Nevirapine: An Option For Preventing as Well as Treating Paediatric HIV Infection

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In Brief

Nevirapine belongs to the class of non-nucleoside reverse transcriptase inhibitors (NNRTI) of HIV. It reduces perinatal HIV transmission when administered as a 2-dose regimen, 1 dose to pregnant women during labour and 1 dose to the new born infant within 72 hours of birth. This nevirapine regimen was more effective than a short course of intrapartum and neonatal zidovudine in a randomised trial in breastfeeding women in Uganda. The 2-dose mother-infant nevirapine regimen is well tolerated and is more cost effective and easier to administer in resource-poor settings than zidovudine. In the US, guidelines for the prevention of perinatal HIV transmission suggest the use of the 2-dose nevirapine regimen as one of the possible treatment options for pregnant women who have received no previous antiretroviral therapy and whose infection is diagnosed late in pregnancy or during labour.

Data concerning the use of nevirapine for the treatment of children with established HIV infection are still limited. It should only be used in combination with at least 2 other antiretroviral agents. In small numbers of patients nevirapine-containing triple antiretroviral combination regimens have produced reductions of HIV RNA both in plasma and the CSF.

Introduction

It has been estimated that >600 000 children acquire HIV infection or AIDS each year worldwide.[1] The majority of these children are from developing countries and most acquire their infection perinatally.[2] Transmission of HIV occurs mainly around the time of labour and delivery but can also be transmitted after birth in breast milk, with the greatest risk of infection via this route occurring in the first few months of life.[3]

Zidovudine effective . . .

The first antiretroviral intervention shown to reduce mother-to-child transmission of HIV was an intensive treatment regimen of zidovudine given during the last 2 trimesters of pregnancy, during labour and to the newborn infant after birth (see *Differential features* table for dosages).[6]

This regimen reduced perinatal HIV transmission by approximately 66% in the absence of breastfeeding and was rapidly adopted as the standard of care in the US and Western Europe.

. . . But Not Ideal

However, such treatment is impractical and too expensive (approximately $US800) for HIV-infected pregnant women in developing countries where antenatal care is often limited.[2,3] Shorter courses of zidovudine, from 36 weeks gestation and oral rather than intravenous administration during labour, have also reduced HIV transmission; reductions of approximately 50% were seen in a non-breastfeeding population in Thailand[7] and reductions of approximately 37% were seen in breastfeeding populations in Africa.[8,9] Combined administration of zidovudine and lamivudine during labour and for 1 week after delivery also resulted in a similar reduction of mother-to-child transmission (38%).[10] These 'simplified' regimens, although an improvement, are still costly and require some antenatal care.[2,3,11]

Nevirapine Has an Ideal Kinetic Profile

Several features of nevirapine pharmacokinetics make it an ideal candidate for providing a simple dosage regimen to prevent perinatal transmission of HIV (see table 1). A single oral 200mg dose of nevirapine to the mother at the onset of labour and a single 2 mg/kg oral dose to the infant 48 to 72 hours after birth maintains serum nevirapine concentrations above 100µg/L (10 times the *in vitro* 50% inhibitory concentration against wild-type HIV) in the infant throughout the first week of life.[2,3] A single maternal 200mg dose also results in nevirapine concentrations >100µg/L in cord blood and breast milk during the first week of life. However, the total amount of nevirapine provided to the infant from breast milk is small, approximately 0.06 mg/kg on day 2 of life and 0.02 mg/kg on day 7.[12]

Mother-to-Child Transmission Reduced . . .

The 2-dose nevirapine regimen described in the previous section reduced mother-to-child HIV transmission more effectively than a simplified dosage regimen of zidovudine (see *Differential features* table for dosages) in a randomised, nonblind study of 607 mother-infant pairs.[5] The probability of being infected with HIV after 14 to 16 weeks of life was 13.1% for infants in the nevirapine treatment group compared with 25.1% for infants in the zidovudine treatment group.[5] This greater efficacy of nevirapine was sustained after 12 to 18 months in the presence of ongoing breastfeeding.[13]

. . . at Minimal Cost

The 2-dose nevirapine regimen costs approximately $US4.00, making it significantly more cost effective than short courses of either zidovudine alone (Thailand study regimen)[7] or zidovudine plus lamivudine.[10,11]

Resistance May Develop

HIV strains resistant to nevirapine were isolated 6 weeks after delivery from 3 of 15 mothers who had received single intrapartum doses of nevirapine.[14]

None of the mothers had received any previous antiretroviral therapy.[14] The implications for the treatment of the infant and for treatment in subsequent pregnancies are not yet known.

Useful for HIV-infected children?

Suppression of viral replication in HIV-infected infants, children and adolescents (age range 15 days to 20 years) has been achieved with nevirapine, when used in triple combination therapy regimens with 2 NRTIs.[2,15-17] Triple combination of nevirapine, zidovudine and didanosine resulted in greater reductions in HIV RNA than dual therapy with either nevirapine and zidovudine or didanosine and zidovudine in antiretroviral therapy-experienced patients (age range 6 months to 20 years).[15] The same triple drug combination (nevirapine dose 120mg/m^2 once daily for 28 days then 200mg/m^2 twice daily) reduced viral load by $\geq$1.5 $\log_{10}$ copies/ml within 2 to 4 weeks of commencing treatment and remained below baseline for 6 months, in 5 of 6 perinatally infected infants <4 months of age.[16] Another study reported that a triple regimen of nevirapine, zidovudine and lamivudine induced a $\geq$2 $\log_{10}$ reduction in plasma HIV RNA in 12 of 15 treated infants and children aged 15 days to 2 years which was maintained for 12 weeks.[17]

Reduces CSF Viral Load

Triple combination with nevirapine, zidovudine and didanosine has resulted in reductions in CSF viral load $\geq$ 0.5 $\log_{10}$ from baseline sustained for 48 weeks in a small number of children with HIV-associated encephalopathy.[18]

Reasonably Well Tolerated

Tolerability of long term nevirapine administration in children appears to be similar to that reported for adults. Rash is the most commonly reported adverse event which occasionally becomes severe or develops into Stevens-Johnston syndrome.[2] Elevations in liver enzymes may also occur and can lead to severe or life-threatening complications.

The 2-dose nevirapine regimen was well tolerated by mothers and infants resulting in a similar incidence of serious adverse events to zidovudine (4.7 *vs* 4.4%).[5] The incidence of rash was <2% in nevirapine treated mother-infant pairs and no cases of Stevens-Johnston syndrome were reported.[5]

Dosage and Administration

The 2-dose mother-infant nevirapine regimen for the prevention of HIV perinatal transmission is presented in the *Differential features* table. During long term use (i.e. in the treatment of patients with HIV infection), nevirapine elimination increases 1.5- to 2-fold over the first 2 to 4 weeks because of autoinduction of enzymes involved in its metabolism.[2,3] Using a lower lead-in dose for the first 2 weeks of therapy avoids elevated nevirapine concentrations and reduces the occurrence of adverse events such as rash in both adults and children.[2,3] Due to more rapid clearance in younger children dosage administration is age adjusted (see table 2). A 10 mg/ml solution is available for use in children.[2]

Prescribing and Formulary Considerations

With no imminent prospect of a cure for HIV, prevention is of paramount importance. Antiretroviral therapy of HIV-infected pregnant women is an effective way of reducing perinatal HIV transmission, even in populations where breastfeeding predominates. This lead a Technical Consultation Group convened under the auspices of the World Health Organization to conclude that:

- the prevention of mother-to-child HIV trans mission should be part of the minimum stan dard package of care for HIV-infected women and their infants
- the benefit of antiretroviral therapy outweighs concerns about the potential adverse events of drug exposure or concerns related to the development of drug resistance.[19]

The meeting did not state any preference between zidovudine, zidovudine plus lamivudine, or nevirapine treatment regimens.[19] However, it is clear that nevirapine is the least expensive and easiest to administer of the possible treatment options and is most suited to use in resource poor environments. In the US, guidelines for the prevention of perinatal HIV transmission suggest the use of the 2-dose nevirapine regimen as one of the possible treatment options for pregnant women who have received no previous antiretroviral therapy and whose infection is diagnosed late in pregnancy or during labour.[20] For infants and children with confirmed HIV infection US paediatric treatment guidelines currently recommend early and aggressive antiretroviral therapy with 3 antiretroviral drugs.[4] The preferred combination is with 2 NRTIs and a protease inhibitor. However, as there are no long term data in children demonstrating improved efficacy and tolerability of any triple combination regimen over another and there are concerns over the long term safety of protease inhibitors, triple combination regimens with an NNRTI such as nevirapine should not be ruled out. Nevirapine has been shown to reduce viral load in combination with 2 NRTIs and it has the advantage of penetrating the CSF, an important reservoir of HIV infection. Furthermore, it is reasonably well tolerated, and is available in a convenient paediatric dosage formulation which only needs to be administered twice daily.

The results of additional and ongoing studies should help to further define the optimum use of nevirapine for the treatment and prevention of paediatric HIV infection.

Table 1. Nevirapine pharmacokinetic parameters contributing to its suitability as a 2-dose regimen, 1 dose to the mother during labour and 1 dose to the neonate, for the prevention of perinatal HIV transmission[2,3,12]

- Rapid and nearly complete oral absorption
- Even distribution throughout body organs and tissues including CSF
- Prolonged elimination half-life($t_{1/2}$) during labour (mean $t_{1/2}$ 72.5 hours compared with 48.5 hours in non-pregnant adults)
- Prolonged $t_{1/2}$ in the neonate (mean $t_{1/2}$ of maternal dose 64.9 hours)[a]
- Rapid transfer across the placenta
- Ready entry into breast milk

a Neonatal dose is administered within 72 hours of birth.

Table 2. Recommended doses of nevirapine when used as part of a combination antiretroviral therapy regimen in HIV-infected infants and children[2]a

Age	Weeks 1 & 2	>2 weeks
<2 months	No recommendation	
2 months-8 years	4 mg/kg once daily	7 mg/kg twice daily
> 8 years	4 mg/kg once daily	4 mg/kg twice daily

a The maximum daily dose for all age groups is 400 mg/day.

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Adis Evaluation

Key points in the overall evaluation of nevirapine in the prevention of mother-to-child HIV transmission and in the treatment of HIV-infected children.

Clinical Benefits

- A simple monotherapy regimen to mother and infant results in a greater reduction of mother-to-child HIV transmission than zidovudine monotherapy in a breastfeeding population
- The dosage regimen for prevention of mother-to-child HIV transmission is simple and inexpensive
- Reduces viral load in HIV-infected children when used in combination with 2 NRTIs
- Crosses the blood-brain barrier and placenta

Potential Limitations

- HIV-1 resistant strains to nevirapine can develop after monotherapy with only a single dose
- No comparative data are available with other triple antiretroviral combination regimens in children
- Long term safety of exposure to drug in neonates, infants and children is not yet known

Differential Features

Comparison of various features of nevirapine and zidovudine for the prevention of mother-to-child transmission of HIV-1 infection[2,4-6]

Feature	Nevirapine	Zidovudine	
Drug class	Non-nucleoside reverse transcriptase inhibitor	Nucleoside reverse transcriptase inhibitor	
Treatment regimen:		Simplified regimen[a]	In the US and Europe
Mother: during pregnancy during labour	200mg PO at labour onset[b]	600mg PO at labour onset then 300mg PO q3h until delivery	100mg PO 5 times daily from >14 weeks to onset of labour 2 mg/kg IV over 1 hour then continuous IV infusion 1mg/kg/h until delivery
Neonate	2 mg/kg PO within 72 hours of birth hours of birth	4 mg/kg PO twice daily for first 7 days of life	2 mg/kg PO q6h for 6 weeks startin g within 12
HIV-free survival at 14-16 weeks (%)	85.6	72.4	
Incidence of serious adverse events (%)	4.7	4.4	

a Simplified dosage regimen used in the randomised comparative trial with nevirapine.
b Dose used in clinical trials and recommended by US Guidelines.

IV = intravenous;
PO = oral;
qXh = every X hours.