Perspectives on Vertical Transmission

Nevirapine (VIRAMUNE®) is a NNRTI (non-nucleoside reverse transcriptase inhibitor) which has been FDA approved. It has been demonstrated in studies that nevirapine has potent antiviral activity against HIV if used in a well designed treatment regimen suitable for an individual's specific situation, not unlike other antiretroviral drugs. In trial #1046, the combination of AZT+ddI+nevirapine had potent antiviral activity against HIV in treatment naive individuals demonstrated by significant CD4 increases and good suppression of viral load. Nevirapine is being studied in combination with protease inhibitors as part of multi-drug combinations. Nevirapine is generally well tolerated except for the potential of developing a rash (16% incidence rate), which can be severe. The July issue of the NATAP newsletter, NATAP Reports, contains the latest comprehensive data and information available for nevirapine.

Nevirapine has properties, including good bioavailability, that suggest it would be a useful drug to interrupt transmission of HIV from mother to infant if used both during delivery (intrapartum) and immediately after birth (early post-partum). ACTG 250 was a phase I study exploring the safety and pharmacokinetics of using nevirapine in 17 HIV infected pregnant women during labor and in their newborns. The idea was to give a single dose of nevirapine to the pregnant mother when she came in during active labor. The study first explored a 100 mg single dose and then moved to a 200 mg single dose. They found nevirapine to be rapidly absorbed, with high blood levels reached 2 hours after taking the drug, and high levels were immediately transferred to the infant. Levels in the infant at the time of birth were equal to those in the mother. The investigators reported no mother or infant drug related toxicity.

ACTG 250 was conducted to help determine a dosing strategy for ACTG 316. The original goal of 250 was to determine a dose that would maintain a blood level of nevirapine above 100 ng/ml (10 times the in vitro IC50) in the mother during labor and in the newborn during the first week of life. A dose was determined which reached high blood levels of nevirapine in both the mother and the infant.

In fact, the median nevirapine blood concentrations reached high levels of just above 1000 ng/ml in the women, which is 100 times the IC50. The IC50 is a research measure used to see how much drug is required for effective therapy using that particular drug. For example, if the IC50 for a particular drug is 10 ng/ml, that means 10 ng/ml of drug is necessary to inhibit 50% of virus replication. Nevirapine blood concentrations in the newborns remained above 100 ng/ml through the first 7 days of life for all the infants in the study who received the single dose of 2 mg/kg.

Nevirapine has been shown to penetrate cell-free virus, and bind to and inactivate the reverse transcriptase. The reverse transcriptase enzyme is the target of drugs such as AZT, d4T, etc. (reverse transcriptase inhibitors) for the purpose of interrupting the HIV reproduction process.

You may be familiar with the results of study #076, where an AZT treatment strategy was used to try to interrupt HIV transmission from pregnant women to their newborns. In 076, women who received AZT placebo had a transmission rate of 25%; women who received the specially designed AZT treatment had a transmission rate of 8%. In 076, the pregnant women received AZT from week 14. They received AZT by IV during labor, and the newborns received AZT post partum for 6 weeks.

No one is sure exactly how the 076 regimen of using AZT to interrupt HIV transmission works, but it is felt that prophylaxis of the infant is one of the important components of the treatment protocol. In a CDC (Center for Disease Control) study, post exposure prophylaxis of health care workers exposed to HIV reduced the risk of infection by 80% indicating that a prophylaxis strategy may be key to interrupting transmission.

It was reported by Dr. John Sullivan, of the University of Massachusetts, at the recent IDSA medical conference (Sept 15, 1997) that it appears as though 60-80% of transmissions occur during the intrapartum period (during labor). He said, a number of studies suggest this. He cited two studies. A French study which concluded that 65% of the infant infections occurred during the intrapartum period. And a small
South African study of 63 infants observed through the first 6 months of life where the transmission rate was 38%, 79% of the infant infections occurred during the intrapartum period or through breast feeding during the first few months of the infant's life. Additionally, it appears as if even with the reduced rate of vertical transmission due to the 076 AZT treatment strategy, a significant proportion of the transmissions occur intrapartum.

The use of just two oral doses, one for the mother and one for the infant, make the strategy of using nevirapine inexpensive and practical for use in the USA and particularly in developing countries.

All this information is important in planning strategies to interrupt HIV transmission from a pregnant woman to her newborn. Pediatric researchers have set a goal of trying to reduce the HIV vertical transmission rate to below 2%.

ACTG 316 is a study designed to explore if nevirapine can further reduce the transmission of HIV from a pregnant woman to her newborn. It was designed with consideration of the information outlined above. Since it is felt that most transmissions occur during labor and that prophylaxis of the infant may be key, the dosing of nevirapine in ACTG 316 is aimed at these two key rational.

The pregnant woman will receive a single dose of a 200 mg tablet of nevirapine when she comes into the hospital during active labor; and, the newborn will receive a single oral dose of nevirapine of 2 mg/kg between 48 and 72 hours after birth before leaving the hospital. Women participating in 316 can take any other approved antiretroviral therapies they want. They will be randomized to receive either nevirapine or not to receive nevirapine. In fact, in the first 50 women enrolled, most were also taking AZT+3TC, in addition to being randomized to nevirapine or a nevirapine placebo.

The enrollment goal of ACTG 316 was to enroll 800 women. Because the success of the 076 AZT treatment regimen has lowered anticipated transmission rates to 5%, study investigators have had to increase the number needed to enroll to 1200 women so the results will be statistically significant. In order to reach that goal the study has been expanded to France and the United Kingdom.

ACTG 316 is sponsored by the AIDS Clinical Trials Group and funded by the NIH. Drug is being provided by the manufacturer of nevirapine, Boehringer Ingelheim. There is an ongoing Pediatric Expanded Access Program where nevirapine is available for children in tablet or liquid form. More information is available about the Pediatric program by calling 1-800-595-5494. The manufacturer is expected to be soon submitting an application to the FDA for approval of pediatric use of nevirapine.

Added Perspectives

By the year 2000, it's been estimated that 30 to 49 million new HIV infections can be expected with 50% in women aged 14-24 years. This would include 6 million infected pregnant women and 5-10 million infected children. The epidemic in Asia is expected to surpass that in the African continent. Successful treatment for the interruption of vertical transmission is very important to limiting the spread of HIV.

There are two times during which an infant can become infected, in utero or intrapartum (during labor). Additionally, an infant can become infected during breast feeding but this occurs more in some developing countries where breastfeeding is still recommended despite knowing the risks. As stated above, most HIV transmission from mother to a newborn occurs during intrapartum.

In this post 076 period, studies conducted in New York, Connecticut, North Carolina and France have shown a major impact of the results of 076 - transmission rates were reduced to 5-6%. From 076, we also have learned that there is a relationship between the mother's viral load and transmission. Women in 076 with viral load >15,000 copies/ml who received AZT placebo transmitted 42% of the time. Women, who also received AZT placebo, but had viral load <1730 copies/ml had a transmission rate of 7%. But, women with the lowest viral load still transmitted HIV. Women who were at the lowest levels of viral load who received AZT had a reduced transmission rate of 2.5% from 7%. This suggests that the higher a women’s viral load the more likely she is to transmit the virus to her newborn.
In ACTG 180, investigators used a 3-drug regimen of AZT+ddI+nevirapine to treat 8 infants identified with HIV during early primary infection, the first 8-10 weeks of life. Dr. Sullivan discussed the study at the IDSA meeting and said that the idea was to hit them hard with a potent therapy very early in the course of the development of the viral syndrome. 3/8 never before received antiretroviral therapy. The remaining 5 had received prior treatment with AZT. Investigators reported the regimen was well tolerated.

They all had initial dramatic reductions in blood viral load. Prior to starting study drugs the infant's viral load ranged from about 41,000 copies/ml to 1.5 million copies/ml. Within 2 to 4 weeks, 7/8 infants had reductions of at least 1.5 log (96% decrease in viral load). 3 infants had lasting reductions in viral load of at least 1.5 log over six months of the study, while the others' viral load rebounded to or close to where they were prior to therapy. Two of the 3 were twins who had prior AZT-experience and whose viral load fell to <400 copies/ml (undetectable) by days 168 and 56, respectively. So, 2 out of the original 8 infants have had the desired lasting treatment benefits. Both twins were infected intrapartum.

Both infants (twins) had viral load between 300,000 to 400,000 copies/ml just before starting therapy. At 9 days of life both infants were DNA PCR negative. By 5 weeks they were both diagnosed with HIV infection, were still DNA PCR negative but were RNA PCR positive. Both started AZT treatment at 9 days. Nevirapine+ddI were added to AZT at 2.5 months of age to make it a triple therapy. One infant took 6 months to reach undetectable but the other was undetectable within two months after being on triple therapy. After the 3-drug treatment started both infants went <20 copies/ml using the Roche Ultrasensitive test. At 16 months of age, one infant had detectable viral load which was confirmed with a 2nd test (1200 copies/ml). Up to the 16 month point the infant had no detectable HIV maternal antibody. But, now there was detectable antibody and the infant remains ELISA antibody positive. This infant switched therapy to AZT+3TC+ritonavir, but was unable to tolerate it and was switched to d4T+3TC+nelfinavir. The infant then went to back down to undetectable.

The other infant remained undetectable but also switched to d4T+3TC+nelfinavir only because it was more convenient to have both infants on the same regimen.

After 29 months both infants remain healthy, they have normal CD4 counts and undetectable viral load. Other testing indicates they both have a healthy normal immune system. Has HIV been eradicated from these two infants? They have been followed for two years. HIV DNA was detected in both infants earlier in the study and the amount found has never changed. It does not look as if the integrated provirus (HIV DNA) is disappearing. The same situation is occuring with adults. Proviral DNA (provirus) does not seem to be disappearing for adults although their plasma viral load is undetectable. There is some controversy about the significance of the detection of proviral DNA. Some researchers say the proviral DNA that is found is not able to produce infectious virus while others say it is able to produce infectious virus.

The investigators are hoping to treat the two infants with a novel and unique immune therapy, which they are in the process of developing. It is designed to boost their immune response if their viral load starts to rebound.

The following sites are enrolling participants for ACTG 316

- University of Alabama at Birmingham
- UCLA Medical Center in LA, CA
- Long Beach Memorial, San Diego, CA
- UCSD, San Diego, CA
- San Francisco General Hospital
- Moffitt Hospital/UCSF
- Howard University Hospital, Washington, DC
- University of Florida Health Science Center, Jacksonville, FL
- University Hospital, New Orleans
- Tulane Hospital/Charity Hospital of New Orleans
- Tulane University Hospital, New Orleans
- Univ of Massachusetts Medical School, Worcester, Mass
- Duke University Medical Center, Durham, NC
- University Hospital/UMDNJ-New Jersey Medical School
- Bellevue Hospital/NYU Medical School
- Bronx Lebanon Hospital, Bronx, NY
- Children’s Hospital at Albany Medical Center, Albany, NY
- San Juan City Hospital, San Juan, PR