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Updating Estimates of Mother-to-Child Transmission Rates

Session 2: Transmission Data Being Used for PMTCT Models, CHAI Model

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Why use models?

- Models allow us to estimate with immediate results, the EXPECTED outcomes of PMTCT activities.
- Allow us to answer the question, "If we do this, how many infants will be infected?"

- Most importantly, they help us answer, "What can we do to lower that number?"

What is helpful to know about the population and the program?

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Individual level

- How sick is the mother?
- When did she start prophylaxis?
- What was she given?
- Was the baby given prophylaxis? What and for how long?
- Did the mom breastfeed? For how long? In the first 6 months, did she exclusively breastfeed or mixed feed?

Clinic/ program/ district/ national level

- How many pregnant women are HIV+?
- Are they attending ANC? Getting an HIV test? Getting CD4 count? Have access to ARVs for PMTCT?
- What regimens are being offered? Which guidelines are being followed?

Our approach to default MTCT rates

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Methods

- Define regimens
- Establish inclusion criteria
- Literature review
- Random effects meta-analysis
- Apply hazard ratio to calculate role of infant feeding at 6 months through cessation of breastfeeding

Results

- MTCT rates by regimen at 6 weeks, 6 months
- MTCT rates by regimen from 6 months and then monthly, stratified by the pattern of infant feeding the mother adopted during first 4-6 months of infant's life

ARV regimen definitions

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Antiretroviral regimen	Definition
HAART	Triple combination ART using non-PI based regimens received by women for a minimum of 4 weeks of pregnancy; ART continued during the postpartum period for at least 6 months in the breastfeeding population; Infant ARV prophylaxis limited to a max duration of 4 weeks, and limited to sd-NVP +/- AZT.
Dual prophylaxis ARVs	Women received a **minimum of 4 weeks of ART** during the antenatal period, receiving one or two ARV agents; Regimens including PIs excluded; Woman received, at a minimum, NVP or AZT and 3TC during labor; No postnatal ART requirements for women; If ARVs are provided during the postnatal period, limited to $\leq$7 days; Infant antiretroviral prophylaxis is limited to a max duration of 4 weeks.
Single-dose nevirapine prophylaxis	One dose of NVP provided to the mother during labor and/or one dose of NVP provided to the infant within 72 hours of birth, with no additional ARVs provided to either the mother or the infant.
No ARVs	Neither pregnant women nor HIV-exposed infants receive any antiretroviral therapy during pregnancy or during the postpartum period.

Inclusion criteria, all studies

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- Carried out in resource-limited setting in Africa, Asia, South or Central America;
- Kaplan Meier analysis (or comparable statistical analysis technique) used to calculate six month cumulative transmission rates;
- HIV diagnosis <12 mo nths made by RNA- or DNA-PCR;
- Study provided information regarding feeding patterns of study population (ie. proportion of population breastfeeding)

Inclusion criteria, by regimen

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HAART	Pregnant women received triple combination ART (non-PI based regimens) during the antenatal period for a minimum of 4 weeks of pregnancy; Triple combination ART continued during the postpartum period for at least 6 months in the breastfeeding population; Infant antiretroviral prophylaxis limited to a maximum duration of 4 weeks, and limited to sd-NVP +/- AZT.
Dual prophylaxis	Pregnant woman receive a minimum of 4 weeks of antiretroviral therapy during the antenatal period, receiving one or two antiretroviral agents; Regimens including PIs excluded; Woman receives, at a minimum, NVP or AZT and 3TC during labour; No postnatal antiretroviral therapy requirements for women; if ARVs are provided during the postnatal period, duration is limited to seven days or less; Infant antiretroviral prophylaxis is limited to a maximum duration of 4 weeks.
sd-NVP	One dose of NVP provided to the mother during labour and/or one dose of NVP provided to the infant within 72 hours of birth, with no additional antiretrovirals provided.
NONE	Neither pregnant women nor HIV-exposed infants receive any antiretroviral therapy during pregnancy or during the postpartum period.

Results: Cumulative MTCT rates by regimen

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	6 weeks Mean MTCT (95% confidence interval)	**6 months** Mean MTCT (95% confidence interval)
HAART	1.82 (0.6-3.04)%	3.83 (1.62-6.05)%
Dual Prophylaxis	6.48 (4.84-8.12)%	8.08 (4.92-11.23)%
Single-dose Nevirapine	13.05 (8.79-17.31)%	14.22 (9.46-18.99)%
No antiretrovirals	16.74 (12.63-20.86)%	24.95 (21.65-28.26)%

- *Random effects meta-analysis used; accounts for between-study heterogeneity.*
- *Cumulative transmission rates are calculated at 6 weeks and 6 months. Cumulative rates beyond 6 months are calculated using a correction factor for ongoing breastfeeding.*

Adjustment for infant feeding (1)

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- The cumulative transmission rates at six weeks are not disaggregated by feeding pattern, as it is assumed that these numbers reflect pregnancy and delivery transmission, which is not influenced by feeding practice.

- The cumulative transmission rates at six months in the population of women who exclusively replacement feed their infants is equal to the six week cumulative transmission rate, as it is assumed that there is no postnatal transmission in these infants due to no breastmilk exposure.

- We assume that populations represented in the HAART group and the dual prophylaxis ARV group had been counseled to breastfeed exclusively, and that the MTCT rate reported at six months represents an exclusively breastfed population.

- We assume that transmission rate at six months in the single dose nevirapine and no antiretrovirals meta-analysis represents a population of women who practiced mixed feeding.

Adjustment for infant feeding (2)

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- Hazard ratio of 1.56 (0.66-3.69) associated with transmission if mixed feeding during first 6 months compared to exclusively breastfeeding.*

- Approach:
  - *Subtract* MTCT rate at 6 weeks from rate at 6 months to determine postnatal risk for each regimen
  - *Multiply* this by hazard ratio to calculate rate for MF group (for HAART and dual), add to the 6 wk rate
  - *Divide* the postnatal risk by the hazard ratio to calculate the rate for the EBF group (for sdNVP and nothing), add to the 6 wk rate

- Example, sdNVP:
  - 14.2% (6 month rate) - 13.1% (6 week rate) =1.1% (represents postnatal transmission)
  - 1.1% (post-natal transmission) / 1.56% (hazard ratio) = 0.705%
  - 13.05% (6 week rate) + 0.705% = 13.8% (newly calculated rate for EBF and sdNVP at 6 months)

* Coovadia HM, Rollins NC, Bland RM, et al. Mother to child transmission of HIV-1 infection during exclusive breastfeeding during the first six months of life: an intervention cohort study. Lancet, 2007; 369:1107-16.

Adjustment for infant feeding (3)

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- We assume the incremental risk of late postnatal transmission through continued breast-feeding does not change significantly over time, as was reported by the BHITS group*.

- We estimate a 0.75% monthly increase in risk of transmission beyond six months attributed to ongoing breastfeeding (equivalent to the 8.9 transmissions per 100 child yrs of breastfeeding).

- To model beyond 6 months, we determine the duration of breastfeeding, multiply the # of months beyond 6 by 0.75%, and at this late postnatal breastfeeding risk to the 6 month risk.

- Example based on 18 mo of breastfeeding, dual prophylaxis:
  - 18 months – 6 months = 12 months
  - 12 months * 0.75% (monthly risk) = 9.0%
  - 8.1% (6 month risk if EBF) + 9.0% = 17.1% (18 month risk if EBF)

* The Breastfeeding and HIV International Transmission Study Group. Late postnatal transmission of HIV-1 in breastfed children: an individual patient data meta-analysis. Journal of Infectious Diseases, 2004; 189: 2155-66.

Infant feeding estimates at 6 months

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ARV Regimen	Infant feeding patterns	6 month cumulative transmission	95% CI	
HAART	RF	1.8%	0.6%	3.0%
	EBF for 4-6 mo.	3.8%	1.6%	6.1%
	MF during first 4-6 mo.	3.8%	1.6%	6.1%
Dual Prophylaxis ARV	RF	6.5%	4.8%	8.1%
	EBF for 4-6 mo.	8.1%	4.9%	11.2%
	MF during first 4-6 mo.	9.0%	5.8%	12.1%
Single-dose Nevirapine	RF	13.1%	7.9%	17.3%
	EBF for 4-6 mo.	13.8%	9.0%	18.6%
	MF during first 4-6 mo.	14.2%	9.5%	19.0%
No ARVs	RF	16.7%	12.6%	20.9%
	EBF for 4-6 mo.	22.0%	18.7%	25.3%
	MF during first 4-6 mo.	25.0%	21.7%	28.3%

Cumulative rates at 6 weeks are not disaggregated by feeding pattern; assumed to reflect rates at birth and not influenced by feeding practice.

Cumulative transmission rate estimates, up to 24 months

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ARV Regimen	Infant feeding patterns	6 month	12 month	18 month	24 month
HAART	RF	1.8%	1.8%	1.8%	1.8%
	EBF for 4-6 mo.	3.8%	3.8%	3.8%	3.8%
	MF during first 4-6 mo.	3.8%	3.8%	3.8%	3.8%
Dual Prophylaxis ARV	RF	6.5%	6.5%	6.5%	6.5%
	EBF for 4-6 mo.	8.1%	12.6%	17.1%	21.6%
	MF during first 4-6 mo.	9.0%	13.5%	18.0%	22.5%
Single-dose Nevirapine	RF	13.1%	13.1%	13.1%	13.1%
	EBF for 4-6 mo.	13.8%	18.3%	22.8%	27.3%
	MF during first 4-6 mo.	14.2%	18.7$	23.2%	27.7%
No ARVs	RF	16.7%	16.7%	16.7%	16.7%
	EBF for 4-6 mo.	22.0%	26.5%	31.0%	35.5%
	MF during first 4-6 mo.	25.0%	29.5%	34.0%	38.5%

Options A & B

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Regimen	Birth	6 weeks	6 month	12 month
Option A		3.8 (2.0-5.6)% MITRA	4.9 (2.7-7.1)% MITRA	
Option B	1.0 (0.4-1.1)% Mma Bana 1.8 (0.8-3.7)% Kesho Bora	3.3 (1.9-5.6)% Kesho Bora 4.1 (2.1-6.0)% MITRA-Plus	1.0 (0.4-1.8)% Mma Bana 4.9 (3.1-7.5)% Kesho Bora 5.0 (3.2-7.0)% MITRA Plus	5.6 (3.4-8.4)% Kesho Bora

Our conservative estimates to date have been 2% for birth, 5% for 6 months and beyond, with rates equivalent for exclusive and mixed feeding. Our assumption has been that similar to HAART, the risk of transmission beyond 6 months would be close to zero, so rates beyond 6 months would equal the 6 month rates.

Options A & B (cont)

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- The BAN study is not included in these rates because they enrolled uninfected infants at birth, and so far we've been looking at studies reporting cumulative rates, inclusive of the pre- and intra-partum periods. At week 28, transmission rates in BAN were 1.8% for infant NVP, 3.0% for maternal HAART, and 6.4% for the control. There was no statistically significant difference between infant and maternal HAART in this postnatal period. Differences between the 3 arms started to appear ~4 weeks.

- PEPI Malawi is not included as it also starts at delivery and measures postnatal infection. In women with CD4> 350, they found 1.4% and 2.3% in extended NVP, and extended NVP+AZT, respectively, similar to BAN. Rates for lower CD4 categories were higher.

Comparison of rates across groups

	Time	Regimen Type					
		HAART	**Dual prophylaxis**	**sd NVP**	**No ARVs**	**Option A**	**Option B**
CHAI [7]	Birth	1.82 (0.6-0.04)%	6.48 (4.84-8.12)%	13.05 (8.79-17.31)%	16.74 (12.63-20.86)%	2%	2%
	6 mo	RF: 1.8% EBF:3.8% MF: 3.8%	RF: 6.5% EBF: 8.1% MF: 9.0%	RF: 13.1% EBF: 13.8% MF: 14.2%	RF: 16.7 % EBF: 22.0 % MF: 25.0 %	RF: 2% EBF: 5% MF: 5%	RF: 2% EBF: 5% MF: 5%
	12 mo	RF: 1.8% EBF: 3.8% MF: 3.8%	RF: 6.5% EBF: 12.6 % MF: 13.5%	RF: 13.1% EBF: 18.3% MF: 18.7%	RF: 16.7% EBF: 26.5% MF: 29.5%	RF: 2% EBF: 5% MF: 5%	RF: 2% EBF: 5% MF: 5%
UNAIDS Reference Group[5]	Birth	2.0%	4.0%	11.0%	20.0%		
	6 mo	RF: 2.0% EBF: 3.8% MF: 3.8%	RF: 4.0% EBF: 8.2% MF:12.3%	RF: 11.0% EBF: 14.9% MF: 18.7%	RF: 20.0% EBF: 23.5% MF: 26.9%		
	12 mo	RF: 2.0% MF: 5.5%	RF: 4.0% MF: 16.2%	RF: 11.0% MF: 22.3%	RF: 20.0% MF: 30.2%		
PEPFAR. Andrew Auld et al[2]	Birth	1.8%	2.2%	11.0%	20.0%	2.20%	1.80%
	6 mo	RF: 1.8% EBF: 4.7% MF: 6.6%	RF: 2.2% EBF: 7.9% MBF: 14.0%	RF: 11.0% EBF: 16.7% MBF: 22.8%	RF: 20.0% EBF: 25.7% MF: 31.8%	RF: 2.2% EBF: 3.9% MBF: 5.0%	RF: 1.8% EBF: 4.7% MF: 6.6%
	12 mo	RF: 1.8% EBF: 7.6% MF: 11.5%	RF: 2.2% EBF: 13.6% MF: 25.8%	RF: 11.0% EBF: 22.4% MBF: 34.6%	RF: 20.0% EBF: 31.4% MF: 43.6%	RF: 2.2% EBF: 5.6% MBF: 7.9%	RF: 1.8% EBF: 7.6% MF: 11.5%
PEPFAR, Tracy Creek[1]	Birth						
	6 mo						
	12 mo					CD4<200: 9% CD4>200: 6%	CD4<200: 9% CD4>200: 6%

Note: "Birth" rates here are meant to represent transmission during pregnancy and delivery while 6 and 12 month rates are cumulative and represent pregnancy, delivery and the post-natal period.

Inputs used for comparison

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	Botswana	Tanzania	Zambia
# HIV+ pregnant women in 2009	13,534	84,834	71,134
# Women receiving different regimens/nothing			
No ARVs	1,270	5,491	35,970
sdNVP	-	70,000	9,099
Dual	8,693	-	26,065
Triple	3,571	9,343	-
% Women receiving different regimens/nothing			
No ARVs	9.4%	6.5%	50.6%
sdNVP	0.0%	88.2%	25.9%
Dual	70.9%	0.0%	74.1%
Triple	29.1%	11.8%	0.0%
Infant feeding choices, 1st 6 months			
Replacement feeding	95.0%	8.1%	0.0%
Mixed	0.0%	28.6%	85.0%
Exclusive	5.0%	63.3%	15.0%
Median duration (months)	18	22	22
% with access to ARVs for PMTCT	90.6%	93.5%	49.4%

CHAI Model Outputs

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How many HIV-exposed infants born to all of the HIV+ pregnant women in Botswana, Tanzania and Zambia in 2009 do we expect to become infected themselves?

Country	**Number of infections**	***Of women with access to ARVs***	***Of women receiving no ARVs***	***% transmission (women receiving ARVs)***	***% transmission (women NOT receiving ARVs)***	***% overall transmission (within and outside program)***
Botswana	**842**	*629*	*212*	*5.1%*	*16.7%*	*6.2%*
Tanzania	**20,280**	*18,405*	*1,875*	*23.2%*	*34.0%*	*23.9%*
Zambia	**16,692**	*3,374*	*13,318*	*9.6%*	*37.0%*	*23.5%*

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