RESPONDING TO THE FAILURE OF PMTCT PROGRAMMES:

WHAT NEEDS TO CHANGE?

Experts Roundtable
23-24 June 2008
Geneva, Hotel Le Grenil

Background Document

In 2007 an estimated 420 000 children were newly infected with HIV; about 87% of those infections happened in sub-Saharan Africa, 0.001% in North America. The majority of these children become infected during pregnancy, delivery or during the breast-feeding period (mainly in areas where safe and affordable replacement feeding is not available).

The developed world has been successful in reducing the rate of transmission of the HIV virus from mother to child to below 2% or even lower. However, in developing countries transmission rates remain unacceptably high in most places.

Why this is happening?

For sure, the reason for this is two fold: on a public health scale it is a question of coverage: today, the majority of women in resource-poor countries are not accessing PMTCT services, and then within PMTCT services the question of best-practice protocols and their implementation is fundamental. Both these issues become interlinked where complex protocols become a potential obstacle to large scale roll-out.

Different protocols

Current guidelines for PMTCT in the developing world differ from the standards of care for developed countries. In 2006, WHO published The Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Towards Universal Access. In its recommendations WHO suggest a two tier approach making a distinction between women in need for HAART for their own health and those for whom treatment would only be given as prophylaxis to prevent the risk of infection to their child.

This complex protocol requires a high level of understanding by health care workers to correctly apply it and explain it to mothers for an outcome that is sub-optimal compared to the regimen used in the developed world**.**

The 2007 Recommendations for Use of Antiretroviral Drugs in Pregnant Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States recommend HAART for all pregnant women, irrespective of virologic, immunologic or clinical parameters. In these guidelines the single-dose intrapartum or newborn NVP is not recommended as it may be associated with the development of NVP resistance. The minimum duration for AZT prophylaxis for the infant is 6 weeks compared to 1 week for WHO. Other differences in interventions include recommendation of resistance testing prior to initiation for the child (treatment or prophylaxis) and for women on treatment who have persistently detectable HIV RNA levels. In addition, it is advised scheduled caesarean delivery for HIV infected pregnant women with HIV RNA levels >1000 copies/ml and avoidance of breastfeeding.

However, for many reasons including cost, lab capacity and availability of ARV drug many of these additional interventions will not be available or adaptable to the developing world.

Giving HAART to all HIV infected pregnant women not only has the advantage of reducing transmission to lower levels than can be achieved with optimal implementation of existing protocols, it also reflects good medical practice and has the advantage of allowing for a common strategy for all HIV infected women irrespective of CD4 count. This translates into **simplification of protocols**, avoiding confusion of mothers and health-care providers and therefore increasing the probability of success. In many areas human resources is a major limitation and health-care workers are poorly trained. With this strategy protocols could be largely streamlined and implemented at health centre level.

A crucial difference between practices in the "North" and "South" appears in the postnatal period in relation with infant feeding. It is known that exclusive formula feeding is the most effective method to prevent MTCT from HIV+ women in postnatal period. However due to financial and safety reasons (formula preparation, access to clean water, maternal antibodies to infectious disease etc), formula feeding is not considered an appropriate option for most women in the developing world. WHO has recently issued a Consensus statement on HIV and Infant Feeding which confirms the recommendations that mothers should "exclusively" breastfeed for six months and continue breast feeding even further with abrupt weaning only when safe and adequate diet without breast milk can be provided.

It is understandable that knowledge and medical practice from the developed world cannot always be transferred to developing countries. But this does not relieve us from the responsibility of offering the best intervention possible.

The provision of triple ARV prophylaxis to all pregnant women for the prevention of transmission of HIV is a strategy already applied in isolated experiences in developing world and some concerns still exist around this option.

In the table below advantages and limitations of the two regimens are summarised:

ACTUAL RECOMMENDATIONS	**TRIPLE ART FOR ALL PREGNANT**
Advantages: -As efficient in reducing transmission as ART in non-breastfed infants (or if transmission measured at 6 weeks post-partum) born to HIV infected women not in the criteria for ART. -Lower foetal exposure to ARV (shorter duration of exposure; exposure to less drugs). -More forgiving if adherence is not perfect (no risk of emergence of resistance to AZT; for resistance to NVP, see below)	**Advantages**: -Very efficient in reducing transmission (cfr preliminary data of clinical trials) -Simple: same protocol used during pregnancy, labour and post-partum for the mother -Same protocol (3 ARV drugs, although differences in ARV used) used in pregnant women in the criteria for ART and in those not in the criteria for ART; same protocol for infant prophylaxis -No more SD NVP used and therefore no more risk of SD NVP induced resistance -No more need for actively promoting artificial feeding and/or exclusive breastfeeding/early weaning. Would make PMTCT programs much less labour intensive; would prevent the risks linked to AF (increased mortality and morbidity) and reduce the risk link to EW (increase risk of malnutrition and morbidity).
Limitations: -Limited efficiency when breastfeeding: limits transmission compared to no intervention, but transmission remains high (as high as 5 %, although contradictory data) -Needs to be used in combination with either exclusive breastfeeding/early weaning (EBF/EW) or	**Limitations:** - Adherence: most of pregnant women attending ANC who are not in the criteria for ART are asymptomatic and learn about their HIV infection during the course of their pregnancy; breastfeeding women will be asked to take drugs every day for at least 9 months.

artificial feeding (AF) to increase efficiency. - Debatable feasibility (need for intensive counselling, replacement food for weaning, possibility of ensuring safe bottle feeding, etc) and relevance re: benefit/risk and benefit/investment ratios of both strategies in field conditions. -Complex protocol: ARV used vary during the course of pregnancy, labour and post-partum. -Risk of emergence of NNRTI resistant strains of the virus in the mother and the infant, due to the use of SD NVP. Risk of resistance as high as 70-80% in the mother and the infant (with allele specific assays) if no tail protection although the risk is reduced if tail protection properly administered (with AZT/3TC; with TDF/FTC) in the mother; with AZT/(3TC) in the infant. - Negative impact of resistance to NVP on NNRTI based ART outcomes in mothers if ART is started within 6 months of exposure. Negative impact on ART virological outcomes in HIV infected infants whatever the time of ART start after exposure to SD NVP.	-Concerns about NVP induced hepatotoxicity in women with CD4 > 250. Conflicting data about the risk and the threshold above which this risk is significant; recent data (Thailand, Rwanda) reassuring. Pregnant women with high CD4 (indicative threshold: > 350) should not receive a NVP containing regimen anyway. - Operational feasibility in some settings; such a strategy could put too a heavy burden on PMTCT/ART programs in high prevalence settings. -Risk of induction of resistance strains of the virus in the milk and transmission to the infant if some ARV penetrate and other don't or if the concentration of some ARV are sub-therapeutic (AZT and 3TC: breast milk concentration is 2 to 3 time higher than in plasma; D4T, LPV, TDF, EFV: no data in humans; is found in milk of animals). - Uncertainty about the safety of ARV interruption after weaning in mothers not needing ART for themselves.

Existing literature and ongoing studies show that concern about the breastfeeding period is shared with researchers and decision makers. A number of studies using ART during pregnancy and breastfeeding (where applicable) have recently shown encouraging results (AMATA, MITRA +, DREAM+, Kisumu Breastfeeding Study). The AMATA preliminary results point to transmission rates as low as 1.6% with a total of 7/431 children being infected at month 7, only 1 of those post-natally (1/174 → 0.6%). Kisumu Breastfeeding Study presented at the CROI 2008 also showed promising results with a low transmission rate of 3.5% attributable to breastfeeding. Interesting is that infants in this study were not on ARV prophylaxis. At least another three studies are ongoing in Africa (KIBS in Kenya, Kesho Bora in Burkina Faso, Kenya and S Africa and BAN in Malawi) testing ART during the breastfeeding period.

The Drugs

The ideal formulation would be a **robust triple FDC that can be taken once a day.** The aim is to increase adherence with the aim to keep the mother viral load undetectable.

Today the only triple fixed dose combinations available are AZT or D4T/3TC/NVP, AZT/3TC/ABC and TDF/FTC/EFV. The first option includes NVP, which is not suitable for use in the strategy for all pregnant HIV+ mothers. With regards to the second option, it is known to be less powerful and therefore not really indicated for starting treatment. For the last regimen, TDF has been recently reclassified, as Category B by the US FDA and is recommended in the 2007 Perinatal Guidelines. EFV is contraindicated during the first trimester of pregnancy and the issue of contraception for a mother during lactation would need to be addressed. **The TDF/FTC/EFV formulation is available today and could be implemented today.**

Another ARV that has been used in some of the clinical trials listed above is LPV/r, commonly used as a 2nd line treatment. Concerns have been raised regarding the potential creation of resistance for a patient, limiting future drug choices as their disease progresses. This concern is justified only to a certain extent, even more so in view of the fact that LPV/r is more “forgiving” than most other drugs and the duration of use will be limited. A triple treatment always bears a lower risk of resistance than a monotherapy. However, today WHO promotes the use of AZT mono-therapy for pregnant women with a CD4 > 350 hoping that the relatively short exposure to AZT would minimize their resistance to this drug for later use. By offering a robust triple treatment this risk would be reduced even more.

Based on current research and individual characteristics of the drugs, there are a few other combinations that could be explored theoretically. TDF/3TC(FTC)/EFV, AZT/3TC/LPV/r, TDF/3TC/LPV/r. Today these formulations do not exist in FDC, however the manufacture of Co-blisters for ease of use is possible in the short term.

US FDA pregnancy categories for drugs of interest

Drug	Pregnancy (FDA)
Abacavir (ABC)	Category C
Efavirenz (EFV)	Category D
Emtricitabine (FTC)	Category B
Lamivudine (3TC)	Category C
Lopinavir/Ritonavir (LPV/r)	Category C
Tenofovir (TDF)	Category B
Zidovudine (AZT)	Category C

A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the foetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters)
B: Animal reproduction studies fail to demonstrate a risk to the foetus, and adequate but well-controlled studies of pregnant women have not been concluded
C: Safety in human pregnancy has not been determined: animal studies are either positive for foetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the foetus
D: Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despites its potential risk
X: Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Conclusion

Avoiding transmission of HIV to infants should be and is a priority in places where HIV is prevalent. We do have information on what the best medical intervention would be; however its implementation in the developing world lags behind.

The challenge is not to show that the medical intervention works, but that it works on an every-day operational reality and the lessons learnt should be used to advocate for the appropriate drugs to be made available.

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