

# HATiP

HIV & AIDS Treatment in Practice

Issue 57 | 28 October 2005



## In this issue:

---

### Main article: Clinical Care Options discussion on mother-to-child transmission; *page 2*

- Treatment response in mothers previously exposed to single-dose nevirapine
- References

## Main article: Clinical Care Options discussion on mother-to-child transmission

For this special issue of HATIP, we are grateful to Clinical Care Options (<http://clinicaloptions.com/>) for granting permission to reprint part of their comprehensive coverage of the recent 3<sup>rd</sup> International Conference on HIV Pathogenesis and Treatment, held in Rio de Janeiro, Brazil, in July 2005. CCO convened 7 expert panels to discuss and debate new data on key therapeutic issues presented in Rio, including the following analysis of studies of intervention to prevent mother-to-child transmission and access to treatment in resource-constrained settings by Michel Kazatchkine, MD, James McIntyre, MD, and Charles van der Horst, MD.

Free CME credit (or a certificate of participation) for this discussion is available on the CCO site, on successful completion of the online post-test and evaluation. The CCO site also includes Capsule Summaries of all the most important individual studies discussed by the panel, as well as downloadable PowerPoint slides for you to use in your own presentations.

Jointly sponsored by Postgraduate Institute for Medicine and Clinical Care Options, LLC. This program is approved for AMA PRA category 1 credit. CCO's online coverage of the Rio meeting was supported by educational grants from Bristol-Myers Squibb, Gilead Sciences, Roche, Tibotec Therapeutics, and Trimeris. Copyright © 2005 Clinical Care Options, LLC. All rights reserved.

Discussants:

### Michel Kazatchkine, MD

#### Ambassador on AIDS and Transmissible Disease

Ministry of Foreign Affairs  
Paris, France

### Charles van der Horst, MD

Professor of Medicine  
University of North Carolina School of Medicine  
University of North Carolina at Chapel Hill  
Chapel Hill, NC

### James McIntyre, MD

Executive Director  
Perinatal HIV Research Unit  
University of Witwatersrand  
Johannesburg, South Africa  
James McIntyre:

At the 3<sup>rd</sup> International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, our group presented new data from the Treatment Options Preservations Study (TOPS) (<http://www.clinicaloptions.com/HIV/Conference%20Coverage/Rio%202005/Capsules/TuFo0204.aspx>).<sup>[1]</sup> This study randomized antepartur HIV-positive women and their newborn infants, who were not breastfed, to receive single-dose nevirapine at delivery or to receive single-dose nevirapine at delivery plus fixed-dose zidovudine/lamivudine for either 4 or 7 days postpartum. The objective of the study was to test whether the addition of nucleoside

reverse transcriptase inhibitors (NRTIs) would reduce the incidence of HIV transmission and nevirapine resistance in both mother and infant. The hypothesis was that declining nevirapine levels may cause nevirapine resistance in the presence of a significant viral load and that the addition of dual-NRTI therapy may keep the level of virus below that associated with development of resistance.

After an interim analysis of trial data demonstrated a significant reduction in the rate of mother-to-child transmission (MTCT) in the nevirapine plus zidovudine/lamivudine arms compared with the nevirapine-only arm, the nevirapine-only arm was terminated, but recruitment to the nevirapine plus zidovudine/lamivudine arms continued. The findings we presented at this meeting represent new data on a larger group of mothers exposed to zidovudine/lamivudine plus nevirapine.

We continue to find no significant difference in the rate of development of resistance related to the duration of exposure to zidovudine/lamivudine (4 days vs 7 days). Sixty percent of mothers in the single-dose nevirapine group exhibited evidence of nevirapine resistance 6 weeks postpartum, compared with 12% of mothers in the 4-day zidovudine/lamivudine group and 10% of mothers in the 7-day zidovudine/lamivudine group.

Among the infants, the overall transmission rate measured at Week 6 was 10.5%. The rate of nevirapine resistance was low, with 2 of 21 infected infants demonstrating resistance at birth, and an additional 5 infants in the nevirapine-only arm developing resistance by Week 6.<sup>[2]</sup> No infants in the nevirapine plus zidovudine/lamivudine arms acquired nevirapine resistance in the weeks postpartum.

Questions have been asked about why only 4 or 7 days of zidovudine/lamivudine treatment had such a good protective effect when detectable levels of nevirapine may linger for up to 21 days. Indeed, the reduction in the incidence of maternal nevirapine resistance from 60% to 10% with 7 days' treatment is more than we expected. I think we are witnessing the effect of reduction in viral load to < 400 copies/mL in both the 4-day and 7-day zidovudine/lamivudine groups, when assayed at Week 2. We do not have specimens taken between 2 and 6 weeks postpartum so it is not clear how long the duration of undetectable viral load persists. It may be that the reduction in viral load is prolonged beyond 7 days as a result of lamivudine treatment, which has a much longer half-life than zidovudine. It is also not clear how persistent low levels of nevirapine may affect viral replication in these patients.  
Charles van der Horst:

Data presented at the 12<sup>th</sup> Conference on Retroviruses and Opportunistic Infections earlier this year indicated that the development of resistance mutations is driven not by the persistent low levels of nevirapine, but by the high levels of nevirapine in the presence of high viral load at the beginning of the study period.<sup>[3]</sup> That's the key point. The effect of the addition of zidovudine/lamivudine is protection from the development of resistance mutations when both nevirapine concentration and viral load are greatest, not when nevirapine levels are low.  
Michel Kazatchkine:

We have seen this phenomenon in adult clinical practice as well. When an HIV-infected adult initiates a regimen containing nevirapine and experiences intolerance or rash early in treatment, he or she often develops resistance to nevirapine despite short exposure to it because it is present at high levels with accompanying high viral load.  
Charles van der Horst:

Viral load is the key. If we hypothesize that the error rate of reverse transcriptase is about 10% in each replication cycle, and

100,000 copies/mL of the virus exist, then many more mutations will be generated at this high viral load than if, say, only 5000 copies/mL of the virus are present.

James McIntyre:

This suggests that extending antiretroviral treatment beyond 21 days may not be effective in further reducing the amount of resistance. The Ditrane Plus study, which showed an extremely low rate of nevirapine resistance (1.1%) at Week 6, is also consistent with this hypothesis.<sup>[3]</sup> In this study, women had received zidovudine plus lamivudine from week 32 prior to delivery and for three days postpartum, and, therefore, had low viral loads before they were given nevirapine.

Charles van der Horst:

Our research group in Malawi has been encouraged to extend zidovudine/lamivudine treatment beyond 7 days. I'm concerned about doing that because I think it will generate an additional problem. During this time, while mothers are being treated with dual-NRTI therapy only, viral load in the mother will probably increase, and the M184V lamivudine resistance mutation may well develop in that scenario.

James McIntyre:

The other interesting aspect of the TOPS study was the reduction in detectable resistance in the 10% of children who were infected. Among children who received zidovudine/lamivudine as well as single-dose nevirapine, there was no detectable resistance noted at 6 weeks. However, detection of resistance may be a function of the test used.

Additional data were presented by Sarah Palmer at the 14<sup>th</sup> International HIV Drug Resistance Workshop using real-time polymerase chain reaction (PCR) techniques.<sup>[4]</sup> That work showed that when one uses a more sensitive technique to detect resistance, it is possible to show that genotypic resistance is not completely eliminated but, nevertheless is reduced. Nevirapine resistance mutations were detected using real-time PCR in 75% of women who received nevirapine only, compared with 27% of women who also received zidovudine/lamivudine.

Charles van der Horst:

Another poster that we should mention in the context of single-dose nevirapine and MTCT was a presentation looking at the timing of nevirapine dosing in HIVNET 024.<sup>[5]</sup> The data showed that timing variations in either mother or infant dosing did not influence transmission rates, even when the combined pattern of both was taken into account through multivariate analysis. In the subset of women who received nevirapine less than 2 hours before delivery, early nevirapine administration to the infant (within 4 hours of birth) was not associated with lower rates of MTCT when compared with later administration (4 hours or longer after birth). It was possible to administer the infant dose up to 72 hours postpartum without impairing the protective effect against MTCT.

## Treatment response in mothers previously exposed to single-dose nevirapine

James McIntyre:

Marc Lallemand's group has previously presented data showing that women exposed to single-dose nevirapine who subsequently received antiretroviral treatment for their own health exhibited a poorer virologic response to therapy than women who did not receive single-dose nevirapine, although clinical and immunologic outcomes were not significantly different.<sup>[6,7]</sup> At this meeting, 12-

and 18-month follow-up from the same study were presented within an expert talk.<sup>[8]</sup> I found Lallemand's data reassuring. There had been a presumption that the rate of virologic response would continue to deteriorate over time, but Lallemand showed that response at either 12 months or 18 months was very similar to that seen at 6 months.

Additional reassuring data on response to treatment after nevirapine use were presented from the MTCT Plus program in Abidjan, Cote d'Ivoire.<sup>[9]</sup> However, 60% of women in that study had been on a zidovudine/lamivudine regimen before delivery, so a low rate of nevirapine resistance was expected.

Michel Kazatchkine:

The Abidjan study, unfortunately, did not report resistance or virologic response data, but it did show that the increase in CD4+ cell counts, which is associated with important clinical benefit, was similar in women who were pre-treated with nevirapine and in those who were not.

James McIntyre:

It was reassuring to me that the results of these studies suggest that the effect of nevirapine exposure on subsequent treatment outcome does not seem to be marked. It is, of course, always better to avoid the selection of nevirapine resistance than to allow it to happen. However, for the many women who start antiretroviral treatment after exposure to single-dose nevirapine, it seems that responses to therapy are reasonable.

**The remainder of the expert discussion, available at the CCO Web site, covers:**

- HIV-Exposed but Uninfected Infants
- Scaling Up Preventative MTCT Programs
- Male Partner Counseling
- Male Circumcision as an HIV Prevention Measure
- Adverse Pregnancy Outcomes
- Tuberculosis Coinfection

**To read the discussion, view capsule summaries of the data, and complete the post-test and evaluation, visit**

<http://clinicaloptions.com/HIV/Conference%20Coverage/Rio%20005.aspx>

## References

1. McIntyre JA, Martinson N, Gray GE, et al. *Single dose nevirapine combined with a short course of Combivir for prevention of mother to child transmission of HIV-1 can significantly decrease the subsequent development of maternal and infant resistant virus.* Program and abstracts of the 3<sup>rd</sup> IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract TuFo0204.
2. Gray GE, McIntyre JA, Martinson N, et al. *NNRTI-resistant mutations in HIV-infected infants following single dose nevirapine (sd-NVP) are reduced by the addition of short course zidovudine and 3TC.* Program and abstracts of the 3<sup>rd</sup> IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract TuPe5.4P01.
3. Chaix ML, Dabis F, Ekouevi D, et al. *Addition of 3 days of ZDV+3TC postpartum to a short course of ZDV+3TC and single-dose NVP provides low rate of NVP resistance mutations and high*

efficacy in preventing peri-partum HIV-1 transmission: ANRS DITRAME Plus, Abidjan, Côte d'Ivoire. Program and abstracts of the 12<sup>th</sup> Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Massachusetts. Abstract 72LB.

4. Palmer S, Boltz V, Maldarelli F, et al. *Short-course Combivir (CBV) single dose nevirapine reduces but does not eliminate the selection of nevirapine-resistant HIV-1: improved detection by allele-specific PCR.* Antivir Ther. 2005;10:S5. Abstract 3.

5. Chi BH, Wang L, Read JS, et al. *Timing of maternal and infant nevirapine and the risk of mother-to-child transmission of HIV-1: HIVNET 024.* Program and abstracts of the 3<sup>rd</sup> IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract TuPp0405.

6. Jourdain G, Ngo-Giang-Huong N, Tungyai P, et al. *Exposure to intrapartum single-dose nevirapine and subsequent maternal six month response to NNRTI-based regimens.* Programs and abstracts of the 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, California. Abstract 41LB.

7. Jourdain G, Ngo Giang Huong N, Le Couer S, et al. *Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy.* N Engl J Med. 2004;351:229-240.

8. Lallemand M. *Response to therapy after prior exposure to nevirapine.* Program and abstracts of the 3<sup>rd</sup> IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract TuFo0205.

9. Bedikou G, Viho I, Tonwe-Gold B, et al. *6-month immunological response with HAART containing nevirapine in HIV-infected women post exposure to single dose of nevirapine for PMTCT. The MTCT-plus Initiative in Abidjan, Cote d'Ivoire (2003-2005).* Program and abstracts of the 3<sup>rd</sup> IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract MoOa0203.

## 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).

For further information please visit the HATIP section of [aidsmap.com](http://aidsmap.com)