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Rethinking nevirapine revisited

Danger of resistance for mother and infant

There is now clear evidence that some mothers exposed to sdNVP during labour who later took combination antiretroviral therapy had a significantly poorer virological response to treatment. There is also evidence of NNRTI resistance in some of the infants infected despite PMTCT. Final results from the Thai study, presented both at the AIDS conference and published in the *New England Journal of Medicine* (NEJM), showed that 41% of women exposed to nevirapine had evidence of resistance to the drug a median of 12 days after delivery (see

<http://www.aidsmap.com/en/news/1E48C7B9-97EC-4FC8-B6EB-6435E0707609.asp>).

In a second study published in the same edition of NEJM, mothers who received sdNVP + AZT in the Thai study were significantly less likely to achieve a viral load below 50 copies/ml when they subsequently started a nevirapine-based HAART regimen. The study involved 221 women who had received a single dose of nevirapine during delivery and 48 who had not. Although the authors stress that no difference was seen in CD4 cell gain or mortality between the sdNVP/AZT pretreated women and those without prior exposure, this is hardly surprising given the short duration of follow-up (six months) and small number of women included without prior antiretroviral exposure.

But one of the most important questions about the development of resistance after sdNVP is how long it persists. There is a good chance the virus will revert to a susceptible strain once nevirapine has been eliminated from the bloodstream.

The hope is that if NNRTI-based therapy can be postponed long enough, sdNVP-exposed women (and children) might respond nearly as well as if they had never taken nevirapine at all. But how long does therapy need to be delayed for resistance to disappear?

According to Dr. Lynn Morris of South Africa's National Institute for Communicable Diseases (NICD), it may take more than six months after birth for at least 14% (one in six) of sdNVP-exposed women.

Previously, at the 2004 Conference on Retroviruses and Opportunistic Infections (CROI), Morris' team described a study in which 39.4% of sdNVP-exposed women displayed NNRTI resistance mutations seven weeks after exposure to sdNVP. At the Bangkok meeting, she reported that about a third of those resistant at seven weeks still displayed resistance out to month six. The majority of mothers had only one measurable mutation, but it was a mutation that confers clinically significant resistance.

Other factors that increased the risk of persistent resistance included:

- Receiving multiple nevirapine doses due to false labour
- High viral loads
- Lower CD4 counts.

There was also evidence of the persistence of resistance in infants who were infected despite PMTCT. Forty-two percent (20 infants) of these had detectable resistance at seven weeks; twenty-six percent were still resistant at month six.

In a related study from NICD in South Africa presented at the Fifteenth International AIDS Conference, Dr. Candice Pillay evaluated nevirapine resistance mutations among HIV-1 infected infants following single dose nevirapine (Abstract WeOrB1290). This study assessed the rates of resistance among infants enrolled in the standard regimen (SR) where both mothers and infants received NVP compared to those infants who received NVP as post exposure prophylaxis (PEP), either because their mothers had not been diagnosed or the maternal nevirapine dose was not taken at the time of delivery.

Eleven out of 30 sdNVP-exposed HIV-positive infants had NNRTI resistance (Y181C in all cases). Of those exposed to NVP as PEP only three of 23 had resistance. Thus preliminary data suggest that the PEP regimen is associated with a lower frequency of resistance compared to the standard regimen. The amount of resistance seen on sdNVP is disturbing although the clinical significance of resistance remains unclear.

Yet another South African study in matched mother-infant pairs found that NVP resistance occurred more frequently in infants than in mothers (ThPeB7045). The study authors concluded "these findings, together with data from other studies, reinforce the view that although NVP is effective, affordable and simple to administer, the search for safer regimens to prevent MTCT should be intensified."

Another finding in the South African studies (from Dr. Morris) is far more alarming. In the mothers, the mutant/resistant viruses formed a minority of the total viral population infecting each woman at six months, because the nevirapine-resistant virus was gradually outgrown by the fitter `wild-type` virus. But in the infants with resistant virus at six months, the entire population was resistant to NNRTIs. This seems to suggest that resistance in those infants might be far more persistent than in the mothers. What could explain this?

The persistence of resistance acquired during primary infection

The answer might lie in findings reported in the most recent issue of AIDS (see

<http://www.aidsmap.com/en/news/6F767BD1-594B-4D4C-8935-6841CCC2698C.asp>).

Two studies were conducted looking at what happens when an adult is infected with a drug-resistant strain of HIV. Contrary to the conventional wisdom, the transmitted drug-resistant virus didn't quickly evolve into a non-resistant "wild-type" strain in untreated patients, as would be expected in the absence of the active pressure of the drug.

Instead, the resistant virus spread through the body, infecting long-lived chronically infected cells that apparently can churn out this resistant virus for years. One of the patients infected with resistant virus has been followed out to seven years.

These studies should be interpreted cautiously - so far they involve less than forty patients and the median time of follow-up in the larger group is only 12 months.

However, it is possible that resistant virus transmitted during primary infection might be virtually permanent.

If so, then drug resistant virus transmitted from mother to her child may not be as transient in the infant as in the mother. This could explain some of the South African data.

Mother to child transmission of drug-resistant virus after sdNVP may occur more commonly:

- When the mother has a higher viral load or lower CD4 cell count.
- Via breastmilk.
- When the mother has received more than one dose of nevirapine due to false labour.
- When the mother has previously received sdNVP for an earlier pregnancy.
- When a child is infected in utero.

Viral subtypes

One piece of information that is often overlooked when interpreting data from PTMCT trials is that both the risk and the timing of mother-to-child transmission appear to be dependent on the viral sub-type - and women in different parts of the world are infected with different subtypes of HIV. HIV-1C, the subtype responsible for the epidemic in Southern Africa, is not only more easily transmitted from a mother to her child, it is far more likely to be transmitted in utero than other subtypes of virus according to a study in the August 20 edition of AIDS (see <http://www.aidsmap.com/en/news/CD7746D0-5881-410C-B673-6F238BFA81DE.asp>).

The implication of a higher rate of transmission in utero is that short course antiretroviral treatment (including sdNVP given during labour) may not be as effective in regions where subtype C is the dominant form of HIV-1, such as southern Africa, as in regions where other subtypes are dominant. Infants infected in utero who are exposed to sdNVP might also be more likely to develop NNRTI-resistance (and data from South Africa, where subtype C is prevalent, should be viewed accordingly).

The study authors conclude that preventing much mother to child transmission where subtype C virus is prevalent may require treatment earlier during pregnancy. However, HATIP panelist Dr. Mark Cotton, who is Director of the Children's Infectious Diseases Clinical Research Unit at Tygerberg Children's Hospital in South Africa, points out that "In utero transmission [in the study was] high enough with all clades [subtypes of HIV] to warrant antenatal ART strategy."

The safety of nevirapine

But choices for HAART therapy in pregnant women are rather limited in resource-restricted settings. The simplest, lowest cost regimens are fixed dose combinations (FDCs) of nevirapine-based HAART. But a number of studies have noted that nevirapine-based HAART combinations may not be safe in all pregnant women with better functioning immune systems.

A study in the Journal of Acquired Immune Deficiency Syndromes has reported that nevirapine-containing HAART regimens were associated with an increased incidence of severe liver toxicities in HIV-positive pregnant women with a CD4 cell count above 250 cells (see <http://www.aidsmap.com/en/news/C1316A81-32F9-4AA9-A94F-93E3EB4E0D0E.asp>). Australian research presented in Bangkok suggests that a combination of inherited and immunological factors (a CD4 percentage over 25%) may lead to the hypersensitivity reactions (including liver toxicity) associated with nevirapine. (see <http://www.aidsmap.com/en/news/C24D11DE-1C19-48B0-A216-1A62B1DADA9F.asp>).

Since the other widely marketed NNRTI, efavirenz, has been associated with birth defects in animal studies, safe and potent antiretroviral options for many women may thus be limited to a

PI-based regimen - and those are priced far out of the reach of most resource-limited settings.

However, a retrospective review published in AIDS reported that nevirapine is well tolerated in Spanish patients with CD4 cell counts below 200 (see <http://www.aidsmap.com/en/news/69B8100D-9E0A-41D9-9399-B5D28CD0C6E2.asp>). This should reassure clinicians prescribing nevirapine-based HAART in resource-limited settings, where the vast majority of women begin treatment with CD4 cell counts below 200 - especially since these are also the women most likely to develop and transmit nevirapine-resistant virus. Adding other antiretrovirals to sdNVP for a period post-partum.

The fact remains that many settings are still unable to give HAART to every pregnant woman who needs it, especially when her HIV status is discovered only shortly before her child is due to be born. sdNVP still will reduce the likelihood of her transmitting HIV to her infant.

But is there any way to reduce the risk of resistance? Part of the problem with sdNVP is that the drug has a very long half-life - in other words it takes a long time for the drug to be eliminated from the bloodstream.

In Bangkok, further data from the Thai study suggested that significant levels of nevirapine can persist for at least a couple of weeks after sdNVP (ThOrB1352). The study investigated nevirapine levels post-partum in 110 patients in the Thai study. With an assay sensitivity >50ng/ml (>1C50), he found that 56% of mothers had detectable nevirapine levels between 15 and 21 days after delivery but that nevirapine was not detectable in any samples acquired after 21 days. It was suggested that the difference in clearance rates between individuals may be due to inherited differences in metabolism. This means that nevirapine levels high enough to select for resistance could persist for weeks.

However, another South African study presented at the Bangkok meeting suggests that giving zidovudine and lamivudine for just four days after birth of their babies to mothers who have received single dose nevirapine during labour significantly reduces the risk that they will develop resistance to nevirapine, and may preserve their future treatment options (see <http://www.aidsmap.com/en/news/24D285A4-1292-4306-A68A-45BE5ABBF2A9.asp>).

This approach is similar to the advice given patients on NNRTI-based HAART who want to interrupt treatment but preserve their future treatment option: Discontinue the NNRTI first and continue to take the nucleoside analogue backbone for several days (see <http://www.aidsmap.com/en/news/84885C3C-3B1F-414F-9719-F99E4EC3BC31.asp>).

Investigators conducted a prospective trial called the Treatments Options Preservation Study (TOPS) involving 300 mother-infant pairs. The study had three treatment arms 1) sdNVP, or 2) sdNVP plus four days of Combivir (zidovudine/lamivudine 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.

Maternal resistance to the drugs was assessed two and six weeks after labour using genotypic resistance testing. HIV transmission from mother-to-baby was determined by using HIV DNA or RNA testing two and six weeks after birth.

Dr. James McIntyre presented data for the first 61 mothers with six weeks of follow-up and HIV sequencing. On entry to the study the median CD4 cell count was 318 cells/mm³ and median viral load was 32,600 copies/ml. All the women were infected with HIV

subtype C. HIV sequencing 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 only one of the 20 (5%) women randomised to receive single dose nevirapine plus four days Combivir, and three of the 23 women (13%) treated with single dose nevirapine and seven days of Combivir.

In light of the study's preliminary findings, the sdNVP arm has been discontinued. The study will continue in order to determine which of the remaining two arms is superior. A number of other ongoing studies are also evaluating the efficacy of this approach.

What to do next?

WHO's new PMTCT guidelines acknowledged that the preliminary TOPS data were to be presented at the Bangkok conference, but felt that the strategy needed "to be further assessed before any recommendation can be made to use this approach in programmes to prevent mother to child transmission."

At the same time, the guidelines allow wide latitude in the selection of local PMTCT strategies, in line with each country's resources and infrastructure. It is likely that practice will accordingly vary from one place to another. In many settings individual specialists will decide their own approach.

HATIP asked our advisory panel a series of questions to get a reading on what may happen next in clinical practice.

We asked: "Do any of the new data lead you to think that PMTCT programmes should be radically altered now?"

Some panellists think that it could be a bit premature to consider changing practice because of the resistance data.

Dr. Francois Venter from South Africa said: "On a continent where people requiring ARVs are not getting them because of poor health care systems, even in our country, which is relatively well resourced, debates about NVP resistance post sdNVP sometimes seem at best academic and at worst threaten an effective and simple intervention."

Dr. Diana Gibb of the UK's Medicine Research Council: "I would caution being too down on NVP until there is more evidence and debate [as it] risks playing into the hands of those who are against ART anyway, even to MTCT prevention." She supports further research, "in particular looking in more detail at 'covering the tail' with Combivir and short course triple [therapy] (with staggered stop if NVP used). I think the consequences of a single mutation arising in the babies in this manner remains unknown, and this needs urgent investigation."

"Still," says Dr. Venter: "Use whatever it takes to prevent MTCT, and of course try to minimise resistance with strategies like short course AZT/3TC. We should be striving to treat pregnant women with triple therapy, wherever possible. But this is not powerful enough to call into question [sdNVP programmes]. Where sdNVP is all that is available, use it."

Dr. Gerald van Osch, a clinician in the Dutch West Indies, concurs that in the very resource limited areas, sdNVP should continue for now "but with emphasis that better options will have to be researched." He suggests that in addition to the TOPS regimen, a parallel regimen of AZT and 3TC syrup for the baby should be investigated.

Other panellists also expressed a preference for new PMTCT approaches.

Dr. Zvi Bentwich from Israel said: "Overall, we should combine sdNVP with additional retrovirals for a short period of time."

Dr. Mark Cotton: "I favour moving away from sdNVP as soon as possible and support a post delivery short course of dual

nucleosides when sdNVP has been used. [We] need to move to triple therapy where possible as fast as possible."

Dr. Christopher Lee of Malaysia: "Combination ARV therapy has become the favoured option here. Our concern for sdNVP is the risk of NNRTI (one of our preferred ARV agents locally) resistance. I also have problems with ZDV with sdNVP, which to me just increases the risk of ARV resistance across 2 drug classes.

Professor Brian Gazzard of the Imperial College School of Medicine, and HIV Research Director, at Chelsea and Westminster Hospital in London: "The data really do strongly indicate that with newly available cheap combinations, there would be little difference between providing HAART therapy for a very short period, at least to the mother and perhaps AZT monotherapy or perhaps combination therapy for a short period to the baby. I think this is undoubtedly likely to be in the long term the best way forward."

Do you believe that reducing transmission of HIV-1C will require a different strategy?

Most panelists think not because as Dr. Venter points out: "sdNVP been shown to work in SA and in Africa."

Dr. Mark Cotton notes: "Interestingly, Clade C had the lowest percentage of intrapartum transmission; does that mean we should not need an intrapartum strategy for Clade C?"

Yet the study "clearly emphasises the need for early diagnosis [and] to prioritise ART to pregnant women," said Chris Green, a long-time patient advocate in Indonesia.

Doesn't the use of sdNVP alone pose a the danger to subsequent children? Would you prescribe sdNVP to a woman who has previously received it?

Dr. Venter: "I am very worried about subsequent children, but would use best available strategy."

Is the simplicity and economy of PMTCT, and its efficacy in a wide population a good enough excuse to limit the future treatment options of a small proportion of that population?

Dr. Bentwich: Not enough, but there is clearly an alternative with [a short course of background other antiretrovirals post-delivery].

Dr. Venter: "Simple and cheap goes a long way here! Its simple, and South Africa, with all its resources, is only getting sdNVP right in selected areas. I think sdNVP is less than ideal, and needs to be constantly re-evaluated - but the reality is it works better on a mass scale [than combination therapy]."

Informed consent

Chris Green: "There is still a need for simple and cheap options for cases where the complex and more costly options are not feasible, but tempered by much better information provision to both partners to allow them to make an informed decision. If they are unwilling to make a decision, the best option for the baby should be followed. This should take account of care and treatment options that may be available to the child."

What about informed consent counselling? Dr Venter: "I think informed consent is always important, but again, terrifying someone with complex data that scientists barely agree upon is not OK. I think simply saying that the sdNVP works, and that there is a concern that in the future it may be more difficult to treat Mom's HIV (but we're not sure) is the way to go."

Chris Green: "We need to provide much clearer guidance to support informed consent. But we also need to develop a wider dialogue on what we mean by and expect from informed consent in this regard. Can we expect a women in labour to provide meaningful informed consent?"

However, according to Dr. Nyazema, the consent given may not be "informed" at all - that there is a strong bias in favour of sdNVP among southern African women. In one study in which he participated belief in sdNVP was strong "These women were reported to have so much faith in the efficacy of the drug and were not in the least worried about the issue of resistance."

Triple therapy for mothers

HATIP also asked whether the approach to PMTCT should depend upon a woman's immune status? In other words, should PMTCT programs screen for women who qualify and might be able to access HAART in the near future and treat them differently?

Chris Green: "We MUST prioritise pregnant women in selecting candidates for ART, particularly those meeting the normal clinical indication. We currently don't have practical options for pregnant women with CD4 > 250 - we need to develop options for these cases. We also need to confront the challenge of adherence, and of sharing ARVs with the male partner."

Other panellists however thought that this would be impractical or far too complex for most settings.

Nevertheless, WHO and the US Centers for Disease Control will soon investigate just this approach with a study that will stratify women into three groups according to their disease stage:

- Those who qualify for HAART for their own health (with CD4 counts below 200 cells/mm³ and/or symptoms of disease) will receive it through pregnancy, delivery - essentially, as long as they need it.
- Those with CD4 counts above 500 cells, who will receive AZT for the last two months of pregnancy and sdNVP during labour, and probably a short course of nucleoside analogues for four-seven days after birth.
- Those with CD4 counts between 200-500 cells. This group will be randomised to receive either short-course or HAART continued up to six months for those mothers who choose to breastfeed.

Conclusion

It is clear that no one wants to lose the benefit that sdNVP offers where no other PMTCT strategy is available.

However, it also seems clear that there is no longer one single approach to PMTCT.

As Dr Christopher Lee argues: "There should be more than PMTCT regimen recommended globally. Certainly, in Malaysia; our approach has changed with the changing scenario in the country especially with regards to access to ARV. Nevirapine (single dose) did look attractive a few years ago when ARV prices were still high. But since [price reductions] the Ministry of Health approved free HAART to all mothers who were found positive during antenatal screening."

"Each country has to look at its own situation with special attention to: access to ARVs, health infrastructure, patient adherence, ARVs available locally, etc, in deciding its own preferred PMTCT approach / strategy."

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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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