

## POTENTIAL STRATEGIES TO REDUCE THE RISK OF NVP RESISTANCE ASSOCIATED WITH PMTCT REGIMENS

Firm data are lacking to strongly endorse or refute any of the following strategies; however, until further clinical data become available to clarify their relative advantages and disadvantages, the following options are presented for consideration. These strategies should be discussed by national and regional policymakers and, where appropriate, options reviewed with the patients themselves.

1. **Administer a “tail” of two NRTIs for a period of time following the administration of SD NVP.** If the mother begins taking two NRTIs (e.g., AZT and 3TC) immediately after the administration of SD NVP and continues taking the NRTIs for a defined period of time, during that time period the HIV in her serum will be exposed to three ARVs rather than just NVP, which should discourage the emergence of NVP resistance. Indeed, several small clinical trials of this strategy have documented some (but not complete) success in preventing the development of NVP resistance following SD NVP. However, the ideal length of administration of the 2 NRTI tail has not been determined, and may vary between different women because the half-life of NVP varies across individual patients. Administration of a tail that is too short risks promotion of NVP resistance, while administration of too long a tail may promote resistance to one or both of the NRTIs used in the tail. The studies that have shown decreased NVP resistance have used a 3 to 7 days tail of AZT/3TC. In the TOPS study, for example, the rate of NVP resistance was 60% without the tail versus 12% with a 4 day tail of AZT/3TC versus 10% with a 7 day tail of AZT/3TC. The optimal duration of the tail and the optimal components are not known; studies are ongoing to define this. Because there are no data on the safety and efficacy of a prolonged tail (more than 1 week) after SD NVP, if a tail is used a duration of 7 days might be chosen based on the available studies.
2. **Administer short-course AZT boosted by SD NVP (with infant SD NVP given at birth), but omit the maternal dose of SD NVP.** Omitting the maternal dose of SD NVP avoids any risk of inducing maternal NVP resistance. The obvious drawback of this approach is that it might compromise the effectiveness of this intervention in reducing the risk of HIV transmission to the infant. However, results from the Mashhi trial, conducted in a mixed breastfeeding and non-breastfeeding population in Botswana, found that omission of the maternal dose of SD NVP did not result in an increased risk of HIV transmission to the infant, so long as the rest of the regimen (AZT to mother and infant, plus SD NVP to infant at birth) was administered appropriately. Validation from other clinical trials is needed before this approach can be universally endorsed, but clinicians may nevertheless want to consider this option. If this option is chosen, AZT should be initiated at 34 weeks gestation, as in the Mashhi trial, and administered to the infant for 4 weeks postpartum. *Omission of the maternal SD NVP can be considered only if the maternal and infant AZT regimens are properly administered.*
3. **Administer HAART to all HIV-infected pregnant women for PMTCT, regardless of clinical status.** It is important to note that this strategy does not necessarily solve the problem. First, the choice of drug regimen is complicated because the risk of symptomatic NVP-related hepatic toxicity, which can be life-threatening, is markedly increased in women with CD4 counts greater than 250 cells/mm<sup>3</sup> at the time of therapy initiation. Thus, NVP-based HAART would not be an optimal choice for use in such women, and if prescribed the woman would need close monitoring for liver toxicity. Additionally, if NVP-based HAART is prescribed for a pregnant woman who does not herself have clinical indications for starting antiretroviral therapy, then HAART should be discontinued following delivery. When the HAART regimen is stopped, however, serum levels of the NRTIs (e.g., AZT and 3TC) in her HAART regimen will drop much more rapidly than that of NVP, resulting in the same problem of prolonged HIV exposure to just NVP. Indeed, NVP resistance has been documented in a cohort of pregnant women in Mozambique in whom this strategy was employed. If, however, a PI-based HAART regimen is prescribed instead, the risks of NVP toxicity and inducing NVP resistance are avoided altogether. If NVP-based HAART is used, administration of a 7 day “tail” of AZT/3TC following discontinuation of NVP at delivery to reduce the risk of NVP resistance can be considered.
4. **Use PMTCT regimens that do not contain NVP,** such as AZT monotherapy, AZT/3TC combination therapy, or PI-based HAART. Resistance to AZT requires prolonged duration of exposure, and multiple mutations must develop before resistance is observed; thus resistance to AZT following AZT single drug prophylaxis is much less frequent than that observed with NVP or 3TC, for which a single mutation induces

resistance. However, AZT monotherapy for PMTCT is not as effective as AZT boosted by SD NVP. Prepartum/intrapartum/postpartum AZT/3TC combination therapy has similar efficacy to AZT plus SD NVP but is more complex, and risks the promotion of 3TC resistance (which was documented in six of 50 women [12%] who received AZT/3TC prepartum, intrapartum, and postpartum in the PETRA trial). The intrapartum/postpartum AZT/3TC regimen is less effective than AZT plus SD NVP, and antenatal treatment is recommended when possible to prevent in utero transmission as well as peripartum transmission. PI-based HAART, if administered appropriately, constitutes a very potent PMTCT regimen with very little risk of generating resistance, but is generally more expensive and less convenient than other PMTCT regimens. Additionally, appropriate dosing of many PI drugs in pregnancy needs to be defined: SQV boosted with low dose RTV will achieve adequate levels in pregnant women; NFV given twice daily may achieve adequate levels but there is significant variability of levels between women; and LPV/RTV may require an increased dosage in the third trimester due to low levels observed in the third trimester in one study.

5. **Reserve the use of SD NVP PMTCT regimens for women with relatively high CD4 counts and low HIV viral loads.** Studies of SD NVP for PMTCT suggest that the presence of a high HIV viral load and/or low CD4 count in the mother at the time of SD NVP administration elevates her risk of developing resistance to NVP. This underscores the importance of evaluating CD4 cell count in all HIV-infected pregnant women. Limiting the administration of SD NVP to women with relatively low HIV viral loads and high CD4 counts would likely reduce the overall risk of promoting NVP resistance and would also reduce the likelihood that women receiving SD NVP would be initiating HAART within six months of delivery (recent clinical trials suggest that the impact of SD NVP on a woman's subsequent response to HAART may be confined to women who initiate HAART within six months of their exposure to SD NVP). Certainly, all efforts should be made to start HIV-infected women who require therapy for their own health (as indicated by clinical symptoms, low CD4 count, and/or high HIV viral load) on HAART. These women are at highest risk of both disease progression and transmission of HIV to their infants, and HAART will significantly reduce the risk of each of these events. Additionally, such women are at greatest risk for development of NVP resistance following administration of SD NVP; if HAART is started instead and continued postpartum, this risk is avoided. Also, if available, administration of a 7 day "tail" of AZT/3TC following single-dose NVP can be considered to further reduce the risk of NVP resistance.