Hot News

Welcome to "Hot News", a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

Update on the Teratogenicity of Efavirenz

In March 2005, Bristol-Myers Squibb and the FDA notified healthcare professionals of revisions of the prescribing information for efavirenz. The pregnancy category for the drug has changed from category C (risk of fetal harm cannot be ruled out) to category D (positive evidence of fetal risk). This change is a result of four retrospective reports of neural tube defects in infants born to women with first-trimester exposure to efavirenz, including three cases of meningomyelocele and one Dandy Walker syndrome. As efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman, pregnancy should be avoided in women receiving efavirenz.

During the development of efavirenz, animal studies were performed to assess the potential for birth defects. Malformations were observed in three of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (*versus* zero of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20-150) with efavirenz 60 mg/kg daily, a dose resulting in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in one monkey fetus, microphthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to human maternal blood concentrations.

An increase in fetal resorption was observed in rats given efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of efavirenz. It produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of efavirenz.

Limited data are available regarding birth defects occurring after intrauterine exposure to efavirenz. The outcomes of pregnancy have been reviewed for 206 women (207 fetuses) after being exposed to efavirenz-containing regimens, most of which were first-trimester exposures. Birth defects occurred in five of 188 live births with first-trimester exposure, and in zero of 13 live births with second- or third-trimester exposure. None of these prospectively reported defects were neural tube defects. However, there have been four retrospective reports (i.e. after the results of the pregnancy were known) of findings consistent with neural tube defects, including three cases of meningomyelocele. All four mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

In summary, women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and be advised of fetus risk in case they become pregnant. If the drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Although there are no adequate, well-controlled studies in pregnant women, efavirenz should be used during the first trimester of pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

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New Stanford's Guidelines for Interpreting Drug Resistance Mutations

In September 2005, a simple one-page guide was released by the Stanford's team in which the clinical significance of drug-resistance mutations in HIV was updated. Interesting new views about resistance mutations and patterns merit further attention and discussion. Summarized below are some of the main caveats.

1. Resistance mutations to nucleoside analogues are classified in four major groups. First, thymidine analogue mutations (TAMs), which pro-

mote the unblocking of the nascent DNA chain caused by nucleoside analogs, and are mainly selected by AZT and/or d4T, but cause cross-resistance to other nucleoside analogs. Second, TAM-associated mutations (involving codons 44D, 69D, 75I and 118I), which are generally selected in combination with TAMs. Third, discriminatory mutations (65R, 74V, 115F, 184V), which are mainly selected by TDF, ddI, ABC, and 3TC/FTC, respectively. Fourth, Q151M complex, which cause resistance to all nucleoside analogues, although to a lesser extent to 3TC/FTC and TDF.

2. Resistance to non-nucleoside analogues results from changes in three different regions of the RT gene: positions 98-108, 179-190, and 225-238. The most frequent mutations causing intermediate or high-level resistance to these compounds are 103N/S, 181C/I/V, 188L, 190A/S/E/Q/C, and 230L.
3. Resistance mutations to protease inhibitors (PI) are clustered into four groups. First, "major" mutations, which are quite specific: 30N for nelfinavir, 48V/M for saquinavir, 50V for amprenavir, 50L for atazanavir, 82A/T/F/S for indinavir and lopinavir, 84V/A/C for all PI, and 90M for nelfinavir and saquinavir.
4. The second group of PI-resistance mutations are positioned in the flap region and includes for the first time mutation 47A, which characteristically cause high-level resistance to lopinavir.
5. The third group of PI-resistance changes are generally accessory mutations and appear along with "major" mutations. They include mutation 88S, which characteristically cause high-level resistance to nelfinavir and atazanavir.
6. Finally, the last group of PI-resistance mutations is represented by polymorphic changes, with the exception of 10F. They contribute to resistance only when present along with other "major" PI-resistance mutations.
7. The impact of each change in resistance is estimated semi-quantitatively as high, intermediate, or low level, as well as "contributing" to resistance. Moreover, hypersusceptibility is considered for the first time for changes such as rt65R and rt74V for AZT; rt184V for AZT, d4T and TDF; pro88S for amprenavir; and pro50L for all PI but atazanavir.

This update is very useful as a pocket guide for clinicians caring for HIV-infected patients, who often are not experts in the interpretation of resistance mutations. Efforts to translate the complex world of genotypic resistance into simple advice are much appreciated.

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Liver Toxicity is not Increased with Nevirapine Once a Day

In the 2NN study (van Leth, et al. Lancet 2004; 363:1253-63), an international, multicenter, randomized, prospective trial in which nevirapine (NVP) once daily (QD) was compared to NVP twice daily and efavirenz (EFV), a higher incidence of liver enzyme elevations was found in the NVP QD arm with respect to the other two arms. In Dublin, during the 10th European AIDS Conference (EACS 2005), a sub-analysis was presented (Storfer, et al. abstract PE9.6/2) in which it was highlighted that all the cases of excess liver toxicity due to NVP QD in the 2NN trial occurred in a single center from Thailand, which had recruited 162 out of the total 967 HIV-infected patients included in the study who received a single non-nucleoside. Moreover, when only men and women with less than 400 and 250 cells/µl, respectively, were considered (as currently recommended for patients initiating NVP) there were no significant differences between the three study arms in the incidence of liver enzyme elevations outside of Thailand.

This information is relevant since an increasing number of antiretroviral regimens are becoming for once daily use, particularly using combo pills such as Kivexa® (abacavir plus lamivudine) or Truvada® (tenofovir plus emtricitabine). These new data will reassure the use of NVP QD in clinical practice.

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