

APPENDIX C: MANAGING THE RISKS OF RESISTANCE ASSOCIATED WITH PMTCT REGIMENS

Several studies have confirmed the efficacy of short-term ART involving only one or two ARVs in significantly reducing the risk of vertical HIV transmission. The relative simplicity and low cost of these PMTCT strategies make them attractive options in resource-limited settings. However, administration of ART that does not fully suppress HIV replication promotes the development of drug resistance. Therefore, the use of just one or two ARVs in pregnancy can induce ARV resistance that could compromise the efficacy of future HAART regimens for the mother (as well as for the infant, should the infant become infected despite the PMTCT intervention). Drugs that lose efficacy following the development of a single resistance mutation, such as 3TC or NVP, are especially vulnerable to this complication. It is not clear at this time just how serious a problem this poses, making it difficult to establish firm recommendations. However, a brief review of the relevant data is warranted.

Resistance to AZT

Resistance to AZT typically develops only after several months of partially-suppressive ART. Clinical data document a low prevalence of AZT resistance following short-course AZT regimens, hence it is not likely that short-term administration of this agent for PMTCT will compromise the efficacy of this agent in future HAART regimens for the mother.

RESISTANCE TO 3TC

Resistance to 3TC can develop rapidly even when combined with AZT, because a single mutation in the HIV genome can result in high-level resistance to this agent. The ANRS 075 study, a cohort study in France involving the use of AZT with 3TC added after thirty-two weeks gestation, reported an overall resistance rate of 39% to 3TC six weeks following delivery, although the risk of developing resistance depended heavily on the length of exposure to the regimen. No 3TC resistance was reported with the use of this regimen for less than one month, whereas one to two months of prophylaxis was associated with a 20% risk of 3TC resistance, and over two months of prophylaxis was associated with a 50% risk of 3TC resistance. However, in the PETRA trial, 12% of women who received a regimen of oral AZT plus 3TC (starting at thirty-six weeks antepartum and continued intrapartum and postpartum for one week) developed resistance to 3TC.

RESISTANCE TO NVP

Low levels of HIV (approximately 1 in 1,000 viral particles) with mutations associated with NVP resistance are present in treatment-naïve individuals. Following administration of Single-Dose Nevirapine (SD NVP), there is a rapid selection of resistant virus due to the long half-life of the drug: detectable NVP levels can persist for three weeks or longer following a single dose. For example, the HIVNET 012 trial involved SD NVP administered to the mother during labour and another dose to the infant after delivery. 25% of NVP-exposed women had evidence of NVP resistance at six weeks postpartum, as did 46% of the infants who became infected with HIV. Unfortunately, cross-resistance with other agents in the NNRTI class, such as EFV, is very common.

The frequency with which resistance is detected appears to depend upon several variables, including the subtype (clade) of HIV-1 involved; the mother's clinical, immune and virologic status at the time she receives SD NVP; the time at which resistance testing is performed after delivery; and the sensitivity of the resistance assay used. Studies involving clade B virus, the predominant clade of HIV-1 in the Caribbean, have documented detectable NVP resistance following delivery in 15 to 40% of women who received SD NVP (with or without other ARVs) during labour.

The degree to which viral resistance induced by SD NVP is associated with diminished clinical response to subsequent NNRTI-based highly active antiretroviral therapy (HAART) in women has not been clearly established. A preliminary assessment of response to NNRTI-based therapy in women who required initiation of HAART at some time after delivery was performed as a follow-up study of the PHPT-2 trial. The PHPT-2 trial included both AZT and NVP in its PMTCT regimen. AZT was administered to the mother starting at twenty-eight weeks gestation and orally during labour, and one week of AZT was given to the infant following delivery (four to six weeks if the mother received less than four weeks of AZT). SD NVP was also administered to the mother during labour and to the infant following delivery. NVP resistance was detected ten to fourteen days after

SD NVP exposure in 20% of ninety randomly selected trial participants, and was more likely to develop in women with higher HIV viral loads and lower CD4+ T cell counts.

Women who required HAART after completion of the study received a NVP-based HAART regimen (primarily d4T/3TC/NVP). A preliminary analysis compared the virologic outcome after three and six months of NVP-based HAART among women who had received SD NVP as part of their PMTCT regimen versus a small group of women who did not receive SD NVP. No significant differences in clinical response (as demonstrated by weight gain following initiation of therapy), immunologic response at three and six months following initiation of therapy (both groups with an increase of about 100 cells at six months), or in virologic response to <400 copies/mL were seen between women who received or did not receive SD NVP. However, women who received SD NVP and who had genotypic resistance to NVP detected at two weeks postpartum were less likely to achieve an HIV viral load <50 copies/mL after six months of therapy than women who had not received SD NVP (38% versus 68%, respectively). The rate of virologic suppression to <50 copies/mL in women who had received SD NVP but did not have virus with detectable genotypic NVP resistance was intermediate between the two groups (52%).

Response to NVP-based HAART after SD NVP: impact of timing of HAART initiation

Follow-up analysis of women who had developed NVP resistance in the HIVNET 012 trial found that resistance was no longer detectable by conventional resistance assays one year following delivery (conventional assays require 15% to 20% or more of viral quasispecies to contain the mutation to be detectable). However, there has been concern that resistant strains of HIV may remain 'archived' in body compartments (e.g., resting T-cells) at levels undetectable by conventional resistance assays, even after the ARV that induced the resistance is withdrawn. The resistant strain may subsequently re-emerge under selective drug pressure when a HAART regimen containing that ARV is initiated at a later date, potentially resulting in treatment failure.

A recent study from South Africa using highly sensitive resistance assays found that although NVP resistance mutations were present in a high proportion of women who received SD NVP at 6 weeks postpartum, the mutations rapidly faded to low levels over time and resistant variants were detected less frequently in cellular DNA, with persistence in this compartment by 12 months post-SD NVP in only a small minority of women. These data are consistent with recent clinical trials results suggesting that response to NVP-based HAART might not be compromised in women who initiate HAART more than six months after their exposure to SD NVP. In a preliminary report on a study from Botswana in which women received short course AZT with or without SD NVP, virologic response (defined as the likelihood of viral load suppression to less than 400 or less than 40 copies/mL) to subsequent NVP-based HAART varied by the time of initiation of HAART after SD NVP exposure. Women who initiated HAART less than 6 months following SD NVP exposure had a poorer virologic response than women without prior SD NVP exposure; however, women who initiated HAART more than 6 months following SD NVP exposure experienced a virologic response that was similar to the response seen in women without prior SD NVP exposure. Similarly, preliminary data from South Africa indicate that response to NVP-based HAART is similar in women who received SD NVP 18 months or more prior to starting HAART to those without SD NVP exposure (Coovadia, CROI 2006, Abs. 641).

Hence, it is difficult to draw definitive conclusions regarding the relevance of resistance incurred by antiretroviral PMTCT regimens that do not fully suppress HIV replication. It is clear that such regimens can and often do lead to the selection of HIV resistance mutations, but the clinical impact of this resistance on future therapeutic options for the mother awaits further clarification.