Consultative Meeting on

Updating Estimates of Mother-to-Child Transmission Rates of HIV

Co-convened by the M&E Working Group of the Interagency Task Team on Prevention of HIV Infection in Pregnant Women, Mothers, and their Children and the
UNAIDS Reference Group on Estimates, Modelling and Projections

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TECHNICAL REPORT AND RECOMMENDATIONS

World Health Organization

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unicef

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Acronyms

AIDS	Acquired immune deficiency syndrome
ARV	Antiretroviral
ART	Antiretroviral therapy
AZT	Zidovudine (Retrovir)
BF	Breastfeeding
CDC	United States Centers for Disease Control and Prevention
CHAI	Clinton Heath Access Initiative
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
EID	Early infant diagnosis
DHS	Demographic and Health Survey
HIV	Human immunodeficiency virus
IATT	Inter-Agency Task Team
ICER	Incremental cost-effectiveness ratio
MTCT	Mother-to-child transmission of HIV
M&E	Monitoring and evaluation
NVP	Nevirapine
OGAC	Office of the US Global AIDS Coordinator
PEPFAR	The US President's Emergency Plan for AIDS Relief
PMTCT	Prevention of mother-to-child transmission of HIV
sdNVP	Single dose nevirapine
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Session
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Background

The 2001 Declaration of Commitment on HIV/AIDS at the United Nations General Assembly Special Session of HIV/AIDS (UNGASS) committed to reduce the proportion of infants infected with HIV by 50% by 2010. Elimination of mother-to-child transmission (MTCT), with the proxy of less than 5% transmission, is discussed as the goal for the international community as it further intensifies efforts to scale-up PMTCT towards 2015.

We know that most children living with HIV are estimated to be infected through MTCT[1], and progress on the coverage of various intervention components to reduce MTCT is reported and assessed annually[2]. However, the national impact of programmes to prevent mother-to-child transmission (PMTCT) of HIV, measured through vertical HIV infections averted and maternal and child survival, is not well-documented in developing countries except from specific settings or research sites. Thus, alongside trying to improve the direct measurement of impact, international organisations and implementing partners have developed and use models to assess the potential impact of PMTCT programmes.

WHO released new guidelines in 2010 on antiretroviral drugs for treating pregnant women and preventing HIV infection in infants[3]. The updated guidelines include antiretroviral therapy (ART) for all pregnant women with CD4 cell counts <350 cells/μl[3] or clinical stage 3 or 4, and more efficacious prophylactic regimens during pregnancy and breastfeeding for women not needing ART for their own health. Currently there are no standardised internationally-recognised MTCT transmission rates corresponding to the regimen options in these new guidelines. The purpose of this meeting was to bring together modellers, people working on PMTCT programmes, and international partners, to discuss and reach a consensus on MTCT transmission rates under different scenarios based on available data and evidence. A review of available evidence and data, and consensus on MTCT transmission rates will help improve PMTCT models and harmonise transmission assumptions where relevant.

Consultation Participants

M&E Working Group of the Interagency Task Team on Prevention of HIV Infection in Pregnant Women, Mothers, and their Children

The Interagency Task Team on the Prevention of Mother-to-Child Transmission of HIV was established in 1998 following initial reports of the results of the efficacy of antiretroviral drug regimens in preventing transmission from infected women to their infants. In 2001, the Interagency Task Team was renamed the Interagency Task Team on Prevention of HIV Transmission in Pregnant Women, Mothers and their Children. Membership includes UNAIDS secretariat and Cosponsors, bilateral agencies, private foundations and civil society partners supporting education sector responses to HIV. The M&E Working Group was formed in 2006 and its members represent 21 organisations involved with monitoring and evaluation issues related to PMTCT.

The Reference Group on Estimates, Modelling and Projections

The Joint United Nations Programme on HIV/AIDS (UNAIDS) *Reference Group on Estimates, Modelling and Projections* exists to provide impartial scientific advice to UNAIDS, the World Health Organization (WHO) and other United Nations and partner organisations on global estimates and projections of the prevalence, incidence and impact of HIV/AIDS. The Reference Group acts as an 'open cohort' of epidemiologists, demographers, statisticians, and public health experts. It is able to provide timely advice and also address ongoing concerns through both *ad hoc* and regular meetings. The group is coordinated by a Secretariat based in the Department of Infectious Disease Epidemiology, Imperial College London (www.epidem.org).

The consultation was attended by 35 experts representing individuals/agencies using or planning to use models related to mother-to-child transmission of HIV and individuals/agencies familiar with various PMTCT trials and studies or those who have performed literature reviews or collected data on mother-to-child transmission. A list of participants attending this consultation is included in Appendix I.

Consultation Approach

The consultation featured both presentations and group discussions focusing on specific technical issues. Presentations and discussion topics are listed in Appendix II. The recommendations drafted during this Consultation provide guidance on how best to produce estimates of HIV, provide an opportunity to review current approaches and help to identify information needs. This transparent process aims to allow the estimates, statistics and reports published by UNAIDS and WHO to be informed by impartial, scientific peer review.

Consultation Objectives

The specific objectives of this consultation are:

- To discuss assumptions used for mother-to-child transmission rates under various scenarios including by prophylaxis and treatment regimen, infant feeding mode and duration, CD4 count and timing in pregnancy when antiretrovirals (ARVs) are received
- To propose and agree on transmission rate assumptions that can be used as default values in models
- To identify remaining work that needs to be completed in order to further refine transmission rate assumptions

1. Overview of the 2010 WHO Guidelines and implications for estimates of HIV infection

1.I Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants[4]

The new 2010 WHO Guidelines provide revised recommendations for adult and adolescent ART, for the use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants (PMTCT ARV Guidelines) and for HIV and infant feeding. The PMTCT ARV recommendations refer to two key approaches:

1. Lifelong ART for HIV-positive pregnant women in need of treatment
2. Prophylaxis or short-term provision of ARVs to prevent transmission from mother to child during pregnancy and during breastfeeding if this is the optimal infant feeding option.

Approximately 40% of HIV-positive pregnant women have CD4 counts ≤ 350 cells/μl[3] and these women account for greater than 75% of mother-to-child transmission (MTCT) risk and greater that 80% of postpartum transmission. It is now recommended that all HIV-positive pregnant women with a CD4 count <350 cells/μl[3] and those >350 cells/μl[3] with WHO clinical stage 3 or 4 symptoms should be put on ART and all infants should receive prophylaxis to prevent MTCT.

Women who are not eligible for ART or have unknown eligibility should receive ARV prophylaxis from as early as 14 weeks gestation or as soon as possible after this point. There are two recommended options for ARV prophylaxis for mothers who are not eligible for ART – Option A (maternal AZT) and Option B (maternal triple ARV prophylaxis). If breastfeeding is the best infant feeding option, antiretrovirals should be provided to reduce the risk of transmission during breastfeeding. Option A and Option B are specifically detailed in Appendix III.

Potential questions arising from these new guidelines with implications for modelling:

- *How to account for the different transmission risk for mothers with high and low CD4 counts?*
- *Are the current regimen groupings adequate for our models?*
- *What is the duration of the intervention, how important is this and how to account for variance?*
- *Should a range of estimates be used? Point estimates?*
- *What are the appropriate denominators to use?*

Discussion

Countries are currently in the implementation phase and thus will be moving through different treatment regimens in the process and this change over time may be an issue for the modelling. Most high burden countries are moving towards option A, but Option B+ has emerged which is the continuation of lifelong treatment for mothers. Countries may adopt different guidelines for different areas, for example Nigeria is considering implementing both Option A and B, depending upon geographical location. Note that there will be a gap between when the recommendations are in place and when the drugs are actually available in clinics.

There was discussion regarding terminology and it was agreed the appropriate terminology to use when discussing PMTCT differentiates between antiretroviral therapy and ARV prophylaxis. Specific terminology should be used by PMTCT regimen. The previous recommendations (dual prophylaxis) should be referred to as 2006 WHO Guidelines or “2006 prophylaxis”. The term “short course” should not be used.

1.II WHO revised recommendations on HIV and infant feeding[5]

The 2010 HIV and Infant Feeding Guidelines are based on new research evidence and accumulated programme experience with the overall aim to improve HIV-free survival of infants born to mothers who are known to be HIV-infected. The new Guidelines reinforce former principles and recommendations with two significant changes. At the national or sub-national level, health authorities will decide to adopt one of two strategies for mothers known to be HIV-infected:

1. *Breastfeed and receive antiretroviral interventions*
2. *Avoid all breastfeeding*

The decision should be based on international recommendations and consideration of the socio-economic and cultural context of the populations served and the strategy that will give infants the greatest chance of HIV-free survival should be adopted.

In settings where national authorities decide to promote and support breastfeeding and ARVs, the new guidelines are more explicit and harmonised for all mothers (HIV+ and HIV-) for the first 12 months, recommending that all mothers exclusively breastfeed for the first six months of life. Thereafter, all mothers should introduce complementary feeding while continuing to breastfeed. It is recommended that HIV-infected mothers continue breastfeeding up to 12 months (while HIV-uninfected women continue to breastfeed for 24 months). Countries can change the guidelines after the first 12 months of life based on what is nutritionally adequate and safe in the local context. When HIV-infected mothers decide to stop breastfeeding, they should do so gradually within one month.

The potential implications of these revised recommendations are that more HIV-infected mothers will start breastfeeding and more will feed until at least 12 months and more total mothers will partake in exclusive breastfeeding. This will result in improved nutritional intake and HIV-free survival among HIV-exposed infants and overall improved infant survival.

Discussion

Many questions arise regarding coverage of breastfeeding and also coverage by type of feeding and the duration of feeding and how to best obtain this information, whether systems have this information and how far out the data over six months can be extrapolated. The effect of programmes recommending feeding guidelines on actual behaviour was queried and it was discussed that many programmes do not actually monitor exclusive feeding thus the quality of data available are questionable.

It was highlighted that the benefit of the infant feeding guidelines is on survival, while the benefit for reducing HIV transmission will be a result of ARVs. The survival benefit of breastfeeding is 12 months and the modelling done to determine this benefit was based on survival, not based on HIV transmission. It was questioned whether there will there be an additive effect above and beyond the effect from both ARVs and exclusive breastfeeding due to increased survival. Some models have included this (Spectrum does not); it was hypothesised that there might be overall improved survival at the population level as a result of these guidelines. Correspondingly, cost effectiveness analyses need to incorporate infant survival – there is a much better outcome than just HIV transmissions averted, vastly greater benefits when we consider survival and this often gets overlooked or is not incorporated.

Breastfeeding terminology:

- Exclusive breastfeeding
- Partial (or mixed) breastfeeding
- Replacement feeding (non-breastfeeding)
- Complementary feeding
- Cessation of breastfeeding (weaning)

2. Organisation need for transmission rate estimates[6, 7]

UNAIDS works with countries to use mathematical models to produce national HIV estimates and projections every two years. Over 100 countries use the models to create estimates. The estimates are used to provide a detailed summary of the epidemic, to inform national programmes and planning, for monitoring the epidemic and to identify the impact of HIV on the population. At the global level, the estimates are used for advocacy, target setting, determining priorities, and for broad impact monitoring. MTCT rates are an essential component for deriving national estimates of paediatric infections. Mathematical models can be used to look at the impact of various intervention scenarios including reduced incidence, improved access to family planning, increased coverage of ARV prophylaxis or ART among pregnant women, reduced infections through safer feeding and to identify ways to reach "virtual elimination".

It was discussed that the data inputted into the models are nationally representative and while specific CD4 count data are not available, data for the specific PMTCT options used are available. It was mentioned that the country-specific inputs used in Spectrum can be difficult to track down and it was queried whether these data are country owned or whether these data can be made publicly available, something which has not been done in the past, but more recently has occurred and found to be very useful.

PEPFAR uses data on MTCT in their mathematical models which are used at the national level to calculate infections averted in each country (with the goal to avert 480,000 infections by 2013), to support country programme goals (eliminate MTCT and improve PMTCT coverage), to determine the cost of providing PMTCT in each country, and to measure overall programme impact. Data is collected mid-November and reported to Congress at the end of January.

In PEPFAR I, an estimated 240,000 infant infections were averted. This value was derived using the assumption of 19% MTCT for all women who received ARVs regardless of regimen. This MTCT rate was predominantly based on the assumption that women were receiving sdNVP. In PEPFAR II, the number of women receiving specific drug regimens (treatment and prophylaxis) is required along with corresponding transmission rates for each regimen. Data on infant regimens, infant feeding method and drug adherence are not collected thus average transmission rates are needed which incorporate the efficacy of different infant feeding methods and the efficacy of different levels of adherence. The data needs for PEPFAR II include the number of HIV-positive pregnant women in each country (the denominator to determine overall programme coverage), the number of women receiving each regimen (which comes from registers and reports from PEPFAR implementing partners) and the transmission rate for each treatment and prophylaxis regimen.

PEPFAR meets with the Global Fund and WHO biannually to compare PEPFAR reported data to national data in order to validate the results obtained. Currently the PEPFAR focus is on fiscal year reporting as opposed to the UN and Ministry of Health calendar year reporting; it was agreed that these varying reporting time frames need to be addressed and harmonised in the future, but for now, PEPFAR will continue to report on the fiscal year. It was highlighted that PEPFAR is looking at impact and that transmission rates in those reached by PEPFAR programmes might not be the same as the transmission rates in the entire population and thus it will be important to compare the impacts reported to the UN and to PEPFAR.

3. Evidence for mother-to-child transmission rate estimates

3.I Clinical trial data and transmission data supporting WHO 2010 PMTCT Guidelines[8]

Women who meet WHO treatment criteria for their own health are at highest risk for MTCT and thus the largest impact on MTCT will occur in this group. Data from clinical trials demonstrates that ART may reduce overall transmission to 1-5% at six months; the extent of the reduction is partly dependent on the duration of antepartum ART. The contribution of infant nevirapine or AZT in the presence of maternal ART was not studied, but in the absence of maternal ART, it appears to give an absolute reduction of 1-3% in MTCT. It is worth noting that the Mma Bana[9] study which had the lowest overall rate, gave sdNVP and four weeks AZT (and started maternal treatment early, achieved good viral suppression and had a short duration of breastfeeding), while Kesho Bora[10] and the Kisumu the Breastfeeding Study[11] (which reported similar results) only gave sdNVP.

ARV prophylaxis for women who do not need treatment for own health
Both options for PMTCT prophylaxis (Option A and Option B) offer regimens demonstrated to decrease the risk of MTCT and both options have linked maternal and infant regimens. There is no demonstrated superiority of one option over the other and both options have inherent risks associated with them. The two options take into consideration other factors that impact effective PMTCT implementation including feasibility, access, cost, equity, health system capacity and the current in-country approaches. When antepartum ARVs are given, *in utero* MTCT is low (~1-2%) and similar regardless of regimen; however, the duration of antepartum ARVs is important in determining the rate. Either maternal triple ARVs or infant NVP prophylaxis is safe and effective in reducing postnatal MTCT. When antepartum ARVs are given, both appear to reduce postnatal MTCT (between six weeks and six months) to approximately 1-2%. Overall MTCT rates in studies in women with CD4 counts in the range of >200-350 cells/μl[3] and receiving antepartum and postpartum prophylaxis, range from 1% (Mma Bana) to approximately 5% at 6-12 months. If maternal triple ARV started postpartum (or potentially late antepartum), it is less effective against early postnatal MTCT than infant NVP (which works immediately), due to time needed to lower viral load (which takes weeks). For maximum efficacy of any regimen you need to start early in pregnancy to prevent *in utero* transmission; even if the intervention is 100% effective in preventing intrapartum or postpartum MTCT, still have "residual infection" of 1.6% *(in utero)* if starting at 28 weeks – you need to start earlier[12].

The BAN[13] data suggest that breastfeeding transmission risk is not the same over time with an early peak in the first 2-6 weeks– in the control group 0.5% per week which is quite high - then 0.27% per week up to 12 weeks, then approximately 0.12% up to 29 weeks[13]. This early high transmission may be key.

There are several ongoing and new trials which will provide additional data in the near future including HPTN 046, PEP-ANRS, IMPAACT-PROMISE and ANRS.

3.II Considerations related to postnatal HIV transmission and infant feeding[14]

Most postnatal HIV transmission occurs among women who meet eligibility criteria for ART. Postnatal transmission will be influenced by the quality and duration of breastfeeding, the use of antiretrovirals and the severity of maternal disease; therefore, interpreting study results across contexts is not possible without

information on these parameters. Additional considerations include follow-up past the completion of breastfeeding and appropriate adjustment for censoring (left and right and informative censoring).The risk difference over time by different feeding options can be determined using a cohort with comparable populations, establishing an early time point and testing repeatedly with PCR in increments until an ending time point.

Denominators are very important. The denominator commonly used to calculate rates of postnatal HIV transmission is all children born to HIV infected women; however, you need to specify if you are subtracting transmission that occurred during pregnancy and delivery. When calculating postnatal HIV transmission rates, it is not recommended to separate out all HIV transmissions that occurred and then report the proportion that were due to breastfeeding as this will result in very different transmission rates compared to rates calculated using children born to HIV infected women as the denominator.

There is increased transmission due to non-exclusive breastfeeding (4% in first 4 months with exclusive breastfeeding compared to 10% in non-exclusive breastfeeding). The quality of data from non-exclusive breastfeeding needs to be considered. Mixed feeding is complementary feeding when it is developmentally appropriate. Mixed feeding during first 6 months is not developmentally appropriate and thus we may want to consider changing the terminology around this as the rates of transmission will differ. There is a need to go back to why exclusive breastfeeding was recommended in the first place, to focus on mother and the child and survival. In low infant mortality settings, HIV makes a larger contribution to the balance of risk so breastfeeding (in the absence of ARVs) is quite risky. With effective antiretroviral drugs, abstinence from breastfeeding results in worse infant outcomes. In postnatal transmission, the key element is the importance of infant and child mortality. Focussing only on HIV will underestimate the benefits. Mortality needs to be considered either combined with HIV transmission (HIV-free survival) or as an independent outcome (which is likely the more attractive option for programmes).

Discussion

There was discussion regarding the number of females eligible for treatment and the different proportions quoted. CHAI performed a meta-analysis in 2008 to determine the best estimate and found that roughly 40% of pregnant HIV-infected females had a CD4 count <350 cells/μl^3, while a paper from Kuhn et al[15] reports 68% of pregnant HIV-infected females had a CD4 count <350 cells/μl^3 or WHO stage 3-4 disease, and Carter et al found 48%[16]. This proportion will vary depending on whether CD4 data are available as it is not entirely transparent how WHO treatment guidelines for clinical stage are applied. Many settings will err on the side of classifying as stage 3 (ART initiation) when borderline or uncertain, whereas other settings will err on the side of stage 2 classification, delaying ART initiation. The proportion of HIV-infected females eligible for treatment will also vary across settings due to different stages of epidemics and differences in fertility rates. Because it is difficult to generalise from a study population to the general population, the best estimates for the proportion eligible will likely come from treatment sites with CD4 data.

What impact will loss to follow-up have on the transmission rates coming out of these studies? The loss to follow-up from the clinical trials was generally less than 10%, but in programmes this will obviously be much greater.

Is there a genuine peak in early postnatal transmission in the first 4-6 wks (observed in BAN[13])? These data are consistent with others showing early high transmission, then much lower, but none of the data are entirely comparable. Could this early increased transmission be a function of the volume of milk being consumed? There was some disagreement over whether this peak is genuine with the argument that we

do not have the data to make this conclusive statement and will not be able to get this data due to the availability of antiretrovirals**.** It was highlighted that the two key elements for postnatal transmission are the duration of antepartum treatment and the duration of breastfeeding. How you define breastfeeding and categorise weaning is important and can result in different interpretations of the same results (uncertain whether transmission is definitely declining in the longer term). There is very limited information on breastfeeding behaviour; we essentially have no idea what the median duration of breastfeeding is. There is a need to pull all of the available data together to generate very precise estimates by baseline CD4 count, breastfeeding duration and breastfeeding patterns. The difference in breastfeeding patterns for women in programmes (HIV-positive) compared to those not in programmes was probably huge a few years ago (more of a concern retrospectively) but in the future it is likely to be less of a problem as a result of the new Guidelines and the push towards breastfeeding. But note that if you are looking at mortality, this difference will be huge.

4. Mathematical models and mother-to-child transmission

Different models are used for different questions and the function of an individual model will determine the level of detail needed. Having multiple models allows for cross validation but there is also the need to be mindful of how differences in appropriate detail may alter the results generated. Models have different scales and may be international, national, local or programme based, they may be aspirational or realistic. Models are used to generate estimates of disease burden, to determine need, to inform prioritisation and planning and may also be used for advocacy or to identify cost benefits and cost-effectiveness.

4.I Using Spectrum to estimate the effects of PMTCT programmes[17]

For national estimates, HIV incidence is estimated from prevalence trends based on surveillance and survey data. Incidence is inputted into Spectrum along with the coverage of ART and PMTCT and these data are combined with demographic data, epidemic patterns and treatment effectiveness to produce new infections by age and sex, AIDS deaths, treatment and PMTCT need, the number on treatment and orphan estimates. Spectrum version 4.0 incorporates a CD4 bin structure which tracks those infected by CD4 category, progressing to treatment eligibility. The number of births to HIV-infected females (denominator) is calculated by combining population data with age-specific fertility patterns and an age-specific fertility reduction among HIV-infected females. PMTCT regimens over time are inputted as the number of females on each regimen or the coverage level of each regimen. A costing analysis has also been included in Spectrum to incorporate a cost-effectiveness analysis, calculate total costs, costs for treatment and cost-benefit ratios.

Key questions and issues that arise in Spectrum as a result of new data and analyses available and the new 2010 WHO Guidelines include:

- *Perinatal transmission rates for Option A and Option B and monthly breastfeeding transmission rates?*
- *Separate Option A by mother and child or collapse together?*
- *DHS breastfeeding patterns and changing trends in breastfeeding over time?*
- *Assume the same breastfeeding patterns for HIV-positive women?*
- *Can we use information about the distribution of CD4 counts in the general population for pregnant women and assume these are the same?*
- *Do we need to adjust the effectiveness of PMTCT regimens for median starting time on prophylaxis? Will programmes have these data?*
- *Declining monthly transmission rate while breastfeeding after 12 months?*
- *Assume no reduction in fertility for women on ART?*

Discussion

A range of CD4 counts are observed in the available data from HIV-positive pregnant women with a median of approximately 48% having a CD4 count under 350 cells/μl[3].

The use of DHS feeding patterns is a potentially key question that needs to be considered; DHS data are often outdated and there have been substantial changes in infant feeding patterns in the past ten years (e.g., Botswana). From clinical trial data, the duration of breastfeeding seems to be shortening. Should a time trend for breastfeeding patterns be included? Data from Ghana showed that these trends varied greatly in a short amount of time. It is unlikely that programmes have these specific data, but the 3-month breastfeeding indicator currently being piloted might be a potential option to use in the future for breastfeeding patterns and duration. The question arose whether breastfeeding was incorporated in the infant mortality rate, i.e. enhanced survival as a result of breastfeeding, and currently this is not directly incorporated in Spectrum; however there is a separate Spectrum module which can include this. It was discussed that the fertility reduction for HIV-infected women should probably only apply to those who are untreated, but this needs to be looked

into further. The new version of Spectrum will track changing CD4 counts thus there may be an increase in births as a result of increased CD4 counts when on treatment.

4.II Data needs and use for PEPFAR PMTCT impact modelling[18]

The purpose of this modelling was to grossly estimate the population-level MTCT rate using the new WHO 2010 Guidelines and PEPFAR coverage targets (test 80% of females and give ARVs to 85% of those who are positive – 68% overall coverage) representing a best case scenario to use for policy discussion purposes and to estimate the costs associated with this scenario. The data needed include the number of HIV-infected women, the MTCT rates over 12 months of breastfeeding for eligible women on ART and for women on Option A and Option B prophylaxis, the proportion of women eligible for ART and the costs associated with the drugs.

Transmission rate data were compiled from a range of studies. While data exist for rates of transmission while breastfeeding for the first six months, how can you extrapolate after 6 months? The median overall transmission was used (9% for ART and 6% for Option A and B prophylaxis) based on extrapolation which resulted in a population MTCT rate of 16%, and alternatively, Lynne Mofenson's extrapolation method was applied (0.3% for the second 6 months of breastfeeding which resulted in an overall MTCT rate of 5% on ART and 5% for Option A or Option B) which resulted in a population MTCT rate of 15%. Note that there was little difference at the population level using the different MTCT rates. However, if ARV coverage was increased to 85% (instead of 68%), the population MTCT rate decreases to 10%.

This work illustrates that it is the coverage of PMTCT that is driving the population-level MTCT results, not the individual transmission rates while on ART and under the new prophylaxis Options. The vast majority of MTCT occurs in women who receive nothing; therefore, even when you use quite varying assumptions for MTCT rates for women on ART or receiving Option A or Option B prophylaxis, it will not dramatically change the results. Conversely, variance in the coverage of those on treatment or receiving prophylaxis will have a substantial impact thus it is critical the numerators and denominators are correct.

Discussion

These are optimistic or best-case assumptions and yield fairly disappointing results (15% MTCT). These results are important as we consider attempting to get close to elimination (5% MTCT). Triple regimens are not going to make the huge differences to population MTCT rates that are hoped because you still have women who get nothing at all. Extremely high coverage of everything – ANC coverage, treatment and prophylaxis – is needed to even get close to the elimination target which will be extremely difficult to achieve. Note that loss to follow-up will also affect coverage.

Despite the new Guidelines, the 14-week start of ARV prophylaxis is very optimistic; the median start in ANC is 22 weeks (study populations), which will vary greatly and likely towards the later end in the general population. Similarly, MTCT rates will probably also vary greatly outside study populations. Results from Mma Bana[9] demonstrate the promise of what could happen (very low transmission), at least for Option B, but we do not know what will happen. Option A will be most widely used, but is the least studied.

4.III Potential impact and cost-effectiveness of the 2010 WHO PMTCT Guidelines[19]

The purpose of this modelling was to estimate the cost-effectiveness and costs saved in a single year (2010) as a result of implementing Option A or Option B for HIV-positive women ineligible for ART in 15 PEPFAR countries. These two scenarios were compared to the 2006 WHO Guidelines. The model structure divides new HIV infections in exposed infants into those infected at birth and those infected during

breastfeeding with breastfeeding transmission rates extrapolated from 0-5 months, 6-11 months, 12-23 months, 24-35 months divisions.

The assumptions used for MTCT rates (which differed from those in Spectrum) were:

- Option A: 2.2% at birth and 0.28% (exclusive) or 0.47% (mixed) risk per month during breastfeeding
- Option B: 1.8% at birth and 0.48% (exclusive) or 0.81% (mixed) risk per month during breastfeeding)
- 2006 prophylaxis: 2.2% at birth and 0.95% (exclusive) or 1.97% (mixed) risk per month during breastfeeding.

Incremental cost-effectiveness ratios were estimated for Option A and Option B comparing the additional cost per additional life-years gained of implementing either scenario to the 2006 prophylaxis scenario. The results yielded fairly similar results for Options A and Option B in terms of infections averted, life-years gained, but Option B was significantly more expensive than Option A. Implementation of the 2010 WHO Guidelines could nearly triple infections averted compared to 2006 prophylaxis; implementing Option A for ART-ineligible women is highly cost-effective and potentially cost saving in some settings.

4.IV Transmission data used for the CHAI PMTCT model[20]

The CHAI model was used to estimate the expected outcomes of PMTCT activities and explore strategies to reduce the number of expected infant infections. Default MTCT rates were obtained by defining treatment and prophylaxis regimens, conducting a literature review and a random effects meta-analysis (which accounts for between study heterogeneity). Cumulative MTCT rates by regimen were calculated at 6 weeks and 6 months along with cumulative MTCT rates by regimen from 6 months and then monthly, stratified by infant feeding pattern. Rates were similar to those used in Spectrum.

Assumptions of this model include that the cumulative transmission rates at six weeks are a proxy for birth and thus are not disaggregated by feeding pattern. Note that the Kesho Bora data[21] report different rates at birth compared to 6 weeks. The cumulative transmission rate at 6 months in the replacement feeding group is equal to the rate at 6 weeks. For the MTCT rates at 6 months, women receiving ART or dual prophylaxis were assumed to exclusively breastfeed while those receiving sdNVP or nothing at all were assumed to practice mixed feeding. A hazard ratio of 1.56 is associated with transmission if mixed feeding during the first 6 months compared to exclusive breastfeeding[22]. After 6 months of breastfeeding, a 0.75% monthly risk beyond 6 months is attributed to ongoing breastfeeding. Conservative MTCT rate estimates were used for Option A and Option B – 2% at birth and 5% for 6 months and beyond – with rates equivalent for exclusive and mixed feeding. Comparing the MTCT rates used in the models, consolidation of parameter estimates appears most needed for breastfeeding transmission rates. Additionally, all sought guidance for MTCT rates for Options A and B of the 2010 Guidelines, and rates to use when stratifying by CD4 count.

Discussion

Access to programmes is the single most important factor for determining the number of infections in children. Getting this wrong is going to result in the greatest difference. The effect of loss to follow-up is also unknown; women lost to follow-up may have already received sdNVP, or may not have received anything. The models are often quite optimistic with assumptions surrounding adherence, which will greatly impact programme coverage and thus can have a large effect. Will programmes have data on adherence and loss to follow-up? How good is the data on adherence from adults on ART? And when do programme data supersede the model assumptions and model outputs? Some countries have very good data available.

5. From clinical trials to national programme estimates and towards virtual elimination

Data from trials can provide estimates of efficacy and data from programmes can provide estimates of effectiveness. The different endpoints make it difficult to compare data and there is often insufficient data to estimate transmission risk for the many different factors. While the transmission rates in clinical trials and programme data appear similar, the potential caveat is that these are very good programmes and thus may not be generalisable to all programmes.

5.I Estimates of MTCT rates from programmatic data[23]

The inclusion criteria for this analysis were published reports (14) or abstracts (5) of MTCT transmission rates by prophylaxis or treatment regimen. Of these, 15 were PMTCT based and four were EID based representing sub-Saharan Africa, China, Thailand, Ukraine, Russia and Haiti. There were 12 PMTCT reports from sub-Saharan Africa from feasibility studies for provision of multidrug prophylaxis or ART in low-resource settings; most were not powered to compare transmission rates between regimens. CD4 distribution is reported in four studies and infant feeding was described in nine studies. Infant follow-up rates ranged from 65-97% with more around 70%, but note that there is likely a publication bias.

Estimated transmission rates by regimen from programme data in non-breastfeeding settings for mean cumulative transmission at 6 months (range) were:

- sdNVP: 8.8% (7.5, 9.9)
- 2006 prophylaxis: 6.8% (0.0, 10.1)
- ART: 1.9% (0, 3.4)

These transmission rates were comparable to rates used in mathematical models. It was queried whether there was further breakdown by CD4 counts as some of the women given ARV prophylaxis may have ended up in ART programmes, thus potentially entering bias into the transmission rates. For the most part, there is no available data for CD4 count, but in these early studies, women would be less likely to have ended up in ART programmes, but this is something that will change over time. However, loss-to-follow up and the timing around loss-to-follow up (whether women already received some sort of therapy) are important considerations as the assumptions made can introduce bias into the transmission rates.

It was also observed that longer duration on ART is associated with lower MTCT. Hoffman et al[24] reported higher 6-week transmission rates in women receiving ART for a shorter time period (9.3% MTCT in women on ART less than four weeks compared to 5.5% in those on ART for more than four weeks).

Small sample sizes lead to unstable transmission estimates and many studies lack confidence intervals to inform regarding the range of the estimates. High loss to follow-up, including high infant mortality prior to first HIV test, and variability in the timing of the first HIV test for infants who do receive one, make it difficult to interpret age-specific transmission rates and postpartum transmission. The new guidelines result in an increase in women eligible for treatment thus better data are needed for the proportion of eligible pregnant women receiving ART and the duration on ART prior to delivery. Infant feeding practices need to be better described and defined. More complete information is needed on CD4 distribution and the severity of disease among HIV-positive pregnant women in different settings.

The most critical issue for measuring MTCT rates is the number of mother-infant pairs who complete the entire PMTCT cascade – from first attending the ANC clinic, to being counselled and tested for HIV, to receiving prophylaxis or treatment and returning for HIV testing in the exposed infant. Even in an efficient PMTCT cascade, poor infant follow-up will lead to biased transmission estimates. In settings where early infant diagnosis is not widely available this sample is not nationally

representative and has the potential to include more symptomatic children receiving HIV testing and will bias transmission estimates.

It was discussed that previous modelling has focused solely on the regimen the mother had received and did not directly model the infant regimen. Because infant and mother regimens are linked in the new guidelines (Option A and Option B), infant regimens will depend on maternal regimens but the issue of adherence, particularly for Option A, may be a concern for the modelling.

5.II Expected and actual MTCT rates in Botswana[25]

Botswana has had an early infant diagnosis programme since 2005 and these data are fairly easy to interpret because almost all HIV-infected women replacement feed. The most current data is from 2008-9 with nearly 9,000 infants tested out of approximately 13,000 exposed (~68%); the median age of testing is 8 weeks. Of all infants tested, 3.2% were HIV-infected. Of all infants tested who were under 8 weeks of age, 2.7% were HIV-infected. The MTCT rates by regimen can be disaggregated from the EID dataset (self report and infant card) and compared to MTCT rates by regimen in the literature. These data can also be used to project the expected new infant infections in Botswana with a projected total MTCT in Botswana for females who get diagnosed with HIV while pregnant of 4.2% in 2008-9.

In the discussion the question arose regarding incident infections – women who test negative in pregnancy but become infected late in pregnancy. These women will have a high rate of MTCT (Humphrey[26] data suggest extremely high transmission). Incident infections will become an increasingly important proportion of MTCT (this is already the case in Botswana) and will be an important consideration when considering virtual elimination targets.

5.III Clinical transmission rates to national programme transmission: Issues to consider and data gaps[27]

Key factors associated with the effectiveness of PMTCT include CD4 count and receipt of appropriate regimens, duration of, and adherence to, ARV regimens, infant feeding practice by age and duration of breastfeeding. All of these factors will affect transmission but data are not always available at the national level. Most models are not making adjustments for effectiveness, for example, the assumption that full and complete ARV regimens are received. There is also a need to distinguish between retention and adherence. It was discussed that EID and vaccination databases are not representative and need to be used with care, and it was highlighted that there are already many nationally recommended PMTCT indicators thus any additions need to be thoroughly considered.

5.IV Towards virtual elimination[28]

The goals of “virtual elimination” are to reduce MTCT to less than 5% and to reduce global infections by 90% (from 430,000 to less than 50,000). Additional goals include reducing incidence by 50%, meeting 100% of unmet family planning need for all women, achieving greater than 90% coverage of HIV testing in pregnant women and of HIV-positive women on effective ARVs, and greater than 50% ART coverage for eligible HIV-positive women. In realising these goals, mathematical models are needed to produce estimates, establish a baseline and track progress towards these targets and project different future scenarios. WHO is planning a technical and operational consultation in late fall 2010 to discuss and outline this strategy in detail.

The discussion highlighted that child survival should be included in the fall consultation. The focus purely on HIV and not including child survival is cause for great concern. The overall population rates of MTCT will be disappointing due to the high transmission that occurs in women who receive nothing and this undermines the positive impact on survival and HIV-free survival as a result of the 2010 Guidelines.

6. RECOMMENDATIONS

6.I Recommendations for MTCT rates

CD4 count matters and it matters more for women outside of programmes and for women who are not adherent. *In utero* and peripartum transmission rates appear quite similar for ART and combination therapy, but this will also depend upon when you start treatment. Postpartum, if you are actually getting drugs, transmission rates will be very similar; if you are not getting anything then transmission rates will vary by CD4 count. It was noted that nationally representative data are not often available for ARV coverage by CD4 category and whether ART was initiated prior to or during pregnancy.

For postnatal transmission, separating breastfeeding transmission by exclusive vs mixed feeding is confusing and creates a false distinction; data are generally composite thus the separation implies that we have some sort of accuracy when we do not. We have no idea how mixed or how exclusive breastfeeding is.

Perinatal transmission (representing *in utero* and peripartum transmission):

- Stratify transmission rates by CD4 count in those not receiving any PMTCT intervention. Stratify CD4 count by <200, 200-350, >350.
- It is unnecessary to stratify transmission rates by CD4 count for those receiving treatment or prophylaxis (effective regimens).
- Separate perinatal transmission rates by timing of ART initiation – those who began ART before pregnancy and those who began ART after becoming pregnant.

Postnatal transmission:

- Combine all breastfeeding into a single term for calculating MTCT rates – *any breastfeeding.*
- Stratify by CD4 count using a CD4 count of 350 cells/μl^3 as the division.
- Do not separate out the first month of breastfeeding as a time period for increase; this is too much complexity for the limited data available.
- Use hazard rates per month to calculate transmission, which apply to those who were uninfected in the previous month (no longer linear).
- For now, leave all breastfeeding together (0-12 months) and do not separate into rates for 0-6 months and 6-12 months as the data do not definitively support this.
- Use the country-specific guidelines adopted for breastfeeding in the models (for example, the percent feeding until 1 year).

Programme data used in mathematical models

- Continue to use ANC data for treatment coverage for now; however, this may depend on country or type of epidemic (low level epidemic countries may not have these data reported from ANC).
- Data for women who are on ART before they get pregnant will have to come from ANC clinics (note that collecting these data is currently not included as a recommendation in the PMTCT M&E guide).
- For prophylaxis Option A and Option B, separate out mother and child in terms of what they actually receive.
- Incorporate retention in addition to programme coverage.
- EID data and data from vaccine programmes can only be used when combined with regimen and coverage data from programmes. These data are generally not nationally representative and should be interpreted with care.
- Better data on infant feeding practice would be useful

6.II Draft MTCT rates table defined at the Sept 1-2, 2010 Consultation

A draft table of MTCT rates was defined at this consultation as a starting point for a formal justification and documentation process to be conducted by a technical working group.

The product of this working group, including the revised table of MTCT rates, is available at: www.epidem.org/publications/MTCTratesworkingpaper.pdf .

6.III Spectrum

Specific recommendations to be made in Spectrum:

- Spectrum should incorporate different transmission risk by CD4 count *(see MTCT rate table 6.II for specific details).*
- Use CD4 count data to inform the distribution in pregnant women and validate these data (general population distribution of CD4 count vs distribution in pregnant woman distribution).
- Remove the fertility reduction for HIV-positive women on ART and observe the outcomes.
- Spectrum to provide estimates of need for PMTCT for women by CD4 count divided into <350 cells/μl^3 and >350 cells/μl^3.
- Create two breastfeeding patterns for HIV-positive women, those in PMTCT programmes and those not in programmes, use DHS data as the default for both patterns, and if programme data is available this can be inputted in place of the default values.
- For prophylaxis Option A and Option B, separate out mother and child **i**n terms of what they actually receive and add a dropout rate for each. Also record the percent that are following the country-specific breastfeeding guidelines (feeding to 1 year, etc).
- Include total mortality and compare estimates to the data.
- Report HIV-free survival at 12 months.
- Update the variables included in the uncertainty analyses in Spectrum to reflect the changes made.

6.IV Validation of estimates

The validation process is particularly important if all models are using the same, or very similar, assumptions. It is therefore recommended to:

- Use countries with good data to compare with modelled estimates and continue to compare modelled estimates to population-based surveys.
- Publish and make the models publicly available for validation. Format the model descriptions and methods in a way in which the assumptions are well described and can be compared across different models.
- Harmonise reporting timelines to make it easier for countries and to simplify the estimation and validation process.
- All agencies (UN, Ministry of Health, programmes) need to be involved in the estimation process in-country, this leads to greater awareness of the process, greater transparency and better estimates.
- Improved validation of the reports at both the global and country levels.
- A research plan is created outlining a formal validation process.
- Include data for retention in programmes and exlore adherence and whether these data are essential for models.

6.V Research agenda

Specific recommendations for research:

- **MTCT transmission rate table:** Small expert group to spend one month discussing, citing, and validating the MTCT transmission rates by regimen drafted at this meeting and to develop this into a publication. Specific areas for further research regarding the MTCT rates include:
    a) Will women on Option A or Option B have the same transmission rates (perinatal and postnatal) as women on ART for their own health?

   b) Is there increased postnatal transmission in the first 6 weeks while breastfeeding?

- **Implementation of new guidelines:** WHO will provide information on this in the future; the IATT M&E working group may be able to perform the data collection which is needed on both adherence to the regimens and retention in programmes and also on the uptake and duration of breastfeeding.
- **Infant feeding practices:** Recommendation for a special study on infant feeding practices, take this to IATT M&E working group to decide, could potentially use the 3 month indicator used in the recent pilot as this has relatively high uptake (immunization visit). Keep this item on the agenda to re-visit when larger surveys are available.
- **MTCT at long-term breastfeeding:** Some data available to 18 months (Mma Bana, Kesho Bora) but note that the duration of intervention is only 6 months so not exactly the data we are looking for. Re-visit this topic when more data become available.
- **Recommendation for a meta-analysis of MTCT rates:** To tease out the Mma Bana results; to inform by timing of treatment initiation; to pull all of the available data together to have precise estimates by, baseline CD4 count, breastfeeding duration and patterns. Funding for this analysis needs to be identified.
- **Incident HIV infection in pregnancy:** MTCT rates (perinatal and during breastfeeding) as a result of incident HIV infection during pregnancy and the proportion of new infections in children due to incident HIV infection in pregnancy.
- **Timing of ART initiation and PMTCT:** What proportion of HIV-positive women are on ART before pregnancy and what proportion are newly on ART? Data collection question to take to the M&E working group.
- **Denominators:** Comparison of the denominators in surveillance data, programme data and Spectrum data.
- **Adherence:** Adherence (to treatment, prophylaxis, type of breastfeeding practice) might not actually matter in some cases, for example if the woman has stopped breastfeeding. Viral suppression from clinical trials achieved with ~80% adherence. Cohort based reporting (reporting several months after delivery) might be used for testing and validation. Data are available for cohorts in Namibia and Zambia.
- **Infant survival:**
   a) Identify the impact of the new breastfeeding guidelines on underlying (non-AIDS) mortality. Also look at the HIV-free survival at 12 months and 24 months (if possible).
   b) Compare total mortality from mathematical models to the data.
   c) Incorporate infant survival (and not just HIV transmission) in cost-effectiveness analyses.
   d) Include infant survival in the WHO fall 2010 consultation on virtual elimination.

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Appendix II: Meeting Agenda

Wednesday, September 1, 2010

9:00 am ***Welcome, Introductions, logistics***
(Peter Ghys, Nathan Shaffer, & Hanh La)

Overview of objectives, agenda and expected outcome of the meeting; introductions

9:20 am ***PMTCT ARV and Infant Feeding Guidelines***
(Nathan Shaffer & Nigel Rollins)

What are the highlights of the 2010 WHO PMTCT ARV and Infant Feeding guidelines?
How do they differ from previous strategies? What common terminology could we use during the meeting to refer to the different regimens and what do they imply?

9:50 am ***Organization Need for Transmission Rate Estimates***
(Mary Mahy & Rachel Blacher)

Why are these transmission rate estimates important for organizational and global planning?
What is the process that organizations go through to determine transmission?
What are the views, current strategies, and future plans of the UN and PEPFAR?

10:40 pm ***Session 1: Evidence behind MTCT Estimates***
(Chair: Sostena Romano)

1) *Summary of evidence by regimen (Lynne Mofenson)*
   Summary of studies reviewed and transmission rates used to develop the most recent WHO PMTCT guidelines. Comparison of the existing published, presented, and ongoing studies and resulting conclusions. What key clinical trials data need to be reflected in the models?
2) *Infant feeding and MTCT (Louise Kuhn and Nigel Rollins)*
   How do rates change for women that exclusively breastfeed for the first 6 months compared to those that mix feed? Is it most appropriate to look at this on a monthly basis? What IF data is available? How can/should this information be used in models?

Discussion

1:00 pm ***Session 2: Transmission Data Being Used for PMTCT Models***
(Chair: Geoffrey Garnett)

What programmatic and policy questions are being addressed through PMTCT modelling? What are the current approaches to modelling transmission rates? What MTCT default estimates and CD4 distribution are in use currently in Spectrum, CHAI, PEPFAR and other models? How were the defaults chosen? What additional information is needed?

1) *Spectrum model (John Stover)*
2) *PEPFAR model (Tracy Creek)*
3) *PEPFAR model (Andrew Auld)*
4) *CHAI model (Elizabeth McCarthy)*

Summary of key questions to be answered during the meeting: MTCT rates by regimen, feeding mode and duration, CD4 count, number of weeks on prophylaxis during pregnancy; CD4 distribution of HIV+ pregnant women.

3:45 pm ***Session 3: Clinical Trial Compared to Programmatic Estimates***
(Chair: Laura Porter)

How to calculate/estimate programme transmission rates? What key information is required? What estimates can be made when key information is missing? What is the process of moving from clinical trial transmission rate data to programme data? How can field data supplement models? What can be done to improve models?

1) *Programmatic data and transmission rates from the field (Rosalind Carter)*
   Example of real field data: CD4 distribution, regimen provided and observed transmission.
2) *Using Observed MTCT Data in Botswana for Modelling (Tracy Creek)*
3) *Clinical trial transmission rates to programmatic transmission rates: issues to consider (Chika Hayashi)*

Summary of factors to consider going from efficacy to effectiveness; how do transmission rates from clinical trials compare to the estimates in programmatic activities? What data are commonly available? What data is missing or additionally needed for more accurate modelling?

5:00 pm ***Consensus Recap & Review*** *(Nathan Shaffer)*

Thursday, September 2, 2010

9:00 am ***Recap of day 1****(Geoffrey Garnett)*

9:15 am ***Session 4: Discussion on transmission rate estimates***
(Geoffrey Garnett)

Given available data, what consensus can we reach on (standardized) MTCT transmission rates, based on new evidence and the new WHO guidelines, by regimen and key variables (feeding type, duration BF, CD4 group)? What "Best Case Scenario" rates should be used based on data from clinical trials? Can we begin to fill in a matrix with rates by regimen, CD4 and infant feeding mode and duration?

11:00 am ***Session 4: Continued*** *(Geoffrey Garnett)*

1:30 pm ***Session 5: Documenting Consensus***
(Geoffrey Garnett & Peter Ghys)

Discussion and documentation of consensus and rationale behind decisions: MTCT rates by: a) Regimen, b) Feeding type and duration, c) CD4 count. Discussion and agreement on proposed changes to Spectrum resulting from consultation. Agreement on assumptions to make where there is a dearth of data. List of caveats and areas for improvement when data become available. Outline of data needs and research agenda.

3:15 pm ***Session 6: Towards Virtual Elimination***
(Chair: Priscilla Akwara)

How can consensus transmission rates be used to help with target setting for "virtual elimination" and monitoring progress? How will these be harmonized between the UN and PEPFAR and other partners?

Applying meeting outcomes to global target-setting & progress monitoring (Nathan Shaffer)

Discussion on country support (Chair)

4:00 pm ***Consensus Gathering***

What were the main conclusions? Are there any remaining questions to be resolved? What remaining work needs to be completed and what is our plan for getting it done?

4:30 pm ***Closing*** *(Peter Ghys and Paul Bouey)*

Appendix III: ARV Prophylaxis Options

ARV prophylaxis for mothers who are not eligible for ART – Option A and Option B[4]

ARV Prophylaxis Options

Option A	Option B
Mother • Antepartum AZT (from 14 weeks) • sd-NVP at onset of labour* • AZT + 3TC during labour & delivery* • AZT + 3TC for 7 days postpartum*	**Mother** • Triple ARV (from 14 wks until one wk after all exposure to breast milk has ended) – AZT + 3TC + LPV-r – AZT + 3TC + ABC – AZT + 3TC + EFV – TDF + 3TC or FTC + EFV
Infant **Breastfeeding population** • Daily NVP (from birth until one wk after all exposure to breast milk) **Non-breastfeeding population** • AZT or NVP for 4-6 weeks	**Infant** **For all exposed infants** • AZT or NVP for 4-6 weeks

**sd-NVP and AZT+3TC can be omitted if mother receives > 4 wks AZT antepartum*

World Health Organization

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