Prevention of mother to child transmission of HIV

Current challenges

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In 2009, UNAIDS issued a call for the “virtual elimination” of mother-to-child transmission of HIV globally by 2015

This vision has stimulated increased investment in programs for the prevention of mother-to-child transmission (PMTCT) of HIV

The purpose of a PMTCT programme

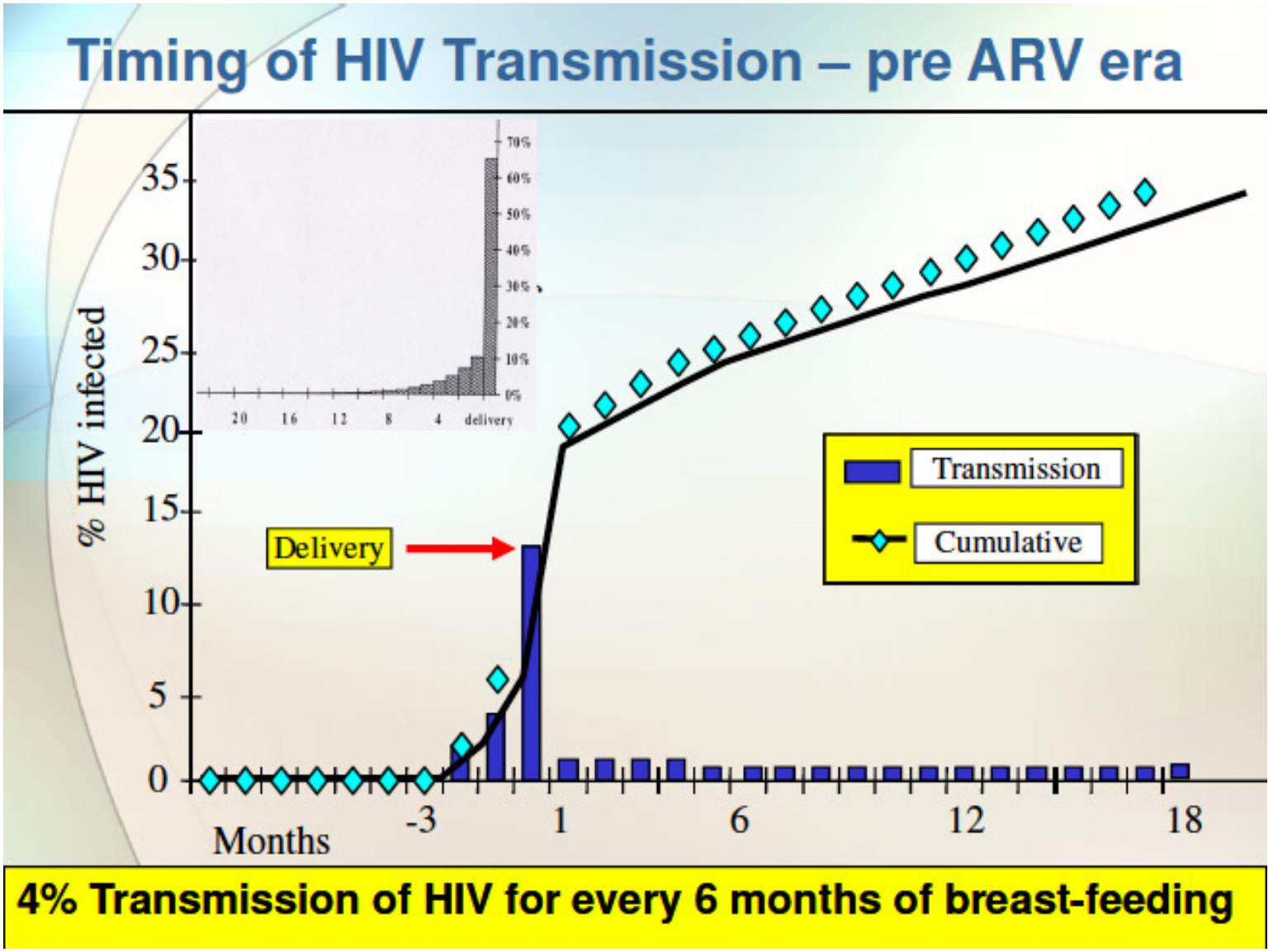
Optimise prevention of mother-to-child-transmission (MTCT)

- cART in pregnancy
- Infant ARV prophylaxis
- Safe feeding

Optimise outcomes for HIV-infected infants

- Infant diagnosis
  - Timing
  - Accuracy
- (Very) early cART initiation

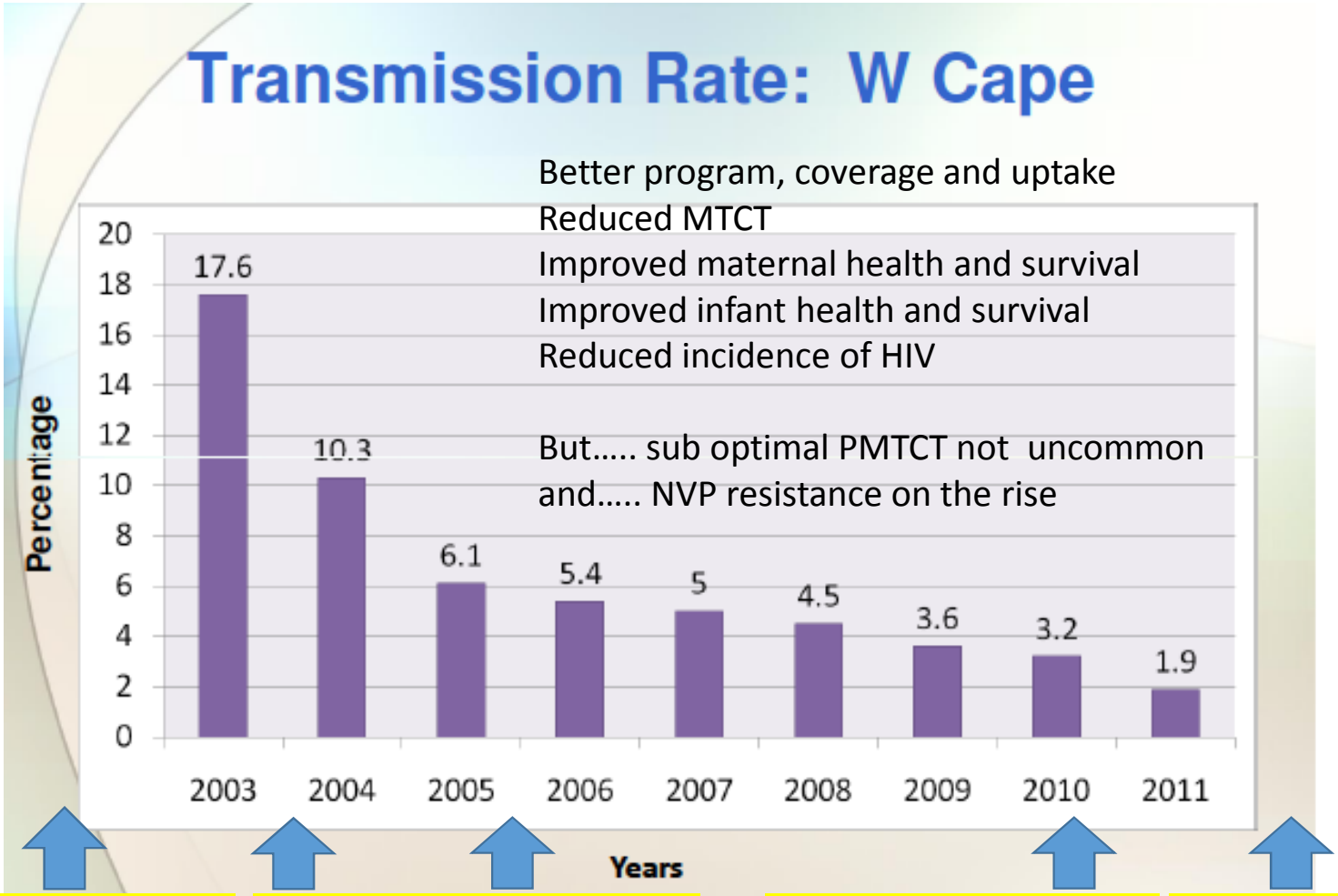
More broadly, a mechanism for improving maternal & family outcomes



From ppt by Prof G Theron

Adapted from ppt by Prof G Theron

Transmission Rate: W Cape



Better program, coverage and uptake
Reduced MTCT
Improved maternal health and survival
Improved infant health and survival
Reduced incidence of HIV

But….. sub optimal PMTCT not uncommon
and….. NVP resistance on the rise

2000: NVP Monotherapy

From 34wk to 28 wk AZT +Targeted ART (CD4<200)

2010: Targeted ART if CD4<350 or 14 wk AZT

2013: Lifelong ART for all

HIV MTCT rates in SA

2011 SAPMTCT Survey

- To evaluate effectiveness of national PMTCT programme to reduce perinatal transmission of HIV from mothers to infants

- National survey of infants aged 4-8 weeks sampled at 585 facilities across all provinces (n=10106)

- **Percentage of infants exposed to HIV (weighted exposure prevalence): 32.2% (95% CI: 30.7-33.6)**

- **Perinatal MTCT rate at 4-8 weeks of age (weighted): 2.7% (95% CI: 2.1-3.2%)**

- Rates differed across provinces:
  - Infant HIV exposure: 15.1-44.4%
  - MTCT: 1.98-6.06%

- Of the HIV-positive mothers: 48% received ARV prophylaxis, 43% received HAART

What drives MTCT of HIV?

- Unsuppressed maternal viral load (not CD4 count)

- New maternal HIV infection during pregnancy (or breastfeeding)
  - Dinh et al. CROI 2014. Impact of maternal incident HIV infection on early HIV vertical transmission, South Africa 2011
    - Weighted national estimate of 3.1% maternal incident HIV infection
    - MTCT rate 10.7% vs 2.2%
    - Represent 6.7% of HIV-infected mothers but account for 26% of MTCT risk
  - W Cape PMTCT guidelines 2014: If HIV test is negative at first antenatal booking, repeat testing to be performed at 32-34 weeks, in labour, in breastfeeding mothers at 6 weeks postpartum and 3-monthly for duration of breastfeeding

- Inadequate maternal or infant ARV prophylaxis

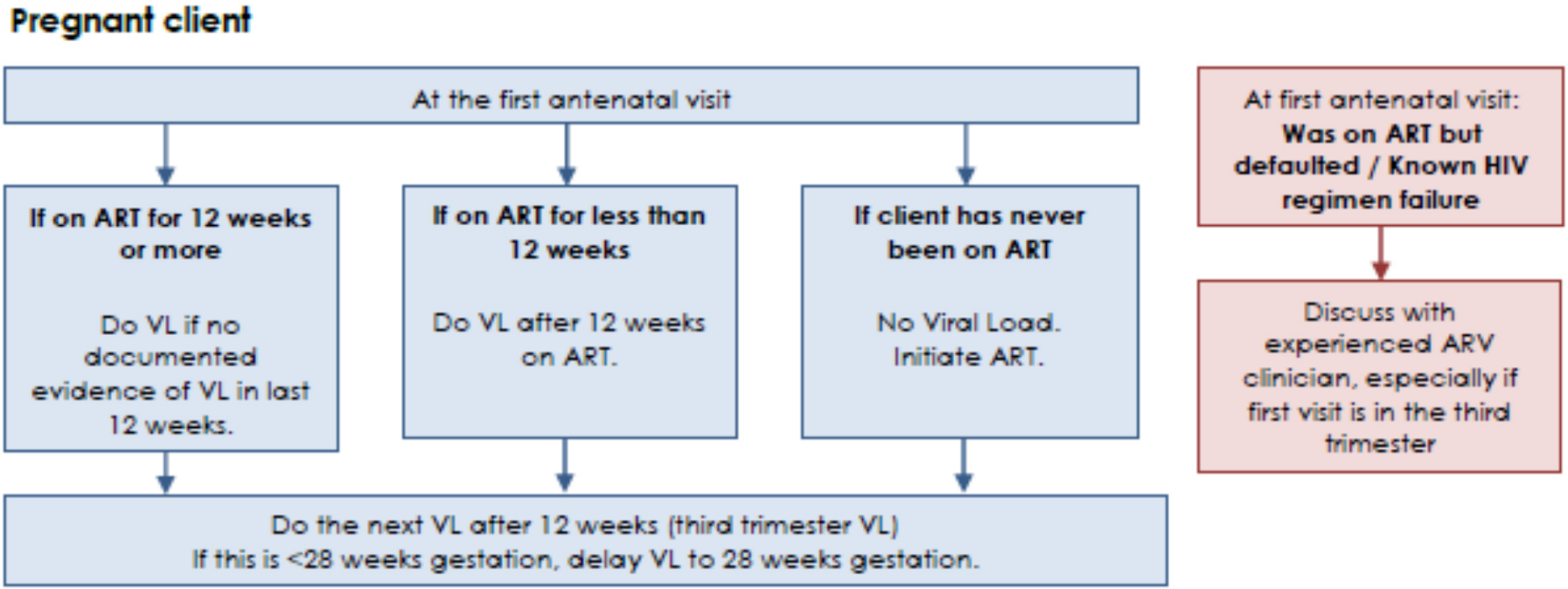
  Nielsen Saines et al. NEJM 2012. Three Postpartum Antiretroviral Regimens to Prevent Intrapartum HIV Infection

Viral load monitoring during pregnancy

- Developed countries
  - BHIVA 2012: In women who commence HAART in pregnancy, VL should be performed 2–4 weeks after commencing HAART, at least once every trimester, at 36 weeks and at delivery
  - US 2014: VL should be monitored at the initial visit; 2 to 4 weeks after initiating (or changing) ARV drug regimens; monthly until levels are undetectable; and then at least every 3 months during pregnancy. VL also should be assessed at approximately 34 to 36 weeks' gestation to inform decisions about mode of delivery
- SA National guidelines (2013)
  - As for non-pregnant patients (month 6, 12, then annually)

Viral load monitoring during pregnancy

W Cape PMTCT guidelines 2014



Criteria for identifying HIV-exposed infants at high risk of MTCT
W Cape PMTCT guidelines 2014

Maternal factors

- Viral load >1000cpm from 28 weeks gestation
- Initiated ART <12 weeks before delivery
- Defaulted ART for ≥1 month at any stage during pregnancy
- Likely NNRTI resistance (failed 1st or 2nd line ART at any stage, or on 2nd or 3rd line during pregnancy)
- Diagnosed as new HIV infection from 28 weeks gestation or in labour/immediate post-partum
- Diagnosed with TB / syphilis during pregnancy or immediate postnatal period
- Clinical signs of chorioamnionitis

Infant factors

- Born before 37 weeks gestational age
- Birthweight <2500g regardless of gestation
- Abandoned newborns / orphans
- Any sick HIV-exposed newborn

Unbooked pregnancies

No antenatal care incl. HIV testing & ART

Metro West, Cape Town	2010	2011	2012	2013
No Antenatal care “UNBOOKED”	5.8%	5.9%	5.1%	5.5%

Thanks to Metro West PPIP Team
Dr C Nelson, Dr L Dietrich, Dr D Nage and Dr L Jacobs

WHO PMTCT Options A & B/B+

	Woman receives:		Infant receives:
	Treatment (for CD4 count ≤350 cells/mm³)	**Prophylaxis (for CD4 count >350 cells/mm³)**	
Option A[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, sdNVP and first dose of AZT/3TC *Postpartum*: daily AZT/3TC through 7 days postpartum	Daily NVP from birth through 1 week beyond complete cessation of breastfeeding; or, if not breastfeeding or if mother is on treatment, through age 4–6 weeks
Option B[a]	*Same initial ARVs for both*[b]*:*		Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
	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*	
Option B+	*Same for treatment and prophylaxis*[b]*:*		Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
	Regardless of CD4 count, triple ARVs starting as soon as diagnosed,[c] *continued for life*		

Infant ARV prophylaxis
Nevirapine (NVP)

- NVP administered once daily in prophylactic dose for 6 weeks is current standard-of-care in SA PMTCT programme (2013 guidelines)

- Extended beyond 6 weeks in breastfeeding mothers who are not yet virally suppressed

Nevirapine prophylaxis

Dosing

Table 8. Nevirapine (NVP) doses for post exposure prophylaxis (PEP) in the first 6 weeks of life

	Birth Weight	Age	Daily Dosage	Daily Volume
Nevirapine (NVP) syrup (10mg/ml)	<2.0kg	Birth to 2 weeks	2mg/kg	0,2 ml/kg
		2 to 6 weeks	4mg/kg	0,4 ml/kg
	2.0 – 2.5kg	Birth to 6 weeks	10mg	1ml
	>2.5kg	Birth to 6 weeks	15mg	1.5ml

Neonates who are Nil per os (NPO) (Necrotizing Enterocolitis (NEC), intestinal anomaly/obstruction) should receive intravenous AZT (Table 9).

Table 6. Nevirapine (NVP) doses for prophylaxis after 6 weeks of age

	Age	Daily Dosage	Daily Volume
Nevirapine (NVP) syrup (10mg/ml)	If 6 weeks to 6 months	20mg	2ml
	If 6 months to 9 months	30mg	3ml
	If 9 months to 12 months	40mg	4ml

Infant ARV prophylaxis
Zidovudine (AZT)

- AZT administered twice daily for 6 weeks is an alternative to NVP
- 4 weeks shown to be as effective as 6 weeks in infants of low risk mothers and with less toxicity
  - Ferguson et al. PIDJ 2011. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting
  - Lahoz et al. PIDJ 2010. Antiretroviral-related hematologic short-term toxicity in healthy infants implications of the new neonatal 4-week zidovudine regimen
- Not recommended for infants of breastfeeding mothers
- Widely used in developed countries

Zidovudine prophylaxis

Dosing

Table 10. Zidovudine (AZT) doses for PEP

	Birth weight / gestational age	Age	Dosage
Zidovudine (AZT) syrup (10mg/ml)	>2 kg	Birth to 4 weeks	12 mg 12 hourly (1.2 ml 12 hourly)
	<2 kg	Birth to 4 weeks	4 mg/kg/dose 12 hourly (0.4 ml/kg/dose 12 hourly)
	If gestational age <35 weeks	Birth to 4 weeks	2 mg/kg/dose 12 hourly (0.2 ml/kg/dose 12 hourly)

Neonates who are Nil per os (NPO) (Necrotizing Enterocolitis (NEC), intestinal anomaly/obstruction) should receive intravenous AZT (Table 9).

Table 9. Intravenous Zidovudine (AZT) doses for PEP

Intravenous Dose of Zidovudine (AZT) **(10 mg/ml in 200mg vial)** Not a multi-dose vial! Prepare in sterile pharmacy for multiple doses.	≥35 weeks gestation	1.5 mg/kg/dose 6 hourly
	<35 weeks gestation	1.5 mg/kg/dose 12 hourly

Infant ARV prophylaxis

Lopinavir/ritonavir (Kaletra) or lamivudine (3TC)

- PROMISE-PEP trial: Burkina Faso, South Africa, Uganda and Zambia

  - To compare the risk of HIV-1 transmission during and safety of prolonged infant PEP with LPV/r versus Lamivudine from day 7 until one week after cessation of BF (maximum 50 weeks of prophylaxis) to prevent postnatal HIV-1 acquisition between 7 days and 50 weeks of age.

  - Dosing:
    - LPV/r: 40/10 mg twice daily if 2-4 kg and 80/20 mg twice daily if >4 kg
    - Lamivudine: Lamivudine: 7,5 mg twice daily if 2-4 kg, 25 mg twice daily if 4-8 kg and 50 mg twice daily if >8 kg

  - 1.3% breastfeeding transmission rate in each arm at 12 months (CROI 2014)

    Nagot et al. BMC Infectious Diseases 2012. Lopinavir/Ritonavir versus Lamivudine peri- exposure prophylaxis to prevent HIV-1 transmission by breastfeeding: the PROMISE-PEP trial Protocol ANRS 12174

UK GUIDELINES

Low risk exposure

Mothers on cART with VL < 50 at ≥ 36 wks gestation

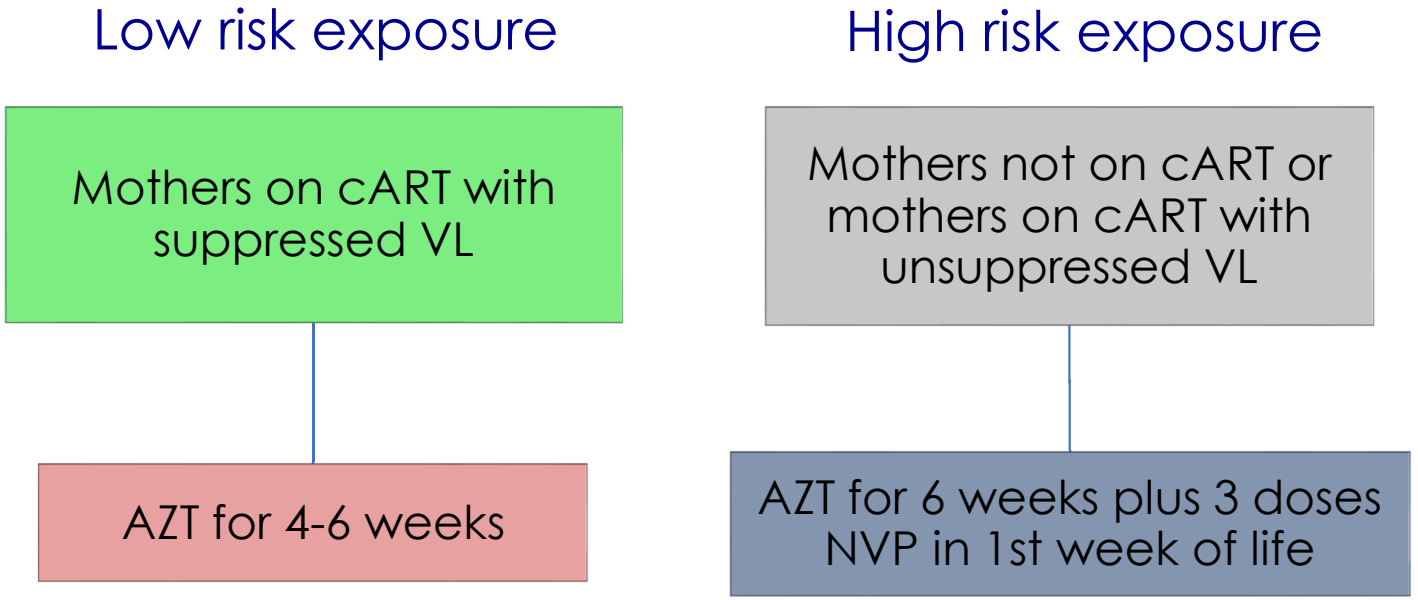
AZT for 4 weeks

High risk exposure

Mothers not on cART or mothers on cART with VL > 50

TRIPLE ARV PROPHYLAXIS (AZT/3TC/NVP) for 4 weeks

US GUIDELINES



Infant ARV prophylaxis

Dual or triple drug prophylaxis

- In infants born to mothers who received no pre-labour ARVs, dual or triple ARV prophylaxis is more effective than Zidovudine (AZT) alone in preventing intrapartum transmission

  Nielsen Saines et al. NEJM 2012. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection

HPTN 040 study

Nielsen Saines NEJM 2012;366: 2368-79

- 1684 infants in Brazil, South Africa, Argentina, United States from 2004-2010
- No antenatal PMTCT (except IV AZT in labour)
- Randomised to 1 of 3 regimens
  - AZT twice daily for 6 weeks
  - AZT + 3 doses of nevirapine in the first week
  - AZT + nelfinavir + lamivudine
- HIV DNA PCR done at study visits: birth, day 10-14, 4-6 weeks, 3 months, 6 months
- Exclusive formula feeding

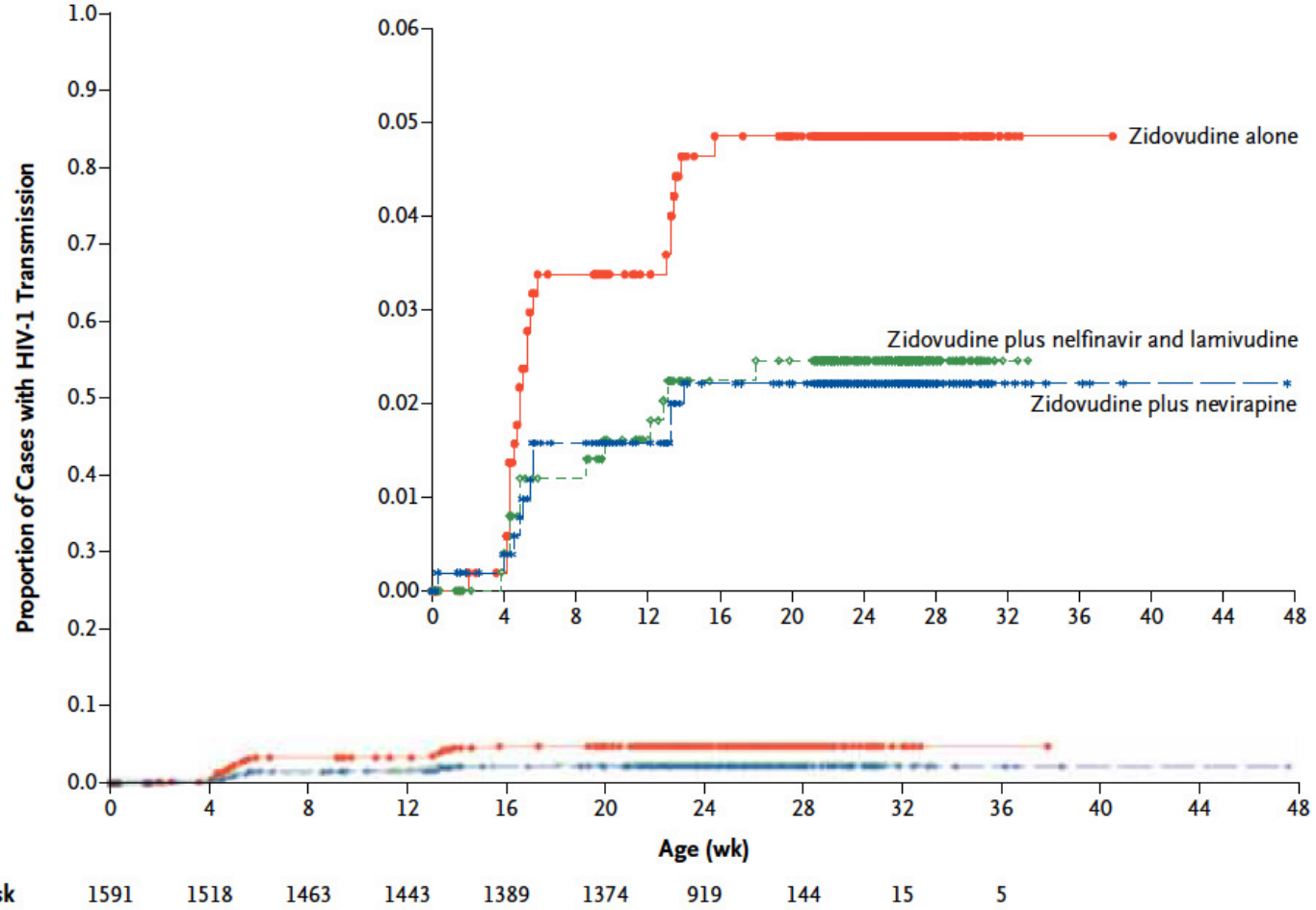


Figure 1. Intrapartum HIV-1 Transmission According to Treatment Group.

Kaplan–Meier curves for intrapartum transmission differed significantly (P=0.03 for the overall comparison). Transmission rates were highest in the zidovudine-alone group (3.4% at 4 to 6 weeks vs. 1.6% in the two-drug group and 1.4% in the three-drug group; 4.8% at 3 months vs. 2.2% in the two-drug group and 2.4% in the three-drug group).

Infant ARV prophylaxis

Role of dual or triple drug prophylaxis?

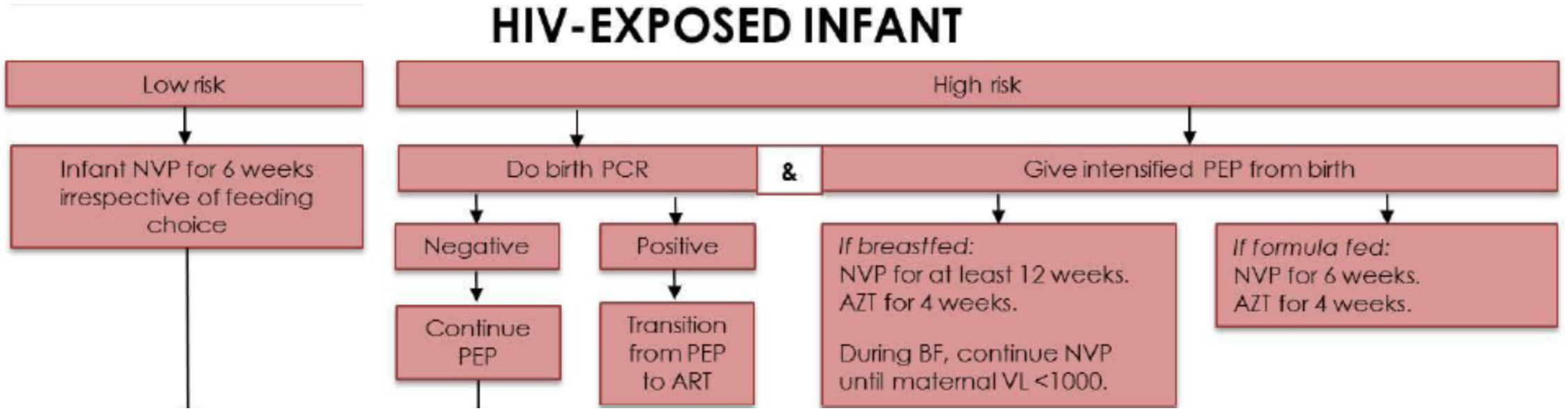
- UK / US infant prophylaxis guidelines
  - Based on a non-breastfeeding context
  - Use of AZT and in high risk transmission scenarios, addition of
    - NVP (US: 3 doses in first week of life)
    - NVP & lamivudine (UK)

- What about our public sector setting where standard infant prophylaxis is with NVP. Should we add AZT for high risk transmission scenario?

- Data is limited
  - NVP single dose + AZT for 1 week was more effective than NVP single dose alone in preventing intrapartum transmission in Malawian infants of mothers who had received no antenatal ARV prophylaxis. Taha et al. Lancet 2003
- Other post-exposure prophylaxis scenarios use dual/triple drugs

Infant ARV prophylaxis

W Cape PMTCT guidelines 2014



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Infant factors

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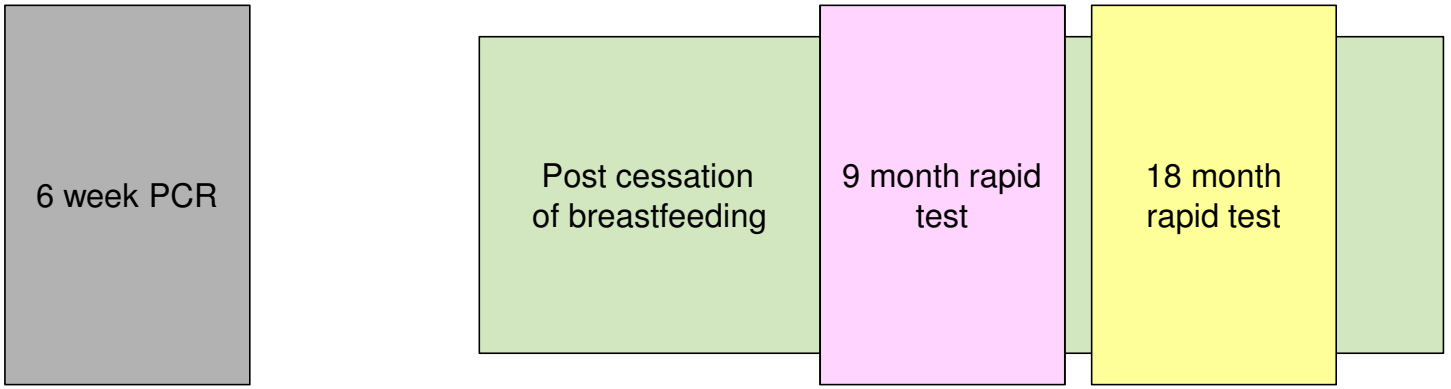
Infant ARV prophylaxis

Role of dual or triple drug prophylaxis?

- Aid for Aids clinical guidelines (10th edition 2014)
  - Recommend AZT+3TC+NVP (NVP twice daily at therapeutic dose) for 4 weeks started as soon as possible after birth
  - Duration may be modified if mother is breastfeeding and based on the viral load of the mother
- NVP therapeutic dose is undetermined for infants <14 days of age (P1115 study will use 6mg/kg/dose twice daily for prevention and treatment)

WHO HIV testing algorithm for infants & young children



The 6-week HIV PCR test

- Why do we do the PCR test at 6 weeks of age?
  - Coincides with routine 6-week immunisation visit
  - Aim to detect all in utero and intra partum infections
  - A single DNA PCR test was 98.8% sensitive & 99.4% specific in 627 infants tested at 6 weeks of age (58 HIV-infected and 569 HIV-uninfected).
  - **PMTCT: sd NVP or nothing (no prolonged NVP)**
  - Repeat testing of all positive HIV PCR tests minimized false positive results. (Sherman et al. 2005)

- In the era of maternal cART, prolonged infant NVP prophylaxis (≥6 weeks) and the need to initiate ART as early as possible in HIV-infected infants, a single PCR test at 6 weeks of age is no longer optimal

Case 1

- A 3-month old exclusively formula fed HIV-exposed infant was admitted with acute gastroenteritis.
- His mother did not access ante-natal PMTCT, but tested HIV positive post-partum; she demised 2 weeks after delivery.
- The baby completed 6 weeks of daily nevirapine prophylaxis.
- Blood drawn at the local clinic on day 44 of life tested HIV DNA PCR negative.
- After admission to hospital on day 82 of life, DNA PCR was positive; confirmatory HIV RNA viral load was >10 million copies/ml (>log 6.7).
- The original specimen had been saved on a dried blood spot card. This card was retrieved and re-tested, and confirmed DNA PCR negative.

Haeri Mazanderani et al. Loss of detectability and indeterminate results: challenges facing HIV infant diagnosis In South Africa's expanding ART programme. SAMJ August 2014

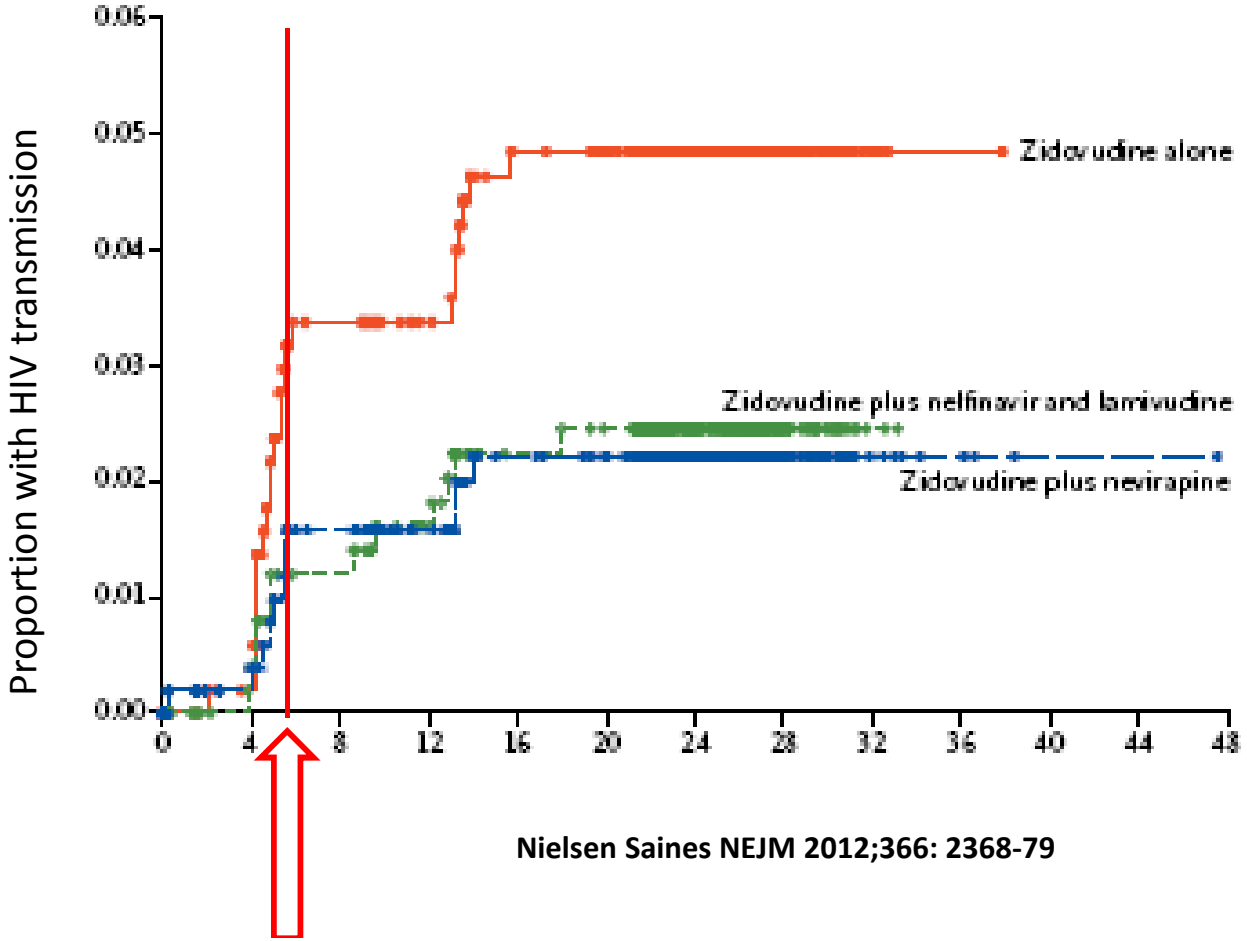
Reduced sensitivity of HIV PCR test with prolonged ARV prophylaxis (≥4 wks)

- French cohort (Burgard et al. J Pediatr 2012)
  - 1567 infants undergoing PCR testing, receiving prolonged postnatal prophylaxis, no breastfeeding.
  - Performance of PCR assessed in relation to 6-month HIV RNA result.
  - Sensitivity
    - At birth: 58% (RNA), 55% (DNA)
    - 1 month: 89% (RNA & DNA)
    - 3 months: 100% (RNA & DNA)
    - 6 months 100% (DNA)

  > At 1 month during prophylaxis, 11% of infected children had negative PCR results.

- French guidelines recommended PCR screening for HIV at birth, 1, 3 and 6 months

HPTN 040 study: in formula fed infants who received 6 weeks of postpartum AZT, with or without other ARVs, 32% of intrapartum-infected infants tested HIV DNA PCR negative at 6-weeks of age but tested positive at 3 months of age



Nielsen Saines NEJM 2012;366: 2368-79

Shortcomings of the 6-week PCR test

- **Too late for early ART initiation**
  - Median age at ART initiation in CHER study was 7.4 weeks
  - 20% death rate/100 person years by 13 weeks in CHER study deferred ART group
  - 62% of 403 infants who initiated cART at median 8.4 weeks of age had advanced HIV disease (CD4 <25% or <1500 cells/mm^3 or WHO Stage 3 or 4. Innes et al. JIAS 2014
  - Loss to follow-up or death before 6 weeks (10-20%)

- **Too early to detect all intrapartum infections**
  - Maternal ARV and infant daily NVP prophylaxis delay detection of HIV at 6 weeks because of a low target of virus failing to detect 10-20% of early infections

- May miss up to 30-40% of all HIV + infants!

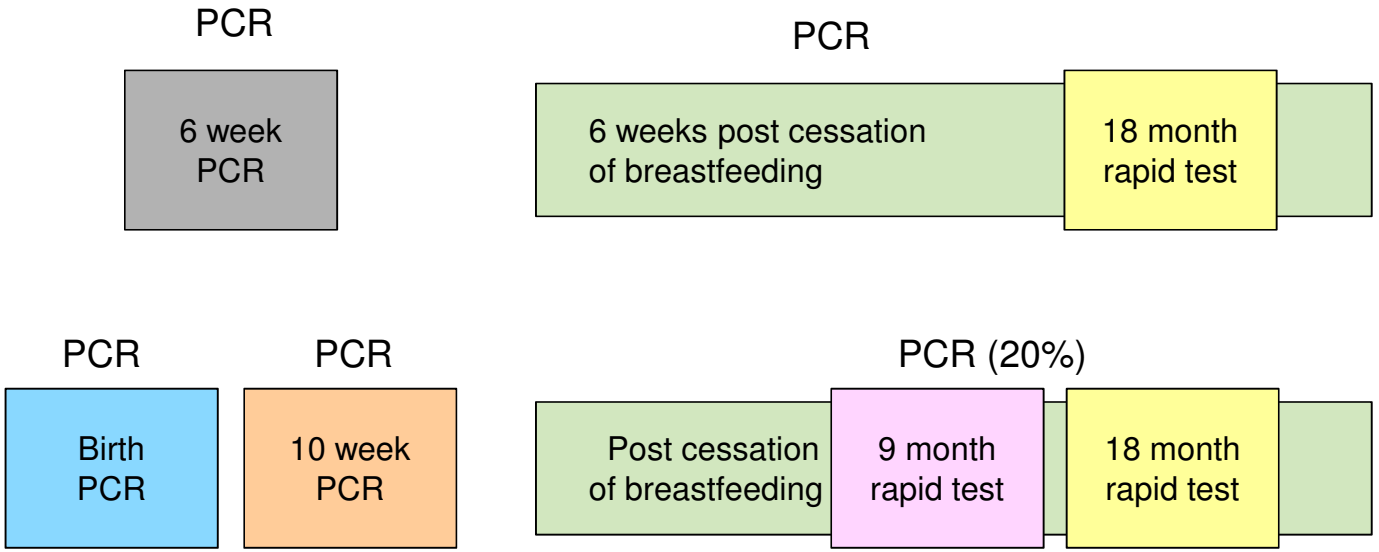
Performance of HIV PCR testing at birth

- Birth testing cannot detect all perinatal transmissions
  - it detects in utero transmissions
  - it does not detect intrapartum transmissions
- Postpartum (breastfeeding) transmissions are separate (v. low)

- Pre-PMTCT & modern HIV PCR assays: birth testing detected 38% of perinatal transmissions (Dunn et al.)

- Antenatal AZT & infant prophylaxis with single dose NVP: birth testing detected 76% of perinatal transmissions: higher total than testing just at 6 weeks (Lilian et al. *J. Clin. Microbiol.* 2012)
  - Improved sensitivity of viral detection assays
  - Ratio of in utero to intrapartum infections increased due to PMTCT interventions targeting late pregnancy & intrapartum transmission

Current vs Ideal HIV Testing Algorithm



If birth HIV PCR test is negative, and prolonged infant prophylaxis (e.g. daily dose NVP to 12 weeks) has been used, then the second PCR should be delayed approximately 4 weeks after NVP is discontinued.

Acknowledgements

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- Prof G Theron
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