

Prevention of Mother-to-Child HIV-1 Transmission—Why We Still Need a Preventive HIV Immunization Strategy

Lynne M. Mofenson, MD

There has been dramatic progress in identification of effective interventions to prevent mother-to-child HIV-1 transmission (PMTCT) in low-resource countries and rapid scale-up to implement these interventions in the last 5 years.^{1–5} The proportion of pregnant women tested for HIV-1 in low-resource countries has increased from 7% in 2005 to 26% in 2009, and the proportion of HIV-1–infected pregnant women receiving antiretroviral prophylaxis has increased from 15% in 2005 to 53% in 2009.^{6,7} A 24% reduction in estimated annual new infant HIV-1 infections was observed between 2005 and 2009 in the 25 low-resource countries, where approximately 91% of HIV-1–infected pregnant women reside.⁸ Joint United Nations Program on HIV/AIDS (UNAIDS) has developed a plan for global virtual elimination of mother-to-child HIV-1 transmission (MTCT), with a goal to reduce the number of new infant HIV-1 infections by 90% and MTCT to <5% between 2009 and 2015.^{8,9}

However, we remain far short of the goal of global MTCT elimination.⁸ In 2009, there remained an estimated 347,000 new infant infections in the 25 countries discussed above,⁸ with 40%–50% of these infections acquired through breastfeeding. Optimal prevention requires identification of maternal HIV-1 infection early in pregnancy with prompt initiation of antiretroviral drugs for treatment or prophylaxis,¹⁰ yet many women in low-resource countries access prenatal care late, only at delivery or do not deliver in medical settings. Provision of the infant PMTCT antiretroviral prophylaxis component remains low, with coverage increasing only slightly from 32% in 2008 to 35% in 2009.⁶ Although current World Health Organization guidelines now recommend breastfeeding for 12 months with concurrent infant or maternal antiretroviral prophylaxis,⁵ new reports suggest weaning before age 18 months is associated with elevated morbidity and mortality and that reduced risk of diarrhea-related morbidity and mortality among HIV-1–exposed uninfected children is associated with continuing breastfeeding after age 12 months even when replacement and complementary foods and counseling are provided.^{11,12} Thus, interventions to allow safe breastfeeding longer than 12 months are important to optimize infant survival. Finally, HIV-1 seroconversion rates of 3%–10% in uninfected pregnant or lactating women have been reported in HIV-1 endemic settings, which are associated with high risk of MTCT^{13–16}; it is estimated that 40% of new infant infections in Botswana are due to acute maternal infection during pregnancy or lactation.¹⁷

Although antiretroviral prophylaxis significantly reduces MTCT, effective implementation is complicated by need for prolonged drug administration and adherence, potential toxicities leading to continued monitoring requirements, potential for drug resistance, and inadequate health-care infrastructure. Additionally, even with maternal triple-drug prophylaxis, most studies demonstrate cumulative residual MTCT rates of 2%–5% at age 6 months.^{4,18–20} Thus, continued investigation of preventive immunologic interventions including maternal and/or infant passive/active immunization to reduce MTCT remains important. Although antiretroviral prophylaxis is the foundation for PMTCT, immunization strategies could provide a safe and durable adjunctive intervention to prevent transmission, particularly during breastfeeding. Immunization strategies, if found to be efficacious, have the advantage of being less reliant on patient adherence and health-care infrastructure than are drug interventions.

From the Pediatric, Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD.

The author has no funding or conflicts of interest to declare.

The conclusions and opinions expressed in this article are those of the author and do not necessarily reflect those of the National Institutes of Health or the US Department of Health and Human Services.

Correspondence to: Lynne M. Mofenson MD, Chief, Pediatric, Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Boulevard, Room 4B11, Rockville, MD 20852 (e-mail: lm65d@nih.gov).
Copyright © 2011 by Lippincott Williams & Wilkins

Immunization is successful strategy for prevention of perinatal hepatitis B virus transmission. Hepatitis B vaccine given as soon as possible after birth leads to a 70% reduction in transmission, and addition of passive immunization with hepatitis B immune globulin results in 94% protection.²¹ The ideal immune-preventive regimen for HIV-1 MTCT would combine passive immunization at birth with antibodies possessing potent and broad HIV-1 neutralization capacity and long half-life to allow the immature immune system time to respond to active HIV-1 immunization added at or sometime after birth. In combination, this platform would optimally provide durable protection against multiple daily low-dose viral exposures throughout breastfeeding.

Passive immunization experiments in nonhuman primates have demonstrated human neutralizing anti-HIV-1 polyclonal and monoclonal antibodies can protect against intravenous, vaginal, rectal, and oral virus challenge, including protection of neonatal rhesus macaques from oral challenge with simian HIV.^{22–30} There are only 2 studies on passive immunization to prevent MTCT in humans; both used polyclonal HIV-1 hyperimmune globulin products. One study, PACTG 185, was conducted in 1993–1997 in the United States among non-breastfeeding HIV-1-infected pregnant women receiving zidovudine for their own health (10% received dual combination drugs); it compared HIV-1 hyperimmune globulin, HIVIG, to immunoglobulin without HIV-1 antibody (IVIG) infused monthly during pregnancy starting at 20 weeks gestation and to the neonate at birth.³¹ The trial was inconclusive because transmission rates in both groups were lower than anticipated, 4.1% in HIVIG and 6.0% in IVIG recipients ($P = 0.36$). There was an intriguing finding that none of 9 infected HIVIG arm infants were infected in utero compared with 5 of 13 infected IVIG arm infants ($P = 0.05$), suggesting a possible biologic effect of HIVIG in reducing in utero but not intrapartum transmission. The viral inoculum may be smaller (and hence more easily prevented by neutralizing antibody) during in utero than intrapartum exposure, when there is intensive infant exposure to virus through mini-blood transfusions occurring during labor and from contact with infectious genital secretions during passage through the birth canal.

This issue of *JAIDS: Journal of Acquired Immune Deficiency Syndromes* reports on the other human trial conducted in a breastfeeding population in Kampala, Uganda, in 2004–2006.³² This study administered a single dose of HIV-1 hyperimmune globulin, HIVIGLOB, to HIV-1-infected pregnant women at 36–38 weeks gestation and to their newborns within 18 hours of birth combined with single-dose nevirapine (sdNVP) compared with sdNVP alone. Transmission rates were higher in this breastfeeding population, but similar to PACTG 185, there was no significant difference in transmission at age 6 months, 18.7% in the HIVIGLOB/sdNVP arm versus 15.0% in the sdNVP arm ($P = 0.29$). In contrast to PACTG 185, in utero infection in the HIVIGLOB/sdNVP arm was significantly higher than the sdNVP arm, 9.1% versus 4.1% respectively ($P = 0.03$). These data raise concern of possible antibody-enhanced risk of transplacental transmission with HIVIGLOB secondary to immunoglobulin Fc-receptor-mediated uptake of antibody-antigen complexes by antigen-presenting cells in the placenta.³³ However, this may be an artifact of the unusually

low in utero transmission rate in the sdNVP control arm; the HIVIGLOB/sdNVP in utero transmission rate was similar to that reported in the HIVNET 012 trial and the control sdNVP arm of the nevirapine and zidovudine trial in Malawi (in utero transmission rate, 8.1%, in both studies).^{34,35}

The products used in these studies were prepared from whole blood from multiple asymptomatic HIV-1-seropositive donors with CD4 count >400–500 cells per cubic millimeter from the United States (HIVIG) or Uganda (HIVIGLOB), fractionated into intravenous HIV-1 hyperimmune globulin and rendered noninfectious for HIV-1.^{36,37} They contained 98% monomeric IgG with high HIV-1 p24 antibody titers. Although both preparations were shown to neutralize some primary patient isolates, polyclonal preparations may not contain sufficiently high concentrations of high-affinity neutralizing antibodies with broad cross-reactivity to effectively provide sterilizing immunity. HIVIGLOB, for example, was shown to neutralize a small number of clade B, C, E, and A isolates but not 2 Ugandan clade D isolates.³⁷

A number of broadly neutralizing anti-HIV-1 monoclonal antibodies have been identified that were generated from clade B-infected individuals (ie, 2G12, 2F5, b12, and 4E10).³⁸ However, several of these monoclonals were tested against clade C primary isolates from infected South African children and 2G12, 2F5, and b12 were found to have none to only limited neutralizing activity, and hence do not seem to be relevant for passive immunization in most parts of the world where clade B viruses are rare.³⁹ Additionally, some weakly interact with membrane components such as phospholipids, raising concerns about potential autoreactivity.^{40,41}

More recently, a number of new monoclonal antibodies with broad neutralization capacity have been identified.⁴² Using high-throughput neutralization screening of activated memory B cells from a clade A-infected donor, 2 monoclonal antibodies (PG9 and P16) were identified with broad neutralizing breadth and potential, neutralizing >70% of 162 multiclade viral strains with median $IC_{50} < 1$ μ g/mL.⁴³ Two additional monoclonal antibodies, VRC01 and VRC02, were identified using molecular probes with antigenic specificity for the structurally conserved initial site of CD4 attachment to gp120 to identify sera with neutralizing antibody to the viral CD4-binding domain and isolate B cells that produce potent neutralizing antibodies to this site.^{44,45} These antibodies neutralized 91% of 190 viral strains representing all major circulating HIV-1 clades and from acute and chronic stages of HIV-1 infection, with geometric mean IC_{50} 0.33 μ g/mL.⁴⁵ Additionally, VRC01 does not display significant human antigen reactivity.^{44,46} Combination of these new and more potent antibodies that target complementary sites on the HIV-1 spike protein may be needed to provide maximal passive immunity against globally diverse isolates of HIV-1.^{47,48}

Identification of these potent and broadly neutralizing anti-HIV-1 monoclonal antibodies has revealed vulnerable targets on the virus that may be able to be exploited not only for passive protection from infection but also for vaccine immunogen design.^{42,49} Nonhuman primate experiments with intramuscular administration of attenuated pox virus-based simian immunodeficiency virus (SIV) vaccines [ALVAC-SIV and

modified vaccine virus Ankara-SIV)] to newborn macaques have shown partial protection against oral challenge and prolonged survival in infants who became infected⁵⁰; oral administration of a recombinant replication-attenuated vesicular stomatitis virus expressing multiple SIV genes followed by an intramuscular boost with modified vaccine virus Ankara-SIV was immunogenic but did not protect neonatal macaques from oral challenge.^{51,52} In humans, the Thailand RV114 HIV-1 vaccine trial (ALVAC-HIV vCP1521 plus booster recombinant glycoprotein 120 AIDSVAZ B/E subunit vaccines) showed the vaccine regimen modestly reduced the risk of transmission (primarily heterosexual) by 31%, providing proof of principle that protection may be possible from an HIV-1 vaccine.⁵³ Clinical trials enrolling HIV-1–exposed infants have been conducted evaluating multiple candidate HIV-1 vaccines, including 3 different recombinant envelope subunit and canarypox vaccines, using a variety of doses, immunization schedules, and product combinations.^{54–60} These trials demonstrate the feasibility and safety of such studies and the ability of neonates to mount both cell-mediated and antibody responses to HIV-1 vaccines despite the presence of potentially attenuating maternal antibody.⁶⁰

Advantages of conducting passive and active HIV-1 immunization trials in the neonatal population include clear potential benefit; even with current more potent antiretroviral prophylaxis regimens, there remains a residual transmission risk as high as 5% at age 6–12 months in HIV-1–exposed breastfeeding infants. Furthermore, transmission rates are even higher in certain populations, such as women diagnosed with HIV-1 around the time of delivery or with acute/recent infection during pregnancy or lactation. Additionally, HIV-1 exposure timing is limited and well defined, and maternal viral quasi-species can be determined and transmitted and nontransmitted viruses evaluated to understand correlates of transmission. Immunization of infants to prevent infectious diseases is part of the established health infrastructure of most countries, making delivery of immunizations to infants easier than in adults. Finally, vaccine response primed during infancy could provide the basis for life-long HIV-1 immunity.

Although the PACTG 185 and HIVIGLOB/NVP studies did not demonstrate efficacy of polyclonal HIV-1 hyperimmune globulin to prevent MTCT, they have demonstrated that such studies can be successfully conducted, including in low-resource settings. New monoclonal antibody candidates with broad neutralizing ability are now available and should be assessed in these populations. Important targets elucidated by these products could be exploited in the design of future immunogens. Elimination of perinatal HIV-1 infection will not be possible with antiretroviral drugs alone. Modeling has suggested that covering of $\geq 90\%$ of HIV-1–infected women with World Health Organization–recommended effective antiretroviral prophylaxis through delivery and breastfeeding, halving new HIV-1 infections among reproductive age women, eliminating unmet need for contraception, and reducing the duration of breastfeeding to 12 months will reduce MTCT risk to 8%.⁸ Although representing significant progress, this would still fall short of the goal of virtual perinatal HIV-1 infection elimination (ie, 90% reduction in new infections and MTCT rate $< 5\%$). The

development of a safe and effective active/passive HIV prophylaxis regimen to prevent MTCT should be a priority.

REFERENCES

1. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med*. 2008;359:119–129.
2. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med*. 2010;362:2282–2294.
3. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med*. 2010;362:2271–2281.
4. Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis*. 2011;113:171–180.
5. World Health Organization. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Recommendations for a Public Health Approach 2010 Version*. Geneva, Switzerland: WHO; 2010.
6. UNAIDS/UNICEF. *Children and AIDS, Fifth Stocktaking Report, 2010*. Geneva, Switzerland: UNAIDS; 2010.
7. UNAIDS. *Towards Universal Access: Scaling up Priority HIV/AIDS Interventions in the Health Sector, Progress Report 2010*. Geneva, Switzerland: UNAIDS; 2011.
8. Mahy M, Stover J, Kiragu K, et al. What will it take to achieve virtual elimination of mother-to-child transmission of HIV? An assessment of current progress and future needs. *Sex Transm Infect*. 2010;86(suppl 2):ii48–ii55.
9. UNAIDS. *Countdown to Zero: Global Plan for the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive*. Geneva, Switzerland: UNAIDS; 2011.
10. Myer L. Initiating antiretroviral therapy in pregnancy: the importance of timing. *J Acquir Immune Defic Syndr*. 2011;58:125–126.
11. Kuhn L, Sinkala M, Semrau K, et al. Elevations in mortality associated with weaning persist into the second year of life among uninfected children born to HIV-infected mothers. *Clin Infect Dis*. 2010;50:437–444.
12. Fawzy A, Arpadi S, Kankasa c, et al. Early weaning increases diarrhea morbidity and mortality among uninfected children born to HIV-infected mothers in Zambia. *J Infect Dis*. 2011;203:1222–1230.
13. Moodley D, Esterhuizen TM, Pather T, et al. High HIV incidence during pregnancy: compelling reason for repeat HIV testing. *AIDS*. 2009;23:1255–1259.
14. Humphrey J, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ*. 2010;341. c6580soi:10.1136/bmj.c6580.
15. Kieffer MP, Nhlabatsi B, Mahdi M, et al. Improved detection of incident HIV infection and uptake of PMTCT services in labor and delivery in high HIV prevalence setting. *J Acquir Immune Defic Syndr*. 2011;57:E85–E91.
16. Moodley D, Esterhuizen T, Reddy L, et al. Incident HIV infection in pregnant and lactating women and its effect on mother to child transmission in South Africa. *J Infect Dis*. 2011;203:1231–1234.
17. Lockman S, Creek T. Acute maternal HIV infection during pregnancy and breast-feeding: substantial risk to infants. *J Infect Dis*. 2009;200:667–669.
18. Thomas TK, Masaba R, Borkowf CB, et al. Triple antiretroviral prophylaxis to prevent mother to child HIV transmission through breastfeeding – the Kisumu Breastfeeding Study, Kenya: a clinical trial. *PLoS Med*. 2011;8:e1001015.
19. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the MITRA Plus Study. *J Acquir Immune Defic Syndr*. 2009;52:406–416.
20. Marazzi MC, Liotta G, Nielsen-Saines K, et al. Extended antenatal antiretroviral use correlates with improved infant outcomes throughout the first year of life. *AIDS*. 2010;24:2819–2826.

21. Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet*. 1983;2:1099–1102.
22. Emini EA, Schleif WA, Nunberg JH, et al. Prevention of HIV-1 infection in chimpanzees by gp120 V3 domain-specific monoclonal antibody. *Nature*. 1992;355:728–730.
23. Van Rompay KK, Berardi CJ, Dillard-Telm S, et al. Passive immunization of newborn rhesus macaques prevents oral simian immunodeficiency virus infection. *J Infect Dis*. 1998;177:1247–1259.
24. Mascola JR, Lewis MG, Stiegler G, et al. Protection of macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies. *J Virol*. 1999;73:4009–4018.
25. Baba TW, Liska V, Hofmann-Lehmann R, et al. Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection. *Nat Med*. 2000;6:200–206.
26. Hofmann-Lehmann R, Vlasak J, Rasmussen RA, et al. Postnatal passive immunization of neonatal macaques with triple combination of human monoclonal antibodies against oral simian-human immunodeficiency virus challenge. *J Virol*. 2001;75:7470–7480.
27. Rupprecht RM, Ferrantelli F, Kitabwalla M, et al. Antibody protection: passive immunization of neonates against oral AIDS virus challenge. *Vaccine*. 2003;21:3370–3373.
28. Ferrantelli F, Rasmussen RA, Buckley KA, et al. Complete protection of neonatal rhesus macaques against oral exposure to pathogenic simian-human immunodeficiency virus by human anti-HIV monoclonal antibodies. *J Infect Dis*. 2004;189:2167–2173.
29. Ferrantelli F, Buckley KA, Rasmussen RA, et al. Time dependence of protective post-exposure prophylaxis with human monoclonal antibodies against pathogenic SHIV challenge in newborn macaques. *Virology*. 2007;358:69–78.
30. Hessel AJ, Poignard P, Hunter M, et al. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. *Nat Med*. 2009;15:951–954.
31. Stiehler ER, Lambert JS, Mofenson LM, et al. Efficacy of zidovudine and human immunodeficiency virus (HIV) hyperimmune immunoglobulin for reducing perinatal HIV transmission from HIV-infected women with advanced disease: results of Pediatric AIDS Clinical Trials Group Protocol 185. *J Infect Dis*. 1999;179:567–575.
32. Onyango-Makumbi C, Omer SB, Mubiru M, et al. Safety and efficacy of HIV hyperimmune globulin for prevention of mother-to-child HIV transmission in HIV-1-infected pregnant women and their infants in Kampala, Uganda (HIVIGLOB/NVP Study). *J Acquir Immune Defic Syndr*. 2011;58:399–407.
33. Beck Z, Prohászka Z, Füst G. Traitors of the immune system-enhancing antibodies in HIV infection: their possible implication in HIV vaccine development. *Vaccine*. 2008;26:3078–3085.
34. Guay LA, Musoke P, Fleming T, et al. 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*. 1999;354:795–802.
35. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA*. 2004;292:202–209.
36. Lambert J, Mofenson LM, Fletcher CV, et al. Safety and pharmacokinetics of hyperimmune anti-human immunodeficiency virus (HIV) immunoglobulin administered to HIV-infected pregnant women and their newborns. Pediatric AIDS Clinical Trials Group Protocol 185 Pharmacokinetic Study Group. *J Infect Dis*. 1997;175:283–291.
37. Guay LA, Mosoke P, Hom DL, et al. Phase I/II trial of HIV-1 hyperimmune globulin for the prevention of HIV-1 vertical transmission in Uganda. *AIDS*. 2002;16:1391–1400.
38. Gorny MK, Zolla-Pazner S. Immunoprophylaxis against mother-to-child transmission of HIV-1. *PLoS Med*. 2006;3:e259–e260.
39. Gray ES, Meyers T, Gray G, et al. Insensitivity of paediatric HIV-1 subtype C viruses to broadly neutralizing monoclonal antibodies raised against subtype B. *PLoS Med*. 2006;3:e255.
40. Haynes BF, Fleming J, St Clair WE, et al. Cardiophilic polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science*. 2005;308:1906–1908.
41. Singh H, Henry KA, Wu SS, et al. Reactivity profiles of broadly neutralizing anti-HIV-1 antibodies are distinct from those of pathogenic autoantibodies. *AIDS*. 2011;25:1247–1257.
42. Burton DR, Weiss RA. A boost for HIV vaccine design. *Science*. 2010;329:770–772.
43. Walker LM, Phogat SK, Chan-Hui PY, et al. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. *Science*. 2009;326:285–289.
44. Zhou T, Georgiev I, Wu X, et al. Structural basis for the broad and potent neutralization of HIV-1 by antibody VRC01. *Science*. 2010;329:811–817.
45. Wu Z, Yang ZY, Li Y, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Science*. 2010;329:856–861.
46. Li Y, O'Dell S, Walker LM, et al. Mechanism of neutralization by the broadly neutralizing HIV-1 monoclonal antibody VRC01. *J Virol*. 2011;85:8954–8967.
47. Koff WC, Berkley SF. The renaissance in HIV vaccine development—future directions. *N Engl J Med*. 2010;363:e7.
48. Euler Z, Bunnik EM, Burger JA, et al. Activity of broadly neutralizing antibodies, including PG9, PG16 and VRC01, against recently transmitted subtype B HIV-1 variants from early and late in the epidemic. *J Virol*. 2011;85:7236–7245.
49. Walker LM, Burton DR. Rational antibody-based HIV-1 vaccine design: current approaches and future directions. *Curr Opin Immunol*. 2010;22:358–366.
50. Van Rompay KKA, Abel K, Lawson JR, et al. Attenuated pox-virus based SIV vaccines given in infancy partially protect infant and juvenile macaques against repeated oral challenge with virulent SIV. *J Acquir Immune Defic Syndr*. 2005;38:124–134.
51. Van Rompay KKA, Abel K, Earl P, et al. Immunogenicity of viral vector, prime-boost SIV vaccine regimens in infant rhesus macaques: attenuated vesicular stomatitis virus (VSV) and modified vaccinia Ankara (MVA) recombinant SIV vaccines compared to live-attenuated SIV. *Vaccine*. 2010;28:1481–1492.
52. Marthas ML, Van Rompay KKA, Abbott Z, et al. Partial efficacy of a VSV-SIV/MVA-SIV vaccine regimen against oral SIV challenge in infant macaques. *Vaccine*. 2011;29:3124–3137.
53. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 2009;361:2209–2220.
54. Jones NG, Ssewanyana I, Kintu K, et al. Immunogenicity of ALVAC-HIV vCP1521 in infants born to HIV-1-infected women in Uganda (HPTN 027). *AIDS Res Hum Retroviruses*. 2010;26:A-17 Abstract OA06.05.
55. Borkowsky W, Wara D, Fenton T, et al. Lymphoproliferative responses to recombinant HIV-1 envelope antigens in neonates and infants receiving gp120 vaccine. *J Infect Dis*. 2000;181:890–896.
56. McFarland EJ, Borkowsky W, Fenton T, et al. Human immunodeficiency virus type 1 (HIV-1) gp-120 specific antibodies in neonates receiving and HIV-1 recombinant gp 120 vaccine. *J Infect Dis*. 2001;184:1331–1335.
57. Cunningham CK, Wara DW, Kang M, et al. Safety of 2 recombinant human immunodeficiency virus type 1 (HIV-1) envelope vaccines in neonates born to HIV-1-infected women. *Clin Infect Dis*. 2001;32:801–807.
58. Johnson DC, McFarland EJ, Muresan P, et al. Safety and immunogenicity of an HIV-1 recombinant canarypox vaccine in newborns and infants of HIV-1-infected women. *J Infect Dis*. 2005;192:2129–2133.
59. McFarland EJ, Johnson DC, Muresan P, et al. HIV-1 vaccine induced immune responses in newborns of HIV-1 infected mothers. *AIDS*. 2006;20:1481–1489.
60. Cunningham CK, McFarland E. Vaccines for prevention of mother-to-child transmission of HIV. *Curr Opin HIV AIDS*. 2008;3:151–154.