Advances and controversies in the prevention of HIV-1 mother-to-child transmission

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Abstract

HIV-1 infection can be transmitted from mother-to-child in utero and intra-partum. In the absence of antiretroviral therapy, chorioamnionitis has been associated with transmission risk, as has duration of rupture of membranes. Chlorhexidine vaginal lavage reduced transmission once membranes were ruptured more than 4 hours however antibiotics given in the 2nd trimester did not reduce transmission. Mode of delivery significantly impacts on transmission in the absence of antiretroviral therapy and when zidovudine is given as a monotherapy. Most risk factors are eliminated by highly active antiretroviral therapy (HAART) and transmission rates well below 1% are achievable. The role of pre-labour caesarean section (PLCS) in women with undetectable HIV viral load on HAART is now uncertain.

The current major controversy is whether HAART, and especially protease-inhibitor containing regimens, are associated with a significant increase risk of severe pre-term delivery. Although some argue the case for full suppression of viral load in all pregnant women, most guidelines maintain an option for zidovudine monotherapy if baseline viral load is low and PLCS is the preferred mode of delivery.

Risk Factors for HIV-1 mother-to-child transmission

Mother-to-child transmission of an infectious agent causing the acquired immune deficiency syndrome was suggested in 1984¹. By December 1985 the Centers for Disease Control in the USA had issued their first advice on prevention of HIV (at that time known as HTLV-III/LAV) perinatal transmission which included a recommendation that infected women should delay pregnancy until more was known about the risks².

HIV-1 was shown to infect the placenta at all stages of pregnancy, and could be found in amniotic fluid and in 2% of foetal thymuses⁴. Subsequently in vitro

studies demonstrated that Hofbauer cells and trophoblasts were CD4 positive and could be infected with HIV-1^{5,6}. However, in the study of Brossard et al HIV was only detected in spontaneously aborted foetuses and not following an induced termination of pregnancy⁴. The data, therefore pointed to the placenta behaving, unless disrupted, as a barrier to infection and to the rarity of foetal HIV infection during the first and second trimesters. This clearly has implications for the timing of any intervention. One risk factor that may contribute to placental disruption is malaria. In a study of 512 mother-infant pairs of which 25% of mothers had malaria during the pregnancy and 19.9% transmitted HIV a high parasite load (>10,000 parasites/ml) was associated with two-fold increase in transmission risk⁷.

Rouzioux et al used the first detection of HIV in newborn infants to model the likely time of infection. Using data from 95 HIV-1 infected infants of whom 17% were positive at birth and 50% by day 10 they postulated that 65% of transmissions occurred intra-partum and 35% in utero during the last 2 months before delivery with less than 2% occurring earlier⁸. Further evidence that detection of HIV infection at, or shortly after, delivery reflects infection in utero and prior to the labour process, is provided by the increase in HLA DR expression, a marker of T-cell activation, on CD8+ cells, in neonates already HIV infected at birth compared with those with a delayed first positive result⁹.

Whether timed pre-partum or intra-partum, the question as to the route of infection remains. Intra-partum infection may in theory occur either through external exposure of the baby as it passages through the birth canal, with ingress of HIV through mucosal membranes or breached epidermis, or via internal exposure with materno-fetal blood transfusion. Pre-partum infection might be trans-amniotic or trans-placental.

HIV can be detected in amniotic fluid¹⁰ and

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chorioamnionitis has been associated with an increased risk of transmission¹¹

. Chorioamnionitis can be further classified as acute or chronic. In a Kenyan study of vaginal lavage with chlorhexidine, the risk of HIV MTCT was increased 3.9 fold if acute chorioamnionitis was present. Where HIV MTCT was attributed to the peripartum period, the adjusted odds ratio (AOR) for transmission was 5.2 ($p = 0.005$). In this setting acute chorioamnionitis carried a higher risk than that attributed to maternal HIV load¹². In a Zambian study, chronic chorioamnionitis was associated with intrauterine HIV transmission with an AOR of 7.6 whereas acute chorioamnionitis, whilst associated with duration of labour and of rupture of membranes, was not associated with an increased risk of transmission. However in this study mothers received intrapartum nevirapine¹³. Thus it appears that acute chorioamnionitis, which is characterised by a neutrophil infiltrate, is associated with intra-partum transmission that can be prevented by intra-partum intervention such as single dose nevirapine. However, despite reducing the prevalence of bacterial vaginosis, which is associated with pre-term labour and chorioamnionitis, randomisation to metronidazole and erythromycin at 20 – 24 weeks was not associated with a reduction in MTCT nor in chorioamnionitis in a controlled study in which all mothers also received single dose nevirapine¹⁴. In the study of chlorhexidine vaginal lavage, transmission was reduced by the intervention if membranes had been ruptured more than 4 hours¹⁵. Chronic chorioamnionitis, which is characterised by a mononuclear cell infiltration, is associated with pre-partum transmission and unaffected by such late intervention. In summary it appears that the risk of HIV transmission associated with chorioamnionitis can be, to a large extent, eliminated by antiretroviral therapy during pregnancy. It remains unclear whether antibiotics should be given earlier in patients with HIV infection than in the general antenatal population but on balance this remains favoured in the recently updated BHIVA guidelines¹⁶.

Since HIV RNA load in the genital tract is a risk for MTCT¹² factors that increase this might also be expected to be associated with transmission. Herpes simplex virus, the most common cause of genital

ulceration, has been investigated as a risk factor. In the North American Women and Infant Transmission Study (WITS) no association with HSV-2 seropositivity was found¹⁷ whilst in Zimbabwe the presence of antibodies to HSV-2 was associated with a 1.5 fold increase in risk¹⁸. Interestingly HIV transmission in the WITS case-control study was not associated with the presence of HSV DNA either but the numbers were probably too small to determine this¹⁷. Although suppressive therapy with valaciclovir for 12 weeks was associated with a decrease in the frequency of detection of HSV DNA this had no impact on the frequency of detection or load of HIV-1 in the genital tract in women taking HAART¹⁹, whereas the same treatment in women not taking HAART was associated with a reduction in both genital tract and plasma HIV-1 viraemia²⁰.

Other evidence of the importance of exposure to HIV by passage through the birth canal comes from studies of twins. Although it might be expected that the second born twin, exposed to the labour process for longer, might be at a higher risk of infection the reverse is true with 35% transmission for the first born delivered vaginally compared with 8% for the second twin if delivered by caesarean section²¹. However although a similar difference in risk was seen in the French cohort (8.5% v 2.4% $p = 0.008$) twins have not been at higher risk than singletons since 1996, with the advent of suppressive antiretroviral therapy (1.0% v 1.8% $p = 1.0$)²².

The other major potential route of transmission, even at the time of delivery, is transplacental. Materno-fetal transfusion has long been recognised²³

Elective (i.e. pre-labour) caesarean section avoids, not only passage through the birth canal, but the labour process with associated inflammation of the placenta and the potential for micro-transfusions during labour. It is worth noting that in some early studies on caesarean sections, the planned timing was for after labour had commenced and therefore focussed on by-passing the birth-canal whilst others were planned pre-labour, sometimes as early as 36 weeks. Thus in some studies 'elective' caesarean section was protective and in others it was not. Rates of transmission with emergency CS are high but the many confounding factors make interpretation difficult. In the European mode of delivery study,

transmission was reduced by 80% with pre-labour Caesarean section (PLCS)³.

Since the advent of antiretroviral therapy, the factors that remain risks for transmission have diminished in number. In a study comparing differing durations of zidovudine monotherapy to mother and baby the only risk factors associated with transmission detected by day 3 of infant life and deemed to have occurred in utero, were maternal plasma viraemia greater than 35,000 HIV RNA copies/ml and delayed initiation of zidovudine. Intrapartum transmissions were also associated with high viral load and additionally with tocolysis for pre-term labour. Considering both groups together pre-term delivery and small birth weight were associated with transmission, as was increased maternal creatinine²⁴. In an analysis of the WITS cohort from 1990 to 2000, encompassing a period prior to the use of zidovudine monotherapy through to the later period with combination therapies, HIV viral load and the lack of any antiretroviral therapy were associated with in utero and intra-partum transmission, low birth weight with in utero transmission, and maternal CD4+ T-lymphocyte count, maternal age and the duration of rupture of membranes with intra-partum transmission²⁵. In the UK and Ireland cohort, the transmission rate with use of three or more therapies in pregnancy was, if the viral load was undetectable at delivery, 0.1% with only 3 transmissions out of 2202 deliveries, of which two at least were thought to have become infected prior to the initiation of therapy. In the same cohort PLCS did not reduce transmission if the mother was already on HAART (0.7%) and although the overall transmission rate was 1.1% this was reduced to 0.8% if treatment was initiated > 14 days prior to delivery²⁶.

Thus, whilst interventions to reduce HIV viral load in the genital tract through treatment of bacterial and viral infections might reduce transmission in the absence of effective antiretroviral therapy these become of marginal importance if maternal viral load is fully suppressed. The remaining question therefore is should all pregnant women infected with HIV be treated with HAART, regardless of health, CD4 T-lymphocyte count and viral load? This appears to be the recommendation of the European AIDS Clinical Society whose guidelines state that viral load should be fully suppressed in all pregnant women²⁷. In Ireland women are generally offered HAART but

zidovudine monotherapy may be considered in selected cases and usually a PLCS is recommended²⁸. The 2007 US guidelines restrict the option of zidovudine monotherapy to pregnant women with a viral load of less than 1,000 HIV RNA copies/ml²⁹ whilst in the 2008 UK guidelines zidovudine monotherapy remains an option for women with a viral load less than 10,000 HIV RNA copies /ml and a CD4+ T-lymphocyte count greater than 200 cells/ml, provided the mother opts to deliver by PLCS¹⁶.

Since the efficacy of HAART is not in doubt, only concerns about safety remain. Whilst some studies have observed an increased incidence of gestational diabetes with HAART, particularly if PI-based^{30,31} this has not been confirmed and recent studies have been reassuring in this regard^{32,33}. Of greater concern is the reported increase in pre-term delivery with HAART. This was first reported by the Swiss³⁴, and has since been noted in the European Collaborative Study (ECS)^{35,36}, the UK cohort³⁷, Italian³⁸, Dutch³⁹ and German⁴⁰ studies. The relative risk varies but the effect seems larger with severe pre-term deliveries (before 32 or 34 weeks). Some studies report a greater effect with protease inhibitors than nevirapine (this being the only NNRTI widely prescribed in pregnant women) and some with first trimester rather than later first exposure. Other factors associated with pre-term delivery were maternal age, CD4 count less than 200 and injecting drug use. In the ECS logistic regression analysis of data from 2279 mother-infant pairs demonstrated that, compared to monotherapy, the adjusted odds ratio for delivery before 37 weeks with HAART was 1.88 (95% CI 1.34 – 2.65 $p < 0.002$) if started antenatally and 2.05 (95% CI 1.43 – 2.95; $p < 0.002$) if commenced prior to pregnancy³⁶.

Data from the USA appear to contradict these findings. Analysis of data from seven clinical studies between 1990 and 1998 found no difference in risk between mothers who received no antiretroviral therapy ($n = 1143$, pre-term delivery rate 17%) and those treated with zidovudine monotherapy ($n = 1590$, pre-term delivery rate 16%). Furthermore no increased risk, compared with monotherapy, was seen with combination therapy ($n = 533$, AOR 1.08 95% CI 0.71 – 1.62) although only 137 mothers were exposed to PI-based HAART⁴¹. Similarly the WIT

study of 2453 mothers did not reveal an association of HAART with pre-term delivery although the timing of therapy was obscured with an undisclosed number of mothers initiating treatment after 32 weeks, which might dilute any effect⁴². Finally in a recent meta-analysis although pre-term delivery was not associated with antiretroviral therapy when compared with no antiretroviral therapy, a small increase in pre-term delivery was seen with PI-based combination antiretroviral therapy compared with non-PI based combination therapy (OR 1.24 (95% CI 0.76-2.02)) and when therapy was started prior to or during the first trimester (OR 1.71 (95% CI 1.09-2.67))⁴³.

Possible explanations for these differences include different baseline risks for pre-term delivery and different antiretroviral prescribing practice. Clearly the timing of therapy during pregnancy will influence the likelihood of an association with pre-term delivery especially if significant proportions of women included in the studies started therapy. It may also be important to discriminate between women who change therapy during pregnancy due to poor viral control and those who have fully suppressed HIV. The importance of clarifying this controversy cannot be underestimated. Pre-term delivery, especially, before 32 weeks is associated with increased neonatal morbidity and requires intensive resources. Rolling out HAART will reduce HIV mother to child transmission but transmission rates with zidovudine monotherapy and single dose nevirapine are already low (1.9%)⁴⁴ and in selected populations zidovudine monotherapy accompanied by PLCS virtually eliminates transmission²⁶. Careful examination of preterm delivery rates and any associated morbidity or mortality should be conducted as HAART is increasingly prescribed to pregnant women who do not have access to neonatal intensive care. If the European experience is replicated and an association with PI-based therapy confirmed, strategies to minimise the risk will be needed.

References

1. Scott GB, Buck BE, Leterman JG, Bloom FL, Parks WP. Acquired immunodeficiency syndrome in infants. *N.Engl.J Med.* 1984;**310**:76-81.
2. Centers for Disease Control (CDC). Recommendations for assisting in the prevention of perinatal transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus and acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep* 1985;**34**:721-6.
3. The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999;**353**:1035-9.
4. Brossard Y, Aubin JT, Mandelbrot L, et.al. Frequency of early in utero HIV-1 infection: a blind DNA polymerase chain reaction study on 100 fetal thymuses. *AIDS* 1995;**9**:359-66.
5. David FJ, Autran B, Tran HC, Menu E, Raphael M, Debre P et al. Human trophoblast cells express CD4 and are permissive for productive infection with HIV-1. *Clin. Exp. Immunol.* 1992;**88**:10-6.
6. Lewis SH, Reynolds-Kohler C, Fox HE, Nelson JA. HIV-1 in trophoblastic and villous Hofbauer cells, and haematological precursors in eight-week fetuses. *Lancet* 1990;**335**:565-8.
7. Ayisi JG, van Eijk AM, Newman RD, ter Kuile FO, Shi YP, Yang C et al. Maternal malaria and perinatal HIV transmission, western Kenya. *Emerg Infect Dis* 2004;**10**:643-52.
8. Rouzioux C, Costagliola D, Burgard M, et.al., and the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Estimating timing of transmission of mother-to-child HIV-1 transmission by use of a Markov model. *Am.J.Epidemiol.* 1995;**142**:1330-7.
9. Rich KC, Chang BH, Mofenson L, Fowler MG, Cooper E, Pitt J et al. Elevated CD8+DR+ lymphocytes in HIV-exposed infants with early positive HIV cultures: a possible early marker of intrauterine transmission. Women and Infants Transmission Study Group. *J Acquir. Immune. Defic. Syndr. Hum. Retrovir.* 1997;**15**:204-10.
10. Mundy DC, Schinazi RF, Gerber AR, Nahmias AJ, Randall HW, Jr. Human immunodeficiency virus isolated from amniotic fluid. *Lancet* 1987;**2**:459-60.
11. St Louis ME, Kamenga M, Brown C, Nelson AM, Manzila T, Batter V et al. Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic, and placental factors. *JAMA* 1993;**269**:2853-9.

12. Mwanyumba F, Gaillard P, Inion I, Verhofstede C, Claeys P, Chohan V et al. Placental inflammation and perinatal transmission of HIV-1. *J Acquir.Immune.Defic.Syindr.* 2002;**29**:262-9.
13. Chi BH, Mudenda V, Levy J, Sinkala M, Goldenberg RL, Stringer JS. Acute and chronic chorioamnionitis and the risk of perinatal human immunodeficiency virus-1 transmission. *Am J Obstet Gynecol* 2006;**194**:174-81.
14. Taha TE, Brown ER, Hoffman IF, Fawzi W, Read JS, Sinkala M et al. A phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission. *AIDS* 2006;**20**:1313-21.
15. Biggar RJ, Miotti P, Taha TE, Mtimavalye L, Broadhead R, Justesen A et al. Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. *Lancet* 1996;**347**:1647-50.
16. de Ruiter A, Mercey D, Anderson J, Chakraborty R, Clayden P, Foster G et al. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med* 2008;**9**:452-502.
17. Chen KT, Tuomala RE, Chu C, Huang ML, Watts DH, Zorrilla CD et al. No association between antepartum serologic and genital tract evidence of herpes simplex virus-2 coinfection and perinatal HIV-1 transmission. *Am J Obstet Gynecol* 2008;**198**:399-5.
18. Cowan FM, Humphrey JH, Ntozini R, Mutasa K, Morrow R, Iliff P. Maternal Herpes simplex virus type 2 infection, syphilis and risk of intra-partum transmission of HIV-1: results of a case control study. *AIDS* 2008;**22**:193-201.
19. Ouedraogo A, Nagot N, Vergne L, Konate I, Weiss HA, Defer MC et al. Impact of suppressive herpes therapy on genital HIV-1 RNA among women taking antiretroviral therapy: a randomized controlled trial. *AIDS* 2006;**20**:2305-13.
20. Nagot N, Ouedraogo A, Foulongne V, Konate I, Weiss HA, Vergne L et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N.Engl.J Med.* 2007;**356**:790-9.
21. Duliege AM, Amos CI, Felton S, Biggar RJ, Goedert JJ. Birth order, delivery route and concordance in the transmission of human immunodeficiency virus type 1 from mother to twins. *J Pediatr* 1995;**216**:625-32.
22. Scavalli CP, Mandelbrot L, Berrebi A, Batallan A, Cravello L, Pannier E et al. Twin pregnancy as a risk factor for mother-to-child transmission of HIV-1: trends over 20 years. *AIDS* 2007;**21**:993-1002.
23. Zilliacus R, De la CA, Schroder J, Tilikainen A, Kohne E, Kleihauer E. Transplacental passage of foetal blood cells. *Scand.J Haematol.* 1975;**15**:333-8.
24. Jourdain G, Mary JY, Coeur SL, Ngo-Giang-Huong N, Yuthavisuthi P, Limtrakul A et al. Risk factors for in utero or intrapartum mother-to-child transmission of human immunodeficiency virus type 1 in Thailand. *J Infect.Dis.* 2007;**196**:1629-36.
25. Magder LS, Mofenson L, Paul ME, Zorrilla CD, Blattner WA, Tuomala RE et al. Risk factors for in utero and intrapartum transmission of HIV. *J Acquir.Immune.Defic.Syindr.* 2005;**38**:87-95.
26. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS* 2008;**22**:973-81.
27. Clumeck N, Pozniak A, Raffi F, and the EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. *HIV Med* 2008;**9**:65-71.
28. Lyons F, Butler K, Coulter Smith S, Mulcahy F. National guidelines for the management of HIV-1 in pregnancy. *Ir Med J* 2006;**99**:152-4.
29. Jamieson DJ, Clark K, Kourtis AP, Taylor AW, Lampe MA, Fowler MG et al. Recommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States. *Am J Obstet Gynecol* 2007;**197**:S26-S32.
30. Gonzalez-Tome, MI., Ramos, J., Solis, I., Munoz, E., Guillen, S., Almeda, J., Bates, I., Miralles, P., Pena, J., Del Barrio, P., Garaulet, C., Gonzalez-Espinola, A., Onate, S., Salcedo, N., Segovia, P., and for the Spanish Cohort of HIV infected mother-infant pairs. Gestational Diabetes and ART in Pregnant HIV-1-infected women. 12th Conference on Retroviruses and Opportunistic Infections, 22 - 25 February 2005, Boston, Ma. USA, #68. 24-2-2005.
31. Justman JE, Benning L, Danoff A, Minkoff H, Levine A, Greenblatt RM et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *AIDS* 2003;**32**:298-302.

32. Tang JH, Sheffield JS, Grimes J, McElwee B, Roberts SW, Laibl V et al. Effect of Protease Inhibitor Therapy on Glucose Intolerance in Pregnancy. *Obstetrics Gynecology* 2006;**107**:1115-9.
33. Hitti J, Andersen J, McComsey G, Liu T, Melvin A, Smith L et al. Protease inhibitor-based antiretroviral therapy and glucose tolerance in pregnancy: AIDS Clinical Trials Group A5084. *American Journal of Obstetrics and Gynecology* 2007;**196**:331.
34. Lorenzi P, Spicher VM, Laubereau B, Hirschel B, Kind C, Rudin C et al. Antiretroviral therapies in pregnancy: maternal, foetal and neonatal effects. *AIDS* 1998;**12**:F241-F247.
35. European Collaborative Study, Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS* 2000;**14**:2913-30.
36. Thorne C, Patel D, Newell M-L, and the European Collaborative Study. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS* 2004;**18**:2337-9.
37. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS* 2007;**21**:1019-26.
38. Chiesa, E., Repetto, D., Melzi, S., and et al. Increasing risk of preterm delivery with more potent antiretroviral therapy (ART). 6th International Congress on Drug Therapy in HIV Infection (Abstracts) 17-21 Nov, P322. 18-11-2002.
39. Boer K, Nellen JF, Patel D, Timmermans S, Tempelman C, Wibaut M et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *Br J Obstet Gynaecol* 2007;**114**:148-55.
40. Grosch-Woerner I, Puch K, Maier RF, Niehues T, Notheis G, Patel D et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. *HIV Med.* 2008;**9**:6-13.
41. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD et al. Antiretroviral Therapy during Pregnancy and the Risk of an Adverse Outcome. *The New England Journal of Medicine* 2002;**346**:1863-70.
42. Tuomala RE, Watts DH, Li D, Vajaranant M, Pitt J, Hammill H et al. Improved Obstetric Outcomes and Few Maternal Toxicities Are Associated With Antiretroviral Therapy, Including Highly Active Antiretroviral Therapy During Pregnancy. *JAIDS* 2005;**38**:449-73.
43. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS* 2007;**21**:607-15.
44. Lalléman M, Jourdain G, Le Coeur S, Mary J, Ngo-Giang-Huong N, Koetsawang S et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004;**351**:217-28.