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Prevention of mother-to-child transmission with nevirapine: time for a rethink?

Introduction

Short-course nevirapine treatment forms the mainstay of programmes to prevent mother to child transmission in resource-limited settings. It is cheap, convenient and requires only two doses one to the mother during delivery and one to the infant within 72 hours of birth. It reduces the risk of transmission by about 50% compared with AZT during labour and for one week to the infant.

However, recent evidence from a study conducted in Thailand has forced experts to rethink their guidance on using this drug, following two discoveries: AZT during the last two months of the pregnancy, plus one dose of nevirapine appears almost as effective as triple combination therapy (the gold standard in rich nations), but at the same time, maternal exposure to a single dose of nevirapine compromises the mothers virologic response to treatment, especially if treatment begins within six months of birth.

The findings raise some difficult questions for programmes designed to reduce rates of mother to child transmission. This article reviews the key issues.

New WHO Guidance

A recent WHO expert consultation called to review the findings made the following key recommendations:

- Women who need ARV treatment for their own health should receive it, following the revised ARV treatment guidelines recently issued by WHO. The use of ARV treatment when indicated during pregnancy will improve the health of the mother and substantially decrease the risk of transmission of HIV to the infant.
- Women who do not need treatment or do not have access to treatment should be offered ARV prophylaxis to prevent MTCT using one of a number of ARV drug regimens known to be safe and effective.
- The most effective regimen is zidovudine from 28 weeks of pregnancy plus single dose nevirapine at the onset of labour for the mother and a single dose of nevirapine for the infant within 72 hours of birth plus one week of zidovudine.

Alternative but less effective regimens include:

- Zidovudine alone from week 28 of pregnancy, and throughout labour for the mother, plus zidovudine for one week after delivery for the infant.
- Zidovudine plus lamivudine from week 36 of pregnancy and throughout labour, and for one week after delivery for the infant.
- A single dose of nevirapine for the mother at the onset of labour, plus a single dose of nevirapine for the infant within 72 hours of delivery.
- The selection of the ARV drug regimen should be made at the national level, based on issues of efficacy, safety, drug resistance, feasibility and acceptability.

Dr Diana Gibb of the UK's Medical Research Council Clinical Trials Unit runs trials in resource-limited settings. She told HATIP: It think it

will be practical to do the AZT plus nevirapine regimen in Thailand because they are very organised and politically committed to it. People

will be able to do it in many middle income countries, and in Brazil they are likely now to be asking whether they should be using HAART, but in many resource-poor countries in Africa it may not be so practical.

I was quite depressed by some of the roll-out data from MTCT intervention programmes I heard at the African AIDS Conference in Nairobi, particularly in terms of the number of women who came back for their test results and the number of women who actually took short-course regimens prescribed to them. There are practical issues, stigma issues and cost issues that need to be addressed if this more complicated regimen is to work in practice. For example, given that one of the main reasons cited for not taking perinatal nevirapine is stigma and fear of disclosure to partner and family, how practical is it to introduce a regimen which starts at 28 weeks?

Nevirapine resistance: evidence confirms widespread fears

The recent WHO guidance comes as a result of a study conducted in Thailand, which found that future treatment options for mothers were compromised by exposure to short course nevirapine treatment, even when given with AZT from week 28 of pregnancy. The same study found that a combination of AZT, given from week 28 of pregnancy, and a single dose of nevirapine, appears to be almost as effective as Highly Active Antiretroviral Therapy for the mother in blocking HIV infection of the infant. The findings were presented at the Eleventh Conference on Retroviruses and Opportunistic Infections in San Francisco on February 9th.

The study, called PHPT-2, recruited 1844 pregnant HIV-positive women, and randomised them and their newborns to receive either:

- **one dose of nevirapine for the mother at delivery and nevirapine within 72 hours of birth for the infant (the nevirapine/nevirapine arm)
- **nevirapine for the mother at delivery and a placebo for the infant (the nevirapine/placebo arm)
- **placebos for both mother and infant (the placebo/placebo arm)

All mothers received AZT for the last three months of their pregnancy, and all infants received AZT syrup for the first week of life. No infants were breastfed.

The placebo/placebo arm of the study was stopped after an interim analysis showed a higher rate of HIV transmission from mother to child in this arm (6.3% vs 1.1% in the nevirapine/nevirapine arm, $p=0.00026$).

The final analysis of the study showed that the nevirapine/nevirapine

regimen proved only slightly superior to the nevirapine/ placebo arm in reducing the rate of transmission (2.0% vs 2.8%). This difference was not statistically significant. HIV DNA testing was carried out at birth, week 6 and months 4 and 6 to determine if the child had become infected.

A random sample of 90 women exposed to nevirapine showed that

NNRTI-associated mutations were present in 18% of women tested 12 days after delivery, whilst a pharmacokinetic study showed that 77% of the women had detectable levels of nevirapine 5-15 days after delivery, and detectable levels of nevirapine were still present in one woman 19 days after delivery.

A sub-analysis of mothers (n=255) who needed to start triple antiretroviral therapy with d4T/3TC/nevirapine due to CD4 counts below 250 cells/mm³ after delivery showed that women exposed to nevirapine at delivery had significantly poorer virologic responses after six months of treatment if they showed evidence of nevirapine resistance six weeks after delivery, with a trend towards poorer response also evident in women who

were exposed to nevirapine without developing detectable resistance to the drug.

A quarter of women who participated in PHPT-2 needed antiretroviral treatment after delivery, and the researchers found that when virologic response was measured using an ultrasensitive viral load assay, only 34% of women with at least one nevirapine-associated mutation had viral load below 50 copies/ml after six months of treatment (n=65), compared to 75% of women not exposed to nevirapine (n=42) (p=0.001). 53% of women exposed to nevirapine without evidence of resistance had viral load below 50 copies at this point, leading Professor John Mellors of Pittsburgh University School of Medicine to note that this trend mirrored results from a study presented by his group in the same session.

Dr Mellors group found that participants in the ACTG 398 study who added efavirenz to HAART were significantly more likely to experience virologic failure if they had been exposed previously to another NNRTI, even in the absence of resistance detectable by normal assays. Using a highly sensitive resistance assay, the ACTG 398 researchers found that between 0.6% and 7% of the virus population in previously exposed patients already carried the same mutation at baseline that would later emerge upon failure of the efavirenz-containing regimen. This result would be missed by standard genotypic resistance testing, which cannot detect minority populations that comprise less than 10-20% of the total virus population in a blood sample.

In the PHPT-2 sub-study women who started treatment more than six months after delivery had a better response to treatment, suggesting that starting treatment earlier is likely to result in a sub-optimal response.

Although treatment responses appeared equivalent when measured by CD4 cell response, experts argue that poorer virologic responses at six months signals a higher risk of treatment failure.

Dr Diana Gibb urged some caution over interpretation of these results. I think these results need to be replicated on a larger scale for longer before we throw out nevirapine short course treatment. One of the questions I have is whether the poorer response was because those women with mutations were also more likely to have advanced disease, and disentangling the effects of these two on response is difficult.

Dr Haruna Jibril of Botswanas MTCT programme told us that investigators in the MASHI study of AZT plus nevirapine will look at virologic response to nevirapine in mothers previously exposed to the drug one year after they start HAART. This analysis will evaluate response in approximately 230 women who have begun antiretroviral therapy since being exposed to nevirapine at delivery.

Don't throw out nevirapine

Several speakers at the Retroviruses Conference argued that whilst single dose nevirapine treatment should be continued for the time being, it should be seen as a transitional treatment regimen, and that HAART for pregnant women should be the preferred regimen at the very least around the time of delivery. They also emphasised that the findings should not block the roll-out of nevirapine-based

HAART regimens, given that the majority of women will not receive short-course nevirapine treatment during pregnancy.

Dr. Francois Venter of the University of Witwatersrand Reproductive Health Research Centre agrees. My biggest concern over these data is that they will be seen as a reason not to use nevirapine in programmes. The Thai data are very concerning but they need to be put in context. A lot of babies will die if we wring our hands about a yet to be confirmed problem.

Dr Douglas Wilson of the University of Natal, South Africa, agrees that this evidence should not be permitted to erode hard won gains.

In South Africa the Treatment Action Campaign won its PMTCT case against the government in the Constitutional Court, forcing the government to provide single dose nevirapine for PMTCT. Most of the maternity clinics in the country are now able to offer this service. We cannot walk away from this policy now, but we do have the option of only offering nevirapine to the infant, or offering PI-containing HAART for PMTCT as part of the rollout. I suspect, however, that it will take many years to make the ARV rollout widely available throughout the country.

Further evidence

The Thai study was not the only presentation at the conference to report high levels of detectable nevirapine resistance in mothers after short-course treatment. A South African study found that 39% of women exposed to nevirapine had detectable resistance to nevirapine (and by implication resistance to the other non-nucleoside reverse transcriptase inhibitor efavirenz). Risk factors for resistance were higher viral load and lower CD4 cell count, and taking more than one dose of nevirapine during pregnancy (Martinson).

As a result of their findings, the researchers on this study posed two questions for future research and debate:

- Should nevirapine be given to infants only (the Thai study did not test this question)
- Should nevirapine be given at the time of delivery only with `cover` from two nucleoside analogues in the week after delivery?

Members of the HATIP panel tended to disagree with the view that nevirapine should be reserved for infants. Mark Harrington, Executive Director of Treatment Action Group, New York, strongly disagrees with the suggestion. For those where nevirapine plus AZT/3TC is the only HAART option the benefits of nevirapine within HAART strongly outweigh its risks, even where nevirapine has been used before for PMTCT. Although women previously exposed to nevirapine had an inferior virologic response in the Thai study, there was no significant difference in CD4 cell response at this point. However, longer term follow-up is needed before firm conclusions can be drawn about any differences in clinical outcome as a result of poor virologic response. Dr Diana Gibb was not impressed with the argument that nevirapine be reserved for infants. Why is it any different for the infants in terms of the risk of compromising future treatment?" Given the even more limited number of options for treatment of children compared to adults in resource-limited settings, reserving nevirapine for infants might well spare the mothers from developing drug-resistant virus, but may well be a problem for infants who become infected despite receiving nevirapine after birth, she argues. The degree to which infected infants receiving nevirapine perinatally have future treatment options compromised is an important question which needs to be answered. A possible solution, as NVP resistance appears to be acquired de novo in infected babies and not to be transmitted from

the mother, would be for babies also to receive a short course of triple HAART in the neonatal period.

The second question posed by South African researchers at CROI may have been partially answered by a UK study, which looked at levels of efavirenz in the blood of people who stopped taking the drug whilst continuing to take two nucleoside analogues for at least one week. The researchers found that efavirenz lingered in detectable amounts, potentially high enough to cause some resistance to the drug, for up to two weeks after efavirenz treatment ceased.

However, resistance levels were much lower than those seen in mothers exposed to single doses of nevirapine plus AZT in the Thai study, suggesting that the use of two nucleoside analogues may suppress viral load sufficiently to avoid resistance in most patients. Although nevirapine has a slightly shorter half-life than efavirenz, its long half-life is what causes the high levels of resistance seen after single doses in PMTCT studies.

HAART during pregnancy

All panel members agreed that where long-term HAART for the mother is not possible or necessary, short-term fully suppressive therapy with three drugs would nevertheless be preferable.

For places which can manage it logistically the AZT plus NVP regimen is much more efficacious. But nevirapine resistance could be an issue with this regimen, and so could AZT resistance, says Mark Harrington. Panel members agreed that it was far better to aim for fully suppressive therapy, even if it only lasted for a couple of weeks. Paradoxically a nevirapine-containing triple regimen would be cheaper than the AZT/NVP regimen in countries where generic fixed dose combinations can be used.

In South Africa resources may permit a more sophisticated approach which recognises the utility and ease of implementation of short-course perinatal nevirapine, but which also offers a back-up management strategy if the use of nevirapine causes problems for mothers subsequent treatment options.

The South African government's antiretroviral rollout, which offers HAART to patients with AIDS-defining illness, has a second line regimen containing lopinavir/ritonavir. A case could be made for using this regimen as first-line therapy in women who have taken nevirapine for PMTCT, argues Dr Douglas Wilson.

Another more conservative option would be to start women who have been through the PMTCT programme on the first-line NNRTI-containing regimen, and to check the viral load at 3 months. If the viral load is detectable then the switch to the second-line PI regimen could be made immediately.

Francois Venter believes that a protease inhibitor-containing regimen during pregnancy and after delivery makes sense, leaving an NNRTI-based regimen as a first line option once the woman needs treatment or it becomes more widely available. However, Chris Green in Indonesia points out: Its rare that any protease inhibitors are available in the developing world. Nelfinavir is probably the most suitable alternative but even at its lowest price it is usually unaffordable and Roche clearly have no interest in addressing this.

Mark Harrington, who served on the WHO panel that drew up guidelines for antiretroviral treatment in resource-limited settings, is more provocative, pointing out that women are at significantly higher risk of potentially fatal liver toxicity associated with nevirapine treatment.

Nevirapine-containing HAART may be suitable where monitoring is available but hepatic monitoring does not always pick up the

severe and life-threatening hepatic events associated with the drug, he warns, a view shared by Professor Brian Gazzard of the Chelsea and Westminster Hospital, London.

Dr. Francois Venter is not comfortable with using nevirapine either. I have had several very bad experiences with nevirapine toxicity and would be wary of starting the drug in pregnancy where a non-life threatening bout of hepatitis or skin toxicity could threaten the foetus. I would rather use a protease inhibitor and switch to nevirapine once the baby is born.

Several panel members refused to rule out abacavir-based triple regimens in women not in immediate need of treatment, given that concerns about the use of such combinations have focused on patients with high viral load.

However abacavir raises concerns for others because of the risk that it may cause a potentially fatal hypersensitivity reaction. Communication about this risk and monitoring for this reaction may be more difficult in resource-limited settings especially where health care worker time is limited.

Studies comparing PI-based and NNRTI-based regimens in pregnant women need to be conducted, says Dr Diana Gibb. Similarly questions about tolerability of triple HAART medications need to be addressed in pregnant women.

A potential role for tenofovir?

Tenofovir is a nucleotide analogue manufactured by Gilead. The drug has shown effectiveness in blocking HIV infection in macaques. Although it has a similar half-life to nevirapine, resistance to the drug is unlikely to arise so easily. For these reasons, some are now suggesting that tenofovir should be studied as a short-course prophylactic treatment. However, such research is dependent on the development of a liquid formulation of the drug suitable for dosing of infants.

Treatment around birth: pointless discussion without tackling infant feeding?

The impressive results in the Thai study of AZT plus nevirapine were achieved in a context where mothers were counselled against breastfeeding, and where there appears to have been high compliance with this advice.

Prof. Brian Gazzard expresses pessimism about the value of refining regimens administered in the weeks around birth (peripartum) if the potential transmission of HIV through breastfeeding is not tackled. Up to 40% of mother to child HIV infections occur through breastfeeding, and discontinuation of a HAART regimen in the mother will quickly lead to a rebound of viral load back to its pre-treatment level. Exclusive breastfeeding after treatment stops might increase the risk of transmission.

In settings where it is likely to be feasible to provide HAART during pregnancy, Prof. Gazzard argues, I believe the Ruth Nduati study remains an extremely important one, showing how bottle feeding is possible for the majority of the urban poor in Kenya, and how breastfeeding negatively affects maternal health and mortality in HIV-positive women. In a sense this is of much more importance to the baby, even if there is a slightly increased risk of diarrhoeal illness as a result of bottle feeding. The study he refers to is summarised in a news article published at www.aidsmap.com.

[Click on this link to read about the study.](#)

Treatment during breastfeeding

Research efforts are beginning to focus on giving antiretroviral treatment to the infant during the breastfeeding period. The SIMBA

study tested the use of either 3TC or nevirapine throughout the breastfeeding period (approximately five months). Transmission was estimated to occur at a rate of two infections per 100 baby years compared to an expected rate of ten per 100 baby years (or more) without treatment. A difficulty in interpreting this study, notes Dr Diana Gibb, is that the researchers used a historical control group rather than comparing the results with another parallel intervention, such as exclusive breastfeeding or exclusive formula feeding. In addition, mothers in this study received AZT and ddI for one week after delivery, which could have influenced the rate of transmission by substantially lowering maternal viral load during a period of high transmission risk.

Dr Douglas Wilson points out that more research is needed in this area. We need data from randomised, controlled trials detailing the effectiveness of one or two dose of nevirapine to the infant only, with or without NRTI cover.

[Click on this link to read about the study.](#)

The NVAZ trial tested the use of a single dose of nevirapine and a weeks worth of AZT in infants whose mothers were not treated during pregnancy or labour. The regimen reduced the risk of transmission by 36% (7.7% of infants who received this treatment were found to be infected six to eight weeks after birth, compared to 12.1% of infants who received nevirapine alone). In terms of clinical practice, this trial may represent a realistic strategy where it is difficult to diagnose HIV infection before delivery and where formula feeding is difficult for cultural, hygienic or financial reasons.

[Click on this link to read about the study.](#)

References

about HATIP

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

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