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Estimates of peripartum and postnatal mother-to-child transmission probabilities of HIV for use in Spectrum and other population-based models

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ABSTRACT

Background The Global Plan Towards the Elimination of New HIV Infections among Children and Keeping Their Mothers Alive aims to reduce by 2015 the number of new infections in children, in 22 priority countries, by at least 90% from 2009 levels. Mathematical models, such as Spectrum, are used to estimate national and global trends of the number of infants infected through mother-to-child transmission (MTCT). However, other modelling exercises have also examined MTCT under different settings. MTCT probabilities applied in models to populations that are assumed to receive antiretroviral interventions need to reflect the most current risk estimates.

Methods The UNAIDS Reference Group on Estimates, Modelling and Projections held a consultation to review data on MTCT probabilities. Published literature, recent conferences and data from personal communications with principle investigators were reviewed. Based on available data, peripartum and postnatal transmission probabilities were estimated for different antiretroviral drug regimens and maternal CD4 levels including for women with incident infection.

Results Incident infections occurring during pregnancy are estimated to be associated with a 30% probability of MTCT; incident infections during breast feeding lead to a 28% probability of postnatal MTCT. The 2010 WHO recommended regimens (Options A or B) are estimated to be associated with a 2% peripartum transmission probability and 0.2% transmission probability per month of breast feeding. Peripartum and postnatal transmission probabilities were lowest for women who were taking antiretroviral therapy before the pregnancy namely 0.5% peripartum and 0.16% per month of breast feeding, respectively.

Discussion These updated probabilities of HIV transmission (applied to Spectrum in April 2011) will be used to estimate new child HIV infections and track progress towards the 2015 targets of the Global Plan.

INTRODUCTION

Modelling approaches are routinely used to estimate national and global trends of the number of infants infected through mother-to-child transmission of HIV (MTCT).[1 2] Such models depend on input data from individual countries such as the number of HIV-positive women receiving antiretroviral drug (ARV) interventions.[3 4] Models apply HIV transmission probabilities (both peripartum and postnatal) by ARV intervention and by timing of maternal infection (either incident or prevalent) to derive population-based HIV infection rates.

WHO guidelines for preventing MTCT are updated to reflect the most current research evidence and recommend the most effective and safe interventions. The 2010 WHO guidelines for ARVs for treating pregnant women and preventing HIV infection in infants introduced several important revisions and, for the first time, recommended ARVs to prevent postnatal transmission of HIV through breast feeding.[5] These guidelines presented two main ARV regimens, namely Options A and B, which both include starting HIV-infected women with CD4 counts less than 350 cells/ml on lifelong antiretroviral therapy (ART). In Option A, women not eligible for ART should receive daily zidovudine (AZT) from the first trimester until delivery and, in breastfeeding populations, HIV-exposed infants should receive daily nevirapine until 1 week after all breast feeding. In Option B, women not eligible for ART should receive daily triple ARVs from the first trimester until delivery and, in breastfeeding populations, continue with these ARVs until 1 week after all breast feeding. In non-breastfeeding populations, both options recommend that HIV-exposed infants receive ARV prophylaxis for the first 6 weeks post partum.

The Global Plan Towards the Elimination of New HIV Infections among Children and Keeping Their Mothers Alive has set a target that by 2015 the number of new HIV infections in children will be reduced, in each of 22 priority countries,[i] by at least 90% from 2009 levels.[6] The Plan has also set a target of reducing HIV-associated pregnancy-related deaths by 50% in the same countries. Progress towards these targets is modelled using the AIDS Impact Module (AIM) within the Spectrum demographic modelling package.

In order to track progress towards the targets of the Global Plan, MTCT probabilities applied to populations in models need to reflect the most current transmission risk estimates.[4] In particular, models need to include the probability of transmission in children due to new incident infection among pregnant and lactating women, and reflect the potential impact of ARV interventions that reduce transmission through breast feeding. Here we

[i]Angola, Botswana, Burundi, Cameroon, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

present the evidence for the revised transmission probabilities applied in Spectrum since April 2011.

How Spectrum uses the transmission probabilities

The transmission probabilities described in this paper were specifically intended for use in the Spectrum computer package or other similar models that estimate the impact of prevention of mother-to-child transmission of HIV (PMTCT) programmes. A detailed description of Spectrum is available elsewhere.[4] The peripartum transmission probabilities are applied to all deliveries among HIV-positive women to estimate the number of peripartum infections. The postnatal transmission probabilities are applied to the estimated proportion of HIV-negative children who are breast feeding among HIV-positive mothers. Postnatal transmission is calculated based on the per cent of women still breast feeding by months since birth. A monthly transmission probability is applied for each month that the child is breast feeding (see figure 1).

METHODS

The probabilities of peripartum and postnatal MTCT of HIV according to ARV regimen and maternal CD4 count among women with prevalent infection and among women with incident infection were reviewed for a meeting that aimed to update modelling approaches and assumptions used in Spectrum that was held in Washington, DC, September 2010. A process to agree on estimates of transmission probability was agreed by the authors following a critical review of available evidence. While the initial meeting was held in September 2010, data from studies reported in peer-reviewed journals from 1990 until the beginning of 2012 were considered for inclusion.

Studies included in the analysis

Data used for this analysis included published literature, conference presentations and data from personal communication with researchers when data were not otherwise available. The authors reviewed these data for quality, internal consistency and relevance. Data from randomised studies were prioritised but cohort and observational data were also included providing the reports indicated rigorous study methods, appropriate sample sizes and provided direct transmission estimates from relevant study populations. Details of these reports are summarised in an annotated bibliography (see working paper in online supplementary appendix).

Definitions and assumptions underlying estimates of HIV transmission probabilities

Peripartum HIV transmission reflects combined in utero and intrapartum transmission and is measured by HIV status of infants at 4–6 weeks of age. It assumes no additional early transmission due to breast feeding. In non-breastfed infants, HIV status of infants at 4–6 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 breast feeding.

Postnatal HIV transmission reflects infections in infants or children who were HIV uninfected through pregnancy and delivery (identified through a negative HIV test at 4–6 weeks) and who subsequently become HIV-infected while breast feeding.

Postnatal transmission rates captured for each study were either those directly reported by investigators, even if the age at which peripartum transmission was measured differed between studies namely 2, 4, 6 or 8 weeks post partum, or were calculated from data included in the reports. Some investigators reported point or cumulative transmission at birth, 6 weeks and other postnatal time points such as 3, 6, 12 and 18 months. In these situations, HIV transmission due to breast feeding was estimated by subtracting HIV infections (or transmission rates) among 6-week-old HIV-exposed infants from HIV infections (or transmission rates) among HIV-exposed breastfeeding infants identified any time thereafter.

Depending on data provided, monthly postnatal transmission probabilities were calculated by dividing the cumulative transmission per cent measured over a particular time interval by the number of months in that time period minus 4 weeks. Four weeks was deducted from the breastfeeding exposure period as HIV DNA laboratory assays only reliably detect infections that occur up to about 4 weeks prior to measurement. For example, if transmission was measured at 6 months, then the breastfeeding exposure period was deemed to be 1 month less, or 5 months. If the transmission rates at 6 weeks and 6 months were 5% and 8.5%, respectively, then 3.5% HIV transmission would be attributed to 5 months of breast feeding, or 0.7% per month of breast feeding.

Alternatively, if studies reported the median breastfeeding period as less than the time at which HIV status was determined, then the cumulative transmission per cent by the time of measurement was divided by the median duration of breast feeding. For example, if postnatal transmission was estimated to be 9% at 12 months with a median breastfeeding period of 7 months, then the monthly transmission probability

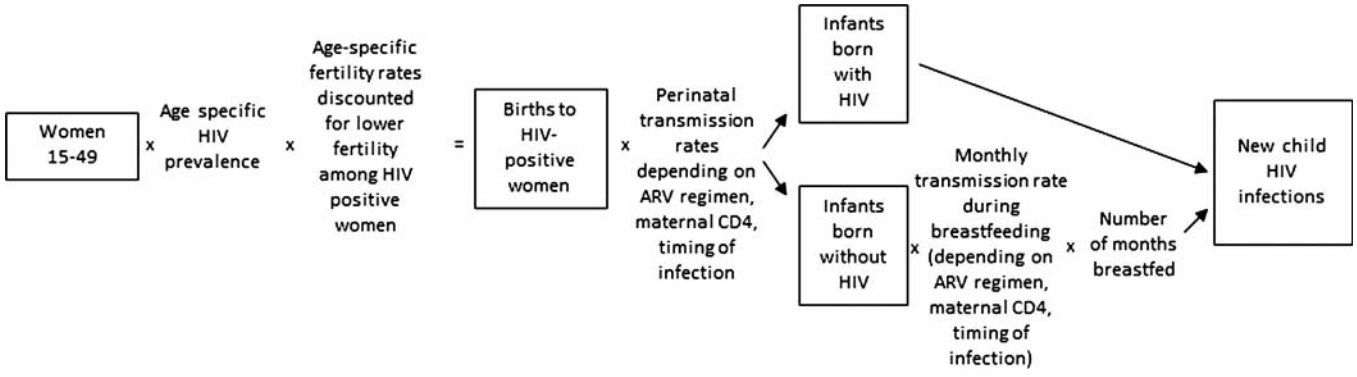

Figure 1 Calculating new HIV infections among children in Spectrum.

associated with breast feeding would be 9/7=1.29% per month of breast feeding.

This simple, and easily applied, calculation does not account for the conditional probability of postnatal infection, for example, the conditional probability that the child is not infected in the previous month or at birth, which will have a significant impact when multiplied over several months of exposure or to large probabilities. Spectrum currently only includes two decimal spaces of accuracy for the monthly transmission probabilities. Thus, a more accurate calculation (see example in footnote[ii]) would have no impact on the overall rates in the current model.

Incident infection refers to newly acquired infections in pregnant or lactating women. Methods used for identifying these women were different between studies and the investigators' approach for inclusion of this population was accepted. Incident infection was usually identified through seroconversion of women who previously tested negative for HIV. Transmission probabilities were not disaggregated by maternal CD4 count as, although women with incident infection have high viral load similar to women with longstanding HIV infection, their CD4 counts are not depleted in the early stages of infection.

We did not estimate a monthly transmission probability for lactating women with incident HIV infection as the reported high risks of transmission, associated with high viral load in mothers during primary viraemia, may only be present for 1–2 months. It was considered inappropriate to apply an average monthly probability over a duration of breast feeding, whether long or short, within a model.

ARV regimens were defined according to WHO recommendations that were valid at the time of respective studies. 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 breast feeding 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 h). While not included in WHO recommendations at that time,[7] this practice was reported in some studies.

Any breast feeding includes exclusive, predominant and partial breast feeding (mixed breast feeding=predominant and partial breast feeding). No attempt to further disaggregate was made given limitations in the data.

Estimating HIV transmission probabilities

The median peripartum and postnatal transmission probability and ranges for each ARV regimen and CD4 count were determined from reported data. Exceptions to this approach are separately presented and justified. In some instances, the median value was overruled based on other considerations and in these situations the rationale is outlined. The transmission probabilities were not weighted by the size of the study as each study had its own limitations.

When reports presented transmission probabilities separately for mothers with CD4 counts 350–500 cells/ml and >500 cells /ml, these probabilities were averaged and included as the transmission probability for women with CD4 counts >350 cells/ml. This concept was applied similarly in some instances for other grouped ranges of CD4 counts (see online supplementary table 1).

For the purposes of Spectrum it was not necessary to calculate the transmission probabilities for different CD4 distributions for single dose nevirapine (sdNVP) and WHO 2006 dual ARV regimens as these interventions will only be applied to historical populations without reference to CD4 counts when disaggregated data by CD4 distributions were not generally available. Options A and B were only recommended for women with CD4 counts of 350 or higher and thus probabilities for those scenarios were estimated. Although not recommended by WHO for women with CD4 counts below 350 cells/ml, a transmission probability is included for Option A in this population because (i) those data were available from some reports and (ii) some countries were providing Option A to this population before revisions of national guidelines (ie, criteria for ART from a CD4 count of <200 to <350) and (iii) in settings where CD4 testing is not routinely available, some women with lower CD4 counts may only receive this intervention.

Monthly postnatal transmission probabilities were not estimated for a population where CD4 count is 'not specified' (as presented in the first column of table 1 for Peripartum transmission). For modelling postnatal transmission in populations where data on maternal CD4 counts are not known, such as historical cohorts, then assumptions can be made on the distribution of CD4 counts in these populations and an average transmission probability is secondarily estimated and attributed. Since 2011 Spectrum assumes a CD4 distribution among pregnant women to determine which transmission probability will be applied during breast feeding.

Separate monthly postnatal transmission probabilities were not estimated for populations receiving sdNVP or WHO 2006 dual prophylaxis as it was assumed that, although both regimens provide an ARV to infants postnatally, neither is considered to have substantial impact on postnatal transmission through breast feeding.

RESULTS

Table 1 presents the estimated transmission probabilities by ARV regimen and CD4 level. Details of transmission probabilities reported in each study are presented in the online supplementary table 1. An annotated bibliography of studies is included in the working paper (online supplementary appendix).

Transmission probabilities due to incident HIV infection

Four reports provided data on peripartum transmission[8–11] and six reports on postnatal transmission[12–17] among women who had become infected during pregnancy or lactation. The reported transmission probability for peripartum transmission ranged from 13% to 30%. The high value of the peripartum range, that is, 30% was selected in light of other reports that documented high odds ratios for infant transmission associated with maternal incident infection in pregnancy but did not provide transmission probabilities. For postnatal transmission, the range was 14.3%–56% with a median of 28%. These are comparable with transmission probabilities to infants born to mothers with CD4<200 cells/ml, not receiving any treatment, and who have high viral load.

[ii]An example of calculating the conditional probability: if the 4–6 week risk is 5% and the 6-month total risk is 10% then the risk of postnatal infection is 10% minus 5% divided by those infants who were negative at the start of the time period so (10–5)/(100–5). Convert the cumulative risk into a monthly rate [–ln(1-P))]/t where P is the conditional probability and t is the number of months of exposure. Calculate back to a monthly probability 1–e^(–r) where r is the monthly rate calculated in the first step.

Table 1 Summary of transmission probabilities by antiretroviral regimen and maternal CD4 count

	Peripartum transmission				Postnatal transmission per month of any BF* (except incident infection)	
Regimen	**CD4 count not specified**	**CD4<200**	**CD4 200–350**	**CD4 350+**	**CD4<350**	**CD4>350**
Incident infections *(range of reported transmission probabilities)*	30% *(13%–30%)*[6–9]				28% *(14.3%–56%)*[10–15]	
No prophylaxis *(range of reported transmission probabilities)*	22% *(15%–25%)*[16–20]	37% *(22%–54%)*[18 21 22]	27% *(13.1%–32.6%)*[18 21]	15% *(9.7%–20.2%)*[18 21 22]	1.57%/m BF[23–25]	0.51%/m BF [23–25 29 30]
sdNVP *(range of reported transmission probabilities)*	12% *(9.4%–12.1%)*[31–34]				1.57%/m BF[23–25]	0.51%/m BF[23–25 29 30]
WHO 2006 dual prophylaxis *(range of reported transmission probabilities)*	4% *(2.3%–5.3%)*[29 30 35–37]				1.57%/m BF[23–25]	0.51%/m BF[23–25 29 30]
Option A‡			*4%† As WHO 2006*	2%[24 29 36]		0.2%/m BF[39 40]
Option B§				2% *(0.9%–2.9%)*[24 41–44]		0.2%/m BF[24 39 43–45]
ART *(range of reported transmission probabilities)*		2%[24 29 30 41–43]			0.2%/m BF[29 30 43–45]	
ART (before pregnancy)		0.5%[24 42 46 47 48]			0.16%/m BF[24 39 43 44]	

Shading indicates transmission probabilities that are not estimated for a particular regimen either because the regimen is not recommended for women with a particular CD4 count, for example, Option A or B for women with CD4 counts less than 350 cells/ml, or because transmission data were not available for a regimen by CD4 count, for example, sdNVP in women with CD4 350–500 cells/ml.

*For the transmission probabilities associated with breast feeding the values are given to two decimal places since rounding these values up or down would result in significantly greater or lesser transmission rates when multiplied according to the duration of breast feeding.

†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.

‡*In Option A*, HIV-positive pregnant women who are eligible for lifelong ART should be started on treatment in the first trimester of pregnancy. HIV-positive pregnant women who are not eligible for ART should receive daily AZT from 14 weeks gestation until delivery, single dose nevirapine during labour and AZT+3TC during labour and for 7 days post partum. HIV-exposed infants would receive AZT or NVP until 6 weeks of age and if breast feeding then NVP would continue until 1 week after all breast feeding has stopped.

§*In Option B*, HIV-positive pregnant women who are eligible for lifelong ART should be started on treatment in the first trimester of pregnancy. HIV-positive pregnant women who are not eligible for lifelong ART should receive one of four combinations of ARVs during pregnancy throughout the breastfeeding period and 1 week after. Exposed infants would receive either AZT or NVP for 1 week.

3TC, lamivudine; ART, antiretroviral therapy; ARV, antiretroviral drug; AZT, zidovudine; BF, breastfeeding; sdNVP, single dose nevirapine.

Transmission probabilities in the context of no ARV prophylaxis

Five studies reported peripartum transmission probabilities without disaggregating by CD4 count.[18–22] While there were significant geographical variations, there was no clear relationship between transmission rates and either breastfeeding or non-breastfeeding populations. The range of transmission probabilities was 15.3%–25.5% with a median of 22%. Four reports provided data on peripartum transmission among mothers with CD4 counts <200 cells/ml in east, west and southern Africa and also Thailand and France[20 23 24] (Humphrey J, personal communication, 2010). In these populations, the range of transmission probability was 22.4%–54.2% with a median of 37%. Among women with CD4 counts 200–350 cells/ml, the range of transmission probabilities was 13.1–32.6% with a median of 27%[20 23] (Humphrey J, personal communication, 2010). Limited data were available from four reports to inform transmission probabilities in women with CD4 counts >350 cells/ml[20 23 24] (Humphrey J, personal communication, 2010). In one study, an average transmission probability was calculated for women with CD4 counts >350 cells/ml at each site as described in the Methods section.[23] The range of transmission probabilities was 9.7%–20.2% with a median value of 15%.

With respect to postnatal transmission through breast feeding among mothers with CD4 count <350[25–27] (Humphrey J, personal communication, 2010). (Becquet R, personal communication, 2010), when maternal CD4 count is not considered, the monthly postnatal transmission probability is about 0.8% per month of breast feeding[28] or 9.2 infections per 100 child years.[29] Some studies only reported a three to ninefold increased risk as an OR or HR of transmission among mothers with lower CD4 count compared with those with higher CD4 counts.[30] The range of monthly transmission probabilities in mothers with CD4 counts <350 cells/ml was 0.84%–2.5% per month of breast feeding and the median value was 1.57% per month of breast feeding. Seven reports provided postnatal transmission data among mothers with CD4 counts equal to or more than 350 cells/ml[25–27 31 32] (R Becquet, Personal communication, 2010) (Humphrey J, personal communication, 2010). Transmission probabilities from the observational cohorts and the randomised control trial groups in the Kesho Bora study were not averaged as they were derived from distinct populations. The range of monthly transmission probabilities was 0.1%–0.96% per month of breast feeding with a median value of 0.51% per month of breast feeding.

Transmission probabilities in the context of single dose nevirapine

Peripartum transmission probabilities were noted in four reports with a range of 9.4%–12.1%.[33–36] The median value was 12%.

Transmission probabilities in the context of WHO 2006 dual prophylaxis

Peripartum transmission probabilities were noted in five reports with a range of 2.3%–5.3% and a median value of 4%.[31 32 37–39]

Transmission probabilities in the context of Option A regimen

No studies reported transmission probabilities when all components of the ARV interventions recommended in Option A were provided to the population for whom Option A is specifically recommended. Table 2 summarises the elements of Option A that are reported in each study.

Table 2 Elements of Option A regimen reported in each study

	Interventions offered in SWEN,[36] PEPI,[40] BANS[41] and HPTN 046[42]	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 breast feeding (6 weeks, 14 weeks or 6 months)	Nevirapine to infants until 1 month after end of all breast feeding

3TC, lamivudine; ARV, antiretroviral drug.

However, studies did provide data on individual components of Option A. In West Africa, among infants who were primarily given formula feeds and whose mothers had CD4 counts >350 and received AZT from either 28 or 32 weeks + lamivudine (3TC) and sdNVP at birth (infants also received sdNVP and AZT for 7 days), transmission at 4 weeks was 3.1%.[31] 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%.[26] In Thailand, among infants who 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 eight infections among 508 infants=1.6%.[38]

The peripartum transmission probability for Option A should be less than the probability associated with the WHO 2006 dual prophylaxis (4%), 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 and the extended postnatal ARV regimen (AZT or NVP for 6 weeks) to infants would provide additional protection. Hence, a peripartum transmission probability of 2% would be plausible and consistent with published data.

Four randomised studies reported the efficacy of nevirapine given to infants to reduce the risk of HIV transmission while breast feeding. Two of the studies provided only limited data.[36 40] The two other studies reported transmission rates from HIV-exposed, uninfected infants recruited and randomised postdelivery and who received nevirapine for up to 6 months while breast feeding.[41 42] A simple median value from these studies would be inappropriate as both studies, included mothers with CD4 counts 200–350. Considering the population for whom Option A is recommended (>350 cells/ml), an estimate of 0.2% per month of breast feeding is consistent with available data.

Transmission probabilities in the context of Option B regimen

As with Option A, no studies report transmission outcomes when all elements of Option B are implemented in the target population. For example, the Kesho Bora study provided the same ARV interventions but started only at 28 weeks and did not include 6 weeks extended postpartum ARVs to the infants. Several studies provide peripartum transmission probabilities associated with triple ARV prophylaxis in women who are not eligible for lifelong ART and are summarised in the online supplementary table 1.[26 43–46] The range of transmission probabilities was 0.9%–2.9%. A peripartum transmission probability of 2% would be consistent with an earlier initiation of ARVs combined with the postpartum infant intervention.

Three randomised trials and two non-randomised, intervention studies provided data on postpartum transmission.[26 41 45–47] Population characteristics were significantly different and monthly postnatal transmission probabilities were calculated based on data provided. Additional discussion of the studies, interventions implemented and reported transmission are included in the working paper (online supplementary appendix). The range of estimates of postnatal HIV transmission was 0.063%–0.53% per month of breast feeding. These may be even less if mothers with CD4>500 were included. For mothers with CD4 counts >350, an estimate of 0.2% per month of breast feeding would be consistent with published literature.

Transmission probabilities in the context of lifelong ART

Two reports from the 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 among women on ART to be around 1%.[43 44] These mothers generally had caesarean section and no infants were breast fed. ART was sometimes started prior to conception. African studies report a wider range of transmission probabilities (0.6%–3.7%).[26 31 2 45] When lifelong ART is started in pregnant women with CD4 counts less than 350 cells/ml then a peripartum transmission probability of 2% or less is expected.

Limited data were available on transmission risks when women were on ART prior to conception. In the UK and Ireland, among infants born by caesarean section to HIV-infected mothers on triple ARVs from conception the peripartum transmission probability was 0.1%.[44] In Botswana and South Africa, programmes reported peripartum transmission probabilities of 0.3% and 0.7% among infants who were not breast fed and whose mothers were on lifelong ART prior to conception.[48 49] In two randomised 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%.[26 45]

These probabilities are consistent with the strong relationship between low transmission and longer duration of ARV treatment in pregnancy, good adherence to ARVs and effective viral suppression.[50] In the context of HIV-infected mothers being on lifelong ART initiated prior to conception, peripartum transmission probability is estimated to be 0.5%.

There was considerable variation in the reported estimates of postnatal transmission from African studies in mothers on ART.[31 32 45–47] These ranged from 0% to 0.42% per month of breast feeding. Effective viral suppression was associated with low postnatal transmission. Differences in reported transmission probabilities may reflect longer intervals between ART initiation and birth or initiation of breast feeding, and different rates of ARV adherence and associated viral suppression. Although the median value of reported transmission probabilities was 0.16% per month of breast feeding, it would be inconsistent, on therapeutic and programmatic grounds, for postnatal transmission rates in mothers eligible for, and starting ART during pregnancy, to be lower than transmission rates

among mothers with CD4 counts greater than 350 cells/ml and starting similar ARV interventions that are recommended as part of Option B.

Data from four studies help to inform the postnatal transmission probability among women who are on ART prior to conception. In Botswana, no postnatal transmissions occurred in a randomised trial among breastfeeding HIV-infected mothers who received one of two triple ARV regimens and viral suppression was achieved in more than 94% mothers.[45] In Rwanda, there were 0.5% transmission over 8 months breastfeeding exposure (=0.063% per month) among mothers with CD4<350 cells/ml who started on lifelong ART (D4T, 3TC and NVP) and among mothers with higher CD4 (>350 cells/ml) who received AZT, 3TC and efavirenz.[46] In Burkina Faso, Kenya and South Africa, when there was effective viral suppression among mothers who received triple ARVs as prophylaxis, postnatal transmission probability at 6 months was 0.9%.[26] In Malawi, differences in early transmission probabilities in intervention arms suggest that a small percentage of postnatal transmission could be additionally prevented by earlier ART initiation.[41]

In the context of infants also receiving ARV prophylaxis for the first 6 weeks post partum, the postnatal transmission probability is likely to be similar in women who have been on ART from before conception and in women who start ART during pregnancy. In light of these data, the Working group estimated that in the context of HIV-infected mothers being on lifelong ART initiated prior to conception the postnatal transmission probability would be 0.16% transmission per month of breast feeding.

DISCUSSION

The above tables (and online supplementary table 1) summarise the HIV transmission probabilities applied in the AIM module of Spectrum since April 2011 (V.4.3). The source data and process by which the transmission probabilities were estimated, including the range of reported MTCT probabilities by timing of infection, maternal CD4 count and ARV intervention, are described and justified. Providing this information enables better understanding and interpretation of Spectrum modelled transmission rates and the uncertainties around those estimates.

For the first time, Spectrum includes monthly transmission probabilities for the breastfeeding period by ARV intervention and whether women have recently acquired HIV infection. The probabilities are frequently derived from randomised controlled trials and do not necessarily reflect the programmatic challenges of delivering interventions to populations in different geographic or cultural contexts. These factors will be included in modelled estimates as determinants of coverage rather than therapeutic effect of an ARV regimen in individual mothers and infants.

For incident infections occurring when mothers are breast feeding, an overall transmission rate is estimated rather than a monthly transmission probability. The available data tend not to support a relationship between duration of breast feeding and the risk of HIV transmission to the infant among women acquiring HIV during lactation.[17] The lack of relationship is plausible. It may be that an extraordinarily high maternal viral load during incident infection results in most infections occurring during the first weeks of breastfeeding exposure. This period of high risk may only be present for 1–2 months and then may decline to a low risk level. [17] It may therefore be inappropriate to apply an average monthly hazard risk over the duration of breast feeding in this case. In the largest of the studies, which also provided the greatest detail on timing of maternal seroconversion and infant infection, about 14% (95% CI 10.7% to 19.0%) of breastfeeding infants born to mothers who converted at any time in the postnatal period became infected within 6 months after maternal infection. In the subgroup of mothers who were known to have seroconverted within the preceding 90 days, 24% (95% CI 14.15% to 39.48%) of breastfeeding infants became infected within 6 months of maternal infection.[17]

There are several limitations to the estimates of transmission probabilities. Estimating the transmission probabilities when mothers and infants receive PMTCT Option A or B is complicated since no single study implemented all elements of either option. The transmission probabilities for these regimens are therefore extrapolated from findings reported in a number of studies. For interventions such as single dose nevirapine or WHO 2006 dual prophylaxis, transmission probabilities are not disaggregated by maternal CD4 count. It is assumed that these probabilities will only be applied to historical populations where CD4 counts were generally not available, and to regimens that are no longer recommended. A transmission probability is included however for the scenario where PMTCT Option A is provided to mothers who may have a CD4 count between 200 and 350 cells/ml. Even though this is not recommended, it was considered a likely scenario—especially in settings where CD4 counts are not routinely available (in 2010, only 30% pregnant HIV-infected women were assessed for ART eligibility by CD4 measurement [51])—and therefore reasonable to include. A simple method was used to derive the monthly postnatal transmission probabilities which did not take into account whether the child was infected in the previous month. For very small probabilities this will not have an important effect. However when multiplied over several months the result could be significant. Future versions of Spectrum should allow for more decimal places in the monthly transmission probability.

The transmission probability during breast feeding is assumed to be the same among women who are on lifelong ART prenatally or if started on ART during pregnancy. Compared with women who start ART during pregnancy, initiating HIV-infected women on ART before pregnancy is likely to have a greater impact on peripartum transmission than transmission through breast feeding. The postnatal viral load of HIV-infected lactating mothers is not likely to be significantly different whether ART is started before pregnancy or whether it is started within the first or second trimester. However, we are unaware of evidence to inform this transmission risk and additional data are needed to validate these assumptions.

As much as it is important to apply the most accurate transmission probabilities, the quality of input data from national programmes must be optimised for the model estimate to be valid. In particular, it is essential that good quality data differentiate the number of women receiving ARVs, either as prophylaxis or ART, and on the distribution of CD4 counts with different populations. This is needed especially in settings where Option A is implemented and where the transmission probability will be higher than expected if women with lower CD4 counts are not identified and managed appropriately. Where information on the duration of breast feeding among women in the PMTCT programme is not available, Spectrum applies breastfeeding rates and duration to mothers who are HIV-infected according to patterns reported in national Demographic and Health Surveys. This may not be an appropriate assumption for women in the PMTCT programme as

these women might preferentially reduce breastfeeding duration. This highlights the need for better data on infant feeding practices and adherence to recommended ARV interventions during this time period as well as during pregnancy. Last, in order to better estimate and interpret modelled outcomes, it is important for empiric transmission rates to be measured through population-based sampling.

The transmission probabilities presented in table 1 and the new infection rates that will be estimated from the models do not reflect all the considerations on which WHO clinical recommendations need to be based. For example, transmission probabilities do not reflect the full risk–benefit opportunities of mothers being able to breast feed their infant compared with using replacement feeds. The value of interventions to reduce HIV transmission can only be judged when understood in the context of overall maternal and child health and survival. For example, the value of an intervention may be greatly increased if it also improves maternal health and survival or reduces the risk of HIV transmission to another adult. The Spectrum model does not include any measure of viral resistance or drug safety and the consequences of these adverse events on population outcomes is not therefore evident. It is quite likely that new data on other benefits (and potential risks) of ARVs will become available in the next few years and will significantly influence PMTCT recommendations. It is less likely, however, that new ARV interventions with greater therapeutic efficacy to decrease HIV transmission will be developed in the near future.

The Global Plan Towards the Elimination of New HIV Infections among Children and Keeping Their Mothers Alive is the most ambitious initiative for improving the health and survival of HIV-infected mothers and their children in the history of the HIV epidemic.[6] It is therefore essential to be able to track, with confidence, progress towards the targets. Applying rigorously-derived transmission probabilities in models such as Spectrum facilitates interpretation of national and global estimates and trends of the number of children becoming infected with HIV, and will allow better comparisons with programmatic data or estimates from other models.

Key messages

- Publishing the mother-to-child transmission probabilities used in Spectrum allows other modellers to understand and compare their results with Spectrum results.
- Peripartum HIV transmission probabilities depend on maternal CD4, antiretroviral drug regimen, incident or prevalent maternal HIV infection and range from 37% to 0.5%.
- Postnatal HIV transmission probabilities in mothers with prevalent infection range from 1.57% to 0.16% per month of breast feeding. With incident infection, 28% transmission is expected irrespective of duration of breast feeding.

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Disclaimer N Rollins is a staff member of WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of WHO.

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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:

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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%*

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Web table: Summary of studies included in the analysis

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Peripartum transmission: Incident infections in pregnant women								Probability applied in Spectrum	30%			
Birkhead GS	Obstet Gynecol 2010 June;115 (6):1247-55	Cohort	New York	2002-2006	Infants of 41 women who acquired HIV during pregnancy	3102 infants		None	22% (9/41)			
Roongpisu-thipong A	JAIDS 2001 Apr 1;26 (4):348-51	Prospective	Bangkok, Thailand	1992-1994	Infants of 16 women seroconverted during pregnancy	All		None	13.3% (2/15)			
Tovo P-A	Brit J Obstet Gynecol 1991 Sept;98:940-2	Case report	Italy	1980's	Infants of 10 women who seroconverted during pregnancy	All		None	20% (2/10)			
Rollins N	AIDS 2007, 21:1341–1347	Surveillance	South Africa	2004-2005	All infants attending immunisation clinics were tested and information collected from mothers. 172 mothers reported themselves as HIV uninfected but infants were antibody positive	Some	Some	None	30.5% [24.0–37.6]			
Postnatal transmission: Incident infection in breastfeeding mothers								Probability applied in Spectrum	28%			
Van de Perre P	NEJM 1991;325:593-8	Cohort analysis	Kigali, Rwanda	1988	Seronegative women followed prospectively of whom 16 seroconverted while breastfeeding		All	None	56.3% (9/16)			

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Dunn DT	Lancet 1992;340:585-8	Meta-analysis	Africa and Australia	late 1980s and early 1990s	42 mothers infected postpartum		All	None	28.6% (12/42) [16-42%]			
Palasanthiran P	J Infect Dis 1993;167:441-4	Retrospective case studies	Australia	1980s	11 mothers infected postnatally by blood transfusion, one via needles		All	None	27.3% (3/11) [6-61%]			
Ekpini ER	Lancet 1997. Apr 12;349:1054-9	Prospective	Cote d'Ivoire,	1990-94	12 mothers infected postnatally by HIV-1 (7 seroconverted from HIV-2 positive to dual positive)		All	None	16.7% (2/12)			
Liang K	J Infect Dis 2009; 200:682-6	Retrospective case studies	China	2007	Mothers infected postnatally by blood transfusion		All	None	35.8% (38/106)			
Humphrey J	BMJ 2010;341:c6580	Vitamin A intervention cohort	Zimbabwe	1997-2001	334 mothers seroconverted during the breastfeeding period		All	None	14.3% (95% CI 10.7-19.0)			
Peripartum transmission: No prophylaxis peripartum								Probability applied in Spectrum	22%	37%	27%	15%
Petra Study Team	Lancet 2002; 359:1178-86	Randomised Controlled Trial	Tanzania, South Africa, and Uganda	1996-2000	377 HIV-1 infected women attending large public (and one missionary) hospitals		All	Placebo	15.30%			
Wiktor SZ	Lancet 1999; 353:781-5	Randomised Controlled Trial	Cote d'Ivoire	1996-98	140 women HIV-1 infected women attending public ANC in Abidjan		All	Placebo	21.7% (14.0-28.8%) 25/119			

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Dabis F	Lancet 1999; 353:786-92	Randomised Controlled Trial	Cote d'Ivoire, Burkina Faso	1995-98	217 women attending public clinics in Abidjan and Bobo-Dioulasso		All	Placebo	21.8% (15.9-27.6%) 42/145			
Connor EM	N Engl J Med 1994;331:1173-80	Randomised Controlled Trial	US and France	1991-93	183 women in the placebo group with cd4 >200 cells/ml	All		Placebo	25.50%			
Shaffer N	Lancet 1999; 353:773-80	Randomised Controlled Trial	Thailand	1996-97	199 women from two Bangkok hospitals	All		Placebo	18.9% (13-24%) (37/198)	37.5% (n=24)	18.3% (n=104)	
Mayaux MJ	JAIDS 1995 Feb 1;8:188-94	Cohort study	France	1986-1994	848 women on no antiretroviral drugs, most formula feeding but some breastfeeding	98%	2%	None		43%		
Humphrey J	Personal communication. 2010	Randomised Controlled Trial	Zimbabwe	1998-2002	Women enrolled in a postpartum vitamin A trial		All	None		22.4% (123/549)	13.1% (117/891)	
Leroy V	AIDS 2005, vol 19(16); 1865-75	Meta analysis	South Africa N=500	1995-2000	Women attending public hospitals		49-52%	None		36.2% (22-51%)		350-500 27.3% (19-36)
			East Africa N=153		Women attending public hospitals in Dar es Salaam and Kampala		50-74%	None		36.4% (17-59)		30.3% (16-49)
			West Africa N=303		Women attending ANC in Abidjan and Bobo-Dioulasso		92-94%	None		54.2% (33-74%)		30.3% (16-49)

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Postnatal transmission: No prophylaxis postpartum								Probability applied in Spectrum		1.57% per month		0.51% per month
Kuhn L et al.	AIDS 2010 Jun 1;24 (9):1374-7		Lusaka, Zambia N=544		HIV-infected women recruited during pregnancy followed for 24 months			None		<350 1.31% per month		0.31% per month
J Humphrey	Personal communication Zvitambo study		Zimbabwe	2010	see above			None	1.57% per month combined	2.12% per month [18.6-29.1]	1.02% per month [8.7-14.3]	0.51% per month
Kesho Bora Study Group	Lancet Infect Dis 2011;11(3):171-80	Randomized controlled study	Burkina Faso, Kenya and South Africa	2005-2008	Antiretroviral-naïve pregnant women infected with HIV-1 who visited antenatal clinics		All	None			0.84% per month	
Mofenson L et al.	IAS,Capetown, South Africa, July 2009 Abs. TuPEC053 PEPI study		Malawi	2004-2009			96% at 6 months	None		1.89% per month		0.69% per month
Renaud Becquet	Personal communication Vertical Transmission Study and Ditrame Plus Study		South Africa Cote d'Ivoire	2001-2007 2001-2005				None		2.52% per month		0.96% per month

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Tonwe-Gold B et al.	PLoS.Med. 2007;4(8):e257	Observational cohort	Côte d'Ivoire,	2003-2005	Women attending HIV care center in Abidjan		71%	Maternal: AZT+3TC+sdNVP Infant sdNVP+AZT		<350		0.61% per month
Kesho Bora Study Group.	JAIDS 2010 Aug 15:54 (5):533-41	Observational cohort	Burkina Faso, Kenya and South Africa	2005-2006	Antiretroviral-naïve pregnant women infected with HIV-1 who visited antenatal clinics		78%	AZT (28 wks) + sdNVP				<0.1% per month
Kesho Bora Study Group.	Lancet Infect Dis 2011; 11(3):171-80	Randomized controlled study	Burkina Faso, Kenya and South Africa	2005-2008	Antiretroviral-naïve pregnant women infected with HIV-1 who visited antenatal clinics			None				350-500 0.48% per month
Peripartum transmission: Single dose NVP								Probability applied in Spectrum	12%			
Guay LA et al and Jackson JB et al.	Lancet 1999;354(9181):795-802 Lancet 2003 Sept 13;362:859-68 (HIVNET 012)		Uganda	1997-1999;				Sd NVP	11.9%			
Moodley D et al.	J Infect.Dis. 2003;187(5):725-35	Randomized controlled trial	South Africa	1999-2000	HIV-infected women at maternity health institutions			NVP	12.3%			
SWEN	Lancet 2008 July 26;372:300-13	Randomized controlled trial	Ethiopia, Uganda and India	2001-2007	Pregnant women at ANC or delivery		All	Sd NVP	9.4%			

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Peripartum transmission: WHO 2006 recommendation, dual prophylaxis							Probability applied in Spectrum		4%			
Dabis F, Bequet L, Ekouevi DK, et al.	AIDS 2005;19:309-18 ANRS Ditrame	Observational cohort	Côte d'Ivoire,	2001-2002	420 women in Abidjan ANC clinics			AZT, sdNVP, maternal 3TC	5.30%			
Tonwe-Gold B et al.	PLoS.Med. 2007;4(8):e257	Observational cohort	Côte d'Ivoire,	2003-2005	See above	mostly		Maternal: AZT+3TC sdNVP Infant: sdNVP+AZT				3.10%
Lallemant M et al	NEJM 2004 July 15;351 (3):217-28 (PHPT-2)	Randomized controlled trial	Thailand	2001-2003	Pregnant women receiving zidovudine	All		combined AZT+NVP/PI and AZT +NVP/NVP	2.3% (29/1264)			
Kesho Bora Study Group.	JAIDS 2010 Aug 15:54 (5):533-41	Observational cohort	Burkina Faso, Kenya and South Africa	2005-2006	See above		78%	AZT (28 wks) + sdNVP	4.9% [2.2 - 10.6] 6/115			
Shapiro RL et al.	AIDS 2006;20(9):1281-8 MASHI study	Randomized controlled trial	Botswana	2005-2006	HIV-infected women attending district hospitals			Maternal: sdNVP	4.0% (28/694)			
Peripartum transmission: Option A peripartum											Probability applied in Spectrum	2%
Tonwe-Gold B et al	PLoS.Med. 2007;4(8):e257	Observational cohort	Côte d'Ivoire	2003-2005	See above	mostly		Maternal: AZT from 28 or 32 weeks + 3TC + sdNVP Infants: sdNVP+AZT at 7 days				3.10%

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Kesho Bora Study Group.	Lancet Infect Dis 2011;11(3):171-80	Randomized controlled trial	Burkina Faso, Kenya and South Africa,	2005-2008	See above							350-500 3.3% (11/335)
Lallemant M et al.	NEJM 2004 July 15;351 (3):217-28 (PHPT-2)	Randomized controlled trial	Thailand	2001-2003	see above	all		AZT (28 wks) + NVP/NVP			>200 1.6% (8/508)	
Postnatal transmission: Option A postpartum									Probability applied in Spectrum			0.2% per month
Chasela CS et al.	NEJM 2010;362:2271-81 BAN Study	Randomized controlled trial	Malawi	2006-2008	Women at ANC in Lilongwe			Infants received nevirapine increasing according to age, ranging from 10 mg daily in first 2 weeks to 30 mg daily for weeks 19 through 28			>250 0.31% per month	
Coovadia H, et al	18th CROI 2011 HPTN 046		Southern Eastern Africa, multicentre, multicountry study	2007-2010			Almost all at 6 months	NVP daily while breastfeeding				0.12% per month

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Peripartum transmission: Option B peripartum											Probability applied in Spectrum	2%
Townsend CL et al.	AIDS 2008 May 11;22 (8):973-81	Surveillance	UK/Ireland	2000-2006	Women identified through national surveillance system as being HIV-infected	all						0.9% (22/2400)
Tubiana R et al	CID 2010 Feb 15;50 (4):585-96	Case-control study	France	1997-2006	HIV-infected women delivering throughout France	All						1.5% (115/7425) [1.3-2.4]
Kesho Bora Study Group.	Lancet Infect Dis 2011; 11(3):171-80	Randomized controlled trial	Burkina Faso, Kenya and South Africa	2005-2008	See above.		All	triple ARVs				350-500 2.90%
Shapiro et al.	NEJM 2010; 362:2282-94 MMA Bana study	Randomized controlled trial	Botswana	2006-2008	HIV-infected women referred to study locations			protease inhibitor or NRTI triple regimens			>200 0.9% (5/553)	
Peltier CA et al.	AIDS 2009; 23(18):2415-23 Amata study	Non randomized intervention study	Rwanda	2005-2007	Women on ART or triple ARV prophylaxis				1.3% [0.4-4.1]			

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Postnatal transmission: Option B postpartum									Probability applied in Spectrum		0.2% per month	
Chasela CS et al.	NEJM 2010;362:2271-81 BAN Study	Randomized controlled trial	Malawi	2006-2008	see above			Mothers received triple ARV starting after birth			>250 0.53% per month	
Kesho Bora Study Group.	Lancet Infect Dis 2011; 11(3):171-80	Randomized controlled trial	Burkina Faso, Kenya and South Africa	2005-2008	See above		most stopped BF at 6-7 months	triple ARVs			350-500 0.24% per month	
Shapiro et al.	NEJM 2010; 362:2282-94 MMA Bana study	Randomized controlled trial	Botswana	2006-2008	See above						>200 0.1% per month	
Peltier CA et al.	AIDS 2009; 23(18):2415-23 Amata study	Non randomized intervention study	Rwanda	2005-2007	Women on ART or triple ARV prophylaxis			<350 lifelong ART >350 AZT, 3TC + Efavirenz	0.063% per month			
Thomas T.	PLoS Med 2011 8(3): e1001015 KIBS study	Single-arm open label trial	Kenya	2003-2009	HIV-positive women who intended to breastfeed attending ANC at hospitals			HIV-infected pregnant women took zidovudine, lamivudine, and either nevirapine or nelfinavir from 34–36 weeks' gestation to 6 months post partum	0.16% per month			

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Peripartum transmission: ART started during pregnancy peripartum								Probability applied in Spectrum		2%		
Kesho Bora Study Group.	JAIDS 2010 Aug 15:54 (5):533-41	Observational cohort	Burkina Faso, Kenya and South Africa	2005-2006	See above		61%	ART		3.7% (4/104) [1.4-9.5]		
											200-500	
Kesho Bora Study Group.	Lancet Infect Dis 2011;11(3):171-80	Randomized controlled study	Burkina Faso, Kenya and South Africa	2005-2008	See above		All	triple ARVs			3.3%	
Townsend CL et al.	AIDS 2008 May 11;22 (8):973-81	Surveillance	UK/Ireland	2000-2006	See above	All		started triple ART during pregnancy	1.3% (39/2967)			
Tubiana R et al.	CID 2010 Feb 15;50 (4):585-96	Case-control study	France	1997-2006	See above	All		ART	0.5% (22/4281) [0.3-0.8]			
										<350		
Tonwe-Gold B et al	PLoS.Med. 2007;4(8):e257	Observational cohort	Côte d'Ivoire	2003-2005	See above	All				1.0% [0.0-3.1]		
											>200	
Shapiro et al.	NEJM 2010; 362:2282-94 MMA Bana study	Randomized controlled trial	Botswana	2006-2008	See above			cd4 < 200 on ART; cd4>200 randomised to PI or NTRI regimens		0.6% (1/156)	0.9% (5/553)	

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Postnatal transmission: ART started during pregnancy postpartum									Probability applied in Spectrum			0.2% per month
Kesho Bora Study Group.	JAIDS 2010 Aug 15:54 (5):533-41	Observational cohort	Burkina Faso, Kenya and South Africa	2005-2006	See above		0.61	ART		0.38% per month		
Tonwe-Gold B et al	PLoS.Med. 2007;4(8):e257	Observational cohort	Côte d'Ivoire	2003-2005	See above	mostly		maternal ART and infants receiving sdNVP and AZT,		<350 0.42% per month		
Shapiro et al.	NEJM 2010; 362:2282-94 MMA Bana study	Randomized controlled trial	Botswana	2006-2008	See above			ART		0% per month		
Thomas T.	PLoS Med 2011 8(3): e1001015 KIBS study	Single-arm open label trial	Kenya	2003-2009	See above			HIV-infected pregnant women took zidovudine, lamivudine, and either nevirapine or nelfinavir from 34–36 weeks' gestation to 6 months post partum	0.16% per month			
Peltier CA et al.	AIDS 2009; 23(18):2415-23 Amata study	Non randomized intervention study	Rwanda	2005-2007	Women on ART or triple ARV prophylaxis			<350 lifelong ART >350 AZT, 3TC + Efavirenz	0.063% per month			

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Peripartum transmission: ART started before pregnancy								Probability applied in Spectrum	0.50%			
Townsend CL et al.	AIDS 2008 May 11;22 (8):973-81	Surveillance	UK/Ireland	2000-2006	most had caesarean section	All		on triple ART at conception	0.1% (1/928)			
Botswana Ministry of Health	Botswana Ministry of Health Report January 2011	Programme data on early infant diagnosis	Botswana	2010		All			0.3% (N=900)			
Hoffman RM.	JAIDS 2010 May;54:35-41	Observational study	South Africa	2004-2008	observational study of women on ART	97%			0.7% (1/143)			
Kesho Bora Study Group.	Lancet Infect Dis 2011;11(3):171-80	Randomized controlled study	Burkina Faso, Kenya and South Africa	2005-2008	See above		All	ART	1.3% at 6 wks 0% at birth			
Shapiro et al.	NEJM 2010; 362:2282-94 MMA Bana study	Randomized controlled study	Botswana	2006-2008				cd4 < 200 on ART; cd4>200 randomised to PI or NTRI regimens		0.6% (1/156)		
Postnatal transmission: ART started before pregnancy (studies included did not all start ART pre-pregnancy – see commentary)								Probability applied in Spectrum	0.16% per month			
Kesho Bora Study Group.	JAIDS 2010 Aug 15:54 (5):533-41	Observational cohort	Burkina Faso, Kenya and South Africa	2005-2006	see above		61%	ART		0.18% per month		
Shapiro et al.	NEJM 2010; 362:2282-94 MMA Bana study	Randomized controlled trial	Botswana	2006-2008	see above			ART		0% per month		

Author	Journal ref	Study type	Setting	Year	Population	Feeding practices		ARV regimen	Transmission by maternal CD4 count			
						#FF	#BF		Overall or not defined	<200	200-350	>350
Thomas T.	PLoS Med 2011 8(3): e1001015 KIBS study	Single-arm open label trial	Kenya	2003-2009	see above			HIV-infected pregnant women took zidovudine, lamivudine, and either nevirapine or nelfinavir from 34–36 weeks' gestation to 6 months post partum	0.16% per month			
Peltier CA et al.	AIDS 2009; 23(18):2415-23 Amata study	Non randomized intervention study	Rwanda	2005-2007	Women on ART or triple ARV prophylaxis			<350 lifelong ART >350 AZT, 3TC + Efavirenz	0.063% per month			
Chasela CS et al.	NEJM 2010;362:2271-81 BAN Study	Randomized controlled trial	Malawi	2006-2008	see above			see above			>250	