Working Paper on

Mother-to-Child HIV Transmission Probabilities

for use in Spectrum

Updated on 6 September 2012

UNAIDS Reference Group on Estimates, Modelling and Projections

Every two years UNAIDS and partners request countries to submit information on the status of the HIV epidemic in their countries. Countries are trained to use tools to estimate and project the impact of the HIV epidemic on their countries. The primary tool for the estimates is Spectrum computer package (www.futuresinstitute.org). The software estimates the transmission of HIV between HIV-positive women and their children. To make these calculations information on the probability of transmitting HIV is required.

This working paper describes the evidence used to derive the transmission probabilities given different CD4 levels during the peripartum period and the postnatal period. In addition the probabilities are described by prophylaxis regimen.

Table 1. Mother to Child HIV Transmission Probabilities by CD4 level for peripartum and postnatal period by regimen

REGIMEN	PERIPARTUM TRANSMISSION*				POSTNATAL TRANSMISSION** per month of any BF § *(except incident infection)*	
	CD4 count not specified	CD4 <200	CD4 200-350	CD4 350+	CD4 <350	CD4 >350
Incident infections	30% [1] *(13-30%)*				28% [2] *(14.3-56%)*	
No prophylaxis	22% [3] *(15-25%)*	37% [4] *(22-54%)*	27% [5] *(13.1-32.6%)*	15% [6] *(9.7-20.2%)*	1.57%/m BF [7]	0.51%/m BF [8]
SD-NVP	12% [9] *(9.4-12.1%)*				1.57%/m BF [7]	0.51%/m BF [8]
WHO 2006 dual prophylaxis	4% [10] *(2.3-5.3%)*				1.57%/m BF [7]	0.51%/m BF [8]
Option A			*4% †* *As WHO 2006[10]*	2% [11]		0.2%/m BF [12]
Option B				2% [13] *(0.9-2.9%)*		0.2%/m BF [14]
ART		2% [15]			0.2%/m BF [16]	
ART (before pregnancy)		0.5% [17]			0.16%/m BF [18]	

General notes

The probabilities were derived by an expert working group which was formed specifically to develop mother to child HIV transmission (MTCT) probabilities for the Spectrum computer package (http://www.futuresinstitute.org/Pages/Spectrum.aspx). The group was formed following a consultation held on Sept 1-2, 2010 in Washington DC, USA. (Report available at http://www.epidem.org/Publications/UpdatingMTCTratesReport.pdf). The working group consisted of:

Dr Renaud Becquet,	*INSERM, Unité 897, Institut de Santé Publique Epidémiologie Développement (ISPED), Université Bordeaux Segalen, Bordeaux, France*
Dr Tracy Creek,	*Formerly of the Global AIDS Programme, Centers for Disease Control, Atlanta, GA, USA*
Dr Louise Kuhn,	*Mailman School of Public Health, Columbia University, New York, NY, USA*
Dr Mary Mahy,	*Epidemic Monitoring and Analysis Unit, UNAIDS, Geneva, Switzerland*
Dr Lynne Mofenson,	*Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA*
Dr Nigel Rollins,	*Department of Maternal, Newborn, Child and Adolescent Health, WHO, Geneva, Switzerland*

The group based the estimates on the literature cited in the accompanying notes. These reflect the current published literature, data from personal communication and conferences. A formal systematic review was not conducted. Once the estimates were developed the table and notes were reviewed by an additional expert, Dr. Elaine Abrams.

* Peripartum HIV transmission reflects combined in-utero and intrapartum transmission and is measured by HIV status of infants at 6 weeks of age. It assumes no additional early transmission due to breastfeeding. In non-breastfed infants, HIV status of infants at 6 weeks or any time thereafter would represent peripartum transmission. In breastfed infants, any additional transmission that occurs after 6 weeks of age would be regarded as postnatal transmission and attributable to breastfeeding.

** Postnatal HIV transmission reflects infections in infants or children who were HIV uninfected at birth (identified through a negative HIV test at 6 weeks) and who subsequently become HIV infected while breastfeeding. Postnatal transmission rates attributable to breastfeeding may be reported among infants who were deemed to be uninfected through peripartum transmission. Investigators reported the different time points at which they tested infants for peripartum transmission namely 2, 4, 6 or 8 weeks postpartum. For the purpose of the estimates for Spectrum, the postnatal transmission probabilities were used irrespective of the age of infants used in those studies at which all peripartum was deemed to have been measured.

Alternatively, some investigators reported cumulative transmission probabilities at birth, 6 weeks and other postnatal time points such as 3, 6,12 and 18 months. In this situation HIV transmission due to breastfeeding was estimated by subtracting HIV infections (or transmission probabilities) among 6 week old HIV-exposed infants from HIV infections (or transmission probabilities) among HIV-exposed breastfeeding infants identified any time thereafter.

Monthly transmission probabilities were thereafter calculated by dividing the % postnatal transmission rate by the breastfeeding exposure period related to that transmission rate.

- If the transmission rate was measured at 6 months, then the breastfeeding risk exposure period was deemed to be one month less than this i.e. 5 months as HIV DNA laboratory assays only reliably detect, with high sensitivity and specificity, infections that occur about 4 weeks prior to measurement. For example if the transmission probabilities at 6 weeks and 6 months were 5% and 8.5% respectively, then 3.5% HIV transmission would be attributed to 5 months of breastfeeding = 0.7% per month of breastfeeding;

- Alternatively, if the median breastfeeding period of infants reported in studies is less than the time at which HIV status was determined, then the % transmission at the time of measurement was divided by the median duration of breastfeeding without any adjustment since the full duration of breastfeeding would have contributed to the risk. For example, postnatal transmission estimated to be 9% at 12 months with a median breastfeeding period of 7 months, then the monthly transmission risk associated with breastfeeding would be 9/7 = 1.29% per month of breastfeeding.

Any breastfeeding includes exclusive and mixed breastfeeding. Data is generally composite and by trying to separate creates a false sense of accuracy of data.

It was noted that when data on duration of breastfeeding is not available from women enrolled in PMTCT programs, Spectrum applies breastfeeding rates from national household surveys (such as the Demographic and Health Surveys or Multiple Indicator Cluster Surveys). These may not accurately reflect practices among HIV-infected mothers. However, in the absence of data specifically from HIV-infected mothers, household survey data will continue to be used.

§ For the transmission estimates associated with breastfeeding the values are given to 2 decimal places since rounding these values up or down would result in significantly greater or lesser transmission probabilities when multiplied according to the duration of breastfeeding.

† Providing option A to breastfeeding mothers with CD4 counts 200-350 is not recommended. However, it is noted that this situation may arise in settings where systems to perform CD4 counts are not in place and women needing to be on lifelong ART are not being readily identified. The inclusion of a MTCT rate for this scenario is for modelling purposes only and does not reflect a WHO recommendation.

Column 2, reflects populations in which CD4 counts are unknown. This column will only be applied to historical versions of Spectrum as the current and future versions will always provide estimated CD4 distributions and associated transmission estimates. (Exception. See note † above) For current WHO recommended interventions, no categories include mothers for whom CD4 count is unknown. Option A and B are assumed to be provided to mothers with CD4 counts >350.

Cells which will not therefore be populated are shaded.

For most cells, median values were calculated. Weighted averages were considered to provide a false level of precision.

Notes for individual transmission estimates *(the numbers reflect the superscript numbers included in each cell of the table on page 1*)

1. Peripartum transmission risk due to incident HIV infection in pregnant women 30%

A number of studies report increased risk of HIV transmission to infants when women/mothers become infected during pregnancy or while breastfeeding i.e. incident infection. However, there is limited research data from which to accurately estimate these risks. Infections in the fetus or infant probably occur in the early stages of incident infection presumably due to the high viraemia at this time.

In contrast to women/mothers with longstanding HIV infection who also have high viral load, the CD4 counts of women with incident infection are not depleted. It is therefore inappropriate to disaggregate transmission risk in this group of mothers and infants by CD4 counts. The risk of transmission to infants may vary with the timing of the incident infection i.e. early or later in pregnancy. This may explain the variation in transmission estimates reported in the published papers.

Four reports, three in formula feeding mothers/infants and one in a breastfeeding population, were identified that provided infant transmission probabilities among women/mothers who had become infected during pregnancy. The reported transmission risks ranged between 13-30%. Other studies reported high odds ratios among the same population but had not provided a % transmission rate.

Among all formula feeding infants included in the three reports, there were 13 infection in total among 66 sero-converting formula feeding mothers = 19.6%. This reported risk contrasted with the higher transmission risk in infants born to mothers with CD4 < 200 cells/ml and not receiving any treatment (37%). The Working group initially considered that the two groups should have transmission risks which would be roughly equivalent.

Data from a surveillance study in a predominantly breastfeeding community was more consistent with the view of expert group. Among 172 mothers who reported themselves as HIV uninfected but whose infants were antibody positive the transmission rate was 30.5% (95% confidence interval [CI], 24.0–37.6).[1]

The Working group recommended that a transmission risk of 30% should be used in Spectrum. This was considered to be justifiable given the high odds ratios reported for infant transmission associated with incident infection in pregnant women, that the transmission risk in infants born to mothers with CD4 < 200 cells/ml and not receiving any treatment is about 37% (considered to be a reasonable comparison risk) and the limited data available that directly quantifies this transmission rate.

Birkhead GS et al. Obstet Gynecol 2010 June;115 (6):1247-55[2]: Cohort analysis, New York, USA 2002-2006; 3,102 formula feeding HIV-exposed infants; 41 mothers acquired HIV during pregnancy, 22% (9/41) of infants were infected.

Roongpisuthipong A et al. JAIDS 2001 Apr 1;26 (4):348-51[3]: Prospective study. Bangkok, Thailand, 1992-1994; formula-fed population, 16 women seroconverted during pregnancy, 13.3% (2/15) infants of seroconverting mothers were infected with HIV (not significantly different than infants born to previously HIV infected women, 66/266, 24.8%, p=0.5)

Tovo P-A et al. Brit J Obstet Gynecol 1991 Sept;98:940-2[4]: Italy, 1980s; formula fed population, report on 10 infants of mothers who seroconverted during pregnancy; 20% (2/10) were infected.

Rollins N et al. AIDS 2007, 21:1341–1347[1]: South Africa, 2004-2005; Surveillance tested all infants attending immunisation clinics and asking information from mothers. Among 172 mothers who reported themselves as HIV uninfected but whose infants were antibody positive, the transmission rate at 6 weeks was 30.5% (95% CI, 24.0–37.6).

2. Postnatal transmission risk due to incident HIV infection in breastfeeding mothers 28%

Similar to the peripartum transmission risk (#1 above), postnatal transmission estimates are not disaggregated by CD4 count. In addition, the duration of breastfeeding was not reported consistently between studies.

The available data does not generally report a relationship between duration of breastfeeding by sero-converting mothers and the risk of HIV transmission to the infant. The lack of relationship is plausible and it may be inappropriate to consider a monthly transmission risk among this group of mothers and infants. It may be that, for infants who are going to be infected, an extraordinary maternal viral load during incident infection results in all infections occurring during the first weeks of breastfeeding exposure. Hence it may not make sense to estimate a monthly transmission rate. Also the very high risk of infection in incident infection mothers may only be present for 1-2 months and then drop down to a different risk level. It may therefore be inappropriate to apply an average monthly hazard risk over a duration of breastfeeding (long or short) within a model.

Six papers were identified that reported transmission to infants of breastfeeding mothers who sero-converted postpartum; transmission probabilities ranged from 14.3-56%. In the largest of the studies, which also had the greatest level of detail available in terms of timing of infant infection and maternal sero-conversion, about 14% (95% CI 10.7-19.0) of breastfeeding infants born to mothers who converted in the postnatal period became infected within 6 months of maternal infection. In the subgroup of mothers with seroconversion interval <= 90 days, 24% (95% CI 14.15-39.48) of breastfeeding infants became infected within 6 months of maternal infection.

Other reports [5] provide estimates of the increased transmission risk (expressed as odds or hazard ratios) that infants of mothers experiencing incident HIV infection while breastfeeding. In these reports, the transmission risk is reported to be about 3-5 times greater than among mothers who were infected prior to breastfeeding.

The Working group estimated the median value of the values reported in the papers (*14.3%, 16.7%, 27%, 29%, 35.8%, 56%*), namely 28%. In Spectrum this will be combined with projected incident infection probabilities and median breastfeeding periods to estimate the additional infections that will occur in infants.

Van de Perre P et al. NEJM 1991;325:593-8[6]: Kigali, Rwanda, 1988; Seronegative women followed prospectively, 16 seroconverted postpartum while breastfeeding; 56.3% (9/16) infants became infected.

Dunn DT et al. Lancet 1992;340:585-8[7]: Meta-analysis, Africa and Australia; Mothers infected prior to pregnancy and breastfed, postnatal transmission 14% (7-22%); 42 mothers infected postpartum, 12 infants infected with postnatal transmission 28.6% (16-42%).

Palasanthiran P et al. J Infect Dis 1993;167:441-4[8]: Australia, 11 mothers infected postnatally by blood transfusion, one via needles; 3 of 11 infants infected, postnatal infection rate 27.3% (6-61%)

Ekpini ER et al. Lancet 1997. Apr 12;349:1054-9[9]: Cote d'Ivoire, 1990-94. 12 mothers infected postnatally by HIV-1 (7 seroconverted from HIV-2 positive to dual positive), 1 of 5 children whose mothers seroconverted from HIV negative to HIV-1, and 1 of 7 children whose mothers seroconverted from HIV-2 to dual reactivity became HIV-1 positive. Thus 12 had acute HIV-1 (5were originally HIV-2 positive but HIV-1 negative); 2 of 12 infants infected, postnatal infection rate was 16.7%

Liang K et al. J Infect Dis 2009;2009:200:682-6[10]: China, 2007; Mothers infected postnatally by blood transfusion, 38 of 106 infants infected, postnatal infection rate 35.8%., average duration of breastfeeding was 16.5 months.

Humphrey J et al. BMJ 2010;341:c6580[11]: Zimbabwe, 1997-2001. 334 mothers seroconverted during the breastfeeding period and was associated with an average of 34.56 infant infections per 100 child years. However the risk decreased over the months that followed incident infection in the mother. Sixty percent of the infections occurred in the first 3 months following incident infection in the mother and 12 months after maternal incident infection there were no infant transmissions. The median duration of breastfeeding in the population was just over 1.5 years (median 578 days). In this population, 14.3% (95% CI 10.7-19.0) of breastfeeding infants born to mothers (n=334) who converted in the postnatal period became infected within 6 months of maternal infection. In the subgroup of mothers with seroconversion interval <= 90 days, 24% (95% CI 14.15-39.48) of breastfeeding infants became infected within 6 months of maternal infection.

3. Peripartum transmission, no prophylaxis, CD4 count not specified 22%

Transmission probabilities (among placebo groups) from studies conducted in US, France, east and southern Africa and Thailand ranged from 15-25%. While there were significant geographical variations, there was no clear relationship between transmission probabilities and either breastfeeding or non-breastfeeding populations. Data were presented for all mothers and no CD4 counts were available. The values (*15.3, 18.9, 21.7, 21.8, 25.5*) result in a median transmission rate is 22%.

Petra Study Team. Lancet 2002;359:1178-86[12]: Tanzania, South Africa, and Uganda, 1996-2000. Breastfeeding population, measured transmission rate at 6 weeks in the placebo group was: 15.3%

Connor EM et al. N Engl J Med 1994;331:1173-80[13]: US and France, 1991-1993; formula feeding population; 18 month transmission rate assumed to be "peripartum" (i.e. in utero + intrapartum), placebo group all CD4 groups: 25.5%.

Shaffer N et al. Lancet 1999 Mar 6;353:773-80[14]: Thailand, 1996-1997, formula feeding population; 6 month transmission rate assumed to be "peripartum" (i.e. in utero + intrapartum), placebo group all CD4 groups: 37/198, 18.9% (13-24%).

Wiktor SZ et al. Lancet 1999 Mar 6:353:781-5[15]: Cote d'Ivoire, 1996-1998. Breastfeeding population, measured transmission rate at 4 weeks in placebo group was: 25/119, 21.7% (14.0-28.8%).

Dabis F et al. Lancet 1999 Mar 6:353:786-92[16]: Cote d'Ivoire, Burkina Faso, 1995-1998. Breastfeeding populations, transmission rate at 6 weeks in the placebo group was: 42/145, 21.8% (15.9-27.6%).

4. Peripartum transmission, no prophylaxis/treatment, CD4 count <200 37%

Three reports included that reflect data collected in east, south and west Africa and Thailand. African sites represented significant breastfeeding populations (49-94%) while Thai population was entirely formula feeding. Range of transmission probabilities was 22-54% with a median value of 37% (*22.4, 36.2, 36.4, 37.5, 43, 54.2*).

Leroy et al, AIDS 2005, vol 19(16); 1865-75[17]: Data disaggregated from three regions in Sub-Saharan Africa, 1995-2000; 6 week transmission probabilities among women with CD4 counts <200: South Africa (N=500) (49-52% breastfeeding) 36.2% (22-51), East Africa (N=153) (50-74% breastfeeding) 36.4% (17-59) and West Africa (N=303) (92-94% breastfeeding) 54.2% (33-74) respectively.

Shaffer N et al. Lancet 1999 Mar 6;353:773-80[14]: Thailand, 1996-1997; formula feeding population. 6 month transmission rate assumed to be "peripartum" (i.e. in utero + intrapartum): Placebo group CD4 <200: N=24, 37.5%.

Humphrey J et al. Personal communication 2010: Zimbabwe 1998-2002, Zvitambo study. Among prevalent cases, the perinatal transmission rate stratified by CD4: <200 (123/549) = 22.4%.

Mayaux MJ. JAIDS 1995 Feb 1;8:188-94[18]: France, 1986-1994, 848 women on no antiretroviral drugs, most formula feeding but some breastfeeding. Transmission at 18 months stratified by CD4: <200 = 43%.

5. Peripartum transmission, no prophylaxis/treatment, CD4 count 200-350 27%

Similar to cell 4, three reports provide data collected in east, south and west Africa and Thailand. African sites represented significant breastfeeding populations (49-94%) while the Thai population was entirely formula feeding. The range of transmission probabilities was 13-33% with a median value of 27% (*13.1, 18.3, 27.3, 30.3, 32.6*).

Leroy et al, AIDS 2005, vol 19(16); 1865-75[17]: Data disaggregated from three regions in Sub-Saharan Africa, 1995-2000. 6wk transmission probabilities in each region in mothers with CD4 200-350 were: South Africa (N=500) 27.3% (19-36) (49-52% BF), East Africa (N=153) 30.3% (16-49) (50-74% BF) and West Africa (N=303) 32.6% (19-48) (92-94% BF).

Shaffer N et al. Lancet 1999 Mar 6;353:773-80[14]: Thailand, formula feeding . 6 month MTCT rate assumed to be "peripartum" (i.e. in utero + intrapartum): Placebo group CD4 200-499: N=104, rate 18.3%

Humphrey J et al. Personal communication 2010 : Zimbabwe 1998-2002, Zvitambo study. Among prevalent cases, the perinatal transmission rate stratified by CD4 200-350 (117/891) = 13.1%.

6. Peripartum transmission, no prophylaxis, CD4 count >350 15%

There is limited data specifically disaggregated according to this range of CD4 counts. It is important to consider the likely overall transmission probabilities when data from populations with CD4 350-500 are collapsed with those from population with CD4 >500.

The Working group considered that the value used previously in Spectrum, namely 17%, was possibly high, i.e. appropriate for the population with CD4 count 350-500, but high for the entire population with CD4 counts >350. Other studies [17] report that the transmission risk in women with CD4 counts <350 is 3-4 times greater than in women with CD4 counts >350.

When the transmission probabilities for 350-500 and >500 for each site were collapsed and averaged, the range of transmission probabilities was 9.7%-20.2% (*9.7, 13.2, 13.4, 17.3, 17.5, 20.2*) with a median value of 15%.

Leroy et al, AIDS 2005, vol 19(16); 1865-75[17]: Data disaggregated from three regions in Sub-Saharan Africa, 1995-2000. 6wk transmission probabilities in mothers with CD4 350-500 were: South Africa (N=500) 17.6% (12-25) (49-52% BF), East Africa (N=153) 16.7% (6-33) (50-74% BF) and West Africa (N=303) 21.7% (12-34) (92-

94% BF). In mothers with CD4 >500 transmission probabilities at 6 weeks were 17.0% (12-23), 9.7% (5-17) and 18.5% (13-25) respectively. The average transmission probabilities for 350-500 and >500 in the respective populations are South Africa 17.3%, East Africa 13.2% and West Africa 20.2%

Shaffer N et al. Lancet 1999 Mar 6;353:773-80[14]: Thailand, 1996-1997; formula feeding population. 6 month MTCT rate assumed to be "peripartum" (i.e. in utero + intrapartum), placebo group CD4 >500: N=67, 13.4%

Humphrey J et al. Personal communication 2010: Zimbabwe 1998-2002, Zvitambo study. Among prevalent cases, the perinatal transmission rate among women with CD4 count >350 = 9.7% (203/2094)

Mayaux MJ. JAIDS 1995 Feb 1;8:188-94[18]: France, 1986-1994, 848 women on no antiretroviral drugs, Mothers were advised not to breastfeed (2% breastfed). Transmission at 18 months stratified by CD4: 400-600 = 20%; cd4 >600 = 15%; average transmission rate for >400 is 17.5%.

7. Postnatal transmission, no prophylaxis/treatment, CD4 count <350 1.57% per month BF

A few reports serve as benchmarks against which to interpret the estimated postnatal transmission reported for the population with CD4<350.

- The Breastfeeding and HIV International Transmission Study Group (BHITS) performed an individual patient meta-analysis of 4,085 mother infant pairs[19]. This included mothers with CD4 count <200 and also some women who were receiving ART. The analysis indicated a transmission of 8.9 transmission per 100 child years of breastfeeding (= 0.74 % per month of breastfeeding) with an adjusted hazard ratio of 2.08 for mothers with CD4 less than 200.
- Iliff reported outcomes among 2060 infants in the Zvitambo trial in which the median breastfeeding was more than 18 months[5]. Between 6 weeks and 18 months there were 199 infections with an estimated postnatal transmission rate (PNT) of 9.2/100 child years. In mothers with CD4 cell counts less than 200 cells/ml (n=216), postnatal transmission was 33.7% (95% CI 22.9–44.1) though it was not explicitly stated that this was at 18 months. The hazard ratio for CD4<200 for HIV transmission at 6, 12 and 18 months were 9.12, 6.24 and 5.28 respectively.
- In South Africa, Coovadia [20] reported the increased risk of postnatal transmission between 6 weeks and 6 months, in mothers with CD4<200, as an adjusted hazard ratio of 3.79.

Data were available from several studies to estimate the risk of postnatal transmission through breastfeeding among mothers with CD4 count <350. As background, the monthly postnatal transmission risk for breastfeeding infants when the mothers CD4 count is not considered is 0.8% per month of breastfeeding [19] and 9.2 infections per 100 child years in the Zvitambo study[5]. Other studies expressed the increased risk as an odds ratio or hazard ratio and reported a 3 to 9 fold increase in transmission risk in this group of mothers but were not able to provide an percentage transmission rate.

In the Zambia Exclusive Breastfeeding study (ZEBS) the median duration of breastfeeding was 12 months[21]. A crude monthly transmission risk in mothers with CD4 counts <350 calculated from these data is 1.96%/month of breastfeeding. However, this does not account for losses to follow up during the study. The author recalculated the estimates to account for drop-outs and the transmission risk was 1.31% per month of breastfeeding.

In two studies (Kesho Bora and PEPI), control group infants received 1 week postnatal prophylaxis but no further prophylaxis. Transmission probabilities occurring between 6 weeks

and 6 months were used to estimate the transmission rate, as no infant prophylaxis was being received during that time.

On reviewing studies that were able to provide the necessary data on mothers with CD4 counts less than 350, the range of monthly transmission probabilities was 0.84-2.5% per month of breastfeeding (*i.e. 0.84, 1.31, 1.57, 1.89, 2.52*). The median value was 1.57% per month of breastfeeding.

Kuhn L et al. AIDS 2010 Jun 1;24 (9):1374-7[21]: Zambia, N=554. Postnatal infection probabilities were estimated *after age 6 weeks*, with follow-up to 24 months. Median duration of breastfeeding was 12 months, therefore estimated monthly infection probabilities between 6 week-12 months i.e. 11 months of breastfeeding: CD4 <350: 20.6% in 10.5 mo = 1.96%/month. However, this does not account for losses to follow up during the study. The author recalculated the estimates to account for drop-outs and the transmission risk was 1.31% per month of breastfeeding.

J Humphrey. Personal communication. Nov 2010: Zimbabwe, Zvitambo study. Among prevalent cases, the postnatal transmission rate stratified by CD4: <200, 23.3% (18.6-29.1) at 12 months = 11m breastfeeding exposure = 2.12% per month of breastfeeding; 200-350, 11.2 % (8.7 -14.3) = 1.02% per month of breastfeeding. Combining the transmission rate in the <200 and 200-350 groups, the average transmission rate (2.12+1.02% / 2) is 1.57% per month of breastfeeding.

Kesho Bora. Lancet Infect Dis 2011;11(3):171-80[22]: Burkina Faso, Kenya and South Africa, 2005-2008; among control group infants born to women with CD4 200-350, transmission probabilities were 6.3% at 6 weeks and 10.5% at 6 m = 4.2% additional transmissions due to 5 months breastfeeding exposure = 0.84%/month. Note. Women in the Kesho Bora Observational cohort with CD4 <200 were placed on ART and therefore cannot contribute data to this estimate.

Mofenson L et al. IAS,Capetown, South Africa, July 2009 Abs. TuPEC053 [23]: Malawi, PEPI study, 2004-2009; 96% of women still breastfeeding at 6 months. Among control group infants born to women with CD4 <200, transmission probabilities were 10.7% at 6 weeks and 21.9% at 24 weeks = 11.2% additional transmission due to 4.5 months of breastfeeding exposure = 2.49% per month. Among women with CD4 200-350, transmission probabilities were 5.6% at 6 weeks and 11.4% at 24 weeks. 5.8% additional transmission over 4.5 months of breastfeeding exposure = 1.29% per month. The average of these two rates is 1.89% per month.

Renaud Becquet. Personal communication. Nov 2010: Vertical Transmission Study, (South Africa, 2001-2007) and the Ditrame Plus Study (Cote d'Ivoire, 2001-2005) (N=1151). Among mothers with CD4 count <350, the transmission rate was 12.6 at 6 months = 5 months breastfeeding exposure = 2.52% per month of breastfeeding

18m postnatal transmission of HIV-1 among children uninfected at 4 weeks of age according to maternal antenatal CD4 count. Median duration of breastfeeding - 6 months

Antenatal maternal CD4 count, cells/mL	No. of children	No. children infected through breastfeeding	HIV-1 postnatal transmission (95%CI), %
<200	119	15	15.3 (9.5-24.2)
≥200	1032	57	6.2 (4.9-8.0)
<250	181	20	11.0 (5.3-16.2)
≥250	970	52	5.4 (3.5-6.5)
<350	353	38	12.6 (9.3-16.9)
≥350	798	34	4.8 (3.4-6.6)
<200	119	15	15.3 (9.5-24.2)
200-349	234	23	11.3 (7.6-16.5)
350-500	320	18	6.3 (4.9-9.1)
≥500	478	16	3.7 (2.3-6.0)

Table adapted from data reported in:

Becquet R, Ekouevi DK, Arrivé E, Stringer JS, Méda N, Chaix ML, Treluyer JM, Leroy V, Rouzioux C, Blanche S, Dabis F. Universal antiretroviral therapy for pregnant and breastfeeding HIV-infected women: Towards the elimination of mother-to-child transmission of HIV-1 in resource-limited settings. Clinical Infectious Diseases 2009;4(12):1936-45.[24]

Becquet R, Bland RM, Leroy V, Rollins NC, Ekouevi DK, Coutsoudis A, Dabis F, Coovadia HM, Salamon R, Newell ML. Duration, pattern of breastfeeding and postnatal transmission of HIV: pooled analysis of individual data from a West and South African cohort study. PLoS One 2009;4(10):e7397.[25]

8. Postnatal transmission, no prophylaxis, CD4 count >350 0.51% per month BF

The Working group used the same data sources and similar rationale as for #7 above. As mentioned above, when maternal CD4 counts are not considered, the transmission risk associated with breastfeeding was reported to be 0.8% per month of breastfeeding from the BHITS study[19] and 9.2 infections per 100 child years in the Zvitambo study[11].

In the Zambia Exclusive Breastfeeding study (ZEBS) (see Kuhn et al below) the crude monthly transmission risk in mothers with CD4 counts >350 is 0.4%/month of breastfeeding. However, this does not account for losses to follow up during the study. The author recalculated the estimates to account for drop-outs and the transmission risk was 0.31% per month of breastfeeding.

On reviewing the studies that were able to provide the necessary data in mothers with CD4 counts equal to or more than 350, the range of monthly transmission probabilities was 0.1-0.96% per month of breastfeeding (*<0.1, 0.31,0.48, 0.51, 0.61, 0.69, 0.96*). The median value was 0.51% per month of breastfeeding.

Note the transmission probabilities from the two reports from Kesho Bora were not averaged as with data from Zvitambo as they derived from two distinct sources, an observational cohort and a randomized control trial group. In Zvitambo, the data originated from a single study population though disaggregated by maternal CD4 count.

Kuhn L et al. AIDS 2010 Jun 1;24 (9):1374-7[21]: Zambia, N=544 median duration of breastfeeding 12 months. Postnatal infection probabilities *after age 6 weeks*, with follow-up to 24 months. Estimated monthly infection probabilities between 6 weeks and 12 months represents 11 months of breastfeeding exposure risk: CD4 >350: 4.4% in 11 mo = 0.4%/month. Recalculated by author to account for drop-outs i.e. transmission risk = 0.31% per month of breastfeeding.

Tonwe-Gold B et al. PLoS. Med. 2007;4(8):e257[26]: Côte d'Ivoire, 2003-2005; primarily formula fed population. CD4>350. Maternal AZT+3TC and sdNVP. Infant sdNVP and AZT. 4 week transmission was 3.1%. Thereafter, 3 of 86 infants infected over 5.7 months of breastfeeding = 0.61%/month.

Kesho Bora Study Group. JAIDS 2010 Aug 15:54 (5):533-41[27]: Burkina Faso, Kenya and South Africa, 2005-2006. Observational cohort with 78% breastfeeding, maternal CD4 >500. AZT (28 weeks) + sdNVP: Birth (in utero) : 2/125, 1.6% (0.4-6.3). Cumulative 6 week (intrapartum + early postpartum): 6/115, 4.9% (2.2-10.6). Considering only those infants uninfected at 6 weeks, 1 infection at 12 months = 1 during 11 mo breastfeeding exposure = <0.1%/month breastfeeding.

Kesho Bora Study Group. Lancet Infect Dis 2011;11(3):171-80[22]: Burkina Faso, Kenya and South Africa, 2005-2008; *after 6 weeks* CD4 350-500, 3.4% at 6 weeks and 5.8% at 6 m = 2.4% additional transmissions due to 5 months breastfeeding exposure = 0.48%/month of breastfeeding.

Renaud Becquet. Personal communication. Nov 2010 : Western and southern Africa, 2001-2003. Mothers with CD4 count ≥350, the transmission rate was 4.8% at 6 mo = 5 months breastfeeding exposure = 0.96% per month of breastfeeding.

J Humphrey. Personal communication, Nov 2010: Zimbabwe, Zvitambo study. Among prevalent cases, the postnatal transmission rate stratified by CD4: 350+, 5.6% (4.5-7.0) at 12 months = 11 months of breastfeeding exposure = 5.6/11 = 0.51% per month of breastfeeding.

Mofenson L et al. IAS,Capetown, South Africa, July 2009 Abs. TuPEC053 [23]: Malawi, PEPI study, 2004-2009; 96% of women still breastfeeding at 6 months. Among control group infants born to women with CD4 >350, transmission probabilities were 3.3% at 6 weeks and 6.4% at 24 weeks = 3.1% additional transmission due to 4.5 months of breastfeeding exposure = 0.69%/month.

9. Peripartum transmission. sd-NVP only, CD4 count not specified 12%

Three randomized controlled studies provided data for this estimate in which the CD4 count of pregnant women/mothers was not considered. The range of transmission probabilities was 9.4 - 12.1% (*9.4, 11.9, 12.1*) with a median of 12% (11.9%).

Guay LA et al. Lancet 1999;354(9181):795-802 and Jackson JB et al. Lancet 2003 Sept 13;362:859-68 (HIVNET 012)[28-29]: Uganda, 1997-1999; breastfeeding, sdNVP group: Birth (in utero): 8.2%; cumulative 6-8 weeks (in utero + intrapartum + early postpartum): 11.9%

Moodley D et al. J Infect.Dis. 2003;187(5):725-35[30]: South Africa 1999-2000, a multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine. 8 week transmission in NVP group was 12.3%

SWEN. Lancet 2008 July 26;372:300-13 (SWEN)[31]: Ethiopia, Uganda, India, 2001-2007. Breastfeeding population, sdNVP group (no extended infant prophylaxis), all CD4 levels. The transmission rate at birth (intra uterine) was 4.1%. There were 5.27% additional transmissions by 6 weeks. The cumulative peripartum transmission rate was 9.4%.

10. WHO 2006 dual prophylaxis. CD4 not known 4%

The term *WHO 2006 dual prophylaxis* is applied to a range of ARV interventions that were included in the recommendations at that time. This included settings in which breastfeeding was the dominant infant feeding practice and also settings where replacement feeding (formula feeds) were the default recommendation. It also includes settings where single dose nevirapine may, or may not have been given to infants in the immediate postnatal period (within 72 hours). This transmission rate estimate will only be applied to historical data. Because of the diversity of ARV interventions that were used at that time in widely differing settings, it is not possible (or necessary for the purposes of Spectrum) to differentiate further.

Among the studies considered, the range of peripartum transmission probabilities, measured in infants either at 6 weeks of age in breastfeeding populations or possibly later when infants were given formula feeds only, was 2.3-5.3% (*i.e. 2.3, 3.1, 4.0, 4.9,5.3*) with a median of 4%.

Dabis F, Bequet L, Ekouevi DK, et al. AIDS 2005;19:309-18[32]: Côte d'Ivoire, 2001-2002. ANRS Ditrame. Slight breastfeeding predominance, open label, maternal and infant AZT and sdNVP, 6 week transmission rate of 6.5%; addition of maternal 3TC 6 week transmission 4.7% (95% CI, 2.4–7.0%). No significant difference. In total there were 38 infections among 711 exposed infants at 6 weeks = 5.3%.

Tonwe-Gold B et al. PLoS.Med. 2007;4(8):e257[26]: Côte d'Ivoire, 2003-2005. Primarily formula fed population, maternal AZT+3TC and sdNVP. Infant sdNVP and AZT. Among infants born to women with CD4>350 the transmission rate at 4 weeks was 3.1%.

Lallemant M et al. NEJM 2004 July 15;351 (3):217-28 (PHPT-2)[33]: Thailand, 2001-2003; formula feeding population, 6 month MTCT rate assumed to be peripartum (in utero + intrapartum):
AZT (28 weeks) + NVP/Pl group: 19/697 (as randomized), 2.8% or 17/628 (per protocol), 2.8%
AZT (28 weeks) + NVP/NVP group: 14/705 (as randomized), 2.0% or 12/636 (per protocol), 1.9%
In total, combining transmissions in both intervention arms, 29 infections occurred in 1264 evaluable infants (per protocol) = 2.3% (CD4 ≤200: 4/119, 3.3%, CD4 >200: 8/508, 1.6%)

Kesho Bora Study Group. JAIDS 2010 Aug 15:54 (5):533-41[27]: Burkina Faso, Kenya and South Africa, 2005-2006, observational cohort, 78% breastfeeding, maternal CD4 >500. AZT (28 weeks) + sdNVP: Birth (in utero) : 2/125, 1.6% (0.4-6.3). Cumulative 6 week transmission (in uteru + intrapartum + early post partum): 6/115, 4.9% (2.2-10.6)

Shapiro RL et al. AIDS 2006;20(9):1281-8[34]: Botswana, 2002-2003; MASHI study. Maternal single dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission. Randomised controlled trial of breastfeeding plus infant zidovudine prophylaxis for 6 months versus formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission. No difference between arms. In total 28 of 694 infected at 4 weeks = 4.0%.

11. Peripartum transmission. Option A, CD4>350 2%

There are no studies that report specifically on all components of the ARV interventions recommended in Option A in the population for whom Option A is recommended.

	Interventions offered in SWEN, PEPI, BANS and HPTN 046	2010 WHO Option A for breastfeeding communities
Antenatal ARVs to pregnant HIV-infected women	*Generally single dose NVP to mother* *Some mothers also started on lifelong treatment*	*AZT during pregnancy , +* *sdNVP during labour, +* *AZT / 3TC from start of labour until 7 days after*
Time when ARVs started antenatally	*Onset of labour*	*AZT from 14 weeks*
Maternal CD4 count	*Included women with CD4 counts as low as 200 cells/ml*	*Only for women with CD4 >350 cells/ml*
ARV intervention to infants to prevent peripartum transmission	*sdNVP after delivery*	*NVP daily for 6 weeks*
ARV intervention to infants to prevent postnatal transmission	*Nevirapine to infants while breastfeeding (6 wks, 14 wks or 6m)*	*Nevirapine to infants until one after end of all breastfeeding*

However, there are studies that provide useful data and allow reasonable estimates of likely protection that the recommended ARV interventions will provide against peripartum transmission.

- In West Africa, among infants that were primarily given formula feeds and whose mothers had CD4 counts >350 and received AZT from either 28 or 32 weeks +3TC and sdNVP at birth (infants also received sdNVP and AZT for7 days), transmission at 4 weeks was 3.1%.[26]
- In Kenya, Burkina Faso and South Africa, among breastfed infants whose mothers had CD4 counts 350-500 and received either triple ARVs or AZT from 28 weeks, there were 11 infections among 335 infants at 6 weeks of age = 3.3%.[22]
- In Thailand, among infants that were formula fed and whose mothers had CD4 counts >200 and received AZT from 28 weeks and sdNVP at birth (infants also received sdNVP), there were 8 infections among 508 infants = 1.6%.[33]

The Working group considered that the estimate of peripartum transmission rate associated with the antenatal interventions recommended as part of Option A should be less than the rate associated with the WHO 2006 dual prophylaxis (= 4%, range 2.3-5.3%). As outlined above this is justified on the grounds that the option would:

- apply only to mothers with CD4>350,
- the ARV interventions would be started earlier in pregnancy from 14 weeks gestation,

- the extended postnatal ARV regimen (AZT or NVP for 6 weeks) to infants would provide additional protection.

The Working group considered that a peripartum transmission rate of 2% would be plausible and consistent with data from published studies.

Tonwe-Gold B et al. PLoS.Med. 2007;4(8):e257[26]: Côte d'Ivoire, 2003-2005; primarily formula fed population. Among infants born to women with CD4>350 who were provided maternal AZT (from either 28 or 32 weeks) +3TC and sdNVP. Infant were provided sdNVP and AZT (at 7 days), the 4 week transmission rate was 3.1%.

Kesho Bora Study Group. Lancet Infect Dis 2011;11(3):171-80[22]. Burkina Faso, Kenya and South Africa, 2005-2008. Among infants born to mothers with antenatal CD4 350-500 and who received triple ARVs, the transmission rate at 6 weeks was 2.9%; among infants whose mothers received only AZT and sdNVP the transmission rate at 6 weeks was 3.4%. The difference was not significant. In total, there were 11 infections among 335 infants in these two groups = 3.3%. *Note, if mothers with CD4 counts >500 were included, the transmission rate would likely be less than this.*

Lallemant M et al. NEJM 2004 July 15;351 (3):217-28 (PHPT-2)[33]: Thailand, 2001-2003; formula feeding population, 6 month transmission rate assumed to be peripartum (in utero + intrapartum): Among the AZT (28 weeks) + NVP/NVP group: transmission rate was 2.0% (14/705) if analysed as randomized, or 1.9% (12/636) if analysed per protocol,. In infants of mothers with antenatal CD4 count >200: 8/508 infections = 1.6%

12. Postnatal transmission. Option A, CD4>350 0.2% per month breastfeeding

There have been four randomised studies that have reported on the efficacy of nevirapine given to infants to reduce the risk of HIV transmission while breastfeeding. The protective effect of other ARVs given to infants for the same purpose have also been studied - AZT was found to have no protective benefit [35-36] while 3TC was found to provide similar benefit to NVP in one study (*1.2% transmission with median 18 weeks of breastfeeding i.e. 1.2/4.5 = 0.26%/m*) but this finding needs to verified in more studies[37].

Two of the four studies that examined the protective efficacy of nevirapine when given to infants while breastfeeding provided limited data for estimating monthly transmission probabilities when breastfeeding infants were given daily nevirapine:

- in SWEN, the intervention was only given for 6 weeks despite continued breastfeeding[31].
- In the PEPI study, conducted in Malawi, nevirapine was given to infants for three months only. A few women (2.6-3.2% by intervention arms) were started on lifelong ART before 14 weeks postpartum. While the intervention was given for only 3 months and infants were generally breastfed until some time between 6 and 9 months, the primary endpoints (transmission and death) were measured at 9 and 18 months. Postnatal transmission at 9 months was 5.2% (95% CI, 3.9 to 7.0) in the extended NVP group and 6.4% (95% CI, 4.9 to 8.3) in the NVP/AZT group. However, among infants receiving either of these interventions, there were minimal additional transmissions in these groups between 3 and 6 months of age. Monthly transmission probabilities restricted to the period of intervention and breastfeeding were not estimated.[35]

The two other studies reported transmission probabilities from infants who received nevirapine for up to 6 months while breastfeeding. In both studies, HIV-exposed, uninfected infants were recruited and randomised post delivery and included mothers with CD4 counts 200-350. A proportion of mothers were also initiated on lifelong ART.

- In BAN, also conducted in Malawi, NVP was given to breastfeeding infants until 24 weeks of age and HIV status was determined at 28 weeks of age. Among infants that were HIV uninfected at 2 weeks, there were 12 additional HIV transmission at 28 weeks in 687 breastfeeding infants (reflecting 24 weeks breastfeeding risk exposure i.e. 5.5 months) i.e. 1.7%/5.5 months = 0.31%/month. BAN included mothers with CD4 counts from 250 cells/ml or above. If the intervention is restricted to infants of HIV-infected mothers with CD4 count >350 then it is likely that the rate of transmission will be less than this[38].
- In HPTN 046, (multicountry study) breastfeeding infants were randomized to receive daily nevirapine for either 6 weeks, 14 weeks or 6 months. Among infants of mothers with CD4 >350 who were HIV uninfected at 6 weeks and who received extended daily nevirapine, MTCT at 6, 9 and 12 months was 0.7% (95%CI, 0-1.5), 0.9% (95%CI, 0-1.9) and 1.5% (95%CI, 0.3-2.7) respectively. Almost all mothers were still breastfeeding at 6 months. Monthly transmission attributable to breastfeeding was estimated to be 0.7%/5 months breastfeeding exposure = 0.12%/months[39].

The Working group considered that it was not appropriate to estimate a simple median value from these studies as the CD4 count characteristics of the two populations were different. Considering the population for whom Option A is recommended (>350 cells/ml), the Working group agreed that an estimate of 0.2% per month of breastfeeding was consistent with these data and may even be less than this.

Kumwenda N et al. NEJM 2008; 359 (2):119-29[35]: Malawi, 2004-2007, PEPI study. Mothers eligible for ART referred but not explicitly excluded. However median CD4 across all groups was about 400 and IQR 260-580. The extended infant interventions (NVP or NVP/AZT) were given for 3 months only. Among infants that were HIV uninfected at birth, HIV transmission rate at 9 months in the extended NVP group was 5.2% (95% CI, 3.9 to 7.0) and in the NVP/AZT group was 6.4% (95% CI, 4.9 to 8.3). At 14 weeks, cumulative postnatal transmission was 2.8% in the extended infant prophylaxis groups. There was minimal additional transmission between 14 weeks and 6 months. More than 90% of infants were breastfeeding at 6 months while about 29% were breastfeeding at 9 months.

Chasela CS et al. NEJM 2010;362:2271-81[38] : Malawi 2006-2008, BAN study. Maternal CD4 >250, among infants uninfected at 2 weeks, the infection rate in the infant NVP group 1.7% at 28 weeks, so 1.7% in 24 weeks (5.5 months) of breastfeeding exposure = 0.31%/month.

Coovadia H, et al. # 123LB. CROI 2011[39]: Southern Eastern Africa, multicentre, multicountry study, 2007-2010. 1522 infants were randomized to receive either 6 weeks, 14 weeks or 6 months of nevirapine daily while breastfeeding. In infants of mothers with CD4 >350 and not on ART, and who were HIV uninfected at 6 weeks and received extended daily nevirapine, transmission probabilities at 6, 9 and 12 months respectively was 0.7% (95%CI, 0-1.5), 0.9% (95%CI, 0-1.9) and 1.5% (95%CI, 0.3-2.7). Almost all mothers were still breastfeeding at 6 months. Monthly transmission attributable to breastfeeding = 0.7%/5months breastfeeding exposure = 0.12%/month.

13. Peripartum transmission. Option B. CD4 >350 2%

As for estimating the peripartum transmission rate associated with the 2010 WHO recommended Option A above, there are no studies that provided the identical intervention. The Kesho Bora study provided the same ARV interventions but started only at 28 weeks compared with 14 weeks as recommended in Option B. The Kesho Bora study also did not include 6 weeks extended postpartum ARVs to the infants irrespective of feeding practices.

One of the main findings from the Kesho Bora study was that in women with CD4 counts more than 350 cells/ml, peripartum transmission probabilities were not significantly different among infants of mothers who received triple ARV prophylaxis (AZT, 3TC and Kaletra) or only AZT from 28 weeks and sdNVP at birth. While other studies have reported lower transmission probabilities in women with the same CD4, no other studies have directly compared these interventions in the same population. Among women with CD4 counts >350, the efficacy of the antenatal ARV interventions of Options A and B to prevent peripartum transmission are considered equivalent. (This does not consider any potential benefit or adverse events to mothers or infants). With Option B, the rationale for giving HIV-infected mothers with higher CD4 counts, triple ARVs as prophylaxis, is to ensure that they have low viral loads when they start to breastfeed. The additional ARVs do not provide significant additional protection against peripartum transmission compared to extended AZT in combination with the intrapartum ARVs recommended by WHO as part of Option A.

Several studies inform the peripartum transmission rate that can be expected with triple ARV prophylaxis in women who are not eligible for lifelong ART.

- In European sites, where caesarean section and formula feeding was standard of care for HIV-infected women, peripartum transmission probabilities of 0.9% and 1.5% have been reported.[40-41]
- In Kesho Bora (Kenya, Burkina Faso and South Africa), among breastfeeding infants whose mothers with CD4 counts 350-500 and received triple ARVs, transmission at 6 weeks of age was 2.9%.[22]
- In Botswana, infants of mothers with CD4 counts >200 and who received either a NRTI or PI based triple ARV regiment, in utero transmission was 0.9%.[42]
- In Rwanda, Women with CD4<350 were started on lifelong ART (D4T, 3TC and NVP) while mothers with higher CD4 (>350) were given AZT, 3TC and Efavirenz. Among 227 breastfeeding women on either ART or triple ARV prophylaxis, 6 week transmission was 1.3% (95%CI, 0.4-4.1) at 6 weeks. Transmission probabilities were not disaggregated by CD4 count and maternal intervention (lifelong ART or triple ARV prophylaxis).[43]

The Working group reviewed the range of transmission probabilities (*0.9-2.9%*) and what could be expected with earlier initiation of ARVs combined with the postpartum infant intervention. The Working group agreed that for the purpose of Spectrum, Option B would be associated with a peripartum transmission rate of 2%.

Townsend CL et al. AIDS 2008 May 11;22 (8):973-81[41]: UK/Ireland, 2000-2006; formula feeding, all CD4 counts. Several also had caesarean sections. Some started triple drugs during pregnancy while others were on ART pre-conception. Among mothers with CD4 counts more than 350 cells/ml and receiving one of several different triple ARV combinations, there were 22 infections at 6 weeks of age among 2400 infants = 0.9%

Tubiana R et al. CID 2010 Feb 15;50 (4):585-96[40]: France, 1997-2006, French Perinatal Cohort. Among 7425 mother- infant pairs, all formula feeding, the transmission rate (in utero + intrapartum) was 1.5% (115/7425, 95% CI, 1.3%–2.4%).

Kesho Bora Study Group. Lancet Infect Dis 2011;11(3):171-80[22]: Burkina Faso, Kenya and South Africa, 2005-2008. Among all infants ever breastfed and born to mothers (CD4 200-500) on triple ARVs, transmission rate at 6 weeks = 3.3%. If mother CD4 350-500, transmission rate at 6 weeks = 2.9%. Likely to be less than this if include mothers with CD4 >500.

Shapiro et al. NEJM 2010;362:2282-94[42]: Botswana, 2006-2008, Mma Bana study. Mother CD4>200 on protease inhibitor or nucleoside reverse-transcriptase inhibitor triple regimens. Good adherence and viral suppression (92-96%). 5/553 infants infected in utero (0.9%).

Peltier CA et al. AIDS 2009;23(18):2415-23[43]: Rwanda, 2005-2007, Amata study. 532 women included in non-randomised, interventional study. Women with CD4<350 started on lifelong ART (D4T, 3TC and NVP) and mothers with higher CD4 (>350) given AZT, 3TC and Efavirenz. Among 227 breastfeeding women on either ART or triple ARV prophylaxis, 6 week transmission was 1.3% (95%CI, 0.4-4.1) at 6 weeks. Transmission probabilities were not disaggregated by CD4 count and maternal intervention (lifelong ART or triple ARV prophylaxis).

14. Postnatal transmission. Option B. CD4>350 0.2% per month BF

Three randomized trials and two non-randomised, intervention studies provide data to inform this estimate.

- In Malawi, mothers with CD4 counts >250 were started on triple ARVs as prophylaxis after birth as their infants started breastfeeding. HIV status of infants was determined at 28 weeks of age. Among infants that were HIV uninfected at 2 weeks, postnatal transmission (measured at 28 weeks) associated with 24 weeks of breastfeeding was 0.53% per month of breastfeeding. If the ARV intervention was started antenatally and was restricted to mothers with CD4 count >350 then it is likely that the rate of transmission will be less than 0.53% per month.[38]
- In Kesho Bora, in breastfeeding infants born to mothers with CD4 count 350-500 and who received triple ARVs antenatally, transmission was 2.9% at 6 week and 4.1% at 6 months. The additional 1.2% represents 5 months of breastfeeding risk exposure = 0.24% per month of breastfeeding.[22]
- In Botswana, mothers with CD4>200 were randomised to one of two triple ARV regimens (NRTI or PI based). There was good adherence and viral suppression with both regimens (92/93% throughout the breastfeeding period). There were only 2/553 late postnatal transmissions by 6 months in infants who were uninfected after birth. This represents a transmission risk of about 0.07% per month of breastfeeding.[42]
- In a non-randomised, interventional study in Rwanda, 532 women with CD4<350 were started on lifelong ART (D4T, 3TC and NVP) and mothers with higher CD4 (>350) were given AZT, 3TC and Efavirenz. Among 227 breastfeeding women on either ART or triple ARV prophylaxis, 6 week transmission was 1.3% (95% CI, 0.4-4.1) at 6 weeks and 1.8% (95%CI, 0.7-4.8) at 9 months. Incremental transmission i.e. 0.5% over 8 months breastfeeding risk exposure = 0.063% per month. (No median breastfeeding duration reported).[43]
- In KIBS, a non-randomised study in Kenya, mothers were initiated on either lifelong ART if they met eligibility criteria or triple ARVs during pregnancy and breastfeeding. Among 487 breastfed infants, cumulative HIV-transmission probabilities at birth, 6 weeks, and 6, 12, and 24 mo were 2.5%, 4.2%, 5.0%, 5.7%, and 7.0%, respectively. The 24-month HIV-transmission probabilities stratified by baseline maternal CD4 cell count <500 and >500 cells/mm3 were 8.4% (95% CI 5.8%–12.0%) and 4.1% (1.8%–8.8%), respectively (p = 0.06). Overall, 0.8% additional transmission between 6 weeks and 6 months (5 months breastfeeding exposure risk) = 0.16% per month.[44]

The range of estimates of postnatal HIV transmission reported in these studies was 0.063-0.53% per month of breastfeeding. These may be even less if mothers with CD4>500 were included. The Working group agreed that an estimate of 0.2% per month of breastfeeding would be an appropriate estimate to associate with Option B among mothers with CD4 counts >350 for use in Spectrum.

Chasela CS et al. NEJM 2010;362:2271-81 [38]: Malawi, 2006-2008, BAN study; Maternal **CD4 >250**, in infants who were uninfected at 2 weeks and mothers received triple ARV starting after birth, transmission at 28 weeks was 2.9%. This reflects 24 weeks (5.5 months) of breastfeeding risk exposure i.e. 2.9/5.5 = 0.53%/month. Note, intervention was started only after birth. If they had started antenatally and viral load was effectively suppressed at the time infants started breastfeeding, the transmission rate would likely be lower.

Kesho Bora Study Group. Lancet Infect Dis 2011;11(3):171-80 [22]: Burkina Faso, Kenya and South Africa, 2005-2008. Among all infants ever breastfed and born to mothers (CD4 200-500) on triple ARVs, transmission at 6 weeks was 3.3% and 12 months was 5.4%; difference of 2.1%. Most stopped breastfeeding at 6-7 months. The approximate monthly transmission risk was 0.3% per month. Among infants born to mothers with CD4 350-500 and on triple ARVs, 6 week transmission was 2.9% and 6 month transmission was 4.1%, difference of 1.2%. The approximate transmission risk = 1.2/5 = 0.24%/month.

Shapiro et al. NEJM 2010;362:2282-94 [42]: Botswana, 2006-2008, Mma Bana study. Mother CD4>200 on triple ARVs. Good adherence and viral suppression (92/93% throughout breastfeeding period). 2/553 late postnatal transmissions in these infants by 6 months results in a 0.36% transmission rate over 5 months or <0.1% per month.

Peltier CA et al. AIDS 2009;23(18):2415-23 [43]: Rwanda, 2005-2007, Amata study. 532 women included in non-randomised, interventional study. Women with CD4<350 started on lifelong ART (D4T, 3TC and NVP) and mothers with higher CD4 (>350) given AZT, 3TC and Efavirenz. Among 227 breastfeeding women on either ART or triple ARV prophylaxis, 6 week transmission was 1.3% (95%CI, 0.4-4.1) at 6 weeks and 1.8% (95%CI, 0.7-4.8) at 9 months. Incremental transmission = 0.5% over 8 months breastfeeding risk exposure = 0.063%/month.

Thomas T. PLOS 2011. PLoS Med 8(3): e1001015 [44]: Kenya, 2003-2009; KIBS study. A single-arm open label trial in which HIV-infected pregnant women took zidovudine, lamivudine, and either nevirapine or nelfinavir from 34–36 weeks' gestation to 6 months post partum. Among 487 live-born, singleton, or first-born infants, cumulative HIV-transmission probabilities at birth, 6 weeks, and 6, 12, and 24 months were 2.5%, 4.2%, 5.0%, 5.7%, and 7.0%, respectively. The 24-mo HIV-transmission probabilities stratified by baseline maternal CD4 cell count <500 and >500 cells/mm3 were 8.4% (95% CI 5.8%–12.0%) and 4.1% (1.8%–8.8%), respectively (p = 0.06). Overall, 0.8% additional transmission between 6 weeks and 6 months (5 months breastfeeding exposure risk) = 0.16%/month.

15. Peripartum transmission. ART. CD4 <350. 2%

Two reports from UK, Ireland and France and three studies from west, south and east Africa provide data that inform this estimate.

- Studies from Europe indicate peripartum transmission probabilities around 1%. These mothers generally had caesarean section and almost all infants were given formula feeds. ART was sometimes started pre-conceptually. African studies report a wider range of transmission probabilities (0.6-3.7%).[40-41]
- In the Kesho Bora Study conducted in Kenya, Burkina Faso and South Africa, women with CD4 counts <200 cells/ml were started on lifelong ART during pregnancy. Women with CD4 counts 200-350 were started on triple ARV prophylaxis. Most infants were breastfed. At 6 week of age, transmission probabilities among infants of mothers on ART and those on triple ARVs were 3.7% (4/104 infants. 95%CI, 1.4-9.5) and 3.3% respectively.[22 27]
- In West Africa, among infants of mothers with CD4<350 and who were started on lifelong ART, 6wk transmission was 1.0% (95% CI 0.0%–3.1%).[26]
- In Botswana, pregnant HIV-infected women with CD4<200 were started on ART and those with CD4>200 were randomised to either PI or NRTI triple ARV regimens. There was excellent ARV adherence and viral suppression (92-96%). Only 1/156 (0.6%) infants became

infected peripartum if mother was receiving ART and 5/553 (0.9%) infants were infected when mothers with higher CD4 count received either PI or NRTI regimen.[42]

The Working group agreed that a peripartum transmission rate of 2% should be applied in Spectrum to mother and infants pairs when mothers had CD4 counts less than 350 and were started on lifelong ART:

Kesho Bora Study Group. JAIDS 2010 Aug 15:54 (5):533-41 [27]: Burkina Faso, Kenya and South Africa, 2005-2006, 61% breastfeeding, observational cohort CD4 <200. Birth (in utero): 2/110, 1.8% (0.5-7.1). Cumulative 6 week (in utero + intrapartum + early post partum): 4/104, 3.7% (1.4-9.5) but include intrapartum + early post partum.

Kesho Bora Study Group. Lancet Infect Dis 2011;11(3):171-80 [22]: Burkina Faso, Kenya and South Africa, 2005-2008. Randomised controlled study. Among all infants ever breastfed and born to mothers (CD4 200-500) on triple ARVs, transmission at 6 weeks =3.3%.

Townsend CL et al. AIDS 2008 May 11;22 (8):973-81 [41]: UK/Ireland, 2000-2006, formula feeding, all CD4 counts. Most mothers also had caesarean section. Some started triple drugs during pregnancy while others were on ART pre-conception. Transmission from women on ART for at least the last 14 days of pregnancy was 0.8% (40/4864, 95% CI: 0.6–1.1%), regardless of type of therapy or mode of delivery. Among mothers with CD4 counts less than 350 cells/ml and receiving one of several different triple ARV combinations, there were 18 infections at 6 weeks of age among 1562 infants = 1.1%. Among those who started triple drugs during pregnancy, 39/2967 infected, 1.3% in utero + intrapartum.

Tubiana R et al. CID 2010 Feb 15;50 (4):585-96 [40]: France,1997-2006; mainly formula feeding, all CD4 count. Overall transmission, 115/7425 infected, 1.5% in utero + intrapartum. Among infants of mothers with effective viral suppression (on ART), caesarean section and infants more than 37 weeks gestation and receiving formula feeds there were 22 infections among 4281 infants = 0.5% (95% CI, 0.3%–0.8%)

Tonwe-Gold B et al. PLoS.Med. 2007;4(8):e257[26]: Côte d'Ivoire, 2003-2005; Primarily formula fed. Among infants born to women with CD4<350 receiving maternal ART and infants receiving sdNVP and AZT, 4 week transmission was 1.0% (95% CI 0.0%–3.1%).

Shapiro et al. NEJM 2010;362:2282-94 [42]: Botswana, 2006-2008, Mma Bana study. Mother CD4<200 on ART. Mothers with CD4>200 randomised to PI or NRTI triple regimens. There was good adherence and viral suppression (92-96%). Only 1/156 (0.6%) infants infected peripartum if mother was receiving ART and 5/553 (0.9%) infants infected when mothers with higher CD4 count received either PI or NRTI regimen.

16. Postnatal transmission. ART. CD4<350. 0.2 per month BF

There was considerable variation in the reported estimates of postnatal transmission through breastfeeding from African studies. These ranged from 0-0.42% per month of breastfeeding (*0%, 0.063%, 0.16%, 0.38%, 0.42%*). Very effective viral suppression was associated with very low postnatal transmission probabilities. Differences in transmission risk may reflect longer intervals between ART initiation and birth (+start of breastfeeding), and different rates of ARV adherence and associated viral suppression. WHO guidelines now recommend that eligible women should start ART as soon as possible in pregnancy which should achieve effective viral suppression well before birth. Postnatal transmission risk should therefore become less if this is achieved at population level.

The Working group agreed not to apply a simple median value (0.16%). Instead Spectrum should allocate a transmission risk of 0.2% per month of breastfeeding by women who are on lifelong ART. The group considered that it would be inconsistent, on therapeutic and programmatic grounds, for postnatal transmission probabilities in mothers eligible for, and

starting ART during pregnancy to be lower than transmission probabilities among mothers with CD4 counts greater than 350 cells/ml and starting on Option B also during pregnancy.

Kesho Bora Study Group. JAIDS 2010 Aug 15:54 (5):533-41 [27]: Burkina Faso, Kenya and South Africa, 2005-2006, 61% breastfeeding, observational cohort CD4 <200. Birth (in utero): 2/110, 1.8% (0.5-7.1). Cumulative 6 week (in utero + intrapartum + early post partum): 4/104, 3.7% (1.4-9.5). If uninfected at 6 weeks, +1.9% at 6 months = 5 months risk exposure from breastfeeding = 0.38%/month.

Tonwe-Gold B et al. PLoS.Med. 2007;4(8):e257 [26]: Côte d'Ivoire, 2003-2005; Primarily formula fed. HIV status determined at 4 weeks and 12 and 15 months. Among infants born to women with CD4<350 receiving maternal ART and infants receiving sdNVP and AZT, 4week transmission was 1.0% (95% CI 0.0%–3.1%). There was one infection among 52 infants (1.9%) who were uninfected at 4 weeks and breastfed for a median of 4.6 months = 0.42%/month.

Shapiro et al. NEJM 2010;362:2282-94 [42]: Botswana, 2006-2008, Mma Bana study, Mothers with CD4<200 on ART. Good adherence and viral suppression (94%). 1/156 infants infected in utero. No additional transmissions in these infants by 6 months even with breastfeeding.

Thomas T. PLoS Med 8(3): e1001015 [44]: Kenya, 2003-2009; KIBS study. A single-arm open label trial in which HIV-infected pregnant women took zidovudine, lamivudine, and either nevirapine or nelfinavir from 34–36 weeks' gestation to 6 months post partum. Among 487 live-born, singleton, or first-born infants, cumulative HIV-transmission probabilities at birth, 6 weeks, and 6, 12, and 24 mo were 2.5%, 4.2%, 5.0%, 5.7%, and 7.0%, respectively. Of the HIV-negative infants in study at 6 months, 87% (379/434) reportedly had stopped breastfeeding by 6 months, in accordance with study recommendations. Between 6 weeks and 6 months and 6 weeks and 12 months there was 0.8% and 1.5% additional transmission respectively. 0.8%/5 month breastfeeding risk exposure = 0.16% per month.

Peltier CA et al. AIDS 2009;23(18):2415-23 [43]: Rwanda, 2005-2007, Amata study. 532 women included in non-randomised, interventional study. Women with CD4<350 started on lifelong ART (D4T, 3TC and NVP) and mothers with higher CD4 (>350) given AZT, 3TC and Efavirenz. Among 227 breastfeeding women on either ART or triple ARV prophylaxis, 6 week transmission was 1.3% (95%CI, 0.4-4.1) at 6 weeks and 1.8% (95%CI, 0.7-4.8) at 9 months. Incremental transmission = 0.5% over 8 months breastfeeding risk exposure = 0.063% per month.

17. ART before pregnancy. Peripartum transmission 0.5%

There is very limited data available to directly inform this estimate. In the UK and Ireland, among infants born by caesarean section to HIV-infected mothers on triple ARVs from conception the peripartum transmission rate was 0.1%[41]. In Botswana and South Africa, programmes reported peripartum transmission rate of 0.3% and 0.7% among infants who were formula fed and whose mothers were on lifelong ART prior to conception [47 45]. In two randomized studies conducted in Botswana, Kenya, Burkina Faso and South Africa, among women who started ARV interventions during pregnancy but where there was good ARV adherence and effective viral suppression, peripartum transmission probabilities were 0.63% and 1.3% [22 42].

These probabilities are consistent with the strong relationship between low transmission probabilities in HIV-exposed infants and longer duration of ARV treatment in pregnancy, good adherence to ARVs and effective viral suppression[46].

The Working group agreed that, in the context of HIV-infected mothers being on lifelong ART initiated prior to conception, an estimate of 0.5% peripartum transmission would be consistent with published reports.

Townsend CL et al. AIDS 2008 May 11;22 (8):973-81[41]: UK/Ireland, 2000-2006, formula feeding, all CD4 counts. Most had C/S. On triple drugs at conception, 1/928, 0.1% IU+IP.

Botswana Ministry of Health Report. January 2011[47]: Botswana, programmatic data. 0.3% (N=900, non-breastfeeding). Report from the national program for Early Infant Diagnosis of HIV. 2010. Botswana, Ministry of Health, Department of HV/AIDS Prevention and Care.

Hoffman RM. JAIDS 2010 May;54:35-41[45]: South Africa, 2004-2008, 97 % formula fed. Observational study of infant infection status in 873 pregnant women in Johannesburg; 143 women became pregnant while receiving ART with 1 infant infection at 4-6 weeks = 0.7%.

Kesho Bora Study Group. Lancet Infect Dis 2011;11(3):171-80 [22]: Burkina Faso, Kenya and South Africa, 2005-2008. Randomised controlled study. Among infants breastfed by mothers receiving triple ARVs with effective viral suppression, indicated by a viral load <300 copies per ml at birth, transmission probabilities at birth and 6 weeks were 0% and 1.3% respectively.

Shapiro et al. NEJM 2010;362:2282-94 [42]: Botswana, 2006-2008, Mma Bana study, Mothers with CD4<200 on ART. Good adherence and viral suppression (94%). 1/156 (0.64%) infants infected in utero. No additional transmissions in these infants by 6 months.

18. ART before pregnancy. Postnatal transmission 0.16% per month BF

There is limited data in the peer-reviewed literature to directly inform this estimate. As with peripartum transmission, there is a relationship between the risk of postnatal transmission probabilities in HIV-exposed infants and maternal CD4 count and systemic viral load.

The rationale for attributing a different postnatal transmission rate to mothers who have been on ART prior to conception vs. mothers who start ART during pregnancy is that they would have effective viral suppression at the time of birth and during the first 2-3 months of breastfeeding. After 2-3 months of age, it would be reasonable to assume that the protection afforded by ART would be similar whether a mother had been on ART before conception or started during pregnancy. Furthermore, WHO guidelines recommend that all breastfeeding HIV-exposed infants receive at least 6 weeks of postnatal nevirapine, regardless of maternal CD4 count and ARV intervention. Hence it is likely that starting ART before pregnancy will have lesser benefit for postnatal transmission compared to peripartum transmission.

In considering the potential benefit of ART started prior to conception, data from studies that have achieved effective viral suppression in mothers provide a range of estimates of potential effect.

- In Botswana, no postnatal transmissions occurred in a randomized trial among breastfeeding HIV-infected mothers who received one of two triple ARV regimens and viral suppression was achieved in more than 94% mothers.[42]
- In Rwanda, there were 0.5% transmission over 8 months breastfeeding risk exposure (= 0.063% per month) among mothers who with CD4<350 started on lifelong ART (D4T, 3TC and NVP) and mothers with higher CD4 (>350) given AZT, 3TC and efavirenz.[43]
- In Burkina Faso, Kenya and South Africa, when there was effective viral suppression among mothers who received triple ARVs as prophylaxis, postnatal transmission risk at 6 months was 0.9%.[22]
- In Malawi, in mothers who started triple ARVs at birth to prevent postnatal transmission, transmission probabilities at 2.5, 4 and 6.5 months among infants who were HIV uninfected at 2 weeks were 1.7%, 1.9% and 2.9% respectively. If infants who were randomised to receive nevirapine, transmission probabilities at the same time points were 0.5%, 0.5% and 1.7% respectively. These data suggest that the difference between efficacy of regimens was

due to transmissions that occurred in the first 2.5 months of life because no additional difference was seen at later time points. The transmissions that might therefore be prevented by earlier initiation of ART would be about 1.7-0.5 = 1.2%. Based on the monthly transmission probabilities derived from this study and applied to a 12 month breastfeeding period namely 0.53%/month breastfeeding x 12 = 6.36% (see note 14 above), 1.2% might be considered as 20% postnatal transmission (*1.2/6.36=18.9%*) that could be additionally prevented by earlier ART initiation.[38]

In extrapolating these estimates for the purposes of Spectrum, the benefit of starting ART prior to pregnancy would be in the assurance that effective viral suppression is present from the time of birth of the infant and during the first 2-3 months of breastfeeding.

In light of these data, the Working group agreed that, in the context of HIV-infected mothers being on lifelong ART initiated prior to conception, a postnatal transmission rate of 0.16% transmission per month of breastfeeding, namely an additional 20% reduced transmission (vs. 0.2% per month), would be consistent with known transmission risk factors and the limited published reports.

Kesho Bora Study Group. Lancet Infect Dis 2011;11(3):171-80[22]: Burkina Faso, Kenya and South Africa, 2005-2008. Randomised controlled study. Among infants breastfed by mothers receiving triple ARVs with effective viral suppression, indicated by a viral load <300 copies per ml at birth, transmission probabilities at 6 weeks, 6 and 12 months were 1.3%, 2.2% and 2.7% respectively. In this population, additional postnatal transmission risk at 6 months was 0.9%. This represents 5 months breastfeeding exposure risk = 0.18% per month of breastfeeding.

Shapiro et al. NEJM 2010;362:2282-94 [42]: Botswana, 2006-2008, Mma Bana study; mothers with CD4<200 on ART. Good adherence and viral suppression (94%). 1/156 infants infected in utero. No additional transmissions in these infants by 6 months even with breastfeeding.

Thomas T. PLoS Med 8(3): e1001015 [44]: Kenya, 2003-2009; KIBS study. A single-arm open label trial in which HIV-infected pregnant women took zidovudine, lamivudine, and either nevirapine or nelfinavir from 34–36 weeks' gestation to 6 months post partum. Among 487 live-born, singleton, or first-born infants, between 6 weeks and 6 months and 6 weeks and 12 months there was 0.8% and 1.5% additional transmission respectively. 0.8%/5 month breastfeeding risk exposure = 0.16% per month.

Peltier CA et al. AIDS 2009;23(18):2415-23 [43]: Rwanda, 2005-2007, Amata study. 532 women included in non-randomised, interventional study. Women with CD4<350 started on lifelong ART (D4T, 3TC and NVP) and mothers with higher CD4 (>350) given AZT, 3TC and Efavirenz. Among 227 breastfeeding women on either ART or triple ARV prophylaxis, 6 week transmission was 1.3% (95%CI, 0.4-4.1) at 6 weeks and 1.8% (95%CI, 0.7-4.8) at 9 months. Incremental transmission = 0.5% over 8 months breastfeeding risk exposure = 0.063% per month.

Chasela CS et al. NEJM 2010;362:2271-81 [38]: Malawi, 2006-2008, BAN study; Maternal **CD4 >250**, in infants who were uninfected at 2 weeks and mothers received triple ARV starting after birth, transmission at 28 weeks was 2.9%. See table below.

Estimates of the cumulative risk of HIV-1 infection among infants who were HIV-1–negative at 2 weeks

Transmission at:	Maternal triple ARV regimen Probability of end point	Infants nevirapine Probability of end point	Control Probability of end point
42 days	*0.9%*	*0.1%*	*2.0%*
84 days (2.5 mo)	*1.7%*	*0.5%*	*3.6%*
126 days (4 mo)	*1.9%*	*0.5%*	*4.4%*
203 days (6.5 mo)	*2.9%*	*1.7%*	*5.7%*

REFERENCES

1. Rollins N, Little K, Mzolo S, et al. Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening. *AIDS* 2007;21(10):1341-7.
2. Birkhead GS, Pulver WP, Warren BL, et al. Acquiring human immunodeficiency virus during pregnancy and mother-to-child transmission in New York: 2002-2006. *Obstet Gynecol* 2010;115(6):1247-55.
3. Roongpisuthipong A, Siriwasin W, Simonds RJ, et al. HIV seroconversion during pregnancy and risk for mother-to-infant transmission. *J Acquir Immune Defic Syndr* 2001;26(4):348-51.
4. Tovo PA, Palomba E, Gabiano C, et al. Human immunodeficiency virus type 1 (HIV-1) seroconversion during pregnancy does not increase the risk of perinatal transmission. *Br J Obstet Gynaecol* 1991;98(9):940-2.
5. Iliff PJ, Piwoz EG, Tavengwa NV, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS* 2005;19(7):699-708.
6. Van de Perre P, Simonon A, Msellati P, et al. Postnatal transmission of human immunodeficiency virus type 1 from mother to infant. A prospective cohort study in Kigali, Rwanda. *N Engl J Med* 1991;325(9):593-8.
7. Dunn DT, Newell ML, Ades AE, et al. Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet* 1992;340(8819):585-8.
8. Palasanthiran P, Ziegler JB, Stewart GJ, et al. Breast-feeding during primary maternal human immunodeficiency virus infection and risk of transmission from mother to infant. *J Infect Dis* 1993;167(2):441-4.
9. Ekpini ER, Wiktor SZ, Satten GA, et al. Late postnatal mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire. *Lancet* 1997;349(9058):1054-9.
10. Liang K, Gui X, Zhang YZ, et al. A case series of 104 women infected with HIV-1 via blood transfusion postnatally: high rate of HIV-1 transmission to infants through breast-feeding. *J Infect Dis* 2009;200(5):682-6.
11. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ* 2010;341:c6580.
12. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2002;359(9313):1178-86.
13. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994;331(18):1173-80.
14. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 1999;353(9155):773-80.
15. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet* 1999;353(9155):781-5.
16. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. DIminution de la Transmission Mere-Enfant. *Lancet* 1999;353(9155):786-92.
17. Leroy V, Sakarovitch C, Cortina-Borja M, et al. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS* 2005;19(16):1865-75.

18. Mayaux MJ, Blanche S, Rouzioux C, et al. Maternal factors associated with perinatal HIV-1 transmission: the French Cohort Study: 7 years of follow-up observation. The French Pediatric HIV Infection Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;8(2):188-94.
19. Coutsoudis A, Dabis F, Fawzi W, et al. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis* 2004;189(12):2154-66.
20. Coovadia HM, Rollins NC, Bland RM, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet* 2007;369(9567):1107-16.
21. Kuhn L, Aldrovandi GM, Sinkala M, et al. Potential impact of new WHO criteria for antiretroviral treatment for prevention of mother-to- child HIV transmission. *AIDS* 2010;24(9):1374-7.
22. Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis* 2011;11(3):171-80.
23. Mofenson Lea. Infant extended antiretroviral (ARV) prophylaxis is effective in preventing postnatal mother-to-child HIV transmission (MTCT) at all maternal CD4 counts. 5th IAS Conference. Cape Town, South Africa. July 2009.
24. Becquet R, Ekouevi DK, Arrive E, et al. Universal antiretroviral therapy for pregnant and breast-feeding HIV-1-infected women: towards the elimination of mother-to-child transmission of HIV-1 in resource-limited settings. *Clin Infect Dis* 2009;49(12):1936-45.
25. Becquet R, Bland R, Leroy V, et al. Duration, pattern of breastfeeding and postnatal transmission of HIV: pooled analysis of individual data from West and South African cohorts. *PLoS One* 2009;4(10):e7397.
26. Tonwe-Gold B, Ekouevi DK, Viho I, et al. Antiretroviral treatment and prevention of peripartum and postnatal HIV transmission in West Africa: evaluation of a two-tiered approach. *PLoS Med* 2007;4(8):e257.
27. Kesho Bora Study Group. Eighteen-month follow-up of HIV-1-infected mothers and their children enrolled in the Kesho Bora study observational cohorts. *J Acquir Immune Defic Syndr* 2010;54(5):533-41.
28. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999;354(9181):795-802.
29. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003;362(9387):859-68.
30. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003;187(5):725-35.
31. Bedri A, Gudetta B, Isehak A, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet* 2008;372(9635):300-13.
32. Dabis F, Bequet L, Ekouevi DK, et al. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *AIDS* 2005;19(3):309-18.
33. Lallemant M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004;351(3):217-28.

34. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS* 2006;20(9):1281-8.
35. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med* 2008;359(2):119-29.
36. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA* 2006;296(7):794-805.
37. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr* 2008;48(3):315-23.
38. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med* 2010;362(24):2271-81.
39. Coovadia H and others. HPTN 046: Efficacy of Extended Daily Infant NVP through Age 6 Months Compared to 6 Weeks for Postnatal PMTCT of HIV through Breastfeeding. 18th Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA 2 March 2011.
40. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis* 2010;50(4):585-96.
41. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS* 2008;22(8):973-81.
42. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med* 2010;362(24):2282-94.
43. Peltier CA, Ndayisaba GF, Lepage P, et al. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. *AIDS* 2009;23(18):2415-23.
44. Thomas TK, Masaba R, Borkowf CB, et al. Triple-Antiretroviral Prophylaxis to Prevent Mother-To-Child HIV Transmission through Breastfeeding-The Kisumu Breastfeeding Study, Kenya: A Clinical Trial. *PLoS Med* 2011;8(3):e1001015.
45. Hoffman RM, Black V, Technau K, et al. Effects of highly active antiretroviral therapy duration and regimen on risk for mother-to-child transmission of HIV in Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2010;54(1):35-41.
46. Sturt AS, Dokubo EK, Sint TT. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. *Cochrane Database Syst Rev* 2010(3):CD008440.
47. Botswana Ministry of Health. Report from the national program for Early Infant Diagnosis of HIV. Gaborone, Botswana: Ministry of Health, Department of HIV/AIDS Prevention and Care, 2011.