Original Article

Vertical Transmission of HIV in Pregnant Patients on ARVs in Relation to Mode of Delivery

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Abstract

Background: Use of antiretroviral drugs have been shown to reduce the risk of vertical transmission of HIV but scheduled caesarean section is still being preferred at some centers.

Objective: To observe the results of intervention with ARVs (antiretroviral drugs) during pregnancy and looking for the difference in the rate of vertical transmission of HIV with the mode of delivery.

Study Design: It was an observational study.

Place and Duration: The study was carried out in the HIV Treatment Center Pakistan Institute of Medical Sciences (PIMS), a tertiary care university hospital during the period January 2007 till October 2015.

Methodology: Sixty three pregnant HIV women registered in the Treatment Center during the period January 2007 till October 2015 were enrolled in the study. All these pregnant females were enrolled for PPTCT (prevention of parent to child transmission) and followed up regularly for obstetric care and management of HIV in accordance with standard clinical and laboratory protocols .Similarly the infants born to HIV mothers were prospectively observed and followed up with standard protocols to prove disease transmission or otherwise .

Results: Sixty three pregnant women were enrolled in the study. Most patients were moderately immuno competent. 26 patients were already on antiretroviral therapy before conception while others started with therapy during pregnancy. Average duration of antiretroviral therapy at term was four months. Most started antiretroviral therapy 14 to 20 weeks of gestational age. Except for one patient who was started on ARVs during pregnancy and was noncompliant to therapy all patients had undetectable HIV RNA levels at 36 weeks of gestation. Overall mother-to-child transmission was 0%. The mode of delivery as caesarean or vaginal delivery did not make any difference

Conclusion: Antiretroviral therapy proves to be very effective in preventing vertical transmission of HIV. All patients on antiretroviral treatment whether delivered via scheduled caesarean section or had normal vaginal delivery did not transmit HIV to their children.

Keywords: Antiretroviral therapy, ARVs, HIV, Scheduled caesarean section, Vertical transmission.

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Introduction

Vertical (perinatal) disease transmission in HIV positive mothers has been a problem ever since the disease existence in human being was found. Intervention with ARVs during pregnancy and obstetric management at

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delivery time has been part of latest PPTCT (prevention of parent to child transmission) guidelines. This has brought significant decrease in the vertical transmission, from as high as 25-30% without intervention to as low as 1-2%. Factors like HIV patients with co-morbidities, high viral load, advanced disease and delay in the use of antiretroviral therapy are associated with increased transmission of HIV from mother to the child.[1, 2] Starting antiretroviral medication during pregnancy, delivery by cesarean section at term, and discouraging breastfeeding, has brought the mother-to-infant transmission to less than 2% in the United States. The mode of delivery by C-section or spontaneous vaginal delivery has been a point of discussion throughout. However conflicting results have been seen in earlier studies regarding transmission risk and cesarean delivery .

Continuing research into vertical transmission of HIV suggests that a substantial number of cases occur as the result of fetal exposure to the virus during labor and delivery. The greatest risk factor for vertical transmission is thought to be advanced maternal disease, likely due to a high maternal HIV viral load[3]. There is strong evidence that indicates that the risk of vertical transmission is proportional to the maternal HIV viral load. Uterine contractions at the time of labor may contribute through micro transfusion the virus transmission and with cesarean delivery this can be prevented .Similarly by avoiding vaginal delivery the exposure to virus in the cervicovaginal secretions and blood at time of delivery can be avoided Patients who receive treatment outside the reference centre have a sevenfold greater risk of HIV transmission[4]. At very low concentrations of virus in maternal plasma (viral load less than 1,000 copies per milliliter), the observed incidence of vertical transmission is as low as less than 2 % .These are findings from a multicenter, randomized clinical trial[5] and from a large data meta-analysis of individual patient.[6] These two studies are from the time when the majority of HIV-infected women received no antiretroviral (ARV) medications or zidovudine as a monotherapy and even before the routine viral load estimation was considered in pregnant mothers. In a randomized clinical trial, 1.8% of infants born to women randomized to undergo cesarean delivery were HIV-infected compared with 10.5% of infants born to women randomized to vaginal delivery (P< .001)[5] In the late 1990s, prospective cohort studies noted a decrease in mother-to-child transmission in women on zidovudine (ZDV) who underwent elective cesarean delivery compared with women who did not take ZDV prophylaxis.[7] So from the results of these studies the risk of vertical transmission in mothers with high viral loads could be reduced by performing cesarean deliveries before the onset of labor and membranes rupture.

However most of the evidence promoting cesarean delivery has been before the use of highly active antiretroviral therapy (HAART) and without any reference data of maternal viral load. Nowadays, pregnancy is no longer a general contraindication for antiretroviral therapy. It is clear that maternal morbidity is greater with cesarean delivery than with vaginal delivery, as is true for women not infected with HIV. Increases in postpartum morbidity seem to be greatest among women infected with HIV who have low CD4 cell counts. Before the current treatment era, approximately 2000 babies were infected with HIV each year in the United States alone. Despite increasing HIV prevalence, that figure now stands at approximately 300 infants per year[9]

Whether cesarean delivery offers any benefit to women on HAART or to women with low or undetectable maternal viral loads is unknown In a report on births to HIV-infected women from the United Kingdom and Ireland between 2000 and 2011, perinatal transmission rates in women on HAART with HIV RNA<1,000 copies/mL with planned cesarean delivery (13/3,814; 0.3%) were not significantly different than those in similar women with planned vaginal delivery (6/2,238; 0.3%).[8] The results from these studies and other studies have helped making current recommendations about the mode of delivery , use of combination highly active antiretroviral therapy (HAART) during pregnancy and viral load estimation near term.

Given the low mother-to-child transmission rates among women on HAART, the additional benefit of delivery by elective Caesarean section remain difficult to evaluate .Neonates of women at highest risk for vertical transmission, with relatively high plasma viral loads, are most likely to benefit from scheduled cesarean delivery. Data are insufficient to demonstrate a benefit for neonates of women with plasma viral loads of less than 1,000 copies per milliliter.

This study is aimed to compare the rates of vertical transmission of HIV among HIV pregnant mothers on treatment with combination antiretroviral therapy. Patients delivered via scheduled caesarian section or had normal vaginal delivery .

Methodology

This observational study was conducted in HIV Treatment Center Pakistan Institute of Medical

Sciences. The selection criteria was all pregnant HIV females registered in the Treatment Center during the period January 2007 till October 2015. Following confirmation of pregnancy the patients were enrolled for PPTCT (Prevention of parent to child transmission) and followed up regularly for obstetric care and management of HIV in accordance with standard clinical and laboratory protocols. Similarly the infants born to HIV mothers were prospectively observed and followed up with standard protocols to prove disease transmission or otherwise.

All mothers were started on Anti retroviral drugs (either as part of treatment or prophylaxis for PPTCT). Information collected included timing of initiation and type of antiretroviral treatment, maternal CD4 cell count and viral load. Data on delivery and neonatal characteristics were recorded, including mode of delivery, sex, birth weight, and gestational age. Laboratory tests, including HIV RNA PCR, serologic testing, and CD4 cell count measurements, were performed in HIV center laboratory in PIMS. Maternal CD4 cell counts and HIV RNA levels nearest to the time of delivery were used in the analyses here. Women were declared "viral loads not detected" on the basis of cut-off values less than 50 copies per mm square. Children were tested for vertical transmission of HIV infection by doing PCR at three months and further by persistence of HIV anti bodies at 18 months. If a child tested negative by PCR and no detection of antibody, they were declared as uninfected.

Results

A total of 63 mother-child pairs were enrolled in the study. Sixty three women overall who received ARVs during pregnancy, 37 started receiving ARVs for the first time during pregnancy, the remaining 26 were already receiving ARVs when they became pregnant. The timing of ARVs started during pregnancy in all cases was between 14 to 20 weeks of gestational age. This was on an average four months of ARV therapy.

Undetectable HIV RNA levels was seen in both groups at 36 weeks of pregnancy except one patient who was started on ARVs during pregnancy but was noncompliant. The viral load results were same in those who initiated ARVs before pregnancy than among women who initiated ARVs during pregnancy.

Overall mother-to-child transmission was 0%. The mode of delivery as caesarean or vaginal delivery did not make any difference.

Table I: Mode of delivery and the rates of vertical transmission (N= 65)

Mode of delivery	Number	Vertical transmission
C-Section	46	0%
Spontaneous vaginal delivery	19	0%

Discussion

The mode of delivery by C-section or spontaneous vaginal delivery has been a point of discussion throughout. However conflicting results have been seen in earlier studies regarding transmission risk and cesarean delivery. The introduction of highly active antiretroviral therapy (HAART) during pregnancy has been the major development which dramatically brought down the vertical transmission . However the continued preference of C-section as the mode of delivery has been discussed keeping in view that majority of females are virologically suppressed at term.

In this cohort of 63 pairs irrespective of mode of delivery the mother-to-child transmission of HIV has been 0%. However all these patients have been on combination HAART. Nearly one-half of the women were already receiving HAART before they became pregnant while the remaining were started during pregnancy before 5 months of pregnancy, however the achievement of undetectable HIV RNA levels at or close to delivery was same in both groups. It is of interest to note that we were able to show no difference in mode of delivery influencing the vertical disease transmission. This remarkable development has been the result of continuously improving interventions during pregnancy and at delivery .In 1994, the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 demonstrated that the administration of zidovudine during pregnancy and labor and then to the newborn decreased the risk of perinatal transmission of HIV by 68%, from 25.5% to 8.3%.[10] In a surveillance data from the United Kingdom and Ireland transmission rates of about 1%, was seen in pregnant women receiving HAART unadjusted for mode of delivery.[9] The low transmission rates achievable with use of maternal HAART, the additional benefit coming from scheduled cesarean sections is difficult to evaluate. A randomized clinical trial[6] and a meta-analysis[7] documenting the benefits of cesarean delivery included mostly women who were receiving either no ARVs or zidovudine alone. However, other data partially address this issue. In the late 1990s, the combined use of 3 or more

antiretroviral medications was found to be highly successful at suppressing viral replication.

The efficacy of ziduvidine therapy during pregnancy to reduce vertical HIV transmission was demonstrated in 1994.[11] Combination ARVs when started in the later months of pregnancy also reduced HIV transmission by 50%.[12-16] A large meta-analysis of data from 15 prospective cohort studies demonstrated a 50% reduction of vertical transmission with the use of elective cesarean delivery for women with HIV, after adjusting for antiretroviral therapy, maternal stage of disease, and infant birth weight.[5] The transmission risk was decreased by about 80% for women who had both an elective cesarean delivery and were taking antiretroviral medication.[17] ACOG issued an opinion in 1999 that elective cesarean delivery should be discussed and offered to all pregnant women who were HIV positive at 38 weeks' gestation to avoid the potential risk of spontaneous labor and rupture of membranes.[18] If cesarean delivery is performed after the onset of labor or rupture of membranes, the benefit of surgery may be lost. In this scenario, a decision regarding the route of delivery should be individualized.[19] Operative risk may outweigh the potential benefit of further reducing HIV transmission. In a study by Louis et al that compared the outcome of cesarean section in 378 women infected with HIV and in more than 54,000 uninfected women, HIV-infected women were found to have higher rate of blood transfusions intra-operatively and increased incidence of postpartum infections like endometritis, sepsis, pneumonia, more intensive care unit admissions and maternal death.[20]

In females where ARVS started late or not started at all the viral loads are high and this group requires proper handling Scheduled cesarean delivery should be discussed and recommended for women with viral loads greater than 1000 copies/mL, whether or not they are taking antiretroviral therapy. Because morbidity is increased in women infected with HIV who undergo cesarean delivery, prophylactic antibiotics should be administered. The use of chlorhexidine as a vaginal cleansing agent in the prevention of HIV transmission has yielded mixed results.[21] In patients attempting a vaginal delivery, all invasive procedures such as amniotomy, internal fetal scalp electrode, or scalp sampling should be avoided, as these may increase the risk of transmission.

Conclusion

Initiating/ maintaining combination antiretroviral drugs during pregnancy plays a key role in preventing vertical transmission of HIV. The concept of scheduled caesarean delivery in HIV infected patients has limited applicability in patients on combination antiretroviral therapy and those who achieve undetectable viral loads.

References

1. Cecchini D, Martinez M, Astarita V, Nieto C, Giesolauro R, Rodriguez C. Prevención de la transmisión vertical del VIH-1 en un hospital público de complejidadterciaria de Buenos Aires, Argentina. Rev PanamSaludPublica. 2011;30:189-195.
2. Pilotto JH, Velasque L, Freidman RK, Moreira RI, Veloso VG, Grinsztejn B, Morgado MG, Watts DH, Currier JS, Hoffman RM. Maternal outcomes after highly active antiretroviral therapy for the prevention of mother-to-child transmission in HIV-infected women in Brazil. Antiviral therapy. 2011;16(3):349.
3. Garcia PM, Kalish LA, Pitt J, Minkoff H, Quinn TC, Burchett SK, Kornegay J, Jackson B, Moye J, Hanson C, Zorrilla C. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. New England Journal of Medicine. 1999;341(6):394-402.
4. Barral Maria F.M., Oliveira Gisele R. de, Lobato Rubens C., Mendoza-Sassi Raul A., Martínez Ana M.b., Gonçalves Carla V. Risk factors of HIV-1 Vertical transmission (VT) and the influence of anti retroviral (ART) in pregnancy outcome Rev. Inst. Med. trop. S. Paulo. 2014; 56(2): 133-138.
5. International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. The International Perinatal HIV Group. *N Engl J Med*. 1999;340(13):977-987.
6. (European Mode of Delivery C. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet*. 1999;353(9158):1035-1039.
7. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, Berrebi A, Bénifla JL, Burgard M, Lachassine E, Barret B, Chaix ML, Bongain A, Ciraru-Vigneron N. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. Jama. 2001;285(16):2083-2093.
8. Townsend CL, Byrne L, Cortina-Borja M, Thorne C, de Ruiter A, Lyall H, Taylor GP, Peckham CS, Tookey PA. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011. Aids. 2014;28(7):1049-1057.
9. Brinkman K, ter Hofstede HJ, Burger DM, Smeitink JA, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS*. 1998 ;12(14):1735-1744.
10. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. New England Journal of Medicine. 1994;331(18):1173-1180.
11. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. New England Journal of Medicine. 1994;331(18):1173-1180.
12. Shaffer N, Roongpisuthipong A, Siriwasin W, Chotpitayasunondh T, Chearskul S, Young NL. et al. Maternal virus load and perinatal human immunodeficiency virus type 1 subtype E transmission, Thailand. Journal of Infectious Diseases. 1999;179(3):590-599.

13. Dabis F, Msellati P, Meda N, Welffens-Ekra C, You B, Manigart Oet al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. The Lancet. 1999 ;353(9155):786-792.
14. Wiktor SZ, Ekpini E, Karon JM, Nkengasong J, Maurice C, Severin ST, Roels TH, Kouassi MK, Lackritz EM, Coulibaly IM, Greenberg AE. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. The Lancet. 1999 ;353(9155):781-785.
15. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. The Lancet. 1999 ;354(9181):795-802..
16. Lallemant M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, Phoolcharoen W, Essex M, McIntosh K, Vithayasai V. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. New England Journal of Medicine. 2000;343(14):982-991.
17. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. The International Perinatal HIV Group. *N Engl J Med*. 1999; 340(13):977-987.
18. American College of Obstetrics and Gynecology. Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. No. 234. *Obstet Gynecol*. 2000.
19. Louis J, Landon MB, Gersnoviez RJ, Leveno KJ, Spong CY, Rouse DJ. Perioperative morbidity and mortality among human immunodeficiency virus infected women undergoing cesarean delivery. *Obstet Gynecol*. 2007 Aug. 110(2 Pt 1):385-90.)
20. Biggar RJ et al. Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. Lancet, 1996, 347: 1647–1650. 1630.
21. Gaillard P, Mwanyumba F, Verhofstede C, Claeys P, Chohan V, Goetghebeur E, Mandaliya K, Ndinya-Achola J, Temmerman M. Vaginal lavage with chlorhexidine during labour to reduce mother-to-child HIV transmission: clinical trial in Mombasa, Kenya. Aids. 2001 ;15(3):389-396.