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Pharmacotherapy of perinatal HIV

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Summary Continued spread of HIV infection among women has led to the use of antiretrovirals in pregnant women and their newborns. Regional strategies to prevent mother-to-child transmission are evolving. Altered drug disposition during pregnancy may require altered dosing or 'boosted' therapies to avoid treatment failure. Maturing drug elimination pathways in newborns must also be considered for effective therapy. Potential teratogenic effects and increased sensitivity to antiretroviral toxicities might be encountered in this population. Use of highly active antiretroviral therapy (HAART) to suppress viral replication combined with formula feeding can reduce the rate of mother-to-child HIV transmission to less than 2%. In resource-limited settings, less intensive regimens including zidovudine, lamivudine and nevirapine still substantially reduce mother-to-child transmission. Although difficult to perform, clinical trials to determine the safety, pharmacokinetics and optimal dosing of antiretroviral in pregnant women and their newborns are urgently needed.

Introduction

As infection with human immunodeficiency virus (HIV) continues to spread throughout the world, HIV/AIDS has become a major contributor to global morbidity and mortality. At the end of 2003, 40 million people worldwide were estimated to be living with HIV infection. Approximately half these people are women, most of whom are of child-bearing age, but 2.5 million of them are children, most of whom acquired HIV infection via mother-to-child transmission.[1] Women are particularly vulnerable to HIV infection because of inadequate knowledge about AIDS, insufficient access to HIV

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prevention services, inability to negotiate safer sex, and a lack of female-controlled HIV prevention methods.

Indications for the use of antiretrovirals in HIV-infected pregnant women and their neonates

The use of combination regimens of three or more antiretrovirals, often referred to as highly active antiretroviral therapy (HAART), has resulted in dramatic improvements in HIV morbidity and mortality. Guidelines have been published on the use of antiretroviral therapy (ART) in HIV-infected adults and children living in areas with wide-scale access to ART (Table 1) and in resource-poor areas where access is limited (<http://www.aidsinfo.nih.gov/guidelines>). In general, HIV-infected pregnant women should initiate ART according to the same criteria as those used in non-pregnant adults. However, ART can also be used in pregnancy to prevent vertical HIV transmission in those women who do not require ART based on their immunologic and clinical status. In the absence of treatment, 15–45% of HIV-infected pregnant women will pass the infection on to their infants, with 5–10% of infants born to HIV-infected women infected across the placenta, 10–20% infected from exposure at or around the time of delivery and 5–20% infected through breast feeding.[2] The later mode is thought to be responsible for up to 50% of HIV infections in children in Africa.[3]

Effective therapeutic strategies to prevent mother-to-child transmission (MTCT) of HIV have been in use for the past decade. In 1994, the PACTG 076 trial demonstrated that administration of a zidovudine regimen comprised of oral dosing initiated at 14–34 weeks gestation, continuous intravenous (IV) infusion during labor and 6 weeks of oral dosing to the newborn, reduced mother-to-child transmission by 67%.[4]

Administration of HAART during pregnancy is associated with reductions in the rate of vertical transmission to 1.5% or less in women who do not breastfeed their infants.[5,6] The use of combination antiretroviral regimens during pregnancy, elective cesarean section with detectable viral load at the time of delivery, and formula feeding have become the standard treatment of HIV-infected pregnant women in areas of the world where resources allow.

Unfortunately, countries most affected by HIV generally lack sufficient resources to make these interventions widely available. Less intensive antiretroviral regimens more practical for use in resource-poor areas have been developed. Shortened zidovudine regimens that start at 36–38 weeks of pregnancy (alone or in combination with lamivudine), use of oral rather than intravenous dosing during labor, and decreased or eliminated postnatal infant dosing have been shown to reduce transmission by 38–50%.[7–12] Understanding the relative contribution of the treatment during these three periods (prenatal, intrapartum, postpartum) in reducing transmission has not been fully defined and is essential for effective utilization of scarce resources. In the PHPT study, early zidovudine therapy in mothers starting at 28 weeks with long therapy (6 weeks) to the newborn significantly reduced transmission as compared to late maternal therapy starting at 36 weeks with short infant therapy of 3 days.[7] However, no differences were noted if the maternal therapy was short but the infant received long therapy or the mother received prolonged therapy and the infant only 3 days.

The least intensive, lowest-cost regimen shown to be effective in preventing mother-to-child HIV transmission involves two oral doses of nevirapine: one to the mother during labor and another one to the infant at 48–72 h postpartum. This nevirapine regimen reduced vertical HIV transmission by 41% in a breast-feeding population.[11] In a South Africa study, mother-to-child transmission at 8 weeks postpartum was equally low (9–12%) with either an abbreviated zidovudine–lamivudine regimen or intrapartum-postnatal nevirapine.[13]

In regions of the world where formula feeding is not a safe option, mother-to-child HIV transmission from breast milk is a major problem. Preliminary data suggest that several strategies can be effective in preventing breast milk HIV transmission, including exclusive breast feeding and postnatal infant ART while breast feeding. However, conclusive demonstration of the efficacy and risk–benefit ratios of these strategies await the completion of further trials.[14]

Effect of pregnancy on drug disposition

Physiologic changes associated with pregnancy can affect all four components of drug disposition: absorption, distribution, metabolism and excretion. Nausea and vomiting, especially pronounced in early pregnancy, may decrease drug absorption. Plasma progesterone increases during pregnancy, leading to decreases in intestinal motility and increase in gastric emptying and intestinal transit times.[15] During an average pregnancy, total body water increases by 8 L, plasma volume enlarges by 50%, and body fat stores increase, changing the distribution of both hydrophilic and lipophilic