Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Original Article

Efficacy of single dose Nevirapine in reducing viral load in HIV positive mother in labour and transmission of HIV infection to new born babies as part of prevention of parent to child transmission

Col Devendra Arora ^{a,*}, Brig R.M. Gupta ^b, Brig S.P.S. Kochar ^c^a Senior Advisor (Obst & Gyn), Specialist in Maternal Fetal Medicine, Base Hospital, Delhi Cantt 110010, India^b Consultant (Pathology & Microbiology), Command Hospital (Northern Command), C/O 56 APO, India^c Consultant (Obst & Gyn & Gyn Oncology), Base Hospital, Delhi Cantt-110010, India

ARTICLE INFO

Article history:

Received 16 October 2011

Accepted 3 September 2014

Available online 22 October 2014

Keywords:

HIV

Nevirapine

Viral load

ABSTRACT

Background: Prevention of parent to child transmission (PPTCT) program was initiated in Armed Forces to reduce the vertical transmission of HIV by instituting single dose Nevirapine (sdNVP) in untreated HIV positive mothers in labour. The aim of this study was to evaluate the role of sdNVP to decrease viral load of HIV infected mother during labour and its efficacy in prevention of mother to child transmission of HIV.

Methods: Thirty antenatal women tested positive for HIV at our PPTCT centre and delivered between Jan 2006 and May 2008 were evaluated. During labour these women were given sdNVP. Newborns were given syrup Nevirapine. The babies were tested for HIV infection at 48 h and six weeks after delivery.

Results: Thirty HIV positive women delivered at our centre and four newborns were found positive for HIV infection at 48 h. After six weeks interval three neonates were detected for HIV infection as one infant at six weeks was found to be negative for HIV infection.

Conclusion: The protection rate of Nevirapine in untreated HIV positive women is not ideal. It is recommended that all HIV positive women should be offered Highly Active Antiretroviral therapy as primary mode for PPTCT.

© 2014, Armed Forces Medical Services (AFMS). All rights reserved.

Introduction

National AIDS Control Organization of India (NACO) declared that the country experienced 72,000 new HIV infections in

2005; nearly triple the 28,000 new cases in 2004. The new data means overall infections grew by 1.4 percent.¹ In 2003, approximately 630,000 children worldwide became infected with HIV and nearly half a million children died of AIDS or AIDS related events.² The overall risk of mother to child

* Corresponding author. Tel.: +91 9540667660 (mobile).

E-mail address: drdarora@hotmail.com (D. Arora).<http://dx.doi.org/10.1016/j.mjafi.2014.09.005>

0377-1237/© 2014, Armed Forces Medical Services (AFMS). All rights reserved.

transmission (MTCT) is 15–30% for non breastfeeding infants and 20–45% in breastfeeding populations for whom interventions to prevent mother to child transmission (PMTCT) of HIV are not implemented.

India is a country having more than one billion population and an estimated more than 5.2 million people infected by Human Immunodeficiency Virus (HIV) by now. Among the HIV infected adults 39% are females. The average HIV prevalence among antenatal women in India is 0.88%. The monogamous relationship with the spouses was identified as the only route of HIV transmission in females who were not sex workers.³ The monogamous women, being infected by HIV via the heterosexual route from their spouses transmit the infection to the next generation through vertical transmission. In 2006, India's Joint Technical Mission estimated that out of 27 million annual pregnancies, 189,000 occur in HIV positive women. An estimated 56,700 HIV positive babies were born each year in the absence of intervention.⁴

PPTCT program was also adapted by all the service hospitals in May 2003. There are four parts of PPTCT program. The first one is the primary prevention of HIV infection, second is prevention of unintended pregnancies among HIV infected women, third is prevention of HIV transmission from HIV infected women to their infants and the last fourth one is the provision of treatment, care and support to the HIV infected women, their infants and their families.⁵ Single dose Nevirapine (sdNVP) is used to prevent mother-to-child HIV transmission in resource-limited settings. The concerns have arisen over the efficacy of sdNVP in repeat pregnancies due to detection of resistant mutants among women who receive sdNVP.⁶ However Highly Active Antiretroviral Therapy (HAART) is clearly the gold standard for PMTCT. The ability of our Indian pregnant women population to access and utilize these complex and costly regimens of HAART may continue to be limited in the foreseeable future.

Materials & methods

Thirty HIV seropositive antenatal patients reporting to our outpatient department and not taking antiretro viral therapy were recruited in our present study. The existing protocols of PPTCT in concurrence with the National Aids Control Organization (NACO) guidelines were followed for these patients. During the antenatal care at our outpatient department all women attending the antenatal clinic were counselled regarding the HIV infection with special reference to the possibility of HIV transmission from the parents to their children. After taking informed consent, the antenatal patients were tested for their HIV status. Those who were found to be seropositive for HIV underwent confidential post test information and counselling regarding the vertical transmission and importance of their delivery in the PPTCT centers. Those couples who wanted to have termination of pregnancy after post test counselling, the termination of pregnancy was carried out.

The antenatal patients who wanted to continue the pregnancy were advised to attend the antenatal outpatient department regularly. All the patients were also referred to the HIV clinic of our hospital where they were followed up

with CD4 counts for the possibility of initiating antiretroviral therapy if CD4 counts went less than 200 per ml. Thirty patients who were willing to participate in this study protocol and were not started on antiretroviral drugs during the period January 2005–January 2008 were included for the PPTCT as per the NACO guidelines.

The patients who were recruited for the study were put on regular follow up in the antenatal outpatient department. The patients were informed and counselled again at 28 weeks and 34 weeks of pregnancy regarding the study protocol of PPTCT. The HIV seropositive patient who reported to the labour room with labour pains was initially examined to ascertain the onset of true labour pains from false labour pains. After confirming true labour pains on history and clinical examination the first blood sample was drawn from the mother in labour for estimation of the viral load. Immediately after obtaining the blood sample sdNVP 200 mg was given orally to the patient. The patient was monitored for labour and time of delivery noted to record the time duration between the administration of sdNVP and the delivery of the baby. The delivery of the baby was conducted by caesarean section with adequate precautions using disposable caesarean kits. The second maternal blood sample was obtained immediately after the delivery of the baby for the viral load. The evaluation of second blood sample estimated the reduction in viral load compared to the first blood sample due to the effect of sdNVP.

The first sample for PCR of the neonatal blood was obtained 48 h after delivery to avoid false positive or false negative report before the administration of syrup Nevirapine to the neonate. The neonate was administered syrup Nevirapine 2 mg/kg after obtaining the blood sample for PCR at 48 h after birth. The second blood sample for PCR to estimate HIV infection in the baby was performed at 6 weeks of age. The HIV seropositive mothers were instructed not to breast feed the baby during the study period and also thereafter for optimal benefit.

All those mothers who came in advanced labour and delivered vaginally or within 2 h of administration of sdNVP were excluded from the study as the Nevirapine dose given to the mother would not give adequate protection against the vertical transmission of HIV.

Results

Out of the total number of antenatal women who were tested for their HIV status during the study period from Jan 2005 to Jan 2008, thirty seven were detected to have HIV infection. Four patients opted for termination of pregnancy after post test counselling session. The remaining thirty three had opted for continuation of pregnancy. Nevirapine was given as per the NACO guidelines for PPTCT protocol during labour. One patient on follow up at HIV clinic of our hospital had to be started on antiretroviral therapy due to low CD4 counts. This patient was excluded from our study protocol. Two patients who came in advanced labour and delivered vaginally within 2 h of sdNVP administration were also not considered for this study protocol. Finally thirty HIV seropositive patients delivered live born babies by caesarean section during the study period. All the live born babies to the HIV seropositive mothers were administered pediatrics drops of Nevirapine at 48 h after birth.

Table 1 – Viral load in HIV positive mothers at the onset of labour with its reduction (in percentage) after Nevirapine administration.

Patient group	Viral load: Copies/ml (onset of labour)	No of HIV seropositive mothers	Percentage of reduction in viral load per group after Nevirapine	Percentage of reduction in viral load in groups 1–6 & 7–9 after Nevirapine (95% confidence interval)
1.	Less than 1000	06	44%	53%
2.	Between 1001 and 10,000	01	47.5%	(32.12, 71.70)
3.	Between 10,001 and 30,000	08	41%	
4.	Between 30,001 and 50,000	03	69%	
5.	Between 50,001 and 70,000	04	55.6%	
6.	Between 70,001 and 90,000	01	61.2%	
7.	Between 90,001 and 1,10,000	02	63%	63.6%
8.	Between 1,10,001 and 1,30,000	02	56.3%	(21.59, 87.72)
9.	Between 1,30,001 and 1,50,000	03	71.6%	

The observations thus obtained are compiled from Table 1–4. The potency of Nevirapine to reduce the viral load that was noticed in this study varied from 44 % to 71.6% (Table 1) after administration of sdNVP. The effectivity of sdNVP to reduce viral load was noticed to be more than 50% in women infected with HIV reported in labour with viral copies more than 30,000 per ml when administered to the patients at least 2 h or more before delivery. The maximum reduction of viral load with sdNVP was seen in the infected mothers with viral load of more than 1,30,000 copies per ml in group 9 reaching upto 71.6%. Overall percentage of reduction in viral load in Groups 1–6 & 7–9 after Nevirapine was 53% (95% CI = 32.12, 71.70) and 63.6% (95% CI = 21.59, 87.72). There was no significant difference in the percentage reduction in group 1–6 and 7–9 ($p = 0.84$).

It was also observed that in the patient group 4 and group 9 the time interval between the administration of tablet Nevirapine and delivery was more than 6 h which was the maximum limit in this study and also revealed maximum decrease in viral load upto 70% (Tables 1 and 4). The minimum time interval was noticed to be 3 h and 13 min in patient group 1 (Table 4). A linear correlation of change was noticed between the viral load decrease against time interval of sdNVP administration and delivery (Fig. 1).

At 48 h of delivery, four babies were found to be infected with HIV on testing with PCR of first blood sample (Table 2). On follow up of all the babies by performing PCR at six weeks on the second blood sample, only three babies were detected to be infected with HIV. One baby who was detected to be infected with HIV at 48 h of birth was later detected to be negative for HIV infection at six weeks of life (Table 3). The role of sdNVP in vertical transmission of infection from HIV infected mother to the neonate at birth is upto 13.3% (95% CI = 4.38, 29.10) in this study (Table 2). However the perinatal transmission of HIV infection is further reduced to 10% (95% CI = 2.61, 24.85) after administering the second dose of Nevirapine to the neonate within 72 h of birth (Table 3).

Discussion

The PPTCT program was adapted in May 2003 in compliance with NACO for all the service hospitals in which sdNVP 200 mg regimen was administered only to those seropositive mothers

at onset of labour and not receiving highly active combination antiretroviral therapy (HAART). This was followed by one dose of 2 mg/kg Nevirapine administered to all babies within 72 h of delivery. Thirty HIV seropositive patients delivered live born babies by caesarean section during the study period in this tertiary care centre. The efficacy of Nevirapine to reduce the viral load in maternal circulation which was noticed in this study had a variable response. The reduction of viral copies in maternal circulation during labour varied from 44% to 71.6% (Table 1). These variable responses probably depended upon the initial viral load before administration of sdNVP. The effectivity of sdNVP 200 mg to reduce viral load was noticed to be more than fifty percent in infected women in labour with viral copies more than 30,000 per ml (Table 1) when administered to the patients at least 3 h or more before the delivery (Table 4). The maximum reduction of viral load with single dose Nevirapine was seen in the infected mothers with viral load of more than 1,30,000 copies per ml which was 71.6%. It was thus observed that the amount of reduction in viral copies was directly proportional to the initial viral load in maternal circulation before administration of sdNVP and also the time interval from the administration of Nevirapine to delivery of the baby which was 6 h and 10 min (Tables 1 and 4). A high reduction of viral load was also seen the patient group 4 with viral load ranging from 30,001 to 50,000 copies per ml as the time interval from administration of sdNVP to delivery of the baby was noticed to be 6 h and 30 min, which was the maximum in this study group. This also suggests that the time interval between the drug administration to delivery of the baby is an important factor in reducing the viral load effectively and thus reducing the incidence of transmission. In group 4 of our study group there was perinatal transmission of HIV infection to the baby (Table 3).

After delivery, four babies were found to be infected with HIV on testing with PCR of first blood sample taken 48 h after birth. Despite the reduction of viral load in mothers with viral copies more than 90,000 per ml in groups 7–9 by 63.6% (Table 1) the transmission of HIV infection to the neonate was noticed in four neonates out of seven neonates born to seropositive mothers in these groups with transmission rate as high as 57.1% (Table 2). In HIV infected mothers with viral copies less than 90,000 per ml in groups 1–6, the reduction of viral load was only 53% but there was no perinatal transmission of infection to the neonate at 48 h of birth with sdNVP

Table 2 – HIV infection status by PCR in the neonate at 48 h of birth.

Group	Viral load: Copies/ml (onset of labour)	No of HIV seropositive mothers	PCR status (Neonate at 48 h)	Vertical transmission of HIV infection in groups 1–6 & 7–9 at 48 h of birth in %	Vertical transmission of HIV infection at 48 h of birth in % (95% confidence interval)
1.	Less than 1000	06	Negative	Nil	13.3%
2.	Between 1001 and 10,000	01	Negative		(4.38, 29.10)
3.	Between 10,001 and 30,000	08	Negative		
4.	Between 30,001 and 50,000	03	Negative		
5.	Between 50,001 and 70,000	04	Negative		
6.	Between 70,001 and 90,000	01	Negative		
7.	Between 90,001 and 1,10,000	02	01 Positive	57.1%	
8.	Between 1,10,001 and 1,30,000	02	02 Positive		
9.	Between 1,30,001 and 1,50,000	03	01 Positive		

prophylaxis. This suggests that the transmission of HIV infection from mother to baby is directly related to high viral load. The administration of sdNVP restricts vertical transmission of infection from HIV infected mother to the neonate at birth to 13.3% in this study (Tables 1 and 2). All the babies were administered a single dose of Nevirapine drops at 48 h of birth and strictly not allowed to breast feed since birth. All the babies were given top feeds to prevent transmission of HIV infection from the breast milk. On subsequent follow up of all the babies the PCR was performed on the second blood sample of the babies at six weeks. Three babies were detected to be infected with HIV out of the four babies who initially acquired the infection. The baby who subsequently tested PCR negative for HIV infection at six weeks and was PCR positive at 48 h after birth was born to the seropositive mother in group 7 who had an initial viral load of 96,000 copies per ml. The perinatal transmission of HIV infection at six weeks after birth thus reduced further to 10% after administering the second dose of Nevirapine to the neonate within 72 h of birth (Table 3).

This study is in order with the study by Thorne et al in which they found that the use of sdNVP reduces transmission by around 50% to a rate of 10–15% at six weeks, depending on early infant feeding.⁷ One baby in our study was detected to be infected with HIV at 48 h of birth in group 7 that was later detected to be negative for HIV infection at six weeks of life. This particular case only suggests the role of administering Nevirapine to the neonate within 72 h to prevent HIV infection in the infant on follow up. However, false positive results of PCR for HIV infection in the neonate at 48 h of delivery cannot be ruled out. The risk of infection after birth was completely

eliminated in our study by exclusive top feeding. This intervention was based on individual patient meta-analysis conducted by Coutoudis et al of PMTCT trials in resource-poor settings showed that 225 of 539 infected children (42%) had late postnatal transmission (at or after four weeks of age) through breastfeeding.⁸ The PCR performed on the babies who were not breast fed after birth, at 6 weeks to detect HIV infection was in order with this study protocol to check for infection by vertical transmission. Most of the studies world wide has shown transmission rates of between 8.7% and 22% with the use of sdNVP in programme settings which is in consistence with our trial results.^{9–15}

A significant technical issue in PPTCT is the drug resistance that mothers develop to Nevirapine. This prevents them from being able to take the drug should they become pregnant again. Nevirapine being relatively cheaper and easy to administer than the more complex combination drug therapies, in a country like ours with resource-poor scenario it may be the only chance for some women to protect their babies. Although there is a concern about the drug resistance but sdNVP remains the best choice in HIV positive mothers for preventing MTCT in areas where medical resources are limited.

A dramatic reduction in MTCT in resource-rich countries has come from the use of HAART not only for women who need treatment, but also for HIV positive women who have higher CD4 counts. In Europe, the use of antiretroviral therapy has increased from 5% in 1997 to 92% in the period 2001–2003, resulting in a transmission rate of 0.99% (95% CI, 0.32–2.30%) in the 2001–2003 period which is a great achievement.¹⁶

Table 3 – HIV infection status in the infant by PCR at 48 h after birth and at 6 weeks of life.

Group	Viral load: Copies/ml (onset of labour)	No of HIV seropositive mothers	PCR status (neonate at 48 h)	PCR status (baby at 6 weeks)	Vertical transmission of HIV infection at 6 weeks age of infant in % (95% confidence interval)
1.	Less than 1000	06	Negative	Negative	10 %
2.	Between 1001 and 10,000	01	Negative	Negative	(2.61, 24.85)
3.	Between 10,001 and 30,000	08	Negative	Negative	
4.	Between 30,001 and 50,000	03	Negative	Negative	
5.	Between 50,001 and 70,000	04	Negative	Negative	
6.	Between 70,001 and 90,000	01	Negative	Negative	
7.	Between 90,001 and 1,10,000	02	01 Positive	Negative	
8.	Between 1,10,001 and 1,30,000	02	02 Positive	02 Positive	
9.	Between 1,30,001 and 1,50,000	03	01 Positive	01 Positive	

Table 4 – Time interval from Nevirapine administration to HIV positive mother to delivery of the baby.

Group	Viral load: Copies/ml (onset of labour)	No of HIV seropositive mothers	Average time interval after Nevirapine administration and delivery (hrs. mins)
1.	Less than 1000	06	3.13
2.	Between 1001 and 10,000	01	3.45
3.	Between 10,001 and 30,000	08	3.56
4.	Between 30,001 and 50,000	03	6.30
5.	Between 50,001 and 70,000	04	4.50
6.	Between 70,001 and 90,000	01	5.20
7.	Between 90,001 and 1,10,000	02	5.43
8.	Between 1,10,001 and 1,30,000	02	5.32
9.	Between 1,30,001 and 1,50,000	03	6.10

Fig. 1 – Change in viral load against time interval of sdNVP administration and delivery.

In our study we had two HIV positive mothers who came to labour room in advanced stage of labour and delivered within 2 h of sdNVP administration. These two patients were excluded from our study protocol as the drug administration to delivery interval of less than 2 h was not adequate for the drug to get fully absorbed and reach ideal systemic levels for optimal viral load reduction.¹⁷

Conclusion

All the live born babies to the HIV seropositive mothers were administered pediatrics drops of Nevirapine. The efficacy of Nevirapine to reduce the viral load in maternal circulation was effective but with a variable response which probably depended upon the initial viral load with a linear correlation between the time interval of administering sdNVP to delivery of the baby. After delivery, four babies were found to be infected with HIV on testing with PCR of first blood sample taken 48 h after birth. In this study the administration of sdNVP restricts vertical transmission of infection from HIV infected mother to the neonate at birth to 13.3%. All the babies were administered a single dose of Nevirapine drops at 48 h of birth and strictly not allowed to breast feed since birth. On subsequent follow up of all the babies the PCR was performed on the second blood sample of the babies at six weeks. Three babies were detected to be infected with HIV out of the four

babies who initially acquired the infection. The perinatal transmission of HIV infection at six weeks after birth thus reduced further to 10% after administering the second dose of Nevirapine to the neonate within 72 h of birth.

The advances in reducing mother to child transmission in resource-poor settings have still to be implemented into Armed Forces. It is no longer appropriate to recommend sdNVP approach in PPTCT programmes as approved by NACO and issued by DGAFMS guidelines issued in May 2003 in present day scenario for the families of Armed Forces. In situations where other antiretroviral drugs (ARV) are accessible, the sdNVP regimen should be combined with additional effective ARVs.

In Armed Forces, HAART may be feasible and affordable for all HIV positive pregnant women. The sdNVP regimen remains the most feasible and least expensive regimen for preventing mother-to-child transmission of HIV and there will be places where this is the only available or possible regimen for some time to come. The long term implications of the Nevirapine resistance following PMTCT regimens are uncertain in resource-poor settings. Alternative strategies to reduce the risk of breast milk transmission are also required if the MTCT rates are to be substantially reduced in resource-poor settings. There is an ability to scale up HAART delivery to seropositive families, with appropriate counselling for adherence and monitoring in many of our service hospitals so that MTCT rate can be optimized below 1%. The role of sdNVP in preventing perinatal transmission of HIV infection to the baby is less than ideal in the present day scenario. However studies with larger sample size needs to be carried out for stronger recommendation and policy change for viral load testing for all positive pregnant women and initiation of HAART to all HIV positive women during pregnancy and their neonates.

Conflicts of interest

All authors have none to declare.

Acknowledgement

This paper is based on Armed Forces Medical Research Committee Project No. 3494/2006 granted by the office of the

Directorate General Armed Forces Medical Services and Defence Research Development Organisation, Government of India.

REFERENCES

1. New HIV Infections in India Almost Triple in 2005 Report. The CDC HIV, STD, TB. Prevention News Updates; April 24 2006. <http://www.cdc.gov/hiv>.
2. UNAIDS. 2004 Report on Global AIDS Epidemic: 4th Global Report. 2004.
3. Gangakhedkar RB, Bentley ME, Divekar AD, et al. Spread of HIV infection in married monogamous women in India. *JAMA*. 1997;278:2090–2092.
4. Nair KS, Piang L, Tiwari VK, Raj S, Nandan D. Prevention of vertical transmission of HIV in India through service integration: lessons from Mysore District, Karnataka. *WHO South-East Asia J Public Health*. 2013;2:121–127.
5. Overview of HIV Prevention in Mothers, Infants and Young Children. PPTCT (India). Revised Training Curriculum. Participant Manual. NACO; December 2004. Module 2-4:44.
6. McConnell M, Bakaki P, Eure C, et al. Effectiveness of repeat single-dose nevirapine for prevention of mother-to-child transmission of HIV-1 in repeat pregnancies in Uganda. *J Acquir Immune Defic Syndr*. 2007;46(3):291–296.
7. Thorne C, Newell ML. Prevention of mother-to-child transmission of HIV infection. *Curr Opin Infect Dis*. 2004;17(3):247–252.
8. Coutsoudis A, Dabis F, Fawzi W, et al. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis*. 2004;189(12):2154–2166.
9. Sherman GG, Jones SA, Coovadia AH, Urban MF, Bolton KD. PMTCT from research to reality-results from a routine service. *S Afr Med J*. 2004;94(4):289–292.
10. Martinson N, Morris L, Gray G, et al. HIV resistance and transmission following single-dose nevirapine in a PMTCT cohort [abstract 38]. In: 11th Conference on Retroviruses and Opportunistic Infections; 8 – 11. February 2004 [San Francisco].
11. Quaghebeur A, Mutunga L, Mwanyumba F, Mandaliya K, Verhofstede C, Temmerman M. Low efficacy of nevirapine (HIVNET012) in preventing perinatal HIV-1 transmission in a real-life situation. *AIDS*. 2004;18(13):1854–1856.
12. Kiarie JN, Kreiss JK, Richardson BA, John-Stewart GC. Compliance with antiretroviral regimens to prevent perinatal HIV-1 transmission in Kenya. *AIDS*. 2003;17(1):65–71.
13. Stringer JS, Sinkala M, Chapman V, et al. Timing of the maternal drug dose and risk of perinatal HIV transmission in the setting of intrapartum and neonatal single-dose nevirapine. *AIDS*. 2003;17(11):1659–1665.
14. Stringer JS, Sinkala M, Goldenberg RL, et al. Universal nevirapine upon presentation in labor to prevent mother-to-child HIV transmission in high prevalence settings. *AIDS*. 2004;18(6):939–943.
15. Ayoub A, Tene G, Cunin P, et al. Low rate of mother-to-child transmission of HIV-1 after nevirapine intervention in a pilot public health program in Yaounde, Cameroon. *J Acquir Immune Defic Syndr*. 2003;34(3):274–280.
16. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2005;40(3):458–465.
17. Microchnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic consideration in children and pregnant women. *Clin Pharmacokinet*. 2000;39:281–293.