation:
2 mg/kg/dose BID	Birth - 2 weeks old: 2 mg/kg/dose BID 2 - 4 weeks of age: 3 mg/kg/dose BID	4 mg/kg/dose BID

- **YES** → **Consult with Local/National ART Expert before Delivery.** Option: Perinatal HIV Hotline: (888) 448-8765

Mother's HIV Status Unknown, or Mother with previous negative HIV test but at risk for acute HIV infection in late pregnancy#

↓

Urgent Maternal and/or Neonatal HIV Test; maternal HIV RNA test if Acute HIV is Suspected

- **NEGATIVE** → **No ARV Prophylaxis Required**
- **POSITIVE** → **Presumptive HIV Therapy or ARV Prophylaxis; Proceed to Higher Risk Perinatal HIV Exposure Algorithm**

  +

  Newborn HIV Testing
  - HIV Virologic Testing (RNA or DNA PCR) at birth
  - Complete Blood Count with Differential

  +

  Perform Supplemental Maternal HIV Testing
  - 4th generation Ab/Ag testing, HIV-1/HIV-2 antibody Differentiation immunoassay, and HIV Virologic Testing (RNA PCR or Viral Load)

#Mothers with previous negative HIV test at risk for seroconversion in late pregnancy are those with:

- Documented STI
- Unprotected Sex
- Partner with HIV
- Multiple Partners
- IV drug use

ART = Antiretroviral Therapy

Algorithm adapted by Paul Spearman, Rana Chakraborty and Athena Kourtis from Management of Infants Born to Women with HIV Infection, in Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States, aidsinfo.nih.gov.

Higher Risk Criteria

- Mothers who received neither antepartum nor intrapartum ARVs **or**
- Mothers who received only intrapartum ARVs **or**
- Mothers who received ante- and intrapartum ARVs but who do not have viral suppression (HIV RNA <50 copies/mL) near delivery, particularly if delivery was vaginal **or**
- Mothers with acute or primary HIV infection during pregnancy or breastfeeding, in which case, the mother should discontinue breastfeeding.

Higher Risk Perinatal HIV Exposure

Select Presumptive HIV Therapy or 2-drug ARV Prophylaxis based on Gestational Age at Birth

^ ARV doses (such as ZDV and Nevirapine) may need to be changed and the ARV regimen may need to be optimized if the infant has confirmed HIV infection. See aidsinfo.nih.gov for full dosing guidelines for infants with confirmed HIV infection.

Gestational Age at Birth

<32 Weeks or <1.5 Kg birth weight

Zidovudine Prophylaxis

- Only Zidovudine dosing established
- Can start Zidovudine 2 mg/kg po BID*
- For combination therapy advice, consult with local/national experts
- Option: HIV Perinatal Hotline, (888) 448-8765

32 to <34 weeks and ≥1.5 Kg birth weight

2-Drug ARV Prophylaxis

Zidovudine for 6 weeks
Birth to 2 weeks of age: 2 mg/kg po BID*
>2 weeks of age: 3 mg/kg po BID*

PLUS

Nevirapine (3 total doses, oral)

Birth weight 1.5-2 kg: 8 mg
Birth weight > 2 Kg: 12 mg

1st dose given within 48 hours of birth
2nd dose given 48 hours after 1st dose
3rd dose given 96 hours after 2nd dose
(i.e. day 1, day 3, day 7 of life)

≥34 weeks

Preferred

3-Drug Presumptive HIV Therapy for 6 Weeks†

Zidovudine
Gestational Age<35 wks at birth:
Birth to 2 weeks of age: 2 mg/kg po BID*
>2 weeks of age: 3 mg/kg po BID*
Gestational Age ≥35 weeks at birth:
4 mg/kg po BID*^

PLUS

Lamivudine (3TC)†
Birth to age 4 wks of age: 2 mg/kg/dose po BID
>4 wks of age: 4 mg/kg/dose po BID

PLUS

Nevirapine
Gestational Age ≥37 weeks
6 mg/kg/dose po BID^

Gestational Age 34-<37 weeks
Birth to 1 week of age:
4 mg/kg/dose po BID
>1 week of age:
6 mg/kg/dose po BID^

OR

Raltegravir&
Gestational age ≥ 37 weeks
Birth to 1 week of age:
1.5 mg/kg/dose po QD
1 week to 4 weeks of age:
3 mg/kg/dose po BID
4 weeks to 6 weeks of age:
6 mg/kg/dose po BID

OR

Optional; not preferred

2-Drug ARV Prophylaxis

Zidovudine for 6 weeks
4 mg/kg po BID^

PLUS

Nevirapine (3 total doses, oral)

Birth weight 1.5-2 kg: 8 mg
Birth weight > 2 Kg: 12 mg

1st dose given within 48 hours of birth
2nd dose given 48 hours after 1st dose
3rd dose given 96 hours after 2nd dose
(i.e. day 1, day 3, day 7 of life)

† All infants at higher risk of perinatal HIV exposure should be tested by HIV RNA or DNA PCR at birth. If birth HIV virologic testing in newborn is negative, some experts would discontinue Lamivudine and Nevirapine after 2 weeks and complete 6 weeks of prophylaxis with Zidovudine alone.

Algorithm adapted by Paul Spearman, Rana Chakraborty and Athena Kourtis from Management of Infants Born to Women with HIV Infection, in Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States, aidsinfo.nih.gov.

Practice of Offering a Child Pre-Masticated (Pre-Chewed) Food: An Unrecognized Possible Risk Factor for HIV Transmission

Gaur AH et al. Pediatrics 2009;124:658-66

3 cases of HIV infection in children diagnosed at ages 9, 15 and 39 months due to symptoms of HIV:

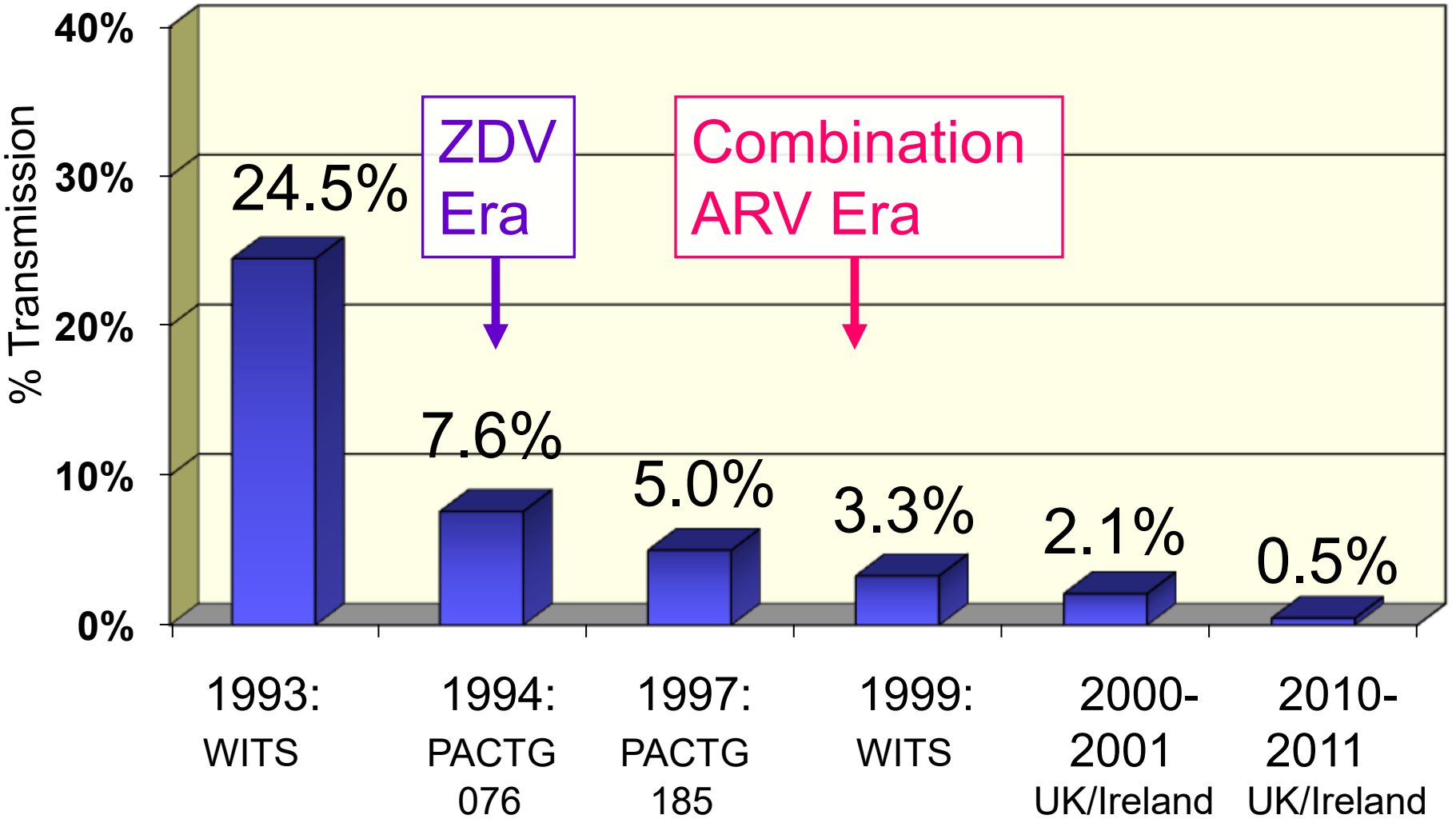
- 2 with HIV+ mother, not breastfed, prior negative PCR
- 1 with HIV- mother, HIV+ great-aunt who cared for child
- All fed pre-masticated food, concurrent oral bleeding
- Phylogenic analysis supported this infection route

- Pre-mastication common in diverse cultures. In US, 29% (*MMWR March 2011;60:273-5 Maritz ER. Pediatrics 2011;128:e579-90).*

SUMMARY SLIDE – U.S.

- ALL PREGNANT WOMEN SHOULD BE TESTED FOR HIV IN THE FIRST TRIMESTER AND AGAIN AT THE END OF THE THIRD TRIMESTER
- WOMEN WITH NO ANC SHOULD RECEIVE A RAPID TEST
- RECEIVE TREATMENT FOR HIV IF THEY TEST POSITIVE SO THAT PLASMA VL IS UNDETECTABLE (RNA LEVEL < 50 COPIES/ML) THROUGH PREGNANCY
- BE OFFERED C-S AND I/V ZDV DURING DELIVERY IF VL IS DETECTABLE OR PRESUMED DETECTABLE (RNA LEVEL > 50 COPIES/ML) AT DELIVERY
- THEIR BABIES SHOULD RECEIVE POSTNATAL PROPHYLAXIS IDEALLY WITHIN 12 HOURS AFTER BIRTH
- PROVIDERS SHOULD INQUIRE ABOUT THE PRACTICE OF PREMASTICATION AND COUNSEL HIV-INFECTED CARERS ABOUT MORE SAFER FEEDING PRACTICES
- FOR INFANTS BORN TO MOTHERS WITH NO PNC OR DETECTABLE VL NEAR DELIVERY, POSTNATAL PROPHYLAXIS SHOULD INCLUDE ZDV, LAMIVUDINE AND NEVIRAPINE. NEVIRAPINE CAN BE REPLACED BY RALTEGRAVIR
- POSTNATAL ARV PROPHYLAXIS IS BASED ON TRANSMISSION RISK FROM MATERNAL HIV RNA
- INFANTS CAN RECEIVE TESTING FOR HIV BY DNA PCR AT BIRTH, 14-21 days of life, 4—6 WEEKS, AND 3 – 6 MONTHS

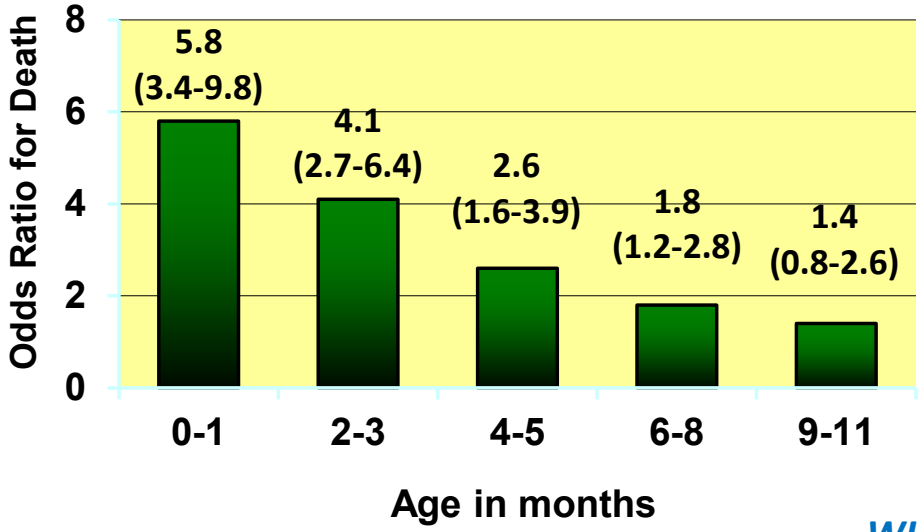
Research to Implementation: VT in Resource-Rich Countries Over Time



Acknowledgement: Dr. Lynne Mofenson

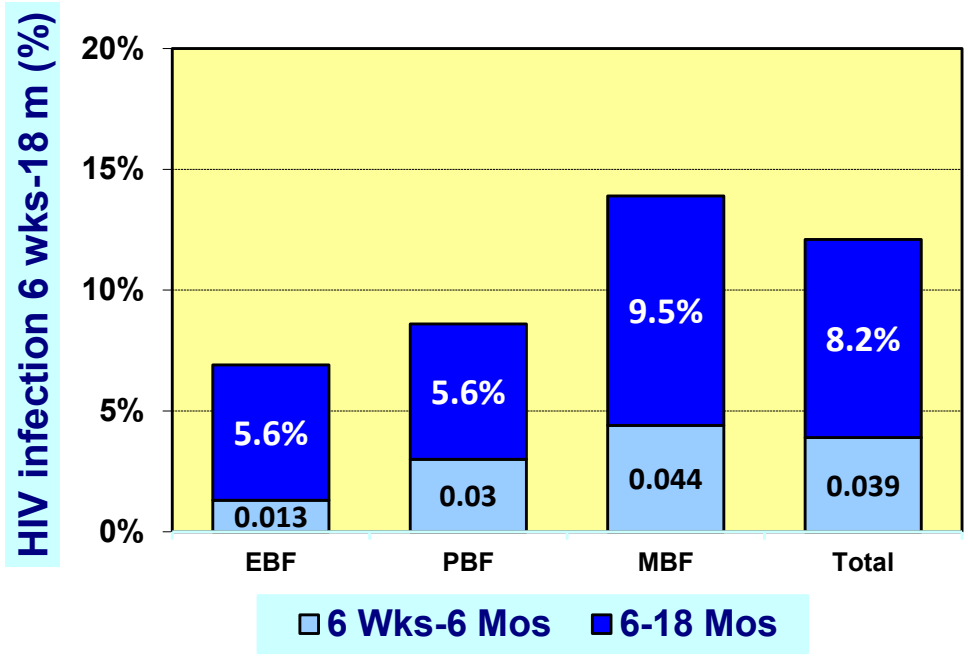
What are the recommendations globally particularly in resource-poor settings where mothers may have to breastfeed, Caesarian Section is not available, viral loads are never measured and where ART may not available? How is a mother supposed to protect her infant?

The Dilemma of Breastfeeding and HIV



Breastfeeding provides optimal nutrition for first 6-12 months and is associated with decreased infant morbidity and mortality over the 1st year of life.

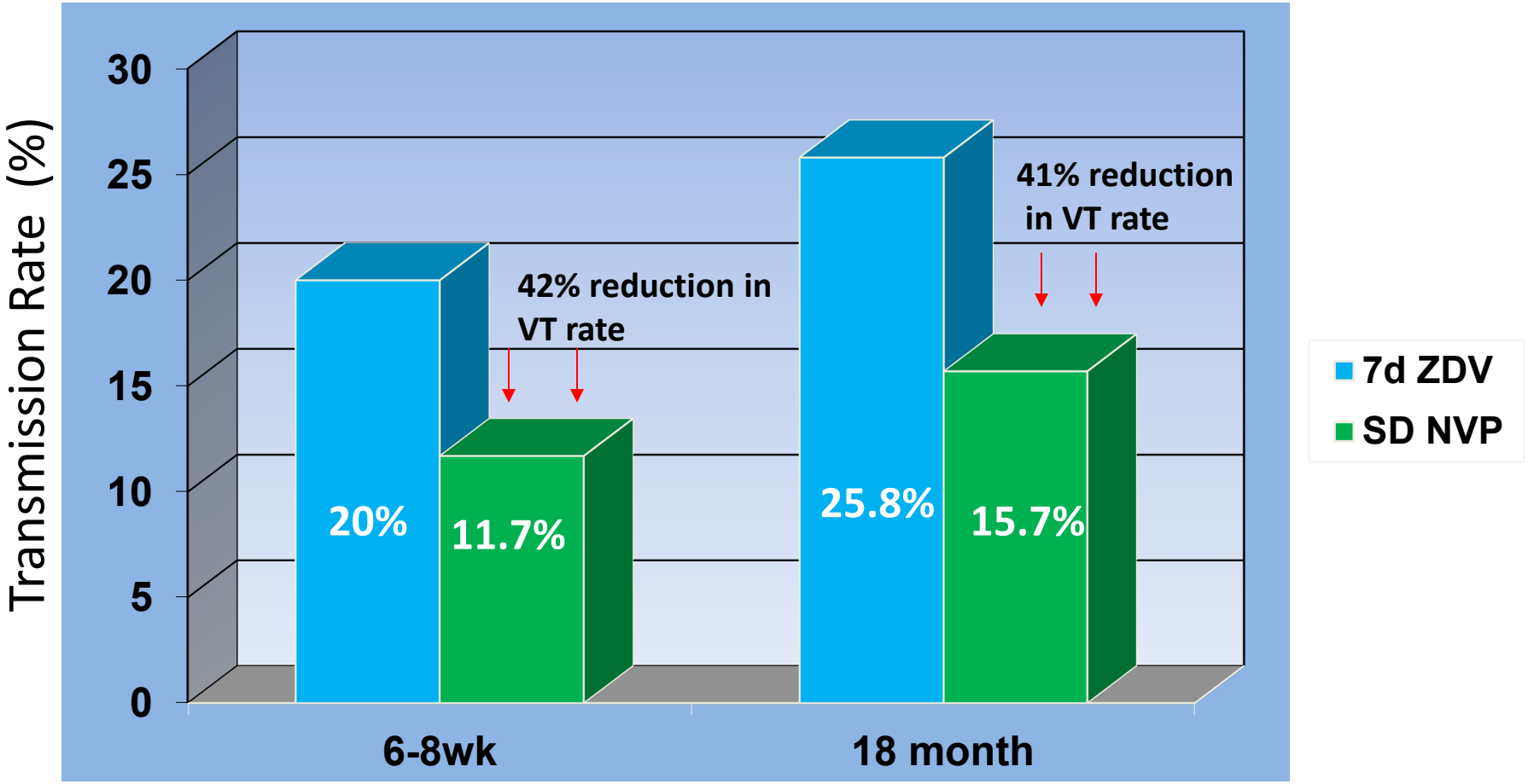
WHO Collaborative Study Team. Lancet 2000;355:451-5



However, prolonged breastfeeding is associated with ~ 10-15% increased risk of HIV transmission

Iliff PJ et al. AIDS 2005;19:699-708

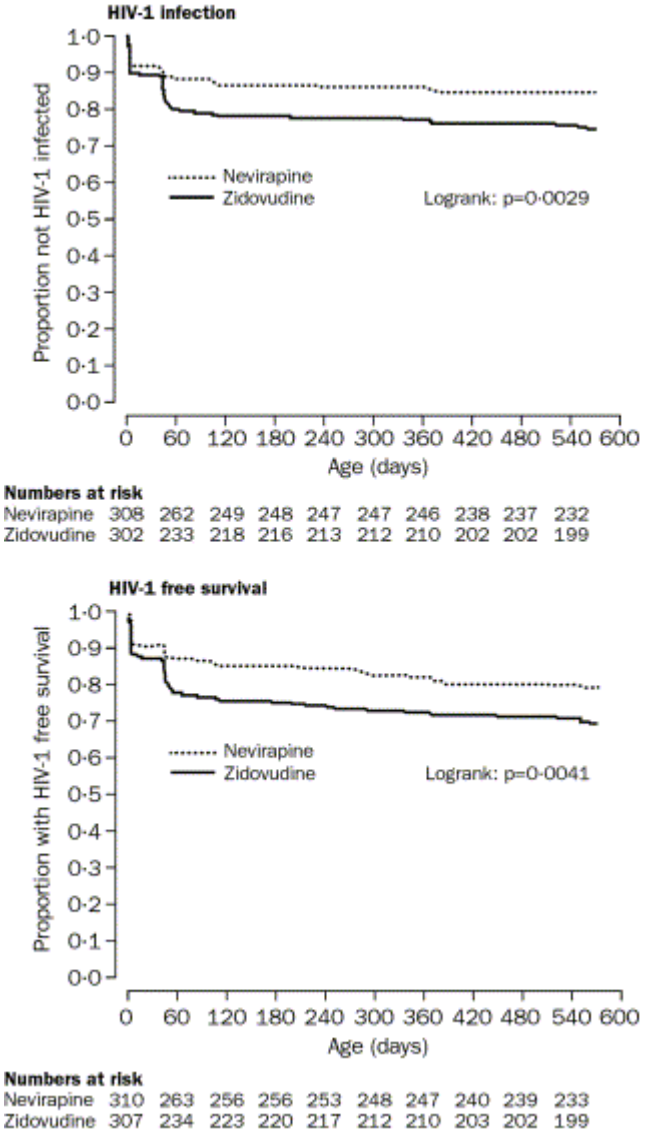
HIVNET 012: Single Dose NVP in Labor and to the Infant Postnatally



Guay et al, Lancet 1999;354:795-803

HIVNET 012: single dose NVP in labor and to the infant

"Intrapartum/neonatal nevirapine significantly lowered HIV-1 VT risk in a breastfeeding population in Uganda compared with a short intrapartum/neonatal zidovudine regimen. The absolute 8·2% reduction in VT at 6–8 weeks was sustained at age 18 months (10·1% [95% CI 3·5–16·6])". Jackson JB, Musoke P, Fleming T et al. *Lancet*. 2003;362:859-68.



Kaplan-Meier estimates of proportion of babies free from HIV-1 infection and with HIV-1 free survival through 18 months.

But what about maternal health? What was being done to keep mums healthy during and after pregnancy? Were there any trials showing that giving ART to mothers during breastfeeding not only kept them healthy but at the same time protected the nursing infant?

The Mma Bana Study – A RCT Comparing HAART Regimens for VT of HIV among Breastfeeding Women in Botswana

Shapiro R et al. N Engl J Med 2007; 356: 135-47

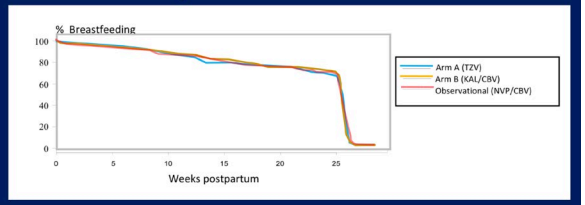
	Antepartum (26-34 wks)	Intrapartum (supplemental AZT)	Breastfeeding (6 months) (Rapid weaning before 6 mo visit)	Follow-up (2 years)
Arm A vs. Arm B	**Trizivir** (Abacavir/AZT/3TC)			
	Kaletra / Combivir (Lopinavair/ritonavir/AZT/3TC)			

170 women with CD4 < 200 cells/mm³ or AIDS enrolled observationally:

	Antepartum (18-34 wks)	Intrapartum (supplemental AZT)	Breastfeeding (6 months) (Rapid weaning before 6 mo visit)	Follow-up (2 years)
Obs Arm	**Nevirapine / Combivir** (Nevirapine/AZT/3TC)			HAART continued for treatment

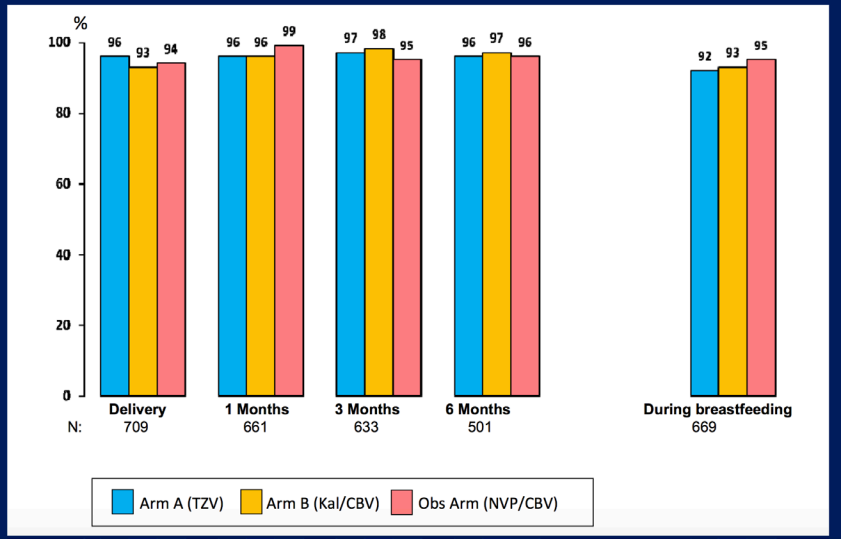
Duration of Breastfeeding and HAART Adherence

- Breastfeeding:
  - 97% of women initiated breastfeeding (all on HAART)
    - 93% exclusively breastfed through the time of weaning
  - 71% breastfed for ≥ 5 months
  - < 1% breastfed beyond the 6 month visit



- HAART Adherence (similar by HAART regimen):
  - 6% missed 3 or more total days of HAART

Maternal HIV RNA Suppression to < 400 copies/mL



Primary MTCT Endpoint

Infections among live-born infants, by maternal arm	Arm A (TZV) N=283	Arm B (KAL/CBV) N=270	Obs Arm (NVP/CBV) N=156
In utero	3 (1.1%)*	1 (0.4%)	1 (0.6%)
Intrapartum	0	0	0
Breastfeeding	2 (0.7%)	0	0
Total at 6 months	**5 (1.8%)***	**1 (0.4%)**	**1 (0.6%)**

1% overall transmission through 6 months

- 95% CI for overall MTCT rate = (0.5%, 2.0%)

P-value for difference in proportions for Arm A vs. B = 0.53

*Results exclude one unconfirmed + birth PCR followed by death in Arm A

- Including this infant as a + PCR: P-value for difference in proportions for Arm A vs. B = 0.42

The Mma Bana Study – A RCT Comparing HAART Regimens for VT of HIV among Breastfeeding Women in Botswana

Shapiro R et al. N Engl J Med 2007; 356: 135-47

- HIV-1 RNA suppression to < 400 copies/mL was similar at delivery and throughout breastfeeding by randomized arm, and for the observational arm
  - 95% suppressed at delivery, 93% throughout breastfeeding
- Among 709 live births, HIV transmission was only 1% overall, and only 2 transmissions occurred during breastfeeding (0.3%)
  - Lowest MTCT rate recorded in a breastfeeding population
- HAART regimens were safe and well-tolerated for women and for their breastfeeding infants

Conclusion

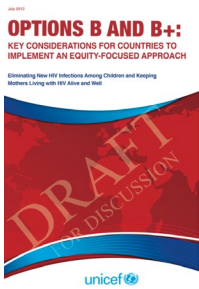
- Maternal HAART from early in the third trimester of pregnancy through 6 months of breastfeeding is a safe and very effective strategy for preventing MTCT while allowing for the benefits of breastfeeding

Postnatal VT by 6 months in Infants Uninfected at Birth: Comparison of Studies of Infant Prophylaxis and Maternal Prophylaxis

Infant Prophylaxis	SWEN	PEPI Malawi	BAN	ANRS 12174
Regimen	6 wk NVP	14 wk NVP	28 wk NVP	50 wks of LPV/rv vs 3TC
6 months	4.4%	2.2%	1.7%	0.7% (1.5% at 12 mo)
Maternal Prophylaxis	**BAN**	**Mma Bana**	**Kesho Bora**	**PROMISE**
Regimen	Maternal HAART (starting IP)	Maternal HAART (starting at 26-34 wks)	Maternal HAART (starting at 28-36 wks)	Maternal HAART (starting at 14 wks)
6 months	2.9%	0.7%	3.1%	? 0.5-0.6% at 2 wks

Acknowledgement: Dr. Athena Kourtis

What are the WHO Recommendations?

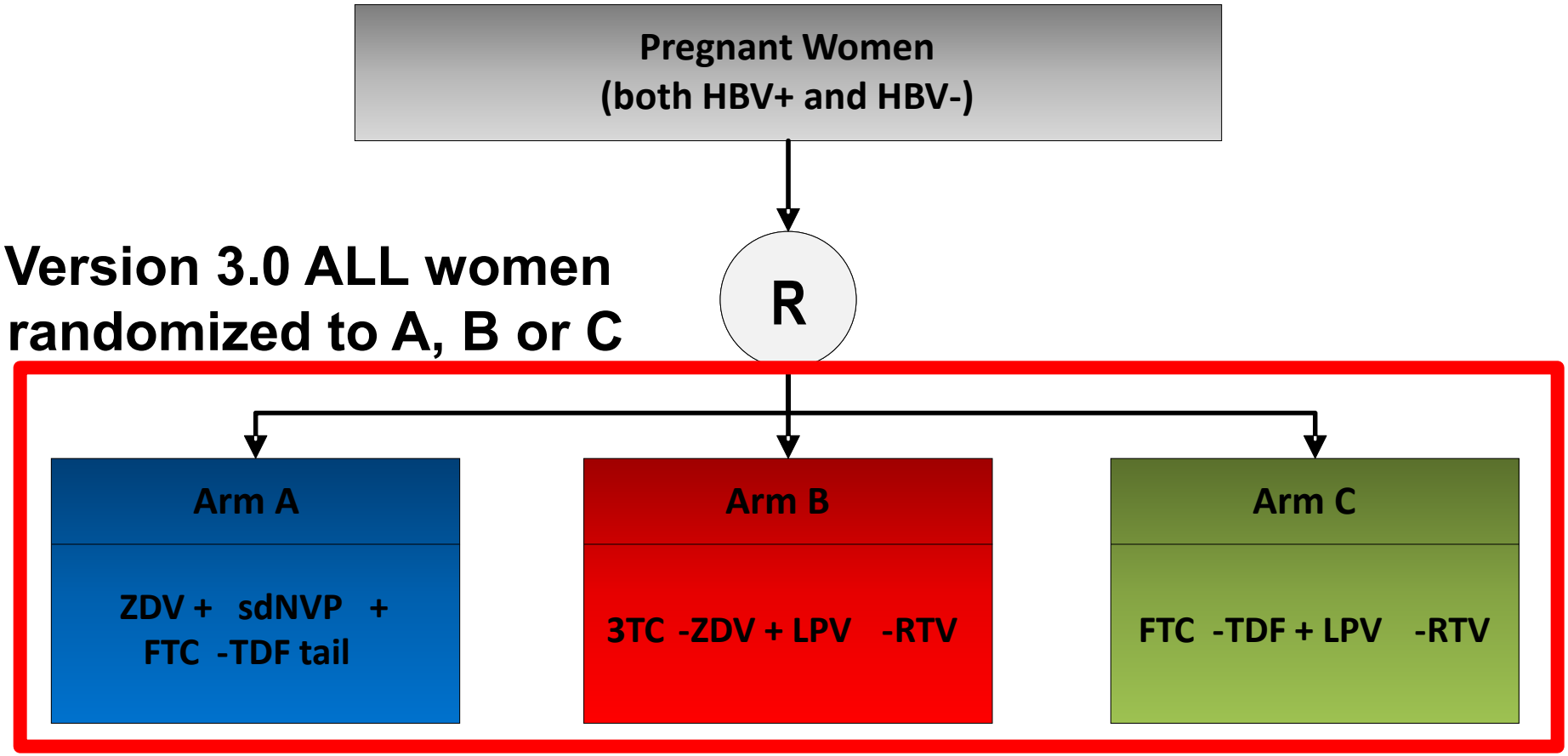


	Treatment (for CD4 count < 350 cells/mm3)	Prophylaxis (for CD4 count> 350 cells/mm3)	Infant receives
Option A	Triple ARVs starting as soon as diagnosed, *continued for life*	*Antepartum*: AZT starting as early as 14 weeks gestation *Intrapartum*: at onset of labour, single-dose NVP and first dose of AZT/3TC *Postpartum*: daily AZT/3TC through 7 days postpartum	Daily NVP from birth until 1 week after cessation of all breastfeeding; or, if not breastfeeding or if mother is on treatment, through age 4–6 weeks
Option B	Triple ARVs starting as soon as diagnosed, *continued for life*	Triple ARVs starting as early as 14 weeks gestation and *continued intrapartum and through childbirth if not breastfeeding or until 1 week after cessation of all breastfeeding*	Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
Option B+	Triple ARVs starting as soon as diagnosed, *continued for life*	Triple ARVs starting as soon as diagnosed, *continued for life*	Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method

PROMISE TRIAL

- Multi site RCT of option A vs B/B+ starting at 14 wks in over 3500 mothers/infants (India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe).

PROMISE TRIAL Antepartum Component
Maternal Randomization

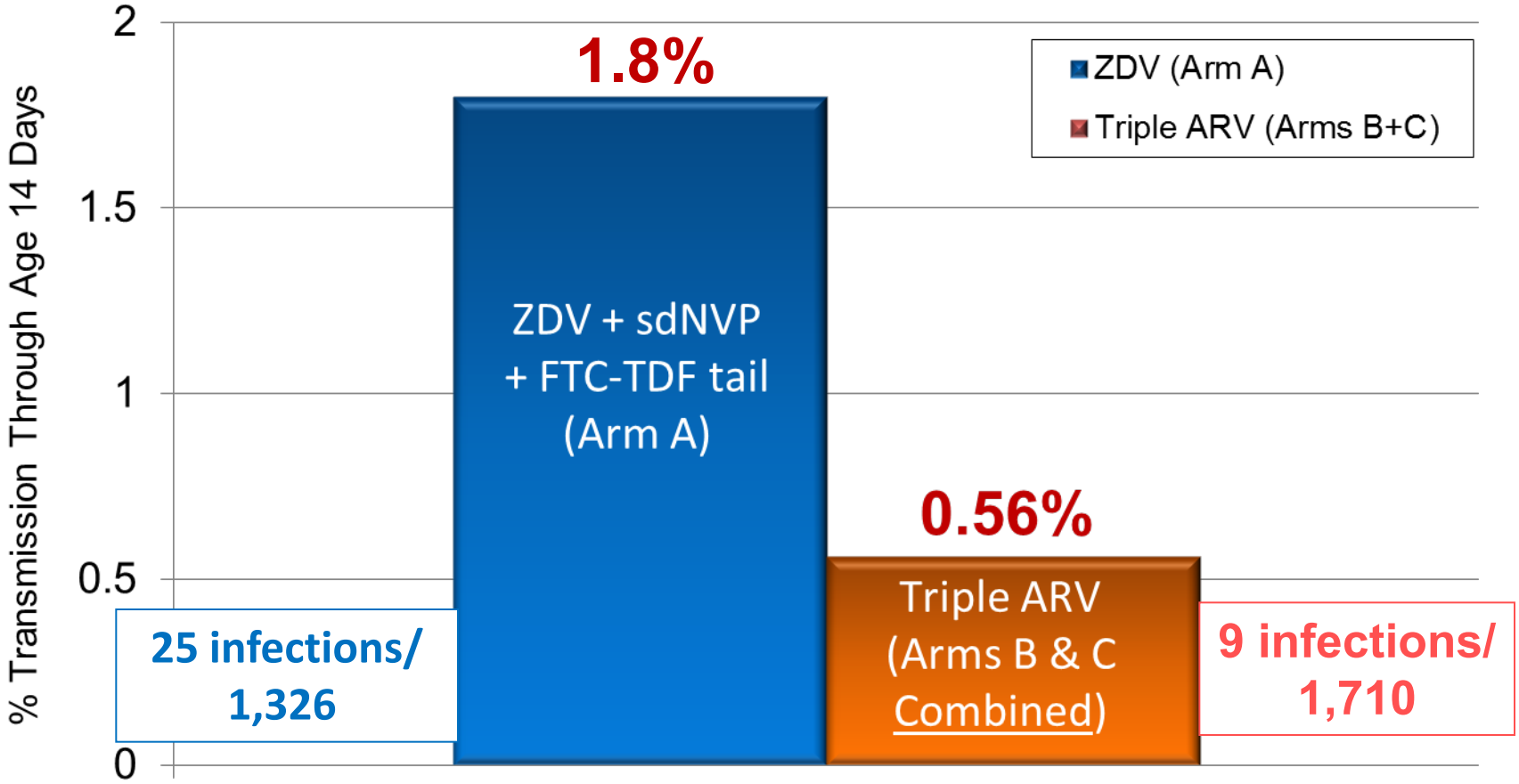


PROMISE TRIAL

- Higher preterm delivery with option B vs A and more very premature delivery in those on TDF/FTC (vs ZDV/3TC) combination.

- Transmission rates : **1.8% vs. 0.5%** @2 wks

VT Through Age 14 Days Significantly Lower in Triple ARV Arms



Difference in VT Risk (Repeated Confidence Interval): -1.28% (95% CI -2.11%, -0.44%)

PROMISE TRIAL - CONCLUSIONS

- Supports the 2013 WHO recommendations for use of triple maternal ARV regimens in pregnancy to achieve the lowest risk of transmission. But……

- Triple ARV regimens were associated with a higher risk of moderate but not severe adverse maternal and pregnancy outcomes including preterm birth and low birth weight.

When does

- **Preconception** U = U if partner living with HIV is taking ART daily and has an undetectable viral load
- **During pregnancy** U = U for her baby **ONLY** if a woman has an undetectable VL at conception, throughout pregnancy, and at delivery.

  If undetectable during pregnancy and at delivery LOW but not ZERO
- **Postpartum** cannot say U = U when it comes to breastfeeding, but if mother on ART and undetectable (same as pregnancy) LOW but not ZERO

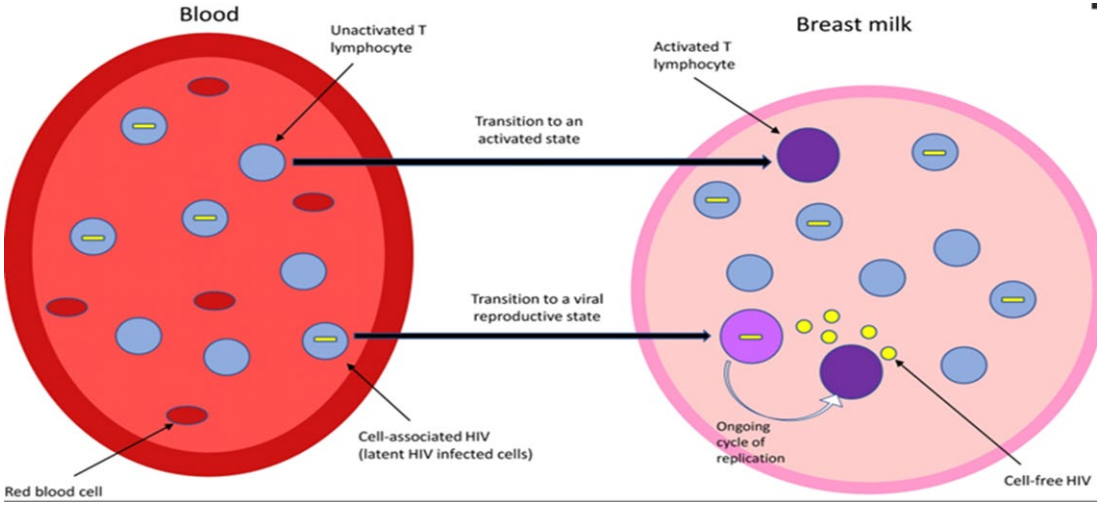
Acknowledgement: Dr. Aida Chaparro

EMORY UNIVERSITY | Center for AIDS Research

Risk of HIV transmission via Breastmilk

Cell-associated vs. cell-free HIV in breastmilk

- Cell-free HIV RNA appears to correlate with plasma viral load (VL)
- Even with undetectable plasma VL and undetectable cell-free RNA, there remains cell-associated HIV in breastmilk
- Whether the cell-associated HIV is infectious or as infectious as cell-free HIV is not known



Who wants to Breastfeed in the U.S.?

Arguments Against and For Breastfeeding

Against

- Maternal ART reduces but does not eliminate the risk of HIV transmission via breast milk
- Safe and affordable infant feeding alternatives are *readily accessible*
- Impact of ARV exposure during breastfeeding
- Adherence to ART often wanes postpartum

For

- Breast is best
- Cultural norms
- Unwanted HIV disclosure
- BF with support and close monitoring is better than hiding
- Patient informed choice
- Harmonization of global recommendations

Maternal Mental Health

Emerging reports of MH outcomes associated with not BF:

- Sadness/Depressive symptoms
- Shame
- Grief
- Lack of empowerment

Health Inequities

In high-income settings, people living with HIV are more likely to be:

- Disadvantaged SES
- Have higher morbidity and mortality related to conditions for which BF is protective (obesity, asthma, diabetes, short interpregnancy intervals)

Acknowledgement: Dr. Aida Chaparro

Panel's Recommendations

- People with HIV should receive evidence-based, patient-centered counseling to support shared decision-making about infant feeding. Counseling about infant feeding should begin prior to conception or as early as possible in pregnancy; information about and plans for infant feeding should be reviewed throughout pregnancy and again after delivery **(AIII).** During counseling, people should be informed that—
  - Replacement feeding with properly prepared formula or pasteurized donor human milk from a milk bank eliminates the risk of postnatal HIV transmission to the infant **(AI).**
  - Achieving and maintaining viral suppression through antiretroviral therapy (ART) during pregnancy and postpartum decreases breastfeeding transmission risk to less than 1%, but not zero **(AI).**
- Replacement feeding with formula or banked pasteurized donor human milk is recommended to eliminate the risk of HIV transmission through breastfeeding when people with HIV are not on ART and/or do not have a suppressed viral load during pregnancy (at a minimum throughout the third trimester), as well as at delivery **(AI).**
- Individuals with HIV who are on ART with a sustained undetectable viral load and who choose to breastfeed should be supported in this decision **(AIII).**
- Individuals with HIV who choose to formula feed should be supported in this decision. Providers should ask about potential barriers to formula feeding and explore ways to address them **(AIII).**
- Engaging Child Protective Services or similar agencies is not an appropriate response to the infant feeding choices of an individual with HIV **(AIII).**

Table 13. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV According to Risk of Perinatal HIV Acquisition at and After Birth[a]

Infants at High Risk	
Criteria for Infants at High Risk	**Age at HIV NAT[b] Testing for Infants at High Risk**
Infants born to mothers with HIV who— • Did not receive prenatal care; • Received no antepartum ARVs or only intrapartum ARV drugs; • Initiated ART late in pregnancy (during the late second or third trimester); • Received a diagnosis of acute HIV infection during pregnancy or in labor; and/or • Had detectable HIV viral loads (≥50 copies/mL) close to the time of delivery, including those who received ART but did not achieve sustained viral suppression	Birth 14–21 days 1–2 months 2–3 months[c] 4–6 months All infants at high risk of perinatal HIV transmission should have specimens obtained for HIV testing at birth before initiating an ARV drug regimen; however, presumptive HIV therapy should not be delayed. If an infant's NAT test result is positive, a repeat test should be performed as soon as possible and ART should be initiated.
Infants at Low Risk	
Criteria for Infants at Low Risk	**Age at HIV NAT[b] Testing for Infants at Low Risk**
Infants born to mothers who— • Received ART during pregnancy; • Had sustained viral suppression (usually defined as <50 copies/mL); *and* • Were adherent to their ARV regimens	14–21 days 1–2 months[d] 4–6 months

Infants With Perinatal HIV Exposure Who Are Being Breastfed
Age at HIV NAT[b] Testing for Infants With Perinatal HIV Exposure Who Are Being Breastfed
Birth 14–21 days 1–2 months 2–4 months[e] 4–6 months
If breastfeeding continues beyond 6 months of age, NAT testing should be performed every 3 months during breastfeeding.
In addition to the standard time points after birth, NAT testing also should be performed at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding, regardless of the age at when breastfeeding ends.
Consultation with an expert is recommended to determine additional testing time points that may be needed for infants with risk factors for HIV acquisition at birth who are being breastfed.
Prompt NAT testing of the infant is indicated if maternal viral load becomes detectable during breastfeeding.

If the mother has a detectable viral load and continues breastfeeding, some Panel members would recommend monthly virologic testing of the infant as an approach to early detection of HIV infection during ongoing exposure.

Does this changing reality apply to Miami?

- More HIV+ women, are choosing to breastfeed their infants, many infants born to HIV+ women have been breastfed successfully…BUT most of those mothers had breastfed prior children in their respective countries or origin…which is NOT the case in Miami

Aim

to Qualitatively describe the barriers and facilitators that Women with HIV in Miami encounter when making feeding choices decisions

…use this information to develop and implement a protocol that supports their choice while assuring the practice occurs under close monitoring and conditions that minimize the risk of HIV acquisition through breastmilk

Acknowledgement: Dr. Aida Chaparro

EMORY UNIVERSITY | Center for AIDS Research

RESEARCH ARTICLE

Breastfeeding in women with HIV infection: A qualitative study of barriers and facilitators

Aida I. Chaparro[1]*, Dieunane Formul[1], Stephanie Vasquez[1], Rosina Cianelli[2], Ivan A. Gonzalez[1], Gwendolyn Scott[1], Joseph P. De Santis[2]

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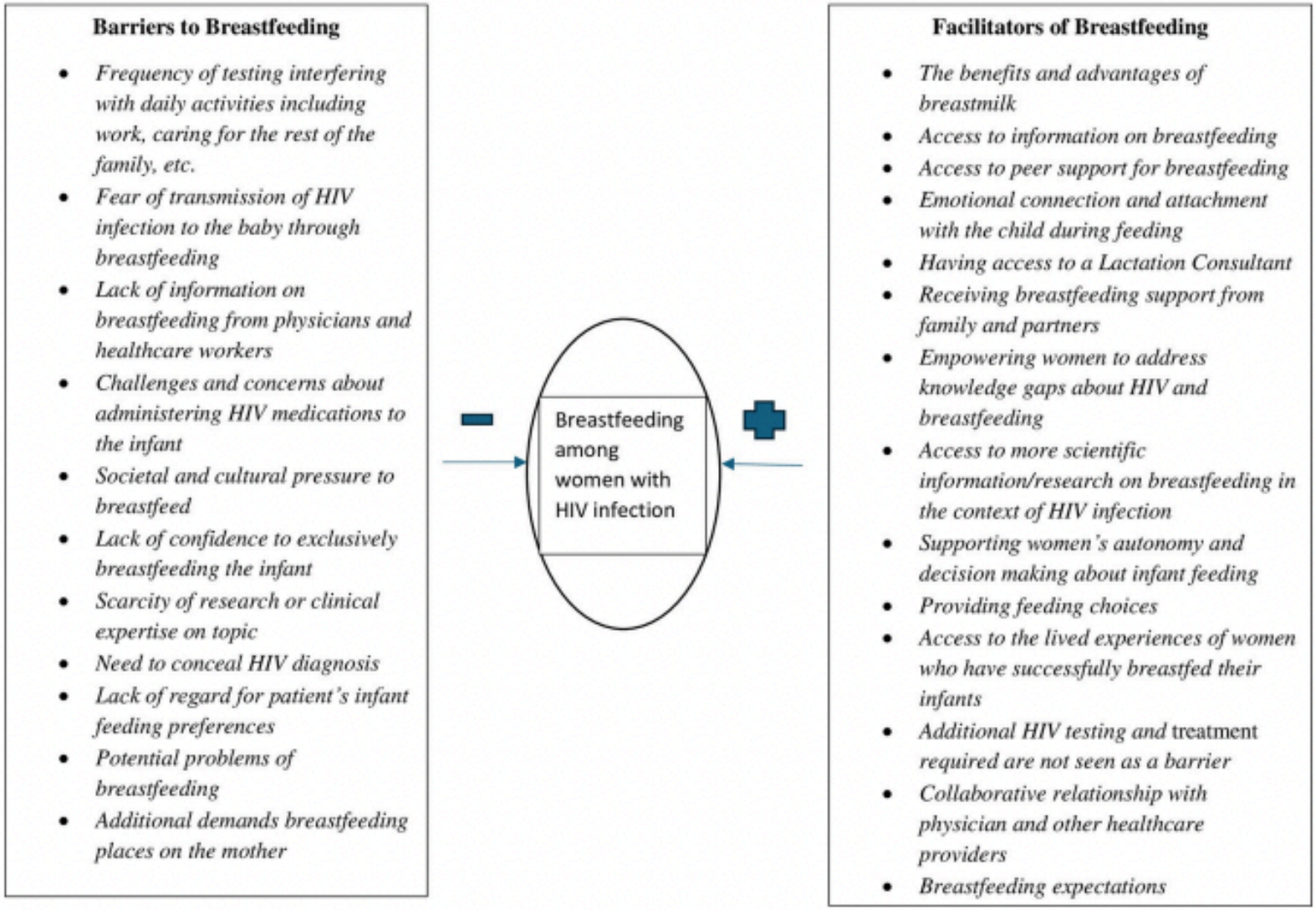

Fig 1. Barriers and facilitators of breastfeeding among women with HIV infection.

https://doi.org/10.1371/journal.pone.0303788.g001

Conclusions

- Study identified multiple barriers & facilitators to breastfeeding among WHIV from a diverse multiethnic and multicultural study population, which may significantly influence their decision-making process.
- Incorporating family and peer support is crucial in assisting mothers in making informed choices that balance the potential benefits of breastfeeding with the need to minimize HIV vertical transmission risk.
- The need for more comprehensive care for WHIV regarding infant feeding remains evident, starting by implementing breastfeeding training to healthcare providers and multidisciplinary team members to ensure that they are knowledgeable and skilled in breastfeeding support.
- The study also highlights the importance of recognizing the autonomy of the mother in the decision-making process and encourages a personalized approach when developing care plans to enhance the overall outcomes for mothers and their infants.

Q1. A pre-labour, pre-rupture of membranes, caesarean section should be recommended if

A. The mother has had a previous CS
B. Maternal HIV viral load >100,000 at first ante-natal visit
C. Maternal HIV viral load is 1000 HIV RNA copies/ml plasma at week 36 gestation on ART
D. Maternal HIV <50 HIV RNA copies/ml plasma at week 36 on HAART
E. None of the above

Q1. A pre-labour, pre-rupture of membranes, caesarean section should be recommended if

A. The mother has had a previous CS

B. Maternal HIV viral load >100,000 at first ante-natal visit

C. Maternal HIV viral load is 1000 HIV RNA copies/ml at week 36 gestation on ART

D. Maternal HIV <50 HIV RNA copies/ml plasma at week 36 on HAART

E. None of the above

Q2. Which of the following is a recognised association with ARVs in pregnancy ?

- A. Gestational Diabetes
- B. Pre-term delivery
- C. Small for Gestational Age
- D. Post-natal Depression
- E. None of the above

Q2. Which of the following is a recognised association with ARVs in pregnancy ?

- A. Gestational Diabetes
- **B. Pre-term delivery**
- C. Small for Gestational Age
- D. Post-natal Depression
- E. None of the above

Q3. An expectant mother with no prenatal care arrives in labour - Do you?

A. Assess her risk factors for HIV
B. Examine her for signs of HIV infection
C. Counsel her to have an HIV test
D. Recommend a Point of Care Rapid HIV test
E. Call the adult ID Team

Q3. An expectant mother with no pre-natal care arrives in labour -Do you?

A. Assess her risk factors for HIV
B. Examine her for signs of HIV infection
C. Counsel her to have an HIV test
D. Recommend a Point of Care Rapid HIV test
E. Call the adult ID Team

HIV Point of Care Test (POCT) – result within 15 minutes

Widely used in:
Resource poor settings
Ob units

Should be offered to:
Women with no OR late PNC in labour

Positive test→

- Intrapartum ART
- Neonatal ARV PPX
- Postpartum ART
- No breast feeding

An alternative to the POCT is a 24 hr lab service

Q4. A Pregnant woman - 38 weeks (CD4 180, viral load 43,542), decides:
She want no medication during pregnancy
She wants a normal delivery
She believes that breast is best
What should you do?

A. Accept her right to choose what she believes is right for herself and her baby
B. Accept her right to choose for herself and inform child protection services regarding the needs of the baby
C. Tell her to find another clinician, you cannot care for her

Q4. A pregnant woman - 38 weeks (CD4 180, viral load 43,542), decides:
She want no medication during pregnancy
She wants a normal delivery
She believes that breast is best
What should you do?

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B. Accept her right to choose for herself and inform child protection services regarding the needs of the baby
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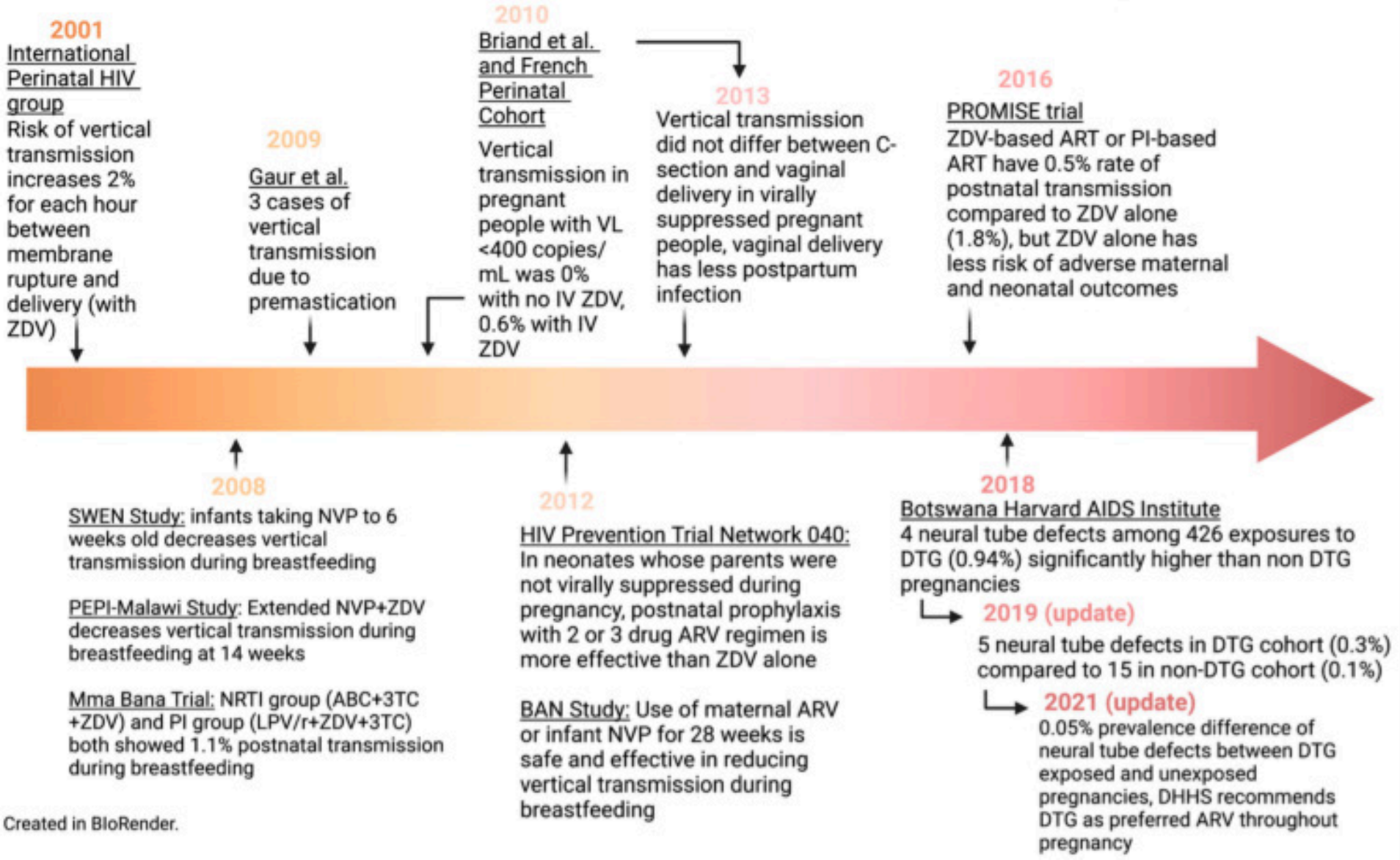
Historical Studies in the Prevention of Vertical Transmission of HIV, 2000-2021

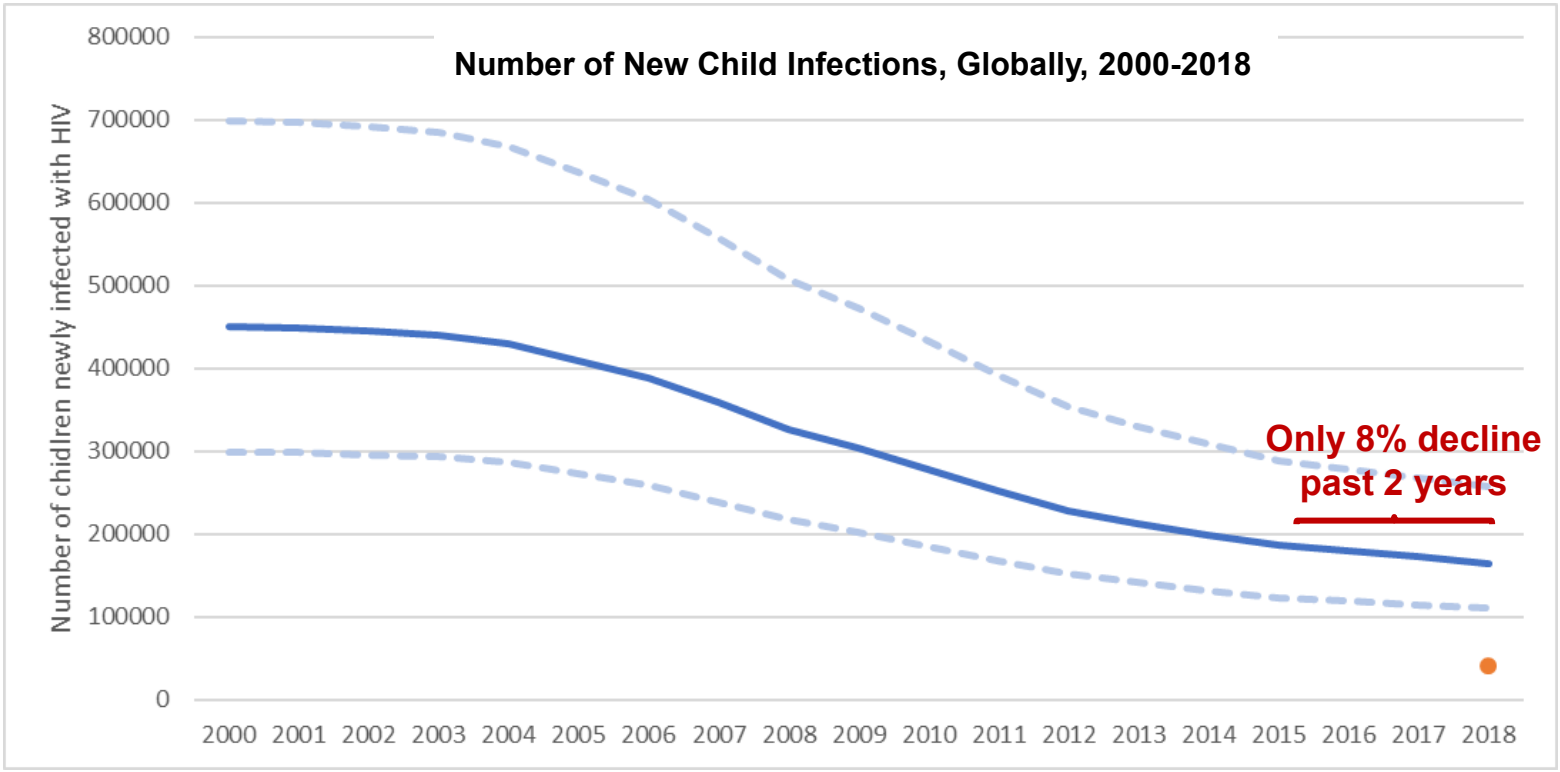


Cardenas MC, Farnan S, Hamel BL, Mejia Plazas MC, Sintim-Aboagye E, Littlefield DR, Behl S, Punia S, Enninga EAL, Johnson E, Temesgen Z, Theiler R, Gray CM, Chakraborty R. Prevention of the Vertical Transmission of HIV; A Recap of the Journey so Far. Viruses. 2023 Mar 26;15(4):849. doi: 10.3390/v15040849. PMID: 37112830; PMCID: PMC10142818.

New Infections in Children

63% Decline New Infections Since 2000 – But Progress Has Stalled

Mahy M et al. Pediatric HIV Workshop, July 2019, Mexico City



160,000 in 2018

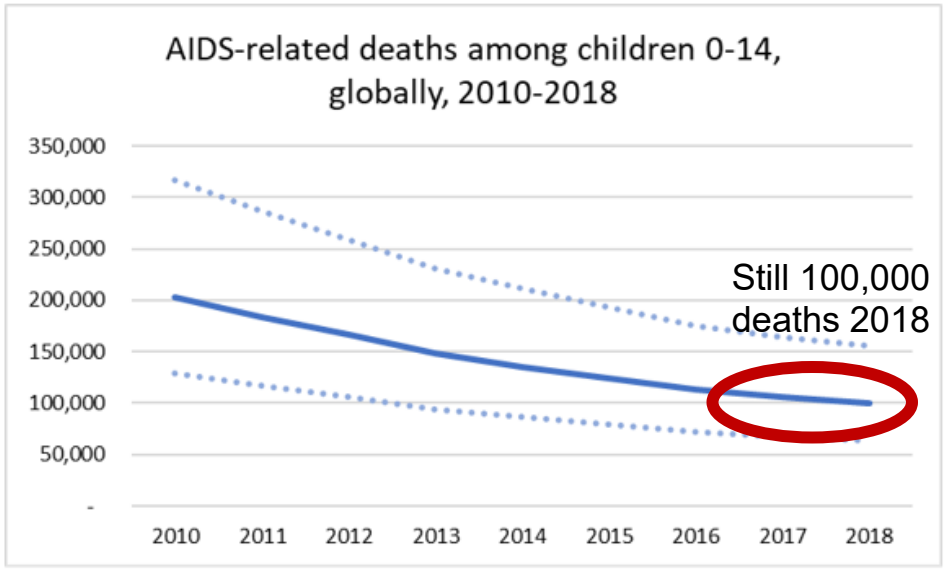
2018 target:
40,000

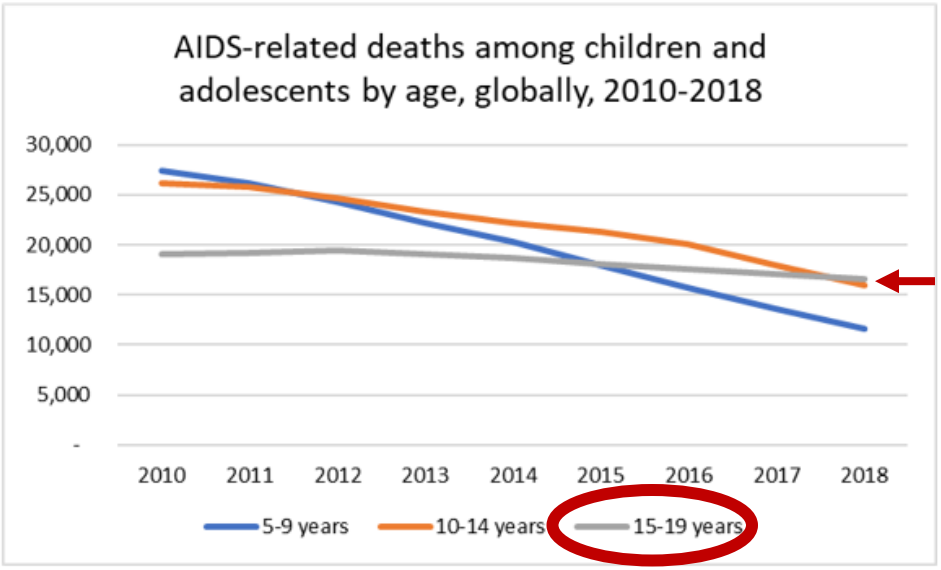
Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019

AIDS-Related Pediatric Mortality

AIDS-Related Deaths Has Declined in Children – But Not Among Adolescents

Mahy M et al. Pediatric HIV Workshop, July 2019, Mexico City





→Decline in pediatric AIDS-related mortality has slowed

→No real decline in AIDS-related mortality in adolescents 15-19 years

Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019

Summary Slide

- PVT is enhanced with early initiation of ART in pregnancy, maintained throughout breastfeeding and indefinitely thereafter.
- Breastfed infants should receive prophylaxis and breastmilk for 6 months.
- Tremendous progress on PVT of HIV in western settings and globally over 2 decades. It's taken a village to get this far!
- Significant challenges remain.


MERRY

Thank You!