Outcomes of Infants Born to HIV-Infected Women Identified by Rapid HIV Testing Late in Pregnancy or at Delivery: The MIRIAD Study

Russell B Van Dyke1*, Susan P Danner2, Sarah Chrestman3, Patricia Kissinger4, Steven Nesheim5, Angela M Amedee6, Gwendolyn Scott7, Mardge H Cohen8, Elaine J Abrams8, Denise J Jamieson9, Mary Glenn Fowler10,11, Athena P Kourits12, Marc Bulterys12,13 for the MIRIAD Study Group

1Department of Pediatrics, Tulane University School of Medicine, New Orleans, LA, USA
2Division of AIDS Prevention, National Center for AIDS, HIV, Viral Hepatitis, STD and Tuberculosis Prevention, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA
3Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA
4Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, CDC, Atlanta, GA, USA
5Department of Microbiology, Louisiana State University Health Sciences Center, New Orleans, LA, USA
6Department of Pediatrics, University of Miami School of Medicine, Miami, FL, USA
7Department of Medicine, Cook County Bureau of Health Services and Rush University, Chicago, IL, USA
8Department of Pediatrics, Harlem Hospital Center and College of Physicians & Surgeons, Columbia University, New York, NY, USA
9Department of Pediatrics, Emory University, Atlanta, GA, USA
10Makerere University Johns Hopkins University (MUJHU) AIDS Research Collaboration, Kampala, Uganda
11US Department of Defense HIV/AIDS Prevention Program (DHAPP), Naval Health Research Center, San Diego, CA, USA

Abstract

Background: Rapid HIV testing late in pregnancy or at delivery provides a final opportunity (among non-breast-feeding mothers) to identify HIV-infected women and initiate antiretroviral drugs to prevent mother-to-child transmission.

Methods: MIRIAD was a CDC-funded study conducted from 2001-2005 at 17 hospitals in 6 US cities. Eligible women had undocumented HIV status when presenting in labor or after 34 weeks gestation and not in labor. We performed both rapid HIV-1 antibody testing of blood and conventional enzyme immunoassay with Western blot confirmation. Women and infants were managed according to the local standard of care. Infant infection status was determined by HIV DNA or RNA PCR testing.

Results: Fifty-one infants (1 pair of twins) were born to 50 women. Among those with data available, 17% of women received prenatal antiretroviral and 71% received intrapartum antiretroviral, including 64% of those identified during labor. All 49 infants with available data received antiretroviral. Forty-four infants had adequate samples to determine their infection status and 5 were infected (11.4%, 95% CI: 1.9 - 20.7%); 3 had in utero, 1 intrapartum, and 1 indeterminate timing of transmission. No infant whose mother received prenatal antiretroviral was infected. The estimated rate of intrapartum transmission among infants with defined infection status was 4.5%.

Conclusions: Rapid HIV testing late in pregnancy or even during labor, allowing the administration of antiretroviral to infected women, reduces intrapartum HIV transmission. This highlights the importance of offering rapid HIV testing to pregnant women, with unknown HIV status late in pregnancy.

Keywords: Antiretroviral therapy; Human immunodeficiency virus; Infection; Mother-to-child-transmission; Perinatal infection; Prevention

Abbreviations: ARV: Antiretroviral Drugs; cART: Combination Antiretroviral Therapy; CDC: Centers for Disease Control and Prevention; DNA: Deoxyribonucleic acid; EIA: Enzyme Immunoassay; MIRIAD: Mother-Infant Rapid Intervention at Delivery Study; MTCT: Mother-to-Child Transmission; PCR: Polymerase Chain Reaction; PBMCs: Peripheral Blood Mononuclear Cells; RNA: Ribonucleic acid; ZDV: Zidovudine

Introduction

In 1994, it was demonstrated that the administration of zidovudine (ZDV) to the HIV-infected pregnant woman during her second and third trimesters and to her newborn reduced the rate of mother-to-child transmission (MTCT) of HIV by two-thirds [1]. ZDV can reduce the rate of MTCT even when initiated as late as 36 weeks gestation [2]. The use of combination antiretroviral therapy during pregnancy and delivery has reduced the rate of MTCT to 2% or less [3-5]. Of the fewer than 150 infants who are estimated to acquire perinatal HIV in the US each year, approximately one-third are born to mothers with unknown HIV status and therefore could not benefit from interventions to prevent MTCT [6-8].

Rapid HIV testing late in pregnancy or at delivery provides a final opportunity (among non-breast-feeding mothers) to diagnose HIV and prevent MTCT. Antiretroviral drugs (ARV) administered to the woman during labor and to her infant following delivery can reduce the risk of MTCT [9]. Even when administered only to the infant following delivery, ARVs can reduce the rate of MTCT [10,11]. The Mother-Infant Rapid Intervention at Delivery (MIRIAD) Study was a Center for Disease Control and Prevention (CDC)-funded multi-site study to evaluate the feasibility and acceptability of rapid HIV testing in late pregnancy or during labor among pregnant women with unknown...
infected child who did not have a blood sample available within 7 days of birth had undefined timing of transmission. A child was defined as HIV-uninfected if the child had never breast fed and had 2 blood samples which were negative for HIV-1 DNA or RNA, one of which was collected when the child was at least 6 weeks of age. In addition, an uninfected child could not have any test indicating the presence of HIV (e.g., culture, p24 antigen, or DNA or RNA PCR). A child who failed to meet these definitions was considered to be of indeterminate HIV infection status.

Viral sequence analysis

The sequence of the V3 region of the HIV envelope gene from reverse-transcribed cell-free virus or PMBC genomic DNA was determined as previously described [14]. Viral diversity was determined by comparing viral sequences from maternal and infant samples using MacVector, version 7.2.3 (Accelrys, San Diego, CA).

Data analysis

Data analysis was conducted using SPSS statistical software. Data was tabulated and presented as proportions, medians, and ranges.

Results

Fifty-four HIV-infected pregnant women were identified, of whom 50, and their 51 infants, were eligible for this analysis (Figure 1). Of the 4 women who were not eligible, 2 were lost to follow-up prior to delivery, 1 did not have rapid testing and was not tested until 5 days after delivery, and 1 was found to be infected 1 month following delivery. Both infants born to the 2 mothers excluded from this analysis but not lost to follow-up prior to delivery were confirmed to be uninfected. Of the 50 eligible women, 11 were in the Late Presenting Group and 39 in the Peripartum Group (Figure 1, Table 1). Four women in the Peripartum Group had a documented primary HIV infection during the pregnancy; 1 was among the 4 ineligible women.

Late presenting group (Table 1)

Nine of the 11 women in the Late Presenting group had ARV data; 5 received prenatal ARV and 9 received intrapartum ARV. All 9 infants with ARV data received preventive ARVs following delivery and all 11 infants were confirmed to be uninfected.
### Peripartum group (Table 1)

Three of the 39 women in the Peripartum Group had premature labor that was stopped, allowing them to receive prenatal ARV, and 25 received intrapartum ARV. Of the 14 women who did not receive intrapartum ARV, 9 were identified as being HIV-infected postpartum, 1 delivered at home, and 4 delivered before they were able to receive ARV’s. One woman delivered twins.

All 40 infants in the Peripartum Group received preventive ARV following delivery. Thirty-three infants had a confirmed infection status with 5 (15%) infected and 28 (85%) uninfected (including both twins).

All 7 infants with an indeterminate HIV infection status were lost to follow-up prior to 6 weeks of age and intrapartum infection could not be excluded. However, 6 had negative PCR results which ruled-out in utero infection (5 at ≤ 48 hours and 1 at 8 days of age). The seventh infant had no PCR testing.

### Characteristics of infants with defined infection status and their mothers (Table 3)

Overall, 44 infants had adequate samples to determine their infection status and five were infected (11.4%, 95% confidence interval 1.9 - 20.7). Details of infants A-C have been published previously [14]. Selected clinical and demographic characteristics of the infected and uninfected infants and their mothers, including risk factors for MTCT, are presented in Table 3. The majority of mothers were African-American; 58% received no prenatal care, most delivered at term and 42% had a Cesarean delivery. Eighteen percent of the mothers received ARVs. One woman delivered twins.

| Women | Late Presenting Group, n (%) | Peripartum Group, n (%) | Total, n (%) |
|-------|-------------------------------|--------------------------|--------------|
|       | Women                         | Mother                   | Infant       |
|       | Late Presenting Group, n (%)  | Post-partum              |              |
|       | Women                         | A                        | B *          | C            | D            | E            |
|       | Timing of HIV diagnosis (hours before delivery) | 5 | 4 | 2.3 | 9 | Post-partum |
|       | Prenatal ARV                  | none                     | none         | none         | none         | none         |
|       | Intrapartum ARV               | ZDV                      | ZDV, NVP     | ZDV          | ZDV          | none         |
|       | VL closest to delivery (copies/mL) (days following delivery) | 8,140 | 2,630 | 10,100 | 44,600 | 18,947 |
|       | CD4 count closest to delivery (cells/µL) (days following delivery) | 241 | 289 | 141 | 163 | 758 |
|       | Duration of ruptured membranes (hours) | 6.1 | NA | 7.9 | 16.2 | 0.1 |
|       | Delivery Mode                 | Vaginal                  | Cesarean     | Vaginal     | Vaginal     | Vaginal     |
|       | Vaginal VL closest to delivery (copies/mL) | 50 | 2,580 | 1,660 | 342 | NA           |
|       | Number of Sexually Transmitted Infections recorded during pregnancy | 4 | NA | NA | 1 | 0 |
|       | Substance use at delivery ‡   | negative                 | NA           | cocaine     | negative    | NA           |
|       | Sex                           | M                        | F            | M            | F            | M            |
|       | Gestational age (weeks)       | 40                       | NA           | 36           | 36           |
|       | Preventive ARV                | ZDV                      | ZDV, SD-NVP  | ZDV, SD-NVP  | ZDV          | ZDV          |
|       | Cord Blood VL (RNA copies/ mL) | 465 | NA | 12,000 | <50 § | NA |
|       | First positive DNA PCR (day of life) | 1 | 1 | 1 | 48 | 16 # |
|       | Timing of transmission        | in utero                 | in utero     | in utero     | Intrapartum & Indeterminate |

NA: Not Available; Date of life: Day of birth is day 1; VL: HIV Viral Load; ARV: Antiretroviral
* Mother had a documented primary HIV infection during pregnancy
† From day 5 post-partum
‡ Urine screen on mother and/or infant
§ Below lower limit of detection
# No newborn testing. Also positive plasma HIV RNA (2392 copies/mL) on day 16 of life & Negative HIV DNA testing on days 1 and 18 of life
prenatal ARV and 69% received intrapartum ARV. All of the infants received preventive ARV in the newborn period. The mothers of the infected infants, as compared to those of uninfected infants, had a lower median CD4 cell count and a higher median HIV plasma viral load around delivery; a greater proportion had membranes ruptured for more than four hours, had a vaginal delivery, and had a sexually transmitted infection during the pregnancy. The rates of substance use were similar in the two groups.

Comparison of viral sequences of infected infants and their mothers (Table 2)

The mother of infant A (in utero transmission) had detectable HIV RNA in plasma and vaginal fluid at delivery and her infant had detectible viral RNA in cord blood (465 copies/mL) and a positive blood DNA PCR at 1 day of age. No amniotic fluid was collected. The V3 amino acid sequences of viruses from baby's plasma were highly similar and were identical to those found in maternal vaginal fluid.
Viral sequences in maternal blood were similar to those found in the infant and vaginal fluid, but varied by up to 6% [14].

The mother of infant B (in utero transmission) had a documented primary HIV infection during pregnancy. She had detectable HIV in plasma, vaginal fluid, and amniotic fluid (50 copies/mL) at delivery. The viral sequences in infant plasma collected one month after birth were identical to those found in amniotic fluid as well as to the proviral DNA sequences found in maternal PBMC DNA at delivery. Viral sequences in maternal plasma and vaginal secretions were more diverse, but contained genotypes highly similar to those found in the infant (3-5% divergent). [14].

The mother of infant C (in utero transmission) had detectable HIV in plasma and vaginal fluid at delivery. Her infant had detectable viral RNA in cord blood (12,000 copies/mL) and DNA in blood obtained at 1 day of age. By sequencing, two virus genotypes were found in both cord blood and the infant’s plasma (obtained at 4 weeks of age) that differed by 33% over the V3 region that was analyzed. One infant genotype was identical to the predominant viral sequences in maternal plasma and vaginal secretions at the time of delivery. The second infant genotype was identical to proviral DNA sequences amplified from the mother’s PBMC at the time of delivery [14].

The mother of infant D (intrapartum transmission) had detectable HIV in vaginal fluid five days post-partum and a plasma viral load of 44,600 copies/mL 19 days post-partum. Her infant had a fetal scalp electrode applied during labor and a vaginal delivery following 16.2 hours of ruptured membranes, both risk factors for intrapartum transmission. The infant had no detectable HIV RNA in cord blood (<50 copies/mL) and HIV DNA PCR testing of blood was negative on day 1 and 19 and positive on day 48 of life. By sequencing, the viruses from vaginal fluid were highly divergent over the V3 region (36% diversity) from those found in baby’s plasma on day 48. No maternal plasma virus was available for sequencing.

The mother of infant E (indeterminate timing of transmission) was found to be infected following delivery and had no intrapartum samples. Her infant had a first DNA PCR test positive on day 16 of life; no blood samples were available prior to day 16. On day 23, the child had detectible HIV RNA in plasma (2,350 copies/mL). The V3 amino acid sequence of the virus from the infant’s plasma at 23 days of age was identical to that found in maternal plasma obtained at 55 days after delivery.

Discussion

The MIRIAD study confirms the feasibility and effectiveness of rapid HIV testing late in pregnancy to identify HIV-infected women, allowing for the initiation ARV for PMTCT. We were able to administer preventive ARV to 71% of all infected pregnant women prior to delivery and to all of their infants with available data. Among the Late Presenting group who were tested prior to the onset of labor, all of the infected mothers and their infants with available data received preventive ARV and no mother transmitted HIV to her infant.

Among the Peripartum Group, rapid testing following the onset of labor allowed 64% of the infected mothers and all of their infants to receive preventive ARV, resulted in a MTCT rate of 15% (Table 1). This rate is similar to that of 11.8% observed in the Uganda HIVNET 012 trial, in which SD-NVP was administered to women following onset of labor and their infants, supporting the value of rapid testing following the onset of labor [17]. Even when administered only to the exposed infant following delivery, ARVs can reduce the rate of MTCT [10]. A study conducted in Brazil and South Africa (HPTN 040) demonstrated that among infants born to HIV-infected mothers who did not receive ARV, postpartum combination ARV is significantly more effective than ZDV alone in preventing intrapartum transmission [11]. Thus, rapid testing of women of unknown HIV status during labor affords a final opportunity to reduce the risk of MTCT.

In the absence of breast feeding and preventive ARV, among infants ultimately shown to be infected, approximately one-third have in utero transmission, defined as having virus detected within the first 48 hours of life [16,18]. The remaining two-thirds of infected infants have virus first detectible at 4-6 weeks of life and are believed to have intrapartum transmission through exposure to maternal blood and secretions during labor and delivery. It is likely that most in utero transmission occur late in pregnancy, explaining why infected infants rarely have clinical abnormalities or suppressed CD4+ lymphocyte counts at birth [19]. Maternal prenatal combination ARV, as currently recommended to prevent MTCT, will prevent both in utero and intrapartum transmission [18,20]. However, interventions initiated near delivery, such as an elective Cesarean delivery or intrapartum ARV, can only be expected to prevent intrapartum transmission.

Fifty of the 51 infants (excluding only infected infant E) had samples necessary to identify an in utero infection – either uninfected or infected with a sample obtained at ≤ 48 hours of age – and 3 had a confirmed in utero infections, giving an in utero transmission rate of 6.0% (3/50) overall and 7.7% (3/39) among those in the Peripartum Group. These rates are similar to the in utero transmission rates reported prior to the use of prenatal ARV [9,21]. This is expected since, in the absence of prenatal ARV, ARV administered during labor cannot be expected to interrupt in utero transmission.

Among the 44 infants with defined infection status (excluding the 7 with indeterminate infection status and assuming that infant E had intrapartum transmission), the upper estimate of the overall intrapartum transmission rate is 4.5% (2/44, including the three infants with in utero transmission) and 6.1% (2/33) among those in the Peripartum Group. This intrapartum transmission rate is similar to that found in studies that administered only maternal intrapartum and newborn ARV and is substantially lower than that observed without ARV prophylaxis [18,22-26].

Comparison of the viral sequences of maternal and infant viruses can help elucidate the mechanism of MTCT [14]. Infant viral sequences were closely related or identical to those of mother’s virus in four of the five mother/infant pairs. In pair C, the infant was infected with two distinct viral genotypes, each corresponding to virus present in different maternal compartments. This suggests that the infant was infected with two distinct maternal viruses [14]. In pair D, maternal virus from vaginal fluid obtained after delivery differed from that present in her infant’s blood, suggesting that, despite intrapartum transmission, the infant was infected by a virus present in a different maternal compartment than the vagina. Although all mothers were advised against breast feeding, transmission by breast feeding cannot be definitively excluded for infant D.

The five transmitting mothers, when compared to non-transmitting mothers, exhibited several of the known risk factors for MTCT, including a low CD4+ count and elevated plasma viral load at delivery, a vaginal rather than a Cesarean delivery, prolonged rupture of membranes, no prenatal ARV, and in one case, a fetal scalp electrode [1,9,27-31]. Because of the small number of infected infants, a formal analysis of risk factors for transmission could not be conducted.
Limitations of the study include missing data, a small number of infected infants, and use of a convenience sample of clinical sites, which may limit the generalizability of the results. However, the sites are experiencing in providing HIV care and have access to large numbers of HIV-infected women. Finally, the estimated rates of MTCT would be misleading if the 7 infants with indeterminate infection status were not representative of the total group.

Conclusions

Rapid HIV testing of women of unknown HIV status late in pregnancy or during labor, with the administration of ARV to infected women, has little effect on in utero transmission of HIV but is effective in reducing intrapartum transmission. This highlights the importance of establishing systems to ensure that all women of unknown HIV status are offered HIV testing during pregnancy, including those in labor, so that effective PMTCT regimens can be initiated [32]. Even when performed after the onset of labor, rapid testing allows for the administration of ARV which will reduce the risk of intrapartum MTCT. These findings also support the importance of repeat HIV testing late in pregnancy for women who tested negative earlier in the pregnancy, as is currently recommended if at increased risk of HIV infection [33].

Acknowledgements

Source of funding: The MIRIAD study was coordinated and funded by the National Center for HIV, Viral Hepatitis, STD and TB Prevention at the CDC under cooperative agreements U46/217724, U46/417719, U46/417735, U46/517715, and U46/617734.

The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

We thank all the study participants, the MIRIAD site investigators and the many people who provided critical input into protocol development, training at the sites and guidance and support throughout the duration of the study. Dr. Alan Greenberg (CDC) provided scientific guidance and support throughout the study. We especially thank Margaret Lampe, RN, MPH, Rosalind Carter, PhD, Yolanda Oliszewski, PhD, MPH, Renata Dennis, RN, MPH, Robert Maupin, MD, Mary Jo O’Sullivan, MD, Mayris Webber, DrPH, Bernard Branson, MD, Michael Lindsay, MD, MPH, Francis Lee, PhD, Pat Garcia, MD, Erin Curtin, PhD, Sivakumar Rangarajan, and Sanjyot Shinde, PhD, for their contributions to the MIRIAD study.

References

1. Connor EM, Sperling RS, Gelber R, Kislew P, Scott G, et al. (1994) Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 331:1173-1180.

2. Saaher N, Chauchoowong R, Mock PA, Bhadrakom C, Sirisawin W, et al. (1999) Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Lancet 353:773-780.

3. Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, et al. (2002) Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr 29: 484-494.

4. Ioannidis JP, Abrams EJ, Ammann M, Bulterys M, Goedert JJ, et al. (2001) Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. J Infect Dis 183: 539-545.

5. Birkhead GS, Pulver WP, Warren BL, Hackel S, Rodriguez D, et al. (2010) Acquiring human immunodeficiency virus during pregnancy and mother-to-child transmission in New York: 2002-2006. Obstet Gynecol 115:1247-1255.

6. McKenna MT, Hu X (2007) Recent trends in the incidence and morbidity that are associated with perinatal human immunodeficiency virus infection in the United States. Am J Obstet Gynecol 197: S10-16.

7. Whitmore SK, Taylor AW, Espinoza L, Shouse RL, Lampe MA, et al. (2012) Correlates of mother-to-child transmission of HIV in the United States and Puerto Rico. Pediatrics 129: e74-81.

8. Centers for Disease Control and Prevention, Mofenson L, Taylor A, Rogers M, Campsmith M, et al. (2008) Achievements in public health. Reduction in perinatal transmission of HIV infection—United States, 1985-2005. MMWR Morb Mortal Wkly Rep 55: 592-597.

9. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, et al. (1999) 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. Lancet 354: 795-802.

10. Wade NA, Birkhead GS, Warren BL, Charbonneau TT, French PT, et al. (1998) Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med 339:1409-1414.

11. Nielsen-Saines K, Watts DH, Veloso VG, Bryson YJ, Joao EC, et al. (2012) Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med 366:2369-2379.

12. Bulterys M, Jamieson DJ, O’Sullivan MJ, Cohen MT, Maupin R, et al. (2004) Rapid HIV-1 testing during labor: a multicenter study. JAMA 292: 219-223.

13. Jamieson DJ, Cohen MH, Maupin R, Nesheim S, Danner SP, et al. (2007) Rapid human immunodeficiency virus-1 testing on labor and delivery in 17 US hospitals: the MIRIAD experience. Am J Obstet Gynecol 199: S72-82.

14. Kourtis AP, Amedee AM, Bulterys M, Danner S, Van Dyke R, et al. (2011) Various viral compartments in HIV-1-infected mothers contribute to in utero transmission of HIV-1. AIDS Res Hum Retroviruses 27: 421-427.

15. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (2015) Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.

16. Bryson YJ, Luzuniaga K, Sullivan JL, Wara DW (1992) Proposed definitions for in utero versus intrapartum transmission of HIV-1. N Engl J Med 327: 1246-1247.

17. Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, et al. (2003) Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. Lancet 362: 859-866.

18. Magder LS, Mofenson L, Paul ME, Zorrilla CD, Blattner WA, et al. (2005) Risk factors for in utero and intrapartum transmission of HIV. J Acquir Immune Defic Syndr 38:87-95. (http://www.ncbi.nlm.nih.gov/pubmed/15608531)

19. Kourtis AP, Lee FK, Abrams EJ, Jamieson DJ, Bulterys M (2006) Mother-to-child transmission of HIV-1: timing and implications for prevention. Lancet Infect Dis 6: 726-732.

20. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (2014) Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States 2014.

21. Chasela CS, Hudgens MG, Jamieson DJ, Kayira D, Hosseinipour MC, et al. (2010) Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med 362: 2271-2281.

22. Taha TE, Kumwenda NI, Gibbons A, Broadhead RL, Fiscus S, et al. (2003) Short postexposure prophylaxis in new born babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. Lancet 362: 1171-1177.

23. Taha TE, Kumwenda NI, Hoover DR, Fiscus SA, Kafululufa G, et al. (2004) Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. JAMA 292: 202-209.

24. Moodley D, Moodley J, Coovadia H, Gray G, McIntyre J, et al. (2003) A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. J Infect Dis 187: 725-735.

25. Petra Study Team (2002) Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. Lancet 359: 1178-1186.

26. Leroy V, Sakarotvitch C, Cortina-Borja M, McIntyre J, Coovadia H, et al. (2005) Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? AIDS 19: 1865-1875.

27. Garcia PM, Kalilah LA, Pitt J, Minkoff H, Quinn TC, et al. (1999) Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. N Engl J Med 341: 394-402.

28. Mofenson LM, Lambert JS, Sieleh EM, Bethel J, Meyer WA, et al. (1999) Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. N Engl J Med 341: 385-393.
29. The International Perinatal HIV Group (1999) 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 340: 977-987.

30. European Mode of Delivery Collaboration (1999) Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. Lancet 353: 1035-1039.

31. Sperling RS, Shapiro DE, Coombs RW, Todd JA, Herman SA, et al. (1996) Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 335:1621-1629.

32. American College of Obstetrics and Gynecology Committee on Obstetric Practice (2008) ACOG Committee Opinion No. 418: Prenatal and perinatal human immunodeficiency virus testing: expanded recommendations. Obstet Gynecol 112: 739-742.

33. Nesheim S, Jamieson DJ, Danner SP, Maupin R, O'Sullivan MJ, et al. (2007) Primary human immunodeficiency virus infection during pregnancy detected by repeat testing. Am J Obstet Gynecol 197:149.