Estimates of MTC Transmission Rates from Programmatic Data

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Inclusion criteria

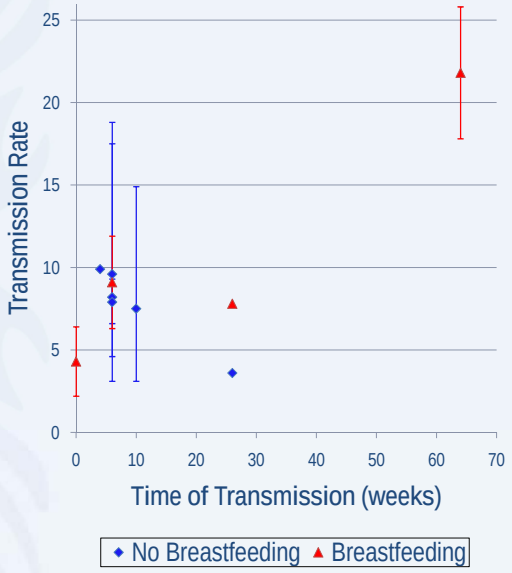
- Published reports (14) or abstracts (5)
  - "grey literature" not included
- Programs: 15 PMTCT program based; 4 EID
- Countries represented: 14 from sub-Saharan Africa; also China, Thailand, Ukraine, Russia, Haiti.
- Had to report transmission rates by regimen.

Program Description of PMTCT reports from sub-Saharan Africa (n=12)

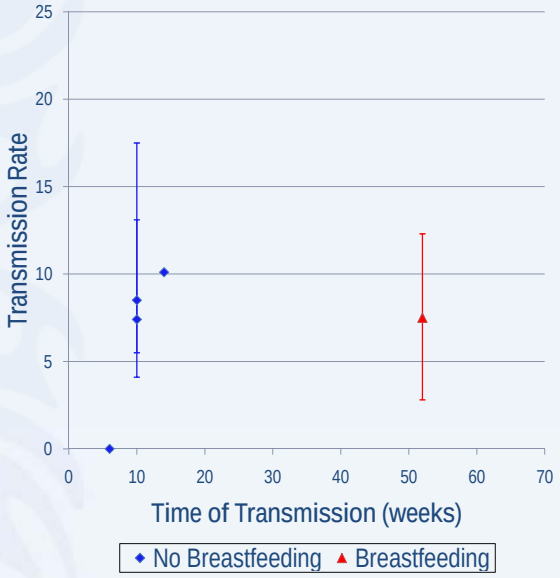
- Sample size ranged from 250 in single hospital to >800 in multi-site study in single country.
- Stated purpose of these studies was to describe feasibility of providing multidrug prophylactic regimens or ART in low-resource settings.
  - Most not powered to compare transmission rates between regimens.
- CD4 distribution reported in 4 (33%) studies; 1 reported VL prior to delivery.
- Infant feeding described in 9 (75%). 6 primarily formula feeding population with program providing free formula for period of time; 3 programs reported high proportion of women EBF in first 3-6 months.
- Infant followup rates ranged from 65 to 97% of original PMTCT cohort.

The next several slides describe the transmission estimates (and 95% confidence intervals) by Regimen, predominant infant feeding practice and time of infant HIV Test

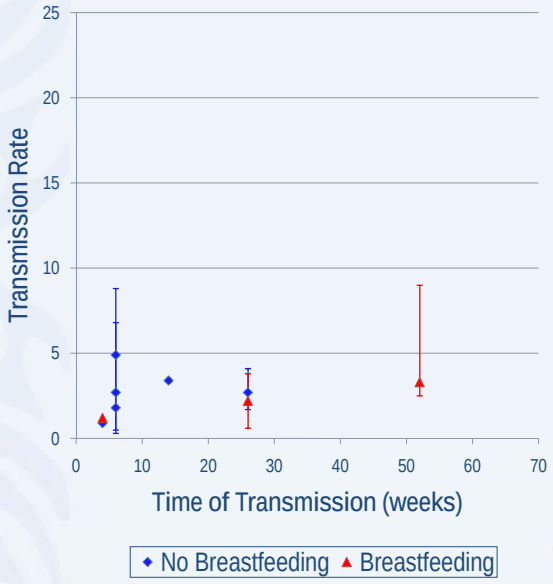
Estimated transmission rates by regimen: SD-NVP



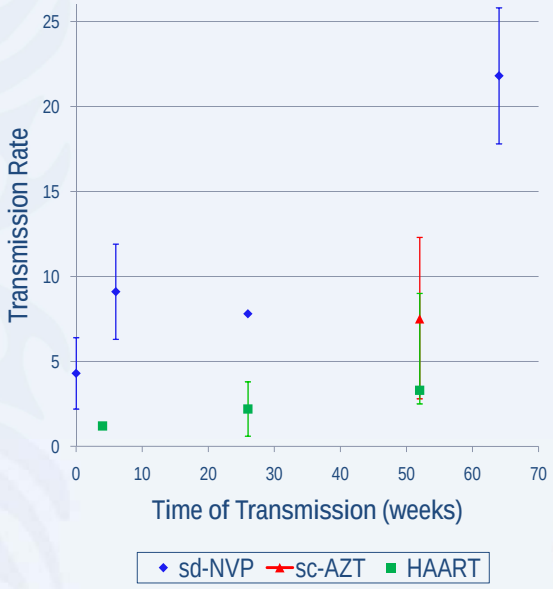
Estimated transmission rates by regimen: 2006 prophylaxis



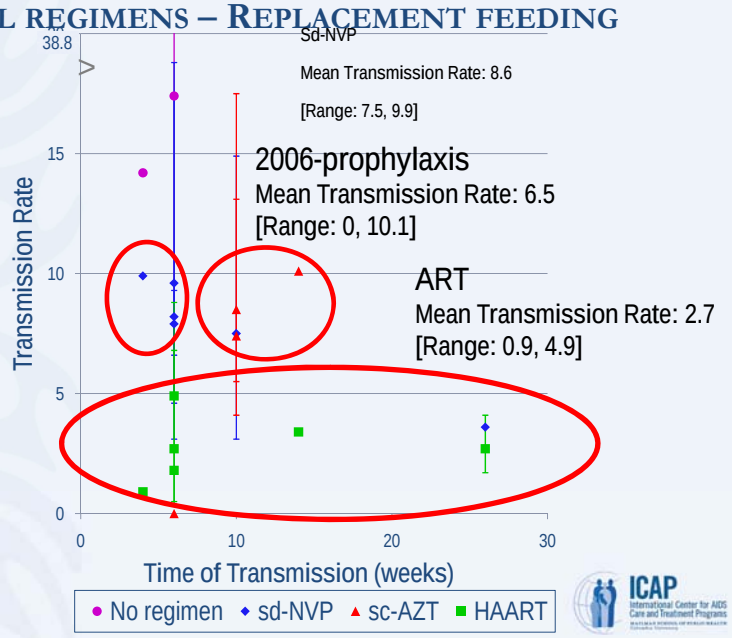
Estimated transmission rates by regimen: ART



Estimated transmission rates, All regimens - Breastfeeding



Estimated transmission rates, All regimens – Replacement feeding



Longer duration of antepartum regimen associated with lower transmission

- Hoffman (2010) observed higher 6wk transmission among women receiving HAART for shorter time period
  <4 weeks (9.3%) vs. >4 wks (5.5%)

LOWER CD4 ASSOCIATED WITH HIGHER TRANSMISSION

- Theron (2009) observed higher transmission at 14 wks among women receiving sc-AZT with lower CD4 count

  CD4<250 [6/21 (28.6%)] vs. CD4>250 [6/98 (6.1%)]

COMPARISON OF TRANSMISSION RATES FROM PROGRAMMATIC DATA WITH MODELS

Regimen	Transmission rates by 6m, cumulative					
	RF			BF		
	Program Data (Mean transmission)	Spectrum model	CHAI Model	Program	Spectrum	CHAI
Sd-NVP	8.8 (7.5, 9.9)*	11.0	13.1	6.1	18.7	14.2
2006 prophylaxis	6.8 (0.0, 10.1)	4.0	6.5	NA	12.3	9.0
ART	1.9 (0.0, 3.4)	2.0	1.8	1.2	3.8	3.8
No regimen	15.8 (14.2, 17.4)	20.0		6.1	26.9	16.7

*range

Mean transmission based on program reports from non-BF settings seem comparable to rates used in Spectrum and CHAI models.

METHODOLOGIC ISSUES RELEVANT TO MODELING:

- Confounding by indication (regimen is determined by CD4 count, which is itself a risk factor for MTCT. [Illustration using MTCT Plus Initiative transmission data]
- Maternal and infant losses to followup for early PCR testing, LTF before determination of final HIV status--and bias in MTCT rates
- Denominator issue with Infant testing programs

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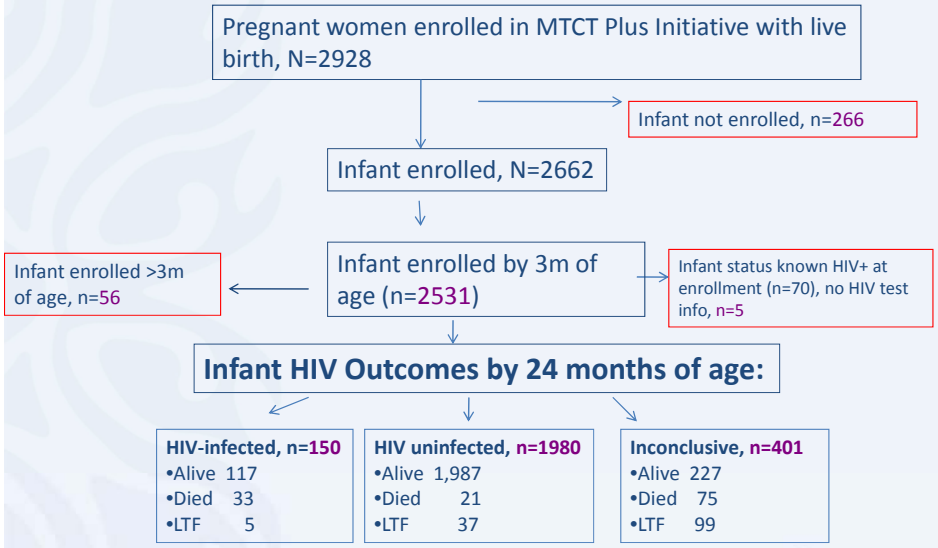
THE MTCT-PLUS INITIATIVE (2004-2008)

- 13 sites in 8 African countries and Thailand enrolled >16,000 women, men and children.
- PMTCT as entry point to comprehensive, family-focused, HIV care and treatment.
- At enrollment, participants received physical exam with WHO clinical staging, and CD4 cell count performed at local labs.
- Women enrolled while pregnant received PMTCT regimens or ART based on WHO (2006) and national guidelines

METHODS

- High proportion of eligible women initiated ART during pregnancy.
- Maternal ART status and PMTCT regimen recorded at each clinic visit.
- PMTCT maternal and infant regimen data also collected at time of HIV exposed infant enrollment.
- Preliminary analysis use 3 broad categories for PMTCT regimen:
  - Sd-NVP at delivery
  - Short course PMTCT: must include antepartum AZT (any duration). Most also had sd-NVP at delivery and some sites provided AZT/3TC tail.
  - Treatment: triple drug regimen [AZT/3TC/NVP] initiated during pregnancy and continued after delivery.
- Defined "breast feeding" as ever (>1 postpartum clinic visit where mother reporting breast feeding) vs. never
- Calculated cumulative transmission at 12, 24 months; HIV free survival

SAMPLE FLOW CHART

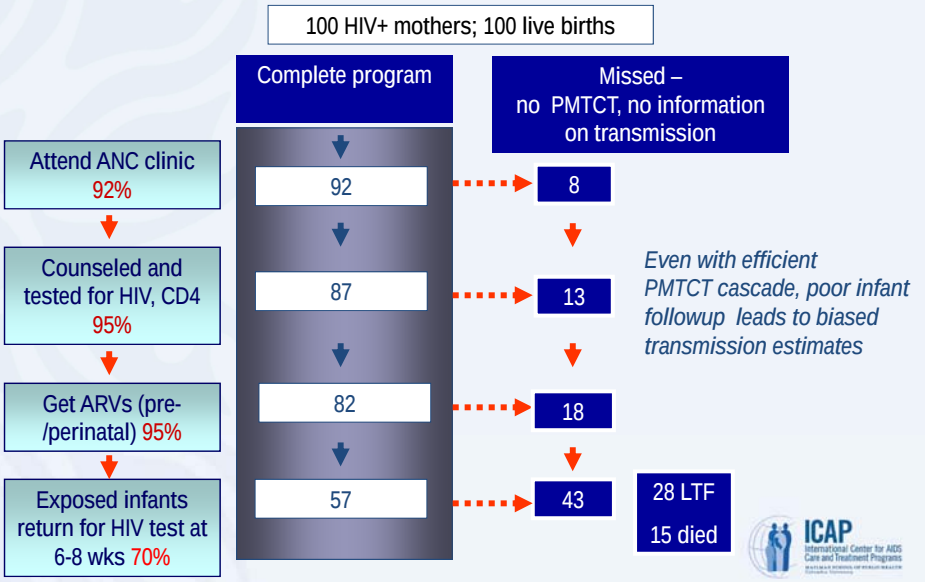


Transmission by 24 months by Maternal regimen and CD4 category closest to delivery, MTCT Plus Initiative cohort, 2004-2008, N=2150

Regimen	Overall transmission by regimen
*Sd-NVP**	*81/646 12.5%*
SC-PMTCT	*45/723 6.2%*
Treatment	*24/761 3.2%*
TOTAL	*150/2130 7.0%*

*includes 84 women whose regimen is missing/unknown; 9 transmissions

Most Critical Issue for measuring MTCT is Number of Mother-Infant pairs Completing PMTCT/EID Cascade

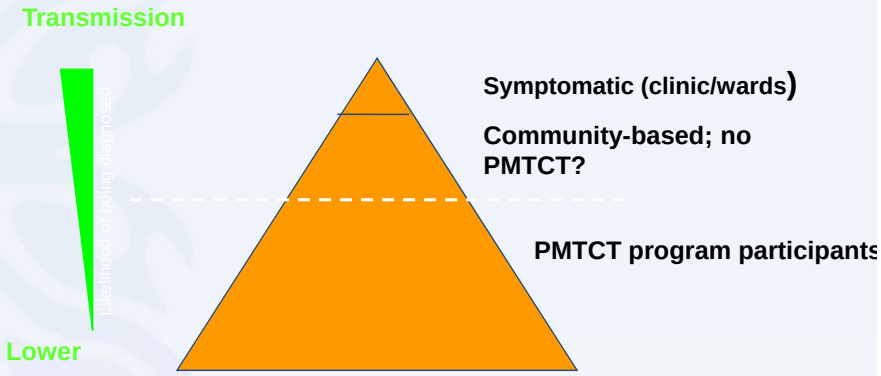


Even with efficient PMTCT cascade, poor infant followup leads to biased transmission estimates

ARE REGIMEN-SPECIFIC TRANSMISSION RATES FROM INFANT HIV TESTING PROGRAMS USEFUL FOR MODELING?

- 3 reports reviewed
- Where sample is representative of national program, and PCR testing widely available and part of standard pediatric care package, and transmission estimates should be minimally biased
- In settings where infant testing not widely available, potential to include more symptomatic children receiving HIV testing thus biasing transmission estimates.

What population is represented in Infant testing programs



Limitations of data on transmission rates from programmatic studies

- Small sample size lead to unstable estimates of transmission and overlapping CI between different regimens in most "program" studies. Also, many studies lack 95% CI to understand range of transmission.
- Selection bias resulting from high losses to followup including high infant mortality prior to first HIV test.
- Difficult to interpret age-specific transmission rates, and post-partum transmission due to variability in when infants received their first HIV test, or returned for followup testing to confirm HIV status.
- Difficult to compare transmission results across different settings in different countries with variable resources and national guidelines for PMTCT and IF.
- Differences in underlying health status of mothers and infants across studies in different countries make it challenging to compare programmatic results.
- Infant feeding practices not always described. Where BF was common, not specified how infant feeding was measured.

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Considerations for modeling transmission rates

- Contribution of infant regimens to transmission rates is of interest historically, but not relevant with new WHO guidelines. Since infant regimens will be conditional on maternal regimens (Option A vs. Option B). But, given our concerns about Option A, consider modeling good vs. poor adherence to infant regimen.
- Priorities: Need more complete information on distribution of CD4 cell count, severity of disease among pregnant HIV+ women in settings. And standards for publishing program PMTCT transmission. Recommendations to countries for representative sampling within programs to better estimate CD4 distrib?
- As more women now "eligible" for ART, need better data on proportion of eligible women receiving ART in addition to duration of ART prior to delivery in order to appropriately model contribution of CD4 (confounding by indication).

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