

# HATiP

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## In this issue:

### Revised 2005 WHO guidelines on prevention of mother-to-child transmission; *page 2*

- More resistance
- Covering nevirapine's tail - sdNVP plus AZT/3TC or AZT
- sdNVP in the infant - but not the mother
- Some thoughts on the WHO revised recommendations

## Revised 2005 WHO guidelines on prevention of mother-to-child transmission

Earlier this month, the World Health Organization issued proposed revisions to its recommendations on the use of antiretroviral drugs for the prevention of mother-to-child transmission (PMTCT) (see [http://www.who.int/entity/3by5/PMTCTreport\\_June2005.pdf](http://www.who.int/entity/3by5/PMTCTreport_June2005.pdf) and [http://www.who.int/entity/3by5/PMTCTtable\\_June2005.pdf](http://www.who.int/entity/3by5/PMTCTtable_June2005.pdf)).

The recommendations were the product of a panel of experts convened by WHO at the end of June, 2005 to discuss important new concerning the development of resistance in women and children using single dose nevirapine (sdNVP) for PMTCT, as well as new clinical findings on strategies that might help reduce the development of that resistance. The panel had the unenviable task of proposing simple, practical evidence-based recommendations that would work in the variety of differently resourced environments and clinical situations that confront healthcare workers trying to help mothers protect their infants from HIV-infection in the developing world.

HATIP published a couple of issues on the subject of sdNVP resistance last year. Since that time, several studies have produced important data.

### More resistance

Initial reports suggested that resistance only occurred in 20-30% of the women exposed to sdNVP-exposed women in HIVNET and other trials and in a higher proportion of women exposed to two doses of the drug in the Saint study.

But recent studies using more sensitive techniques to screen for resistance suggest that it is much more common (see <http://www.aidsmap.com/en/news/379A4719-2FBD-49F8-8353-E3FDFF72F567.asp>, <http://www.aidsmap.com/en/news/A3C49CD6-6951-4B70-B872-887600D5C1D3.asp>). The methods used in some of these studies can detect very small minority populations of drug-resistant virus — which appears to occur in as many as 60-75% of the women who take it, depending on the study and perhaps the viral subtype.

But most of this resistance seems to diminish over time. In one of the studies, nevirapine resistance one year after delivery was seen in only 25% of the women. Encouragingly, HIV DNA in the women's white blood cells did not show any evidence of nevirapine resistance, despite use of the more sensitive lab test. This suggests that archiving of the nevirapine-resistance mutations may be a rare event (HIV DNA represents viral material that has been incorporated into cells that will lie dormant until that cell is activated, at which point new HIV particles are produced. This HIV DNA provides a reservoir that allows drug resistant viruses to persist in the body for long periods).

So it's not clear whether low frequency mutations have much of an impact. It appears to have little impact on the effectiveness of subsequent use of sdNVP, at least for PMTCT in a second pregnancy (see <http://www.aidsmap.com/en/news/0507DD7B-0FD6-4A3F-BB67-5E71638EE5EC.asp>).

But the potential effect on the mothers' treatment outcomes is more troublesome. Prior exposure to sdNVP did compromise at least

some mother's subsequent responses to NNRTI-based antiretroviral therapy in a substudy of the Thai Perinatal HIV Prevention Trial-2 (PHPT-2) (previously reported here <http://www.aidsmap.com/en/news/94EC3850-D045-4420-A7BB-6EE22D9B70AB.asp>). However most of the mothers exposed to sdNVP in that study went onto ART only six months after labour (median).

Virologic responses might not be as impaired in women who have more time to wait until they need antiretroviral therapy for their own health. Yet no subsequent clinical trial has really addressed this. One study presented at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment in Rio de Janeiro last just July, did report on CD4 cell responses to ART in women who waited a median of 17 months after being exposed to sdNVP before starting antiretroviral therapy. (see <http://www.aidsmap.com/en/news/D15A2763-C672-42C2-BE78-34CF7AD207F6.asp>). There were no virologic data from this study but investigators could find no difference in CD4 cell responses between those who were exposed to sdNVP and those who were not. However, these women were drawn from the Ditrane-plus cohort (<http://www.aidsmap.com/en/news/819CD092-3764-4C00-9C68-66E9BA35AA9D.asp>) and also took AZT/3TC for a few days after childbirth.

### Covering nevirapine's tail - sdNVP plus AZT/3TC or AZT

Those few days of combination therapy when AZT/3TC is given to women who have taken sdNVP may make a big difference. The selective pressure on the virus to mutate and become resistant is probably greatest the first few days after dosing (while nevirapine is at its most potent). And the rate of resistance reported by the researchers in the Ditrane Plus study seems almost impossibly low (~1.14%).

The question of whether adding AZT/3TC reduces nevirapine resistance was addressed prospectively in a controlled setting by Dr. James McIntyre, who presented the most recent data from the Treatments Options Preservation Study (TOPS) in Rio. In short, TOPS found that adding four to seven days of AZT/3TC after birth to mothers who have received sdNVP during labour significantly reduces the risk that they will develop resistance to nevirapine, and may preserve their future treatment options.

The study had three treatment arms 1) sdNVP, or 2) sdNVP plus four days of Combivir (AZT/3TC combination tablet), or 3) sdNVP plus seven days of Combivir. Twice-daily Combivir was started in the mothers during labour and in their babies as soon as possible after birth.

The sdNVP arm was discontinued after an interim analysis of HIV resistance data at weeks two and six showed that nine of the 18 women (50%) randomised to receive single dose nevirapine alone had NNRTI resistance compared to 4 out of 43 (10%).

Data on the remaining 226 mothers and 228 infants who were enrolled at the time of the closure of the sdNVP arm are in the table below.

	sdNVP	sdNVP plus 4 days AZT/3TC	sdNVP plus 7 days AZT/3TC
Number who developed	41/68(60)	8/67(12)	7/68(10)

resistance /number in treatment arm (%)			
Baseline viral load (median)	23,200	24,700	35,000
Viral load at nadir (median)	8,300	< 400	436

No resistance to AZT/3TC was detected in the study. However, adding AZT/3TC significantly reduced the rate of NNRTI resistance among mothers from 60% to 12% (4 days) and 10% (7 days). It also greatly reduced the viral load which could be of critical importance. Among the mothers who took only sdNVP, the median viral load (at baseline and nadir) was higher in the mothers who developed resistance, (43,650 and 16,600 copies/ml) than in those who did not, (10,600 and 4,160 copies/ml).

The total infection rate at 6 weeks was 10.5% (24/228) however all but three of these cases were determined to be from in utero transmission.

Two infants had NNRTI mutations at birth, one in the sdNVP and another in the 4-day arm but no new NNRTI mutations emerged in any of the 13 infants who received AZT/3TC. However, 6 out of 9 (66.7%) of the infected infants in the sdNVP only arm developed new NNRTI mutations.

### sdNVP in the infant - but not the mother

Another way to keep a mother's treatment options open would be to simply skip the maternal nevirapine dose, and just give sdNVP to the infant. This idea has been explored in Botswana, where treatment realities are somewhat different than in the rest of Africa.

The Botswana 'Mashi' study has been adjusted several times to reflect changes in the standard of care. Originally, the trial gave all mothers AZT from 34 weeks to delivery, and to the babies from birth to one month. It then randomised participants to sdNVP as per the HIVNET 012 protocol, or a placebo to both mother and infant. Then the placebo was judged unethical due to revisions in Botswana's national protocol. The revised protocol gave nevirapine to all babies as soon as possible (an average of 24 minutes) after birth. Nevertheless, half of the mothers were still placed on placebo. (see <http://www.aidsmap.com/en/news/819CD092-3764-4C00-9C68-66E9BA35AA9D.asp>).

The transmission rates at birth were 2.3% for mother/baby pairs who both received sdNVP and 3.8% where the mother received a placebo. Transmission increased from 3.7% and 4.3% respectively a month after birth.

A resistance sub-study found that 44% of women given sdNVP developed resistance mutations.

The consequences of nevirapine resistance to women in Botswana may be more immediate than in much of the rest of the developing world. In Botswana, a woman with HIV who needs antiretroviral therapy for her own health can access it. For various reasons, though, pregnant women do not always present to an antenatal clinic or have an HIV test result in time before their child is due to start combination antiretroviral therapy. Consequently, women in countries with good treatment access like Botswana who receive single dose nevirapine and who then start treatment shortly afterwards may be at higher risk of a compromised treatment outcome than women in other, less well-resourced settings. Fortunately, there are also increasing data showing that ART can be successfully given to pregnant women in resource limited settings (see section on Dream study in

<http://www.aidsmap.com/en/news/819CD092-3764-4C00-9C68-66E9BA35AA9D.asp>), and from an antenatal clinic in one Pefar-funded study in South Africa (<http://www.aidsmap.com/en/news/0B7338AE-5DBB-43CC-9ABA-9D37F516F012.asp>)

### Some thoughts on the WHO revised recommendations

The revised WHO PMTCT recommendations clearly try to take into account improvements in treatment access, tailoring their recommendations to situations where there is access to the full complement of antiretrovirals and where there is not. When the original PMTCT guidelines were written, such access seemed a remote possibility. Increasing availability to antiretroviral therapy has changed the equation completely – and made continued sdNVP in mothers who can access ART more risky.

Unfortunately, it's not clear what revising the guidelines can do for the vast majority of women who live somewhere in the middle, those who may be able to access nevirapine through the antenatal clinic but not ART.

However, is it wise, especially in a breastfeeding population, to continue recommending the same postnatal treatment regimen (eg, AZT plus sdNVP or AZT/3TC) for the mother and the child? This would seem to be a recipe for the transmission of resistance when it occurs in the mother.

Although there is no reliable well-controlled study demonstrating that the treatments should be switched to decrease the chance of resistant virus being transmitted, do we really need to wait three years for another large trial to tell us that one week of AZT/3TC in the mother, and sdNVP in the child makes more sense?

Finally, WHO should be lauded for their increased emphasis on CD4 cell monitoring in people with HIV – and for recommending the consideration of treatment for pregnant women with 200-350 CD4 cells.

According to Dr. Siobhan Crowley, of WHO's HIV/AIDS Department: "Clearly it is not OK to wait for AIDS before starting ART – this is way too late. Criteria for initiation of ART need to be clinical and immunological and may well change with time and advancing knowledge and experience. Unfortunately in many countries waiting for ART, AIDS-defining conditions (CDC or WHO defined) is how people are recognised as eligible for ART."

## about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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