REVIEW PAPER

Updates to the World Health Organization's Recommendations for the Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants

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SUMMARY

In July 2010, the World Health Organization (WHO) released new guidelines entitled, "Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Towards universal access." Previewed in November 2009 in abridged form, the completed document highlights the key WHO recommendations for antiretroviral treatment (ART) and prophylaxis in pregnant women, and contains substantial changes from the 2006 guidelines. Of note, the new guidelines recommend ART for all pregnant women with a CD4 cell count (CD4) less than 350 cells/mm^3, regardless of their clinical stage; includes tenofovir (TDF) as an acceptable alternative component of an ART regimen in pregnant and breastfeeding women; encourages initiation of both ART and antiretroviral (ARV) prophylaxis early in pregnancy; eliminates single-dose nevirapine (sdNVP) *per se* as a prophylaxis option; lists three-drug ARV prophylaxis as an option for women who do not need ART for their own health; and introduces extended daily infant nevirapine (ED-NVP) as a strategy for prevention of breast milk transmission of HIV. This article reviews these new recommendations and their rationale, and highlights key implications and challenges to their implementation in the Zambian context.

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INTRODUCTION

Pediatric HIV infection remains a substantial problem worldwide, with close to 400,000 new infections occurring yearly primarily as a result of maternal to child transmission.[1] In Zambia alone, an estimated 130,000 children are living with HIV infection and another 85,000-90,000 HIV-exposed babies are born each year, resulting in an additional 28,000 infections.[2] While perinatal HIV transmission has largely been eliminated in the industrialized world, where access to ARVs is nearly universal and safe alternatives to breastfeeding exist, such drastic reductions have not yet been seen in sub-Saharan Africa. Three challenges stand out among many which contribute to the higher rates of maternal-to-child HIV transmission in this setting: early identification of infected pregnant women, timely initiation of effective antepartum prevention, and effective prevention during the breastfeeding period. Additionally, the use of sdNVP on its own has led to high rates of non-nucleotide reverse transcriptase inhibitor (NNRTI)-resistance in both women and children,[3] resulting in limited – and more expensive – treatment options for these patients. Although not without their limitations, the recommendations provided by the WHO in their recently released "Antiretroviral Drugs for Treating Pregnant Women" take a step in the right direction to address these issues.

Key words: Guidelines, HIV, prevention of mother to child transmission, antiretroviral, Zambia.

Key Recommendations: ART for HIV-infected pregnant women who need treatment for their own health

The new recommendations for ART initiation in newly-identified HIV-infected pregnant women are summarized in Table 1.[4] While the 2006 WHO guidelines recommended ART for pregnant women with clinical stage 1 or 2 disease only when the CD4 dropped below 200,[5] the recommendation for earlier treatment is consistent with what has been recommended in Zambia since 2007.[6] Importantly, these new guidelines state that women who need ART for their own heath should start "irrespective of gestational age and continue throughout pregnancy, delivery, and thereafter".[4] This is in contrast to the 2007 Zambian guidelines, which state that ART should not be initiated in women presenting at 36 weeks gestation or later.[6] Adaptation of the WHO guidelines should eliminate the confusion providers have experienced around the Zambian caveat.

Table 1: Summary of Indications for ART in Pregnant Women

WHO Clinical Stage	CD4 (cells/mm^3)	Recommendation
1	> 350	ARV prophylaxis
	≤ 350	ART
2	> 350	ARV prophylaxis
	≤ 350	ART
3	Any	ART
4	Any	ART

One obvious implication of these guidelines is that all HIV-infected pregnant women need timely CD4 testing. This remains a challenge in much of Zambia and, until laboratory services can be scaled up to meet the demand, it is possible that many women who are eligible for ART will be given ARV prophylaxis instead.

The recommended regimens for pregnant women requiring ART for their own health are listed in Table 2. Including TDF as an alternative option is based on the lack of significant associated toxicities found in pregnancy registry data;[7] EFV is also included. While the guidelines state that EFV should not be "newly initiated" during the first trimester, its use in pregnancy is otherwise allowed because the benefits to the mother and the reduction in transmission are felt to outweigh the potential toxicity risks.[4]

Table 2: Recommended Regimens for Pregnant Women in Need of ART for their own Health.

NRTI "Backbone" (2 drugs)	3rd Drug (NNRTI)
Preferred: Zidovudine (AZT) + Lamivudine (3TC)	Nevirapine (NVP) or Efavirenz (EFV)*
Alternative: Tenofovir (TDF) + Emtricitabine (FTC) or 3TC	

*Note: EFV not to be newly initiated during the 1st trimester of pregnancy

In Zambia, TDF has been part of the preferred 1st-line ART since 2007; however, many providers have been reluctant to initiate women of child-bearing age on this drug due to concerns about toxicity in pregnancy and the need to switch to an alternative agent should pregnancy occur. The new guidelines should reassure providers that TDF can be continued during pregnancy and the breastfeeding period.

Interestingly, "Antiretroviral Drugs for Treating Pregnant Women" does not specifically address what to do in either of two common clinical scenarios: first, which regimen should be used for women who need ART for their own health but whose CD4 is greater than 250, the threshold above which NVP toxicity has commonly been associated; and second, what should be done when women already on EFV-containing ART become pregnant. Concerning the first, the guidelines state that NVP can be used for women with a CD4 250-350, but that an alternative 3rd agent should be used if the CD4 is greater than 350 due to the known risks of NVP in such women starting ART.[8] This first scenario also underscores the need to obtain a CD4 count on all women before starting therapy. Concerning the second, no recommendation is given. Options include temporary substitution of EFV during the 1st trimester with either: a. abacavir (ABC), if the woman has been on therapy for at least 6 months with documented good adherence and can therefore be assumed to be virally suppressed (this option has not been studied but presumably should be effective at maintaining suppression); b. lopinavir/ritonavir if the above-noted conditions are not all met; or c. nevirapine if the CD4 remains below 250 (though recent data suggest that such a switch may be safe after immune reconstitution to even higher CD4 counts. EFV should be resumed after completion of the 1st trimester for most women, and appropriate

pregnancy prevention measures should be instituted immediately post partum in all women taking this ARV.

Women on ART for their own health will obviously continue this through the breastfeeding period. This should provide effective prophylaxis for the infant if ART was started early in pregnancy and the mother is adherent, so that viral suppression in both the serum and breast milk has occurred. Nonetheless, the new WHO guidelines recommend some form of infant prophylaxis after delivery for infants born to women on ART. For those who are breastfeeding, six weeks of ED-NVP starting from birth is recommended; and for those who are not, six weeks of either daily AZT or ED-NVP. Neither recommendation is based on data from women on ART; the former can probably be justified by the fact that some women will be starting ART later in pregnancy and viral suppression may not have occurred by the time breastfeeding is initiated. In such cases, the ED-NVP will essentially be acting as pre-exposure prophylaxis and may provide additional protective benefit. It is not clear that AZT or ED-NVP is needed for infants that are not breastfeeding when the mother is already on ART; however, the recommendation may provide coverage for those women planning on replacement feeding who end up mix-feeding or breastfeeding due to difficulties securing sufficient amounts of breast-milk substitute.

Key Recommendations: ARV prophylaxis for all HIV-infected women who do not need treatment for their own health

The new WHO recommendations differ most strongly from those of 2006 concerning women who do not need ART for their own health. Emphasizing the need to provide early access to effective prophylaxis, they list two options for these women, followed by some type of prophylaxis to prevent transmission during the breastfeeding period. Summarized in Table 3, they no longer include sdNVP on its own.

Table 3: ARV prophylaxis options recommended for women who do not need treatment for their own health[4]

Option A: Maternal AZT	**Option B: Maternal triple ARV Prophylaxis**
Mother	Mother
■ Antepartum AZT (from as early as 14 weeks gestation) ■ sd-NVP at the onset of labor* ■ AZT+3TC during labor and delivery* ■ AZT+3TC for 7 days post-partum* *sd-NVP and AZT+3TC can be omitted if mother receives > 4 weeks AZT antepartum	Triple ARV from 14 weeks until 1 week after all exposure to breast milk has ended ■ AZT+3TC+LPV/r ■ AZT+3TC+ABC ■ AZT+3TC+EFV ■ TDF+3TC(or FTC)+EFV
Infant	Infant
Breastfeeding infant ■ Daily NVP from birth until 1 week after all exposure to breast milk has ended *Non-breastfeeding infant* ■ AZT or NVP for 6 weeks	*Breastfeeding infant* ■ Daily NVP from birth to 6 weeks *Non-breastfeeding infant* ■ AZT or NVP for 6 weeks

It is important to note that, whichever option is used, the new recommendation is for women to start taking the prescribed regimen at 14 weeks gestation. This shift was motivated by the all-too-common scenario of women presenting for their first antenatal visit sometime before 28 weeks – the previously recommended start time for "short-course" prophylaxis – only to disappear for the remainder of the pregnancy. Consequently, many known HIV-infected mothers have not been receiving any prophylaxis at all. The new guidelines emphasize starting the chosen prophylactic regimen at the first antenatal visit to avoid such missed opportunities; however, this recommendation is not without its drawbacks.

For women for whom the 3-drug ARV prophylaxis is chosen, beginning this at the first antenatal visit neglects the importance of adequate treatment preparation prior to initiation. While starting earlier in pregnancy will clearly give more time for viral suppression to occur before delivery, and should therefore reduce the risk of transmission, this should not be done at the expense of proper treatment

preparation. Doing so could lead to suboptimal adherence, development of resistance in the mother, and transmission of resistant virus to the child.

For women receiving single-drug prophylaxis with AZT, there are no data to indicate that starting at 14 weeks will reduce *in utero* transmission, and starting this early may potentially lead to increased maternal-fetal toxicity as well as the development of AZT resistance mutations. Anemia in both women and infants exposed to AZT is well-documented.[10] Other cytopenias (lymphopenia, neutropenia), which may persist for several years after birth and which are associated with duration of AZT exposure,[11,12] and mitochondrial toxicities such as hyperlactatemia and neurodevelopmental delay,[13,14] have also been reported.

Prolonged exposure to AZT monotherapy is likely to increase the frequency of AZT-associated resistance mutations in both women and their infants if transmission does occur, resulting in potentially compromised treatment options for both. While one study from Thailand found no AZT-associated resistance in women starting short-course prophylaxis at 34 weeks,[15] data from the US and Europe in the era of mono- and dual-therapy indicate that this will occur in a significant percentage of women and their children when ARV prophylaxis is started early in pregnancy. Among 293 women in the Perinatal AIDS Collaborative Transmission Study (PACTS) who received AZT during pregnancy, 17.3% of the women and 8% of their infected children had at least one AZT-associated resistance mutation.[16] While a lower CD4 count was associated with the risk of developing resistance in this study, the median CD4 of women who had resistance was 389 cells/mm^3, suggesting that even women with CD4 > 350 remain at risk. Additionally, duration of ARV exposure was also significantly associated with resistance: at 24 weeks, the median exposure among those who developed resistance is similar to what will occur if AZT is started at 14 weeks gestation. AZT resistance was found in 25% of women from the Women and Infants Transmission Study (WITS), where – in contrast to the PACTS cohort – this resistance was associated with an increased risk of maternal-to-child transmission.[17] Women from WITS had, however, lower average CD4 counts and higher viral loads than those in PACTS.

The WHO argues that most women will not present as early as 14 weeks gestation, and that the goal of the current recommendation is to get women started on the appropriate prophylactic regimen during the 2nd trimester of pregnancy rather than waiting until late in pregnancy. This makes sense, and we support initiation of 3-drug ARV prophylaxis as early in pregnancy as possible since it is likely to lead to improved suppression rates at the time of delivery and therefore decreased transmission. However, we believe that it would be preferable to make a recommendation that explicitly states the ideal timing of and requisites for initiation of each option, rather than one that could lead to inadequate treatment preparation and an increased risk of toxicity and/or resistance.

There is little debate about the need to provide effective prophylaxis during the breastfeeding period. Most women in sub-Saharan Africa have no acceptable, feasible, affordable, safe, and sustainable (AFASS) alternative to breastfeeding, and HIV-free survival has not been shown to be significantly greater even when they do.[18,19] Furthermore, early weaning to reduce the period of HIV exposure has been shown to be associated with increased mortality.[20] It is therefore clear that most HIV-infected mothers in Zambia need to breastfeed their infants for at least one year. The new guidelines provide two options for prophylaxis during this period: maternal 3-drug ARV (with 6 weeks of infant prophylaxis) or ED-NVP for the infant, both of which are to continue until one week after breastfeeding cessation (see Table 3).

Available data indicate that both strategies are effective,[21-23] though as noted previously the need for additional postnatal prophylaxis in infants born to mothers on 3-drug prophylaxis from early in pregnancy can be debated. It should also be noted that, while it makes sense to continue ED-NVP for the entire duration of exposure, the safety and efficacy of this strategy has only been assessed up to 6 months of life.[18] Daily infant administration of a drug whose dose needs frequent adjustment to remain effective may also prove challenging, and improper implementation of this strategy could lead to higher than expected rates of transmission and large numbers of children with acquired NVP-resistance.

Finally, the regimen options listed for 3-drug prophylaxis include a triple-NRTI, which has been shown to have inferior viral suppression rates in adults when compared to other 3-drug combinations.[7] Given this, it might be helpful for WHO to prioritize the different regimens listed.

CONCLUSION

In the fight against the global HIV epidemic, almost no battle is more critical than that against maternal-to-child transmission of the virus. The greatest reduction in such transmission will occur when the viral load is reduced to undetectable levels prior to delivery, and postnatal exposure in breast milk is eliminated. In the industrialized world, where ART is recommended for all pregnant women and where safe alternatives to breastfeeding exist, rates of maternal-to-child transmission are < 2%.[26] Such dramatic reductions in transmission have been more difficult to achieve in Zambia and other resource-constrained settings largely because access to ARVs is not as widespread, because HIV-infected pregnant women are often not started on prophylaxis until late in pregnancy, and because safe alternatives to breast milk do not exist for most families.

To address these challenges, the revised 2009 WHO guidelines now recommend ART for all women with a baseline CD4 < 350 cells/mm^3, and give two options for those not in need of ART for their own health: antepartum AZT followed by ED-NVP during breastfeeding for the infant, or 3-drug maternal ARV prophylaxis starting early in pregnancy and continuing through the breastfeeding period.

It is still not known which of the two ARV prophylaxis options will result in a greater reduction in transmission. Currently available data suggest that they are similar,[21-23,27-29] but no direct comparative data exist. IMPAACT 1077, a complex mutli-arm, randomized controlled trial has been designed to address this question and should shortly begin enrollment in multiple centers worldwide.[30]

Limitations of these new recommendations include an apparent under-emphasis on the need for adequate treatment preparation of pregnant women prior to beginning any treatment/prophylaxis option, and the risk of increased resistance due to prolonged antepartum exposure to AZT monotherapy – both of which could potentially result in compromised treatment options for women and their infected infants.

In developing these guidelines, the WHO acknowledged that the feasibility of the different options will vary, and they encourage individual countries to adopt specific recommendations based on their socioeconomic situation. In Zambia, where most women present to antenatal clinics later in pregnancy, where stigma still prevents some women from seeking HIV testing, and where CD4 technology is not universally accessible, several challenges to effective implementation of these guidelines exist.

Nonetheless, the revised 2009 WHO recommendations for the use of antiretroviral drugs for treating pregnant women and preventing HIV infection in children provide a reasonable, evidence-based strategy that should significantly reduce new cases of pediatric HIV, resulting in healthier families and communities and a brighter future for Zambia.

REFERENCES

1. UNAIDS 2008 data, available at http://www.unaids.org/en/KnowledgeCentre/HIVData/Epidemiology/epidemiologySlidesAuto.asp.
2. Ministry of Health Zambia. The Zambia Paediatric ART Training Curriculum, 2007.
3. Arrivé, E., Newell, M.-L., Ekouevi, D.K., et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *International Journal of Epidemiology* 2007;36:1009–1021.
4. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access, July 2010. [cited 2010 November 30]. Available from URL:http://www.who.int/hiv/pub/mtct/antiretroviral2010/en/index.html.
5. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, 2006.
6. Ministry of Health Zambia. Antiretroviral therapy for chronic HIV infection in adults and adolescents: new ART protocols, May 2007.

7. The antiretroviral pregnancy registry [database on the Internet]. Antiretroviral Pregnancy Registry Steering Committee. 2009.[Available: http://www.apregistry.com/forms/interim_report.pdf]
8. World Health Organization. Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents, November 2009.
9. Antela A, Ocampo A, Gómez R, et al. Liver Toxicity after Switching or Simplifying to NVP-based therapy is not related to CD4 counts: results of the TOSCANA study. *HIV Clin Trials.* 2010;11(1):11-7.
10. Thorn, C. and Newell, M.-L. Safety of Agents Used to Prevent Mother-to-Child Transmission of HIV: Is There Cause for Concern? *Drug Safety* 2007;30(3):203-213.
11. Le Chenadec, J., Mayaux, M.J., Guihenneuc-Jouyaux, C. et al. Perinatal Antiretroviral Treatment and Hematopoiesis in HIV-uninfected Infants. *AIDS* 2003;17(14):2053-2061.
12. European Collaborative Study. Levels and Patterns of Neutrophil Cell Counts over the First 8 Years of Life in Children of HIV-1 Infected Mothers. *AIDS* 2004;18:2009-2017.
13. Noguera, A., Fortuny, C., Munoz-Almagro, C., et al. Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals. *Pediatrics* 2004;114(5).:e598-603
14. Alimenti A., Burdge D.R., Ogilvie, G.S., et al. Lactic academia in HIV-uninfected infants exposed to perinatal antiretroviral therapy. *Pediatr Infect Dis J* 2003;22(9):782-789.
15 Chalermchockcharoenkit, A., Culnane,M., Chotpitayasunondh, T. et. al. Antiretroviral Resistance Patterns and HIV-1 Subtype in Mother-Infant Pairs after the Administration of Combination Short-Course Zidovudine plus Single-Dose Nevirapine for the Prevention of Mother-to-Child Transmission of HIV. *Clinical Infectious Diseases* 2009; 49:299–305.
16. Palumbo, P., Holland, B., Dobbs, T. et. al. Antiretroviral Resistance Mutations among Pregnant Human Immunodeficiency Virus Type 1–Infected Women and Their Newborns in the United States: Vertical Transmission and Clades. *The Journal of Infectious Diseases* 2001;184:1120–1126.
17. Welles, S.L., Pitt, J., Colgrove, R. et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal±infant transmission in the Women and Infants Transmission Study. *AIDS* 2000;14:263-271.
18. Thior, I., Lockman, S., Smeaton, L.M., et al. Breastfeeding Plus Infant Zidovudine Prophylaxis for 6 Months vs Formula Feeding Plus Infant Zidovudine for 1 Month to Reduce Mother-to-Child HIV Transmission in Botswana A Randomized Trial: The Mashi Study. *JAMA* 2006; 296(7):794-805.
19. Coovadia HM, Rollins,N.C., Bland, R.M., et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet* 2007: 369: 1107–1116
20. Kuhn, L., Aldrovandi, G.M., Sinkala, M. et al. Effects of Early, Abrupt Weaning on HIV-free Survival of Children in Zambia. *The New England Journal of Medicine* 2008;359:130-41.
21. Kumwenda, N.I., Hoover, D.R., Mofenson, L.M. et al. Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission. *The New England Journal of Medicine* 2008;359:119-129.
22. Chasela, C., Hudgens, M., Jamieson, D. et al. Both maternal HAART and daily infant nevirapine (NVP) are effective in reducing HIV-1 transmission during breastfeeding in a randomized trial in Malawi: 28 week results of the Breastfeeding, Antiretroviral and Nutrition (BAN) Study. 5th Conference on HIV Pathogenesis, Treatment and Prevention. *Abstract WELBC* 103.
23. Shapiro, R., Hughes, M., Ogwu, A. et. al. A randomized trial comparing highly active antiretroviral therapy regimens for virologic efficacy and the prevention of mother-to-child HIV transmission among breastfeeding women in Botswana (The Mma Bana Study). 5th Conference on HIV Pathogenesis, Treatment and Prevention. *Abstract WELBB* 101.
24. Gulick, R.M, Ribaudo, H.J., Shikuma, C.M., et. al. Triple-Nucleoside Regimens versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection. *The New England Journal of Medicine* 2004;350:1850-1861.
25. Staszewski, S., Keiser, P.,Montaner, J. et al. Abacavir-Lamivudine-Zidovudine vs Indinavir-Lamivudine-Zidovudine in Antiretroviral-Naive HIV-Infected Adults: A Randomized

Equivalence Trial. *Journal of the American Medical Association* 2001;285(9):1155-1163.
26. Mofeson, L., Taylor, A.W., Rogers, M. et al. Achievements in Public Health: Reduction in Perinatal Transmission of HIV Infection — United States, 1985—2005. *Morbidity and Mortality Weekly Reports* 2006; 55(21):592-597.
27. Arendt V., Ndimubanzi, P., Vyankandondera J., et al. AMATA study: effectiveness of antiretroviral therapy in breastfeeding mothers to prevent post-natal vertical transmission in Rwanda. Cross-track Session: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Abstract no. TUAX102
28. Kilewo, C. Karlsson, K., Ngarina, M. Et al. Prevention of Mother-to-Child Transmission of HIV-1 Through Breastfeeding by Treating Mothers With Triple Antiretroviral Therapy in Dar es Salaam, Tanzania: the Mitra Plus Study. *Journal of Acquired Immune Deficiency Syndromes* 2009;52:406–416.
29. Palombi, L., Marazzi, M.C., Voetberg, A., et al. Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of HIV. *AIDS* 2007; 21 (suppl 4):S65–S71.
30. Douglas Watson, University of Maryland (Baltimore), personal communication, 19 January 2010.