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Feasibility and Safety of ALVAC-HIV vCP1521 Vaccine in HIV-exposed Infants in Uganda: Results from the First HIV Vaccine Trial in Infants in Africa

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Abstract

Background—The development of a safe and effective vaccine against human immunodeficiency virus type 1 (HIV-1) for prevention mother-to-child transmission of HIV would significantly advance the goal of eliminating HIV infection in children. Safety and feasibility results from Phase I, randomized, double blind, placebo-controlled trial of ALVAC-HIV vCP1521 in infants born to HIV-1-infected women in Uganda are reported.

Methods—HIV exposed infants were enrolled at birth and randomized (4:1) to receive vaccine or saline placebo intramuscular injections at birth, 4, 8 and 12 weeks of age. Vaccine reactogenicity was assessed at vaccination, and days 1 and 2 post-vaccination. Infants were followed until 24 months of age. HIV infection status was determined by HIV DNA PCR.

Findings—From October 2006 to May 2007, 60 infants (48 vaccine, 12 placebo) were enrolled with 98% retention at 24 months. One infant was withdrawn, but there were no missed visits or vaccinations among the 59 infants retained. Immune responses elicited by Diptheria, Polio, Hepatitis B and Heamophilus influenzae type B and measles vaccination were similar in the two

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Meetings/conferences at which parts of the data were presented:

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arms. The vaccine was well tolerated with no severe or life-threatening reactogenicity events. Adverse events were equally distributed across both study arms. Four infants were diagnosed as HIV infected [3 at birth (2 vaccine, 1 placebo) and one in vaccine arm at 2 weeks of age].

Interpretation—The ALVAC-HIV vCP1521 vaccination was feasible and safe in infants born to HIV-infected women in Uganda. The conduct of high quality infant HIV vaccine trials is achievable in Africa.

Keywords

HIV vaccine; ALVAC; infants; Africa; breast milk transmission

Introduction

In 2011, an estimated 330,000 children acquired human immunodeficiency virus (HIV) infection through mother-to-child transmission (MTCT).[1] Breastfeeding carries an HIV transmission risk around 15% when continued into the second year of life, accounting for as much as 42% of the overall risk of MTCT of HIV.[2,3] However, in most developing countries, promotion of breastfeeding has been central to reducing infant mortality by providing optimal nutrition and protection against common childhood diseases.[4-6]

Prevention of postnatal pediatric HIV infection is now possible through the extended use of either maternal triple antiretroviral drugs (ARV) or ARV prophylaxis to infants during breastfeeding.[7-12] In 2010, the World Health Organization (WHO) revised HIV prevention of mother to child transmission (PMTCT) and infant feeding recommendations for settings with high infant mortality to encourage HIV-infected women to continue to breastfeed for at least 12 months and receive either infant or maternal ARV prophylaxis to minimize HIV transmission and maximize infant survival.[1,13] However, translating the results of those trials into practice in the field faces considerable challenges.[14] These include limited coverage of adequate comprehensive PMTCT services, poor postnatal follow-up, lack of identification of HIV exposure in infants, cost, supply chain issues, adherence, and weak linkages to HIV care and treatment programs.[13-15] Therefore, identification of a safe and effective HIV vaccine that could be administered to infants along with routine immunizations remains an important goal in the efforts to eliminate HIV infection in children.The study of HIV vaccines in HIV-exposed infants also has the potential to advance the global HIV vaccine research agenda and contribute to the scientific knowledge that will eventually lead to an effective HIV vaccine.

Recombinant canarypox vectored ALVAC-HIV vaccine products have a long history of use in studies with large numbers of adults in various countries and a small number of infants in the US with a good safety profile.[16-21] In 2009, four doses of the ALVAC-HIV vCP1521 vaccine plus two booster doses of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E) showed a preventive efficacy of 31·2% in a modified intent to treat analysis among Thai adult vaccine recipients.[22] This study builds on the previous experience of several clinical trials evaluating different candidate HIV vaccines in infants, mostly conducted in the United States.[16,23-25] These include studies of two different ALVAC-HIV vaccine products and three recombinant envelope subunit vaccines using a variety of doses, immunization schedules, and combinations of products. Pediatric AIDS Clinical Trials Group (PACTG) 230 evaluated the safety and immunogenicity of the Chiron rgp120 (SF-2 strain) with MF59 adjuvant or the VaxGen monovalent rgp120 (MNstrain) adsorbed into alum.[24] PACTG 326 studied the safety and immunogenicity of two different canarypox vectors (ALVAC-HIV vCP205 and vCP1452) with and without a boost with a combination of two recombinant gp120 subunit proteins derived from MN and GNE8 strains (VaxGen

AIDSVAX B/B).[23] These studies also demonstrated the feasibility of conducting HIV vaccine trials in infants, vaccine safety, and the ability of the neonatal immune system to respond to vaccination similar to responses seen in adults in non African populations.

The HPTN 027 trial evaluated the safety, tolerance and immunogenicity of the same ALVAC-HIV vCP1521 product alone in HIV-exposed Ugandan infants. The feasibility and safety of conducting this first infant HIV vaccine trial in a resource limited setting are reported.

Methods

Study Design

HPTN 027 was a phase I randomized, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of ALVAC-HIV vCP1521 among infants born to HIV-1-infected Ugandan women. Eligible infants were enrolled and randomized at birth and followed for two years. The study was conducted by the United States National Institutes of Health (NIH) funded Makerere University-Johns Hopkins University Research Collaboration (MUJHU) clinical trial site, located at Mulago National Referral Hospital in Kampala, Uganda. Study data were managed and analyzed by the Statistical Center for HIV/AIDS Research & Prevention (SCHARP) in Seattle Washington, USA.

The study was approved by the National HIV/AIDS Research Committee in Uganda, the Johns Hopkins Medicine Institutional Review Board, Uganda National Council of Science and Technology and the Makerere-Johns Hopkins Institutional Biosafety Committee and as per Helsinski declaration of 1975 as revised in 2000. Import approval for the study products was provided by the Uganda National Drug Authority. This study is registered with ClinicalTrials.gov, identifier NCT00098163.

Preparation of the Research Site and Community

This was the first study testing an HIV vaccine among HIV exposed infants in Africa. A 12-member Community Advisory Board (CAB) comprised of religious leaders, a former research participant, political leaders, and youth leaders was formed and educated about HIV vaccine trials and HIV infection. The CAB assisted the study team with development of participant education materials, consent forms, and community outreach activities. The study team held interactive sensitization workshops regarding HIV vaccines, which included disposing of fears and myths about vaccine trials. Workshops were held with the Ministry of Health, local scientists, media, other health policy personnel, and hospital health care workers.

Study Population

Study infants were born to HIV-infected pregnant Ugandan women that provided written consent for screening in their third trimester. Inclusion criteria included: age ≥18 years, confirmed HIV infection, CD4 cell count > 500 cells/μL, willingness to visited at home, and intent to deliver at Mulago Hospital. Women who met these criteria received information and counseling about the requirements for infant participation and those willing to continue provided a second written informed consent for screening and enrollment of their infant.

After delivery, maternal consent for the infant's participation in the study was verbally re-confirmed and the infant's eligibility for enrollment was assessed. Infant inclusion criteria included: age ≤3 days, birth weight ≥2,000 g, hemoglobin ≥12·0 g/dL, platelet count ≥ 100,000 cells/mm^3, absolute neutrophil count ≥1,500 cells/mm^3, creatinine ≤1·3 mg/dL, and alanine aminotransferase (ALT) ≤171 U/L. Infants with known HIV infection prior to

vaccination or serious illnesses or medical conditions that would interfere with ability to complete study requirements were excluded. A specimen for HIV testing had to be drawn but infants could be enrolled and vaccinated prior to the results when not yet available.

All study women and infants received the Mulago Hospital standard PMTCT regimens (single dose nevirapine and/or AZT) according to Uganda MOH guidelines, which were consistent with World Health Organization (WHO) 2006 recommendations. Children received routine immunization with BCG and polio at birth, polio and tetravalent Diptheria, Polio, Hepatitis B and Heamophilus influenzae type B at 6, 10 and 14 weeks; and measles at 26 and 52 weeks

Study Procedures

Randomization and Masking

Enrolled infants were randomized 4:1 to ALVAC vaccine or placebo using block randomization. Both the vaccine and placebo products were packaged in identical, sequentially numbered individual kits, each of which contained a complete set of doses required for a single infant. After confirmation of eligibility, the next sequentially numbered kit was assigned to an infant and associated with his/her unique study identification number. Assignment of the kit was the effective point of randomization. Study clinicians and participants were blinded to the identity of study product. To avoid unblinding due to potential differences in appearance between vaccine and placebo products, the syringe had an overlay and the pharmacists and nurses responsible for dispensing and administering the study product did not participate in clinical assessment of participants.

Study products and administration

The ALVAC-HIV vCP1521 is a preparation of a live attenuated recombinant canarypox virus expressing gene products from the HIV-1 clade E *env* and clade B *gag* and clade B *protease* coding sequences. ALVAC-HIV vCP1521 was formulated as a sterile, lyophilized product in single-dose vials that was reconstituted with sterile sodium chloride solution (0·4%). Each vial contained $\geq 10^{6\cdot0} CCID_{50}$ /mL of ALVAC-HIV vCP1521. Sodium Chloride Injection USP, 0·9% was used as the placebo control. One milliliter of study product was administered intramuscularly into the right thigh muscle.

The study products were administered at birth (0-3 days after birth) and at weeks 4, 8 and 12. Each infant was observed in the clinic for at least 1 hour following vaccination and then examined in the clinic or at home for the next two days for assessment of local and systemic reactogenicity events (REs). REs were graded according to the study's Supplemental Toxicity Table for Grading Reactogenicity Occurring within Seven Days of Study Vaccination, specific to infant reactogenicities.[26] Vaccination was withheld in infants with fever > 38°C, abnormal vital signs or clinical symptoms that could mask assessment of vaccine reaction, unresolved Grade 3 adverse events, serious intercurrent infection, or a positive HIV DNA polymerase chain reaction (PCR) test. Vaccination was permanently discontinued in infants with any Grade 4 adverse event, known or suspected disease of the immune system, active tuberculosis, measles, severe malnutrition, immunosuppressive therapy, confirmed HIV infection and confirmed CD4 cell percent <25%. Vaccinations had to be administered within 7 days of the scheduled date, otherwise subsequent vaccinations were permanently discontinued. The number of study vaccinations received did not affect a child's 24 months follow up period.

Schedule of evaluations

Infants were evaluated in the study clinic every two weeks from birth to 14 weeks of age, at 5 and 6 months and then every three months until 24 months of age. Specimens were obtained for laboratory safety evaluation, HIV status determination, or immunologic evaluation at weeks 0, 2, 6, 10, 14 and months 6, 12, 18, and 24 months. Antibody titers to routine immunizations were measured at 6 months (polio, tetanus, hepatitis B and haemophilus influenza type B) and measles at 18 months.

Safety Monitoring and Routine Antibody Tests

At each study visit, children were evaluated for the presence of any clinical or laboratory adverse events (AE), the severity of which were graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004.[27] The study database included information on all AEs through the first 6 months of life; thereafter, only serious adverse event (SAE) data were collected. Safety monitoring was multi-tiered. The first-level site review was performed by the site clinicians and principal investigator. A physician reviewed and reported all serious and expedited adverse events. All AEs ≥Grade 3 were reviewed in real time by a Protocol Chair. Second tier review of AEs was conducted by safety specialists at the data centre and tertiary reviews were conducted by a Protocol Safety Review Team (PSRT) and an external study monitoring committee (SMC). Protocol specified safety pauses were triggered by a potentially related death or multiple similar Grade 3 or higher AE and required review by the PSRT prior to continuing randomization or vaccination.

Methods for measuring immune response to routine vaccination included: Poliovirus Antibody Microneutralization test with neutralizing serum antibodies titers (immunity titer ≥ 1:8), quantitative Hepatitis B surface antibody by chemiluminescence immunoassay (immunity ≥10 mIU), and Enzyme Linked Immunosorbant Assays (ELISA) for tetanus antitoxoid antibodies (immunity ≥0.50 IU/ml), HIB antibodies (immunity ≥1.0 mcg/ml) and measles antibody (categorized as negative, positive, or equivocal).

Definition of infant HIV infection status

Infant HIV infection status was determined using the Roche AMPLICOR® HIV-1 Version 1.5 DNA PCR assay (Roche Diagnostics Corporation, Indiana, USA) with quality monitored through laboratory participation in the DAIDS Virology Quality Assurance Program. HIV DNA testing was performed at birth, weeks 2, 6, 10, 14, and months 6, 12, 18 and 24. Infants were considered HIV infected if they had two positive PCR results on two separate specimens. Rapid HIV testing, followed by confirmatory Western blot testing when necessary, was performed at 18 and 24 months. In the case of a positive antibody test in the absence of documented HIV infection by HIV PCR, antibody testing would be repeated every six months until resolution.

Statistical Analysis

The study target required 50 fully evaluable infants to receive all four scheduled study vaccinations and be HIV uninfected at the 12-month time point. An additional infant was randomized for each infant who was not fully evaluable, up to the prior accepted 10 additional infants. This sample size provides 80% power to detect a ≥57% difference in toxicity rates between the treatment and placebo groups, with alpha level at 0·05. The primary safety endpoint was assessed by comparing overall rates of Grade 3 or higher AE attributable to receipt of the study product between the vaccine and placebo groups. The rates of all AEs, including those considered mild and moderate, were also compared. Given the small sample size, Fisher's exact test and Wilcoxon rank sum test were used for the

comparisons. Frequencies of severe AEs and REs were tabulated. Time to cessation of breastfeeding was analyzed by Kaplan-Meier survival analysis. Both arms produced a known antibody threshold consistent with clinical protection as illustrated by the vertical lines in Figure 2.

Results

The strict eligibility criteria and intensive study schedule of evaluations required for this Phase I safety trial in infants led to a large number of women being assessed for eligibility throughout the multiple stage enrollment process (Figure 1). Among the 222 women who provided informed consent for screening, over half were excluded due to having CD4 cell counts ≤500 cells/μL.

Sixty infants were enrolled in the study and randomized (48 vaccine, 12 placebo) from October 2006 to May 2007 (Figure 1). Characteristics of mothers and infants were similar in both groups except that mothers in the vaccine group were younger (25 vs. 31 years) (Table 1). The median duration of breastfeeding was 155 days for infants in the placebo arm [95% CI: 0 - 638] versus 181 days [95% CI: 154 - 257] for infants in the vaccine arm. One infant was withdrawn from the study before the 2 week visit by the mother for social reasons. All other infants attended all the scheduled study visits and all protocol related evaluations were conducted, including HIV testing by DNA PCR. Retention at two years of age was 98%.

All 60 infants received at least one study vaccination. Forty seven infants (38 vaccine, 9 placebo) received all four study vaccinations and were HIV-uninfected at the 12 month visit. Thirteen infants were discontinued from receiving the full vaccine schedule due to: CD4 cell count < 25% (2 vaccine, 1 placebo); Grade 4 events (4 vaccine); death (1 vaccine); withdrawal of informed consent (1 placebo) and HIV infection (3 vaccine, 1 placebo). Three of the four infants diagnosed with HIV infection during the study received a single study vaccination prior to the availability of the DNA PCR tests results that indicated that they were HIV infected at birth. One infant with a negative PCR at birth received one ALVAC vaccination and then was found to be HIV infected at two weeks of age.

Most reactogenicity events were mild and there were no significant differences between the two study arms (Table 2). There were no severe REs and all events resolved spontaneously within 3 days after vaccination.

No safety pauses were required during the trial. Fifty-nine infants experienced a total of 711 adverse events during study follow-up. Ninety-eight percent of AEs were assessed as not related (74%) or probably not related (24%) to study product. Most AEs (90%) were of mild (62%) or moderate (28%) severity, and included mainly infections or abnormal laboratory results.

There was one Grade 3 asymptomatic elevated liver enzyme that was possibly related to receipt of the vaccine. The most common laboratory abnormalities included decreased neutrophil count, decreased hemoglobin and increased serum bilirubin levels in asymptomatic infants. The frequency of these events was comparable in the two study arms (data not shown).

Six infants (50%) in the placebo arm and 27 infants (56%) in the vaccine arm experienced at least one serious adverse event (p = 0·75) (Table 3). There were a total of 58 SAEs that occurred in these infants; 51 in the vaccine arm and 7 in the placebo arm. The majority of SAEs were common childhood illnesses in developing countries. There were three infant deaths, all judged to be unrelated to study products. The causes of death were: death at home from pneumonia-like symptoms as reported by the infant's caretaker (vaccine arm), cor

pulmonale secondary to congenital heart disease complicated by pneumonia (vaccine arm), and gastroenteritis with electrolyte imbalance (placebo arm).

There were no clinically significant differences found in antibody titers to routine immunizations between the vaccine and placebo recipients for polio, tetanus, hepatitis B, or hemophilus influenza B at 6 months (Figure 2) or measles at 18 months.

Discussion

HPTN 027 is the first HIV vaccine trial conducted in HIV-exposed infants in Africa. This phase I clinical trial demonstrated that high quality HIV vaccine trials in infants are possible in settings with limited resources, where the majority of the world's perinatal HIV transmission occurs. We also found similar and high antibody responses to routine childhood vaccines among infants given the ALVAC-HIV vCP1521 vaccine compared to placebo. Although the numbers are small, this provides some reassurance that the HIV vaccine did not interfere with immune responses to routine immunizations.

The results of the HIV vaccine trial in Thailand that used the same ALVAC-HIV vCP1521 vaccine with the addition of AIDSVAX B/E boosting suggest that vaccination against acquisition of HIV is possible.[22] These and other studies in infants must remain high on the HIV vaccine research agenda both for the unique opportunity that studies of mother to child transmission provide and the critical need for an effective vaccine in this population.[15,28]

HIV-infected Ugandan women were willing to enroll their infants in an HIV vaccine trial for two years, despite the intensive follow-up required. The study achieved a high level of participant retention and visit adherence. Proactive, intensive, and ongoing HIV vaccine and study education was provided to eligible and enrolled participants through a multi-stage informed consent process and throughout the study period. Large numbers of HIV infected women were assessed for eligibility compared to the small number of infants enrolled in the study. However, many of the exclusion criteria, particularly women with CD4 cell counts < 500 cells/μL and the intensive follow-up required for a safety study would not be necessary for future large efficacy studies.

The ALVAC-HIV vCP1521 vaccine was safe and well tolerated in HIV-exposed infants when given monthly vaccinations in the first three months of life. Most reactions to the vaccine were mild to moderate and were consistent with the findings of previous studies of similar ALVAC products in infants and adults[16-21] and those seen with other immunizations. The majority of SAEs and laboratory abnormalities were consistent with background illnesses common in children and variations in normal laboratory values in African setting rather than those from populations used in the DAIDS Adverse Event grading tables.[27,29]

While this study was not an efficacy trial, it is intriguing to note that no infants became infected after the peripartum period, despite the absence of ARV use during the postpartum period for prevention of breast milk transmission at the time and a high rate of breastfeeding in the study population. A study done in a similar population found HIV post partum transmission rates of 3.3 % between 6 weeks and 12 months of age in infants born to women with CD4 cell counts ≥350 cells/μL while in this study there was no HIV transmission between 2 weeks and 24 months of age.[30] However, this may be due to the small study sample size.

Investigations of the immunologic responses to the vaccine are underway and should also provide insight into the generation of the immune responses following vaccination. Follow-up studies with larger numbers of infants will allow evaluation of vaccine efficacy in this

population and collection of additional specimens to evaluate any potential correlates of protection that may be found as scientists investigate immunologic responses in the adult study in Thailand. This phase I study of the ALVAC-HIV vCP1521 in infants was planned as the first step in evaluating the safety of the ALVAC product in African infants. This coupled with the high levels of transplacentally acquired maternal HIV antibodies present in these infants born to HIV infected mothers lead to the study of ALVAC alone in this trial. The expectation was that if this trial was successful, subsequent trials would be conducted with the same or next generation ALVAC with or without a protein boost depending on the outcome of the Thai trial.

There is a significant public health need for an HIV vaccine to protect infants from infection during breastfeeding. Even with the current WHO recommendations for ARV use for PMTCT during pregnancy and breastfeeding, the challenges of sustainability and implementation of increasingly more complex ARV prophylactic regimens for long periods of time postpartum will likely result in ongoing MTCT among breastfed infants living in resource-limited settings. This includes transmission to HIV exposed infants whose mothers are not identified by PMTCT programs, acquire HIV infection during late pregnancy/ breastfeeding, are non-adherent to ARV for the duration of breastfeeding, or are lost to follow up after delivery[15,31,32]. Adding an effective HIV vaccine to the routine childhood immunizations given to all infants, would be a simple and cost effective strategy to reach the global health goal of virtual elimination of HIV infection in children.

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References

1. UNAIDS. UNAIDS Report on the global AIDS epidemic 2010. 2010.
2. Kourtis AP, Jamieson DJ, de Vincenzi I, et al. Prevention of human immunodeficiency virus-1 transmission to the infant through breastfeeding: new developments. American journal of obstetrics and gynecology. Sep; 2007 197(3 Suppl):S113–122. [PubMed: 17825642]
3. Coutsoudis A, Dabis F, Fawzi W, et al. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. The Journal of infectious diseases. Jun 15; 2004 189(12): 2154–2166. [PubMed: 15181561]
4. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. Feb 5; 2000 355(9202):451–455. [PubMed: 10841125]
5. Smith MM, Kuhn L. Exclusive breast-feeding: does it have the potential to reduce breast-feeding transmission of HIV-1? Nutrition reviews. Nov; 2000 58(11):333–340. [PubMed: 11140904]

6. Coutsoudis HMCaA. Problems and advances in reducing transmission of HIV-1 through breast-feeding in developing countries. AIDScience. Jul.2001 1(4) 2001.
7. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. The New England journal of medicine. Jul 10; 2008 359(2):119–129. [PubMed: 18525035]
8. Bedri A, Gudetta B, Isehak A, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. Lancet. Jul 26; 2008 372(9635):300–313. [PubMed: 18657709]
9. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. The New England journal of medicine. Jun 17; 2010 362(24):2282–2294. [PubMed: 20554983]
10. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. The New England journal of medicine. Jun 17; 2010 362(24):2271–2281. [PubMed: 20554982]
11. 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 medicine. Mar.2011 8(3):e1001015. [PubMed: 21468300]
12. Kesho Bora Study Group dV, I. 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. The Lancet infectious diseases. Mar; 2011 11(3):171–180. [PubMed: 21237718]
13. WHO. Rapid advice: revised WHO principles and recommendations on infant feeding in the context of HIV – November 2009.. WHO Library Cataloguing-in-Publication Data. Nov. 2009 2009
14. Guay L. Decreasing HIV transmission through breastfeeding: moving from evidence to practice. J Acquir Immune Defic Syndr. Aug 1; 2011 57(4):258–260. [PubMed: 21602693]
15. Mofenson LM. Prevention of mother-to-child HIV-1 transmission--why we still need a preventive HIV immunization strategy. J Acquir Immune Defic Syndr. Dec 1; 2011 58(4):359–362. [PubMed: 21909031]
16. 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. The Journal of infectious diseases. Dec 15; 2005 192(12):2129–2133. [PubMed: 16288378]
17. Thongcharoen P, Suriyanon V, Paris RM, et al. A phase 1/2 comparative vaccine trial of the safety and immunogenicity of a CRF01_AE (subtype E) candidate vaccine: ALVAC-HIV (vCP1521) prime with oligomeric gp160 (92TH023/LAI-DID) or bivalent gp120 (CM235/SF2) boost. J Acquir Immune Defic Syndr. Sep 1; 2007 46(1):48–55. [PubMed: 17909315]
18. Nitayaphan S, Pitisuttithum P, Karnasuta C, et al. Safety and immunogenicity of an HIV subtype B and E prime-boost vaccine combination in HIV-negative Thai adults. The Journal of infectious diseases. Aug 15; 2004 190(4):702–706. [PubMed: 15272397]
19. Cao H, Kaleebu P, Hom D, et al. Immunogenicity of a recombinant human immunodeficiency virus (HIV)-canarypox vaccine in HIV-seronegative Ugandan volunteers: results of the HIV Network for Prevention Trials 007 Vaccine Study. The Journal of infectious diseases. Mar 15; 2003 187(6):887–895. [PubMed: 12660934]
20. Gupta K, Hudgens M, Corey L, et al. Safety and immunogenicity of a high-titered canarypox vaccine in combination with rgp120 in a diverse population of HIV-1-uninfected adults: AIDS Vaccine Evaluation Group Protocol 022A. J Acquir Immune Defic Syndr. Mar 1; 2002 29(3):254–261. [PubMed: 11873074]
21. Salmon-Ceron D, Excler JL, Finkielsztejn L, et al. Safety and immunogenicity of a live recombinant canarypox virus expressing HIV type 1 gp120 MN MN tm/gag/protease LAI (ALVAC-HIV, vCP205) followed by a p24E-V3 MN synthetic peptide (CLTB-36) administered in healthy volunteers at low risk for HIV infection. AGIS Group and L'Agence Nationale de Recherches sur Le Sida. AIDS research and human retroviruses. May 1; 1999 15(7):633–645. [PubMed: 10331442]

22. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. The New England journal of medicine. Dec 3; 2009 361(23): 2209–2220. [PubMed: 19843557]

23. McFarland EJ, Johnson DC, Muresan P, et al. HIV-1 vaccine induced immune responses in newborns of HIV-1 infected mothers. AIDS. Jul 13; 2006 20(11):1481–1489. [PubMed: 16847402]

24. McFarland EJ, Borkowsky W, Fenton T, et al. Human immunodeficiency virus type 1 (HIV-1) gp120-specific antibodies in neonates receiving an HIV-1 recombinant gp120 vaccine. The Journal of infectious diseases. Nov 15; 2001 184(10):1331–1335. [PubMed: 11679925]

25. 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. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Mar 1; 2001 32(5):801–807. [PubMed: 11229849]

26. HPTN. Supplemental Toxicity Table for grading Reactogenicity Occuring within Seven days of Study Vaccination. 2004.

27. DAIDS. Division of AIDS table for grading the severity of adult and pediatric adverse events. Dec. 2004 1 2004.

28. Cunningham CK, McFarland E. Vaccines for prevention of mother-to-child transmission of HIV. Current opinion in HIV and AIDS. Mar; 2008 3(2):151–154. [PubMed: 19372958]

29. Lubega IR, Fowler MG, Musoke PM, et al. Considerations in using US-based laboratory toxicity tables to evaluate laboratory toxicities among healthy malawian and Ugandan infants. J Acquir Immune Defic Syndr. Sep; 2010 55(1):58–64. [PubMed: 20588184]

30. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. Lancet. Jan 21; 2012 379(9812):221–228. [PubMed: 22196945]

31. Ciaranello AL, Perez F, Keatinge J, et al. What will it take to eliminate pediatric HIV? Reaching WHO target rates of mother-to-child HIV transmission in Zimbabwe: a model-based analysis. PLoS medicine. Jan.2012 9(1):e1001156. [PubMed: 22253579]

32. Mirkuzie AH, Hinderaker SG, Sisay MM, Moland KM, Morkve O. Current status of medication adherence and infant follow up in the prevention of mother to child HIV transmission programme in Addis Ababa: a cohort study. Journal of the International AIDS Society. 2011; 14:50. [PubMed: 22017821]

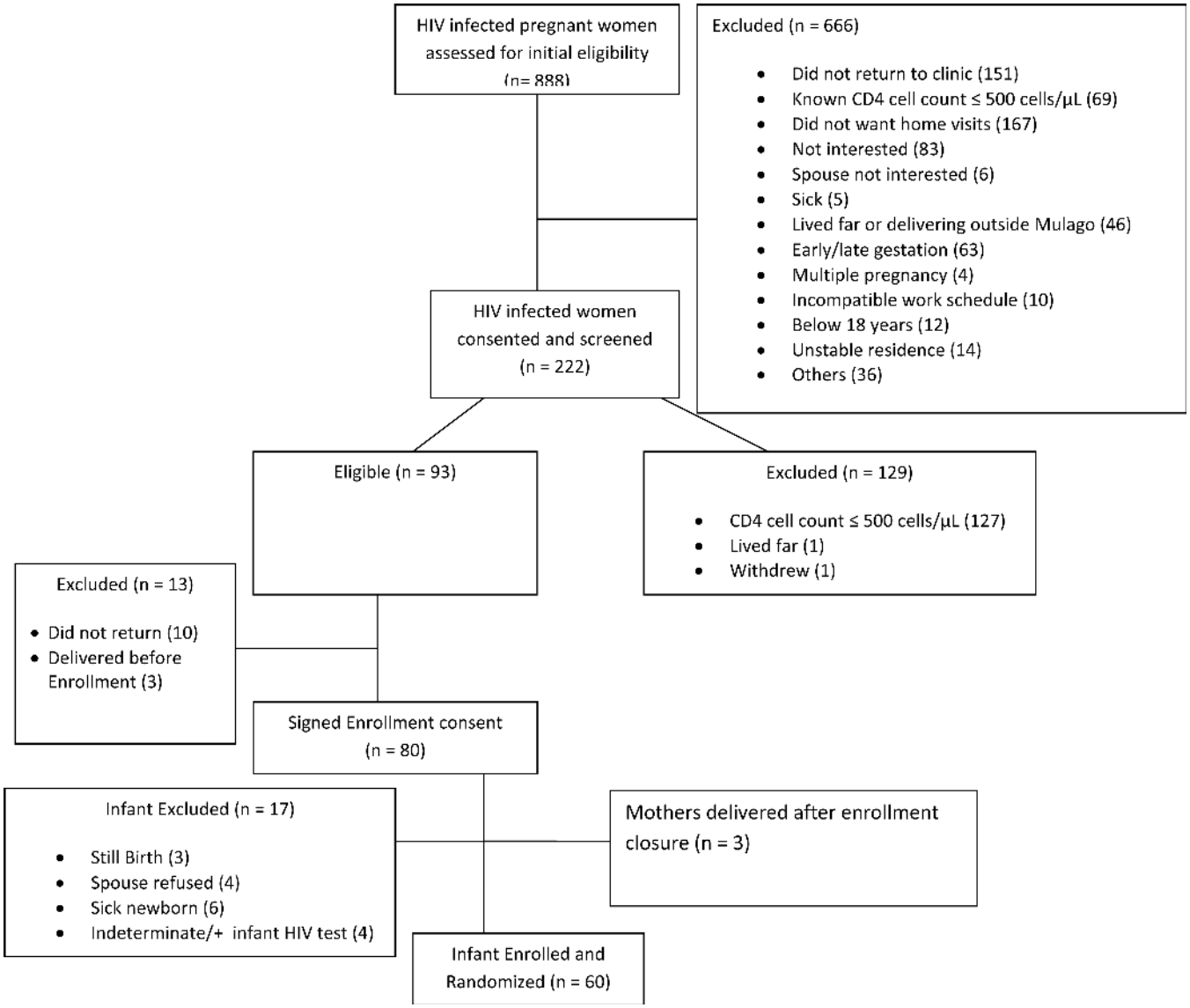

Figure 1.
HPTN 027 Trial Enrollment Profile

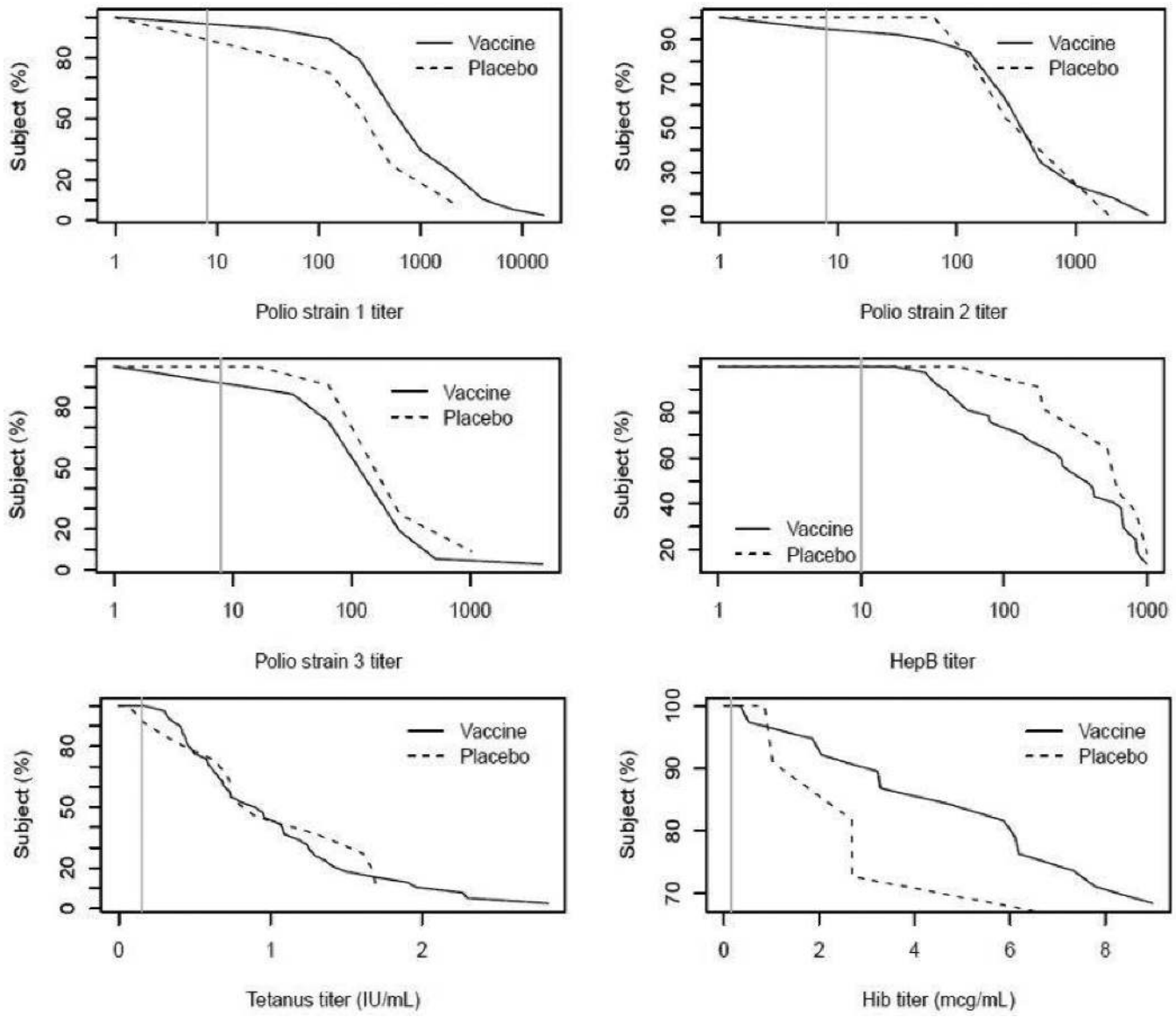

Figure 2.
Protective antibody responses to routine immunizations for all infants in the placebo arm and those that received all 4 vaccines in ALVAC arm

Table 1

Maternal and Infant characteristics

	Vaccine (N=48)	Placebo (N=12)
Age n (%)		
18-24 years	23 (48%)	2(17%)
25-30 years	18 (38%)	5 (42%)
>30 years	7 (15%)	5 (42%)
Median (IQR) [1]	25 (23, 29)	31 (25, 33)
Marital status n (%)		
Never married/not living with partner	5 (10%)	3 (25%)
Married	13 (27%)	3 (25%)
Living with partner	29 (60%)	6 (50%)
Separated	1 (2%)	0 (0%)
Education level n (%)		
No schooling	4 (8%)	0 (0%)
Primary school	27 (56%)	5 (42%)
Secondary school	15 (31%)	5 (42%)
College	2 (4%)	2 (17%)
Working outside home n (%)		
Yes	16 (33%)	3 (25%)
No	32 (67%)	9 (75%)
CD4 cell count (cells/uL)		
Median (IQR) [1]	669 (540, 776)	592 (538, 654)
HIV RNA (log_{10} scale)		
Median (IQR) [1]	3·8 (3·0, 4·2)	4·0 (3·1, 4·2)
Type of delivery n (%)		
Vaginal	40 (83%)	10 (83%)
Cesarean	8 (17%)	2 (17%)
Gender n (%)		
Male	26 (54%)	8 (67%)
Female	22 (46%)	4 (33%)
Birth weight (grams)		
Median (IQR) [1]	3100 (2840, 3425)	3150 (2730, 3300)

[1] IQR = Interquartile range

Table 2

Number of infants with local and systemic reactogenicity events within 7 days of vaccination

Reactogenicity event[1] n (%)	Vaccine (N=48)	Placebo(N=12)	p value[2]
Erythema on right thigh			0·31
None	4 (8·3%)	3 (25%)	
Grade 1 (mild)	43 (89·6%)	9 (75%)	
Grade 2 (moderate)	1(2·1%)	0 (0·0%)	
Induration on right thigh			0·23
None	18 (37·5%)	8 (66·7%)	
Grade 1	29 (60·4%)	4 (33·3%)	
Grade 2	1 (2·1%)	0 (0·0%)	
Right inguinal			1·00
Present	1 (2·1%)	0 (0·0%)	
Not present	47 (97·9%)	12 (100·0%)	
Pain			1·00
None	42 (87·5%)	11 (91·7%)	
Grade 1	5 (10·4%)	1 (8·3%)	
Grade 2	1 (2·1%)	0 (0·0%)	
Fever			0·16
None	24 (50·0%)	10 (83·3%)	
Grade 1	22 (45·8%)	2 (16·7%)	
Grade 2	2 (4·2%)	0 (0·0%)	
Irritability			0·24
None	36 (75·0%)	10 (83·3%)	
Grade 1	11 (22·9%)	1 (8·3%)	
Grade 2	1 (2·1%)	1 (8·3%)	

Note: All Vaccine injections were administered on the right thigh (routine immunizations are given in left thigh).

[1] For infants who experienced multiple occurrences of the same event with different grades at different visits, the maximum grade of the event was reported in this table.

[2] p-value from Fisher's exact test

Table 3

Number of infants with Serious Adverse Events

Serious Adverse Events (SAE)[1]	Vaccine (N=48)	Placebo (N=12)
Any SAE	27 (56·3%)	6 (50·0%)
Malaria	8 (16·7%)	1(8·3%)
Gastroenteritis	7 (14·6%)	1(8.3%)
Pneumonia	8 (16·7%)	0
Pyrexia	5 (10·4%)	1(8·3%)
Anaemia	4 (8·3%)	0
Pulmonary tuberculosis	2 (4·2%)	1(8·3%)
Bronchiolitis	1(2·1%)	2 (16·7%)
Sepsis neonatal	2 (4·2%)	0
Asphyxia	1(2·1%)	0
Diarrhoea	1(2·1%)	0
Metabolic acidosis	1(2·1%)	0
Cor pulmonale	1(2·1%)	0
Malnutrition	1(2·1%)	0
Abscess	1(2·1%)	0
Lymphadenitis	1(2·1%)	0
Urinary tract infection	1(2·1%)	0
Hepatic enzyme, increased	1(2·1%)	0
Somnolence	1(2·1%)	0
Death	2 (4·2%)	1 (8·3%)

[1] A serious adverse event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires impatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability according to ICH guidelines, regardless of relationship to study product.