Two studies in the November 1, 2003 edition of the Journal of Acquired Immune Deficiency Syndromes [JAIDS] address the issue of drug resistance in women taking antiretroviral prophylaxis to prevent mother-to-child transmission [MTCT] of HIV. One found an increased risk of transmission in mothers infected with phenotypic AZT [zidovudine, Retrovir]-resistant virus. The other reported that efavirenz [Sustiva]-based regimens were as effective in women exposed to short courses of nevirapine [Viramune] as in those with no prior nevirapine exposure.

Since ACTG 076, the first study of AZT in pregnant women, dramatic progress in the prevention of MTCT of HIV has been achieved. According to an editorial accompanying the two reports, use of anti-HIV drugs by pregnant women has reduced HIV transmission by more than 70%. Today in North America and Western Europe, some studies report as few as 2% of children born to HIV positive women turn out to be HIV-infected because of antiretroviral prophylaxis and other interventions.

However, the drugs usually employed—AZT, 3TC [lamivudine, Epivir], or nevirapine monotherapy, or dual nucleoside analogues [NRTIs]—are not what anyone would characterize as optimal therapy for the mother herself. Some experts have voiced concerns that these short courses of mono- or dual therapy might lead to resistance, eventually reversing the great strides made in reducing MTCT, and even lead to increasing transmission of resistant HIV to infants. Furthermore, some worry that the development of resistance might limit any benefit that the mother or infant could one day receive from triple-drug therapy, particularly in the developing world where only a limited number of regimens are available.

The first paper reported findings from one of the oldest ongoing perinatal HIV studies in the U.S., the Women and Infants Transmission Study (WITS). This study evaluated the effect of phenotypic AZT resistance on MTCT in 74 AZT-treated mothers enrolled in the study up until September 1994. These women had moderately advanced disease, with a median CD4 cell count of 271 cells/mm³.
and a median viral load of 39,811 copies/mL. Factors independently associated with AZT resistance at delivery included previous use of AZT (before pregnancy), high viral loads, and low CD4 cell counts.

Sixteen of the women (22%) passed HIV on to their infants. After adjustment for other variables known to increase the risk of transmission (such as duration of membrane rupture at delivery), decreasing susceptibility to AZT was shown to be associated with an increased risk of transmission. These findings build on a prior WITS study that identified an increased risk of transmission in women with genotypic AZT-resistant virus (virus known to contain mutations associated with AZT resistance).

There also have been reports that transient mutations associated with nevirapine resistance have been observed in 15–19% of women six weeks after receipt of a single dose (200 mg) of nevirapine administered during delivery to prevent MTCT of HIV. Even though 12-month follow-up of these women revealed no detectable mutant virus in most cases, the rapid emergence of resistance has led to concerns over the increasingly widespread use of nevirapine to prevent MTCT in resource-limited settings.

Since no data are currently available from international MTCT programs on the effect of single-dose nevirapine on future treatment outcomes, authors of the second JAIDS study looked at subjects in an American cohort who had received a short course (less than 28 days) of nevirapine as part of combination therapy that was stopped due to rash or other toxicity (nevirapine resistance mutations have also been observed in such individuals). These subjects were later treated with a regimen containing efavirenz, another non-nucleoside reverse transcriptase inhibitor [NNRTI] that shares a similar resistance profile.

The subjects were drawn from the HIV Outpatient Study (HOPS) which prospectively gathers treatment data on about 3,000 patients from nine urban U.S. clinics. Responses to efavirenz in the nevirapine-pretreated subjects were compared with those of subjects with no prior exposure. Treatment success was defined as achieving viral loads below 400 copies/mL at 1–3, 4–8, and 10–14 months after starting efavirenz-based combination regimens.

Responses to efavirenz-containing regimens were compared between 26 subjects with less than 28 days of nevirapine exposure and 495 subjects with no prior reported nevirapine exposure. The demographic profiles were similar for both groups. The mean interval between stopping nevirapine and initiation of an efavirenz-containing regimen was 518 days.

There were no significant differences in the proportion with treatment success among those cases with prior nevirapine exposure of less than 28 days and those with no prior nevirapine exposure: 42% of both cases and controls achieved undetectable viral loads (less than 400 RNA copies/mL) at 1–3 months after starting efavirenz; 42% of cases and 56% of controls had undetectable viral loads at 4–8 months; and 46% of cases and 53% of controls had undetectable viral loads at 10–14 months.

The authors note that “while these U.S. findings are not directly applicable to the maternal single-dose nevirapine regimens used in international PMTCT [prevention of MTCT] programs, they do suggest that prior exposure to nevirapine may not necessarily result in higher rates of treatment failure for women later treated with efavirenz-containing regimens.”

The accompanying editorial notes that follow-up studies are planned and/or underway in Uganda, Botswana, South Africa, and Thailand to assess whether women exposed to single-dose nevirapine are at increased risk of treatment failure when placed on combination antiretroviral regimens containing NNRTIs and whether viral subtype influences treatment outcome.

Additionally, the editorial’s authors note that “it will also be important to carefully monitor whether there is a heightened risk of adverse events for African women who receive non-nucleoside reverse transcriptase inhibitors as part of combination treatment regimens. Enhanced risk of severe nevirapine-associated rash hypersensitivity and hepatic toxicity has been reported among women as well as among individuals with higher CD4 cell counts, and there have been several case reports of significant nevirapine toxicity among black HIV-infected pregnant women receiving chronic nevirapine therapy.”

Meanwhile, it is well known that efavirenz use should be avoided in pregnant women or women at risk of becoming pregnant because of the risk of birth defects [teratogenicity]. “If high rates of nevirapine toxicity with chronic dosing were to be observed among African women, given the concerns of teratogenicity with the use of efavirenz among women of childbearing age,” they conclude that “careful reconsideration would need to be given as to the optimal first-line antiretroviral therapy for women in resource-limited settings.”

Theo Smart is an AIDS advocate living in South Africa.

This article first appeared on aidsmap (www.aidsmap.com), and the copyright is held by NAM Publications of London. Our thanks to NAM for permission to reprint.

References

