Responding to the Failure of Prevention of Mother to Child Transmission (PMTCT) Programmes

What needs to Change?

Experts Roundtable
Geneva, 23-24 June 2008

Meeting Report

Médecins Sans Frontières - Campaign for Access to Essential Medicines and its partners invited a group of experts to a roundtable discussion in Geneva on the 23-24 June 2008 to discuss the current challenges and limitations in the current strategies for the prevention of mother-to-child transmission (PMTCT) in the developing world and explore ways of improving the current status quo. The objective was to discuss the currently available data in the hope of developing a consensus on outstanding scientific questions and of defining the next steps to accelerate the implementation of an improved strategy.

33 participants were in attendance representing a variety of external organizations including Ministries of Health, Clinton Foundation, University of Bordeaux and Elizabeth Glaser Paediatric AIDS Foundation, in addition to representatives from MSF field projects and headquarters. Dr Lynne Mofenson was unable to attend but provided valuable comments in the preparation of the meeting through email. (See participants list in Annex 1).

All presentations from this meeting are available at the Access Campaign website. www.msfaccess.org

Background:

In 2007, the global number of children newly infected with HIV was estimated to be nearly 420,000, with approximately 90% of these children living in Sub-Saharan Africa.[1] Meanwhile in wealthy countries the number of new paediatric infections has dramatically declined, with less than 250 infants infected each year in the US[2]. The majority of these new paediatric infections occur vertically from the mother.

The WHO guidelines published in 2006 are complicated, dependent on the immunogical status of the mother and difficult to roll out on a large scale.[3] Today convincing evidence is available both for the developed world where infant HIV transmission has nearly been eradicated and in the developing world to support triple antiretroviral therapy for all mothers from week 28 of pregnancy, irrelevant of their clinical, immunological or virological status.[4] However many unanswered questions remain regarding choice of therapy, breast-feeding and implementation.

A background document was given to participants prior to the meeting.and can be found on the Access Campaign website. www.msfaccess.org.

Focus of the Meeting:

The focus of the meeting was to discuss the challenges of PMTCT programs, focusing on the need for a simplified "one size fits all" combination of anti-retrovirals (ARVs). There is consensus that the main risk factor for MTCT is a detectable viral load in the mother, and hence the complete suppression of the VL is the best way for preventing transmission. There is no controversy on the strategy to be adopted for the management of pregnant women with a low CD4 count, who needs ARV therapy for their own health. The uncertainty is what is the best strategy for women who have a CD4 above 350 and who do not need, according to current guidelines, ARV therapy for themselves. Some researchers think that interventions during pregnancy and at the time of delivery may be adequate for women with a CD4 cell count above 500, as there is a perceived reduced risk of transmitting the virus. Data from the Kesho Bora study was presented showing a low rate of transmission for women in this category.[5] Additionally there was no disagreement on the importance of the need to eradicate MTCT in developing countries.

The agenda (see Annex 2) was designed to address to major scientific obstacles and concerns regarding the ARV protocol / regime for these women with who do not need ARV for their own health (CD4 > 350). The presentations and following discussions were scientific-based and did not enter in detail into implementation challenges. The major topics of discussion included:

- Interruption of ART, for women starting ARV therapy with a CD4 > 350.
- Effect on ART for the mother on the children in-utero
- Breast-feeding; ART for the mother vs PEP for the child
- What is the best regime and the cost implications

Current PMTCT programmes have not been very successful and pediatric infections are far from being eradicated in sub-Saharan Africa. A retrospective cohort analysis of women enrolled between 2000 and 2005 in a MSF-supported PMTCT program in Arua, Uganda showed an overall transmission rate of 15.5%.[6] In this analysis 14% of mothers presenting in the Antenatal Clinic (ANC) refused to be tested to determine their status. Of those mothers testing positive, only 50% enrolled in the PMTCT programme. This highlights on the key obstacles to obtaining an effective PMTCT program, namely the loss to follow up at every point of the cascade from when the mother first presents at for antenatal care and learns her status, until diagnosis of the child's status once the breast-feeding period has ceased.

Other obstacles that were raised over the meeting and should be addressed include;

- The lack of interaction between National Aids Programmes and Maternal Child and Health Programmes.
- The lack of human resources at low-level health centres
- The lack of financial resources
- Inadequate Monitoring and Evaluation
- Sub-optimal logistic and supply management
- Policy decisions in countries restricting what qualifications are needed to dispense ARV drugs.
- Lack of availability of PCR machines to accurately diagnose children under 18 months
- Weakness of health systems to cope with evolution of scientific based recommendations.

Presentations from both the Ugandan and Zambian Ministries on the implementation of PMTCT services in the national programs showed just how debilitating an impact these obstacles can have on programmes.[7,8] Nevertheless, while acknowledging these are important topics that need consideration, these did not form the focus of this meeting. This report will thus primarily consider the scientific questions related to protocols and regimens.

Interruption of ART, the impact on the mother

In developed world guidelines today, ARV prophylaxis is recommended for all pregnant women with HIV infection, regardless of viral load.[9] This is based on the knowledge that while rates of peri-natal transmission are low in women with low HIV RNA levels, there is no threshold below which lack of transmission can be assured. Additionally in the developed world, HIV positive women do not breast-feed which removes the risk of transmission to the baby. In this scenario the mother stops her ARV treatment until her disease progresses to a stage where she meets the criteria to start ART.

Data from the PACTG 076 showed that women who received short duration of AZT prophylaxis for PMTCT with stopping postpartum were no more likely to have disease progression, AIDS or death than those receiving placebo[10]. Today however there is no published data on the long-term outcomes of mothers who took HAART through pregnancy. With the use of HAART during pregnancy the "standard of care" in developed world, these women should be followed, and outcomes documented and analyzed to provide insight into this question.

The results of the SMART (Strategies for Management of Antiretroviral Therapies) study are often used in discussion to support the concern of the perceived risk of interrupting ARV treatment to this subset of pregnant mothers. Dr Bernard Hischel gave important insight into interpreting the results from this study.[11] The SMART study was designed to look at the outcomes and possible benefits of the use of CD4+ cell-guided episodic ART (DC strategy) compared with continuous ART (VS strategy).[12] Recruitment started in January 2002 and was suspended early due to a significant number of endpoints (opportunistic infections (OI) or death) in the DC arm. Patients enrolled in this study were on ARV treatment and had been started on ARV treatment when their CD4 was approx 200 (median). The most commonly reported OI was oesophageal candidiasis. In the analysis of the cause of death, more were recorded in the DC arm, but very few of these were AIDS related. Additionally the study shows that at high CD4 the number of years of treatment required to prevent one end point is over 50 years.

It is important to remember the women we are discussing have CD4 counts' above 350, to be contrasted with a median CD4 of 200 in SMART. Most relevant to the discussions related to PMTCT is that the SMART study does not show intermittent treatment is inferior to no treatment.

This information should help decision makers feel more comfortable to respond to this question. The conclusion of from Bernard Hischel was "Mothers with high CD4 can stop ARV treatment without harm"

Aim for Child "HIV Free Survival"

There is no controversy or disagreement that the best result for a child is "HIV-free survival" and this must be remembered in all discussions.

The aim of all interventions is to have the mother's VL undetectable and the "gold standard" is triple therapy for all during pregnancy. This in combination with replacement feeding has resulted in new infections through MTCT to almost disappear. However this is not a feasible option in many resource-limited settings, raising the dilemma of how to overcome the problem of the risk of transmission on the HIV virus through breast milk.

If formula feeding is Acceptable, Feasible, Affordable, Safe and Sustainable (AFASS) it can be considered an option, and has shown good results. Positive results were presented from Maragua District Hospital in Kenya where mothers are given the choice of formula feeding or exclusive breast-feeding. In the study from September 2006 85% of HIV-infected mothers opted to not breast-feed their infants and since April 2007 there has been no new HIV pediatric infections[13]. The cost of the formula feeding is still a limiting factor, and additional resources are needed to ensure the quality of the water.

However in many settings this is not possible and breast-feeding is the best option for "survival" of infants. How to reduce the risk of transmission of the virus to the infant in the breast-feeding period is therefore one of the key questions.

There are two schools of thought; ART prophylaxis to the mother and / or Post Exposure Prophylaxis (PEP) for the child.

The first option is for the mother to continue taking ARV treatment through the breast-feeding period. The theory is to aim to have the mother's viral load undetectable and minimise the risk of transmission. The concerns are the impact of low-level ARV on the development of the infant and the increase risk of resistance if the child does contract the virus. There is a need to follow children born to HIV mothers who were on therapy for themselves during pregnancy and breast-feeding to try to answer questions with regard to child development.

The second option is for the newborn to take ARV as a preventative measure for the duration of breast-feeding. There have been a few studies using either mono or dual therapy for the infant that have shown promising results, but these studies have not been done for the complete duration of breast-feeding. The recently published SWEN study looked at six weeks of NVP for the infant and showed a reduction in transmission compared to single dose NVP.[14] This strategy is more difficult to implement as dosages of ARV for children are weight-dependent, and so dosages will change as the child grows. Dosing with syrups is complex and challenging and treatment success depends to a great extent on the mother's involvement and her capacity to administer the ARVs. In addition, exposing the child to therapeutic levels of ARVs raises the same questions as the first option, the impact on the child's development and the risk of resistance if the child does contract the virus.

Both scenarios appear to reduce the risk of transmission during the breast-feeding period. Programmatically however, they can be quite different. Decision makers must consider the need to simplify protocols and regimes to ensure that PMTCT programs can be rolled out to the lowest level health centers when taking decisions on guidelines.

Resistance concerns for mother and infected infant

It is widely accepted that single dose NVP (sdNVP) given to the mother does create resistance problems and the addition of a short course "tail" to minimize this risk is included in current WHO guidelines.[15] There is a still an unanswered question on the clinical significance of the NVP resistance for subsequent HAART in mothers, but some trials are currently underway to address this.

With successful implementation of PMTCT programs we will see a reducing number of pediatric infections. The dilemma is for the child who does contract the virus, raising the concern over the possible resistance profiles that would limit the choices for treatment to this child. There has been more data presented confirming these concerns; KIBS identified resistance in 67% of infected children and SWEN reported 92% NVP resistance in infected infants in the extended NVP arm.[16]

In April 2008 the WHO Technical Reference Group for Paediatric HIV/Antiretrovial Therapy and Care met to review current data. A recommendation was given that for all HIV infected infants with a history of exposure to single dose NVP or NNRTI containing maternal ART or preventative ARV regimes, a protease inhibitor based triple ART regime should be started.[17]

What regimen?

For simplification the ideal formulation would be a **robust triple fixed-dose combination (FDC) that can be taken once a day.** The aim is to increase adherence in order to keep the mother's viral load undetectable. Today the most commonly used triple FDC for treatment is 3TC/d4T/NVP.[1] This formulation however is not suitable in a "one size fits all" strategy as NVP is contraindicated in women with a CD4 count > 250 due to risk of hepatotoxicity.

There are three other triple fixed dose combinations available today; AZT/3TC/NVP[2], ABC/3TC/NVP[3] and TDF/FTC/EFV.[4] The first two options include NVP, which for reasons explained above is not suitable. With regards to the third option, TDF has been recently reclassified as Category B by the U.S. FDA and is recommended in the 2007 Perinatal Guidelines.[18] EFV is contraindicated during the first trimester of pregnancy and the issue of contraception for a mother during lactation would need to be addressed but the TDF/FTC/EFV formulation is available today and could be implemented today.

While it is known that TDF is not teratogenic, there is still a concern over the use of TDF in pregnancy and in breast-feeding with respect to the potential effect of fetal and later infant and child bone growth. There are children today

[1] 3TC : Lamivudine, d4T : stavudine, NVP : Nevirapine
[2] AZT : Zidovudine, 3TC : Lamivudine, NVP : Nevirapine,
[3] ABC : Abacavir, 3TC : Lamivudine, NVP : Nevirapine
[4] TDF : Tenofovir, FTC : Emtricitabine, EFV : Efavarinz

living in developed countries who have been exposed to TDF inutero. There is a need for the scientific community to monitor these children and document their outcomes to help dispel the fear of the use of TDF.

The cost of implementation of a "one size fits all" regimen is of concern to decision makers. Today the cost of treating a mother with triple therapy from week 28 of pregnancy until abrupt weaning at 6 months depends on the regimen

.

The table below shows the cost of the different regimes for a 9-month period. The prices are from the 11th edition of MSF's *Untangling the Web of Antiretroviral Price Reductions* and are for the cheapest quality-assured generic product, with the exception of the generic triple TDF-based FDC that today is under evaluation at WHO Prequalification.[19]

Regime	Cost in US$	Pills per day
TDF/FTC/EFV (originator)	460	1
TDF/FTC/EFV (generic)	320	1
TDF/3TC/EFV	274	1
AZT/3TC + EFV	200	3
AZT/3TC/ABC	479	2
AZT/3TC + LPV/r	461	6

Perspective and Conclusion

In MSF, there are currently no PMTCT programmes implementing triple therapy prophylaxis for all mothers during pregnancy and the breast-feeding period. Several discussions and debates have taken place within MSF including the Aids Working Group and other key medical staff. MSF plans to start implementation of the triple therapy strategy in some settings with the objective of showing that, even in programme conditions, it is feasible, simpler and more effective than the currently recommended strategy.

In conclusion, there is a urgent need for the scientific community to engage in solving key questions related to triple prophylaxis in pregnant women, but to stress this should not delay the implementation of the best known way to prevent the transmission from the mother to the child so we can aim to have a new HIV free generation.

Future developments

The Department of HIV/AIDs at WHO in collaboration with the Department of Child and Adolescent Health and Development is planning to organize an "Expert consultation on new and emerging evidence on use of antiretroviral drugs for the prevention of mother-to-child transmission of HIV" in Geneva in **November 2008**. The purpose of this consultation will be to review and analyse new evidence that has become available since the last meeting in 2006 regarding the use of ARVs for PMTCT especially during post-natal period. This consultation will also serve as a preparatory meeting for the eventual review of the 2006 WHO PMTCT ARV guidelines.

Data was presented at the IAS 2008 Conference in Mexico City on the neurodevelopmental function of ARV-exposed uninfected children that were enrolled in PACTG 219/219C trials. 1840 infants born between 1993 and 2006 were studied, 92% of whom were exposed to ARV in utero. The results showed no decline in cognitive or motor function for infants with in utero ARV exposure compared to unexposed.[20]

Additional data presented in Mexico City from the PEPI-Malawi study showed daily NVP or NVP + AZT to age 14 weeks could reduce postnatal HIV-1 transmission by >60% during the intervention period.[21]

Furthermore a study published in September 2008 in *Antimicrobial Agents and Chemotherapy Journal* is of relevance: Chronic administration of tenofovir to rhesus macaques from infancy through adulthood and pregnancy: summary of pharmacokinetics and biological and virological effects, demonstrating the safety and sustained benefits of prolonged TDF-containing regimens throughout development from infancy to adulthood, including pregnancy.

Finally a large “PROMISE” trial is planned to address multiple questions with the overall goal to maximize maternal and infant health. Questions to be addressed include comparing short course ARV treatment to HAART for women with CD4 counts over 350, comparing infant prophylaxis to maternal HAART through the breast-feeding period and comparing stopping ART to continuing on HAART for women who start on ART solely for the PMTCT. The study aims to recruit approx 6000 participants across multiple sites and is estimated to have a duration of five years

Annex 1

RESPONDING TO THE FAILURE OF PMTCT PROGRAMMES:

WHAT NEEDS TO CHANGE?

Experts Roundtable
23-24 June 2008

Geneva, Hotel Le Grenil

Participant List

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Annex 2

RESPONDING TO THE FAILURE OF PMTCT PROGRAMMES:

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Experts Roundtable
23-24 June 2008
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AGENDA

Monday, 23rd June 2008

10.00 – 10.15: Welcome and coffee

10.15 – 10.30: Introduction: objectives of the meeting – Alexandra Calmy
10.30 –10.45: Commitment of MSF to improve PMTCT intervention - Isabelle Segui

10.45 – 11.30: **The spectrum of PMTCT intervention – moderator Alexandra Calmy**
National program protocols: where are we? – L Ciaffi
The experience of MSF F in Uganda: a retrospective study – S. Balkan
Discussion

11.30 – 13.00: **Triple therapy for the women: some results, some concerns. Moderator Bernard Hirshel**
The available data: AMATA – V. Arendt
Resistances: the evidences – F. Dabis
Which regimen? – R. Tubiana
When to stop – B. Hirshel
Discussion

13.00 – 14.30: Lunch

14.30 – 16.30: **Obstacles/difficulties in implementation: would a change in protocol make a difference? Moderator: Laura Ciaffi**
PMTCT at different level of care - S. Onyango
The workload and the HR available – B. Putta
The triple prophylaxis in practice – G. Liotta
Discussion

16.30 – 17.00: Coffee Break

17.00 – 17.30: **Costs implications for triple therapy. Moderator Karen Day**
The costs of the triple prophylaxis – S. Romano
Which balance between cost and effectiveness? Perspective from the GF – JP. Moatti

Cocktail

Tuesday, 24th June 2008

9.00 – 10.30: **Scientific open questions: the child – Panel discussion - Moderator François Dabis**
Breast-feeding on triple therapy: Kesho Bora – I. de Vincenzi
The experience of Kenya with artificial feeding – V. Torres
What is the best for the child? – C. Courpotin
The future options for the child – L. Kleynhans

10.30 – 11.00: coffee break

11.00 – 12.30: **Perspectives: need of more evidence or need of more implementation?**
Panel discussion with D. Berman

12.30 – 13.30: Lunch and finish

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[20]Abstract MOAB0102, Aids 2008, Mexico City: Neurodevelopmental status and prenatal antiretroviral exposure in HIV-exposed uninfected infants
[21] Abstract THAC0403, AIDS 2008, Mexico City: Should infants receive antiretroviral prophylaxis throughout breastfeeding? Findings from the postexposure prophylaxis of infants study in Malawi (PEPI-Malawi)