Duration of Human Papilloma Virus (HPV) Type-Specific Antibody after Administration of Quadrivalent HPV Vaccine to HIV-1 Infected Children Previously Enrolled in IMPAACT P1047

A Multi-Center, International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID) and The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

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IMPAACT Complications
Scientific Committee Chair: Sharon A. Nachman, MD
Protocol Chair: Myron J. Levin, MD
NIAID Medical Officer: Edward Handelsman, MD
NICHD Medical Officer: Jennifer S. Read, MD, MS, MPH, DTM&H
Clinical Trials Specialist: Elizabeth Petzold, PhD

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All questions concerning this protocol should be sent via e-mail to actg.teamp1085@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1085@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or via fax at 1-800-418-3544 or 301-897-1701. For EAE questions, e-mail rcscsafetyoffice@tech-res.com or call 1-800-537-9979. For randomization or enrollment questions, contact the Data Management Center at 716-834-0900 or by email at sdac.random.desk@fstrf.org.

Protocol Chair

Myron J. Levin, M.D.
Pediatric Infectious Disease
University of Colorado at Denver and Health Sciences Center
Mail Stop C227; Building 401
1784 Racine Street
Aurora, CO 80045
Phone: (303) 724-2451
Fax: (303) 724-4209
E-mail: Myron.Levin@ucdenver.edu

NIAID Medical Officer

Edward Handelsman, M.D.
HIV Research Branch
NIH, NIAID, DAIDS, TRP,
Room 5107
6700-B Rockledge Drive
Bethesda, MD 20892-7624
Phone: (301) 402-3221
Fax: (301) 480-4563
E-mail: handelsmane@niaid.nih.gov

Clinical Trials Specialist

Elizabeth Petzold, Ph.D.
IMPAACT Operations Office
Social & Scientific Systems, Inc.
1009 Slater Road, Suite 120
Durham NC 27703
Phone: (919) 287-4314
Fax: (301) 628-3304
E-mail: epetzold@s-3.com
Protocol Statistician

Lin-Ye Song, Ph.D.
SDAC, HSPH
651 Huntington Avenue
Boston, MA 02115-6017
Phone: (617) 432-3867
Fax: (617) 432-2843
E-mail: song@sdac.harvard.edu

Protocol Data Manager

Barbara Nowak, B.A.
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226-1056
Phone: (716) 834-0900 X7233
Fax: (716) 834-8675
E-mail: nowak.barbara@fstrf.org

Protocol Field Representative

Nagamah Sandra Deygoo
NYU University School of Medicine
Dept of Pediatrics
Room 8W51
550 First Avenue
New York, NY 10016
Phone: (212) 263-5680
Fax: (212) 263-7806
E-mail: Sandra.deygoo@med.nyu.edu

Protocol Virologist

William A. Meyer III, Ph.D.
Technical Director
Quest Diagnostics Incorporated
Retrovirology Department
1901 Sulphur Spring Rd.
Baltimore, MD 21227-0580
Office Phone: (410) 536-1593
Fax: (410) 536-1639
E-mail: William.A.Meyer@questdiagnostics.com

Protocol Immunologist

Adriana Weinberg, M.D.
Section of Pediatric Infectious Diseases
University of Colorado at Denver and Health Sciences Center
Mail Stop 8604
12700 E. 19th Avenue, Rm 11126
Aurora, CO 80045
Phone: (303) 724-4480
Fax: (303) 724-4485
E-mail: adriana.weinberg@ucdenver.edu

Laboratory Data Coordinator

Carrie Fry, B.S.
Frontier Science and Technology Research Foundation
4033 Maple Rd
Amherst, NY 14226
Phone: (716) 834 0900 Ext. 7437
Fax: (716) 833 0655
E-mail: cfry@fstrf.org

Investigators
Anna-Barbara Moscicki, M.D.  
Department of Pediatrics  
UCSF School of Medicine  
3333 California Street, Suite 245  
San Francisco, CA 94118  
Phone: (415) 476-5139  
Fax: (415) 476-6106  
E-mail: annam@itsa.ucsf.edu

Westat Clinical Research Associate

Scott Watson, B.S., R.N.  
Westat Inc.  
1441 W. Montgomery Ave.  
Rockville, MD 20850  
Phone: (415) 494-5575  
Fax: (415) 859-9029  
E-mail: scottwatson@westat.com

Pharmaceutical Company Representative(s)

Alfred Saah, M.D.  
Merck & Co., Inc.  
PO Box 1000  
UG3CD-28  
North Wales, PA 19454-1099  
Phone: (267) 305-7557  
E-mail: alfred_saah@merck.com

Community Advisory Board  
Representative(s)

David Mburuzabudu  
Phone: +263 23 405 345  
E-mail: mburuzabudu@yahoo.co.uk
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<th>Definition</th>
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<tbody>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical Intraepithelial Neoplasia</td>
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<tr>
<td>CMI</td>
<td>Cell-Mediated Immunity</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
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<tr>
<td>DMC</td>
<td>Data Management Center</td>
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<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
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<tr>
<td>ELISPOT</td>
<td>Enzyme Linked Immunosorbent Spot Assay</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GMT</td>
<td>Geometric Mean Titers</td>
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<tr>
<td>GSK</td>
<td>Glaxo Smith Kline</td>
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<tr>
<td>HAART</td>
<td>Highly Active Anti Retroviral Therapy</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HPV</td>
<td>Human Papilloma Virus</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Group</td>
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<tr>
<td>INF-γ</td>
<td>Interferon gamma</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>NICHD</td>
<td>The Eunice Kennedy Shriver National Institute of Child Health and Human Development</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>OHRP</td>
<td>Office for Human Research Protections, DHHS</td>
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<tr>
<td>PBMC</td>
<td>Peripheral Blood Mononuclear Cell</td>
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<tr>
<td>PID</td>
<td>Patient Identifier</td>
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<tr>
<td>PPD</td>
<td>Pharmaceutical Product Development</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>QHPV</td>
<td>Quadrivalent Human Papilloma Virus vaccine</td>
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<tr>
<td>RCC</td>
<td>Regulatory Compliance Center</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>---------</td>
<td>----------------------------------</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event/Serious Adverse Experience</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>US HHS</td>
<td>United States Health and Human Services</td>
</tr>
<tr>
<td>VLP</td>
<td>Virus-like particles</td>
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<tr>
<td>VQA</td>
<td>Virology Quality Assurance</td>
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SCHEMA

DURATION OF HUMAN PAPILLOMA VIRUS (HPV) TYPE-SPECIFIC ANTIBODY AFTER ADMINISTRATION OF QUADRIVALENT HPV VACCINE TO HIV-1 INFECTED CHILDREN PREVIOUSLY ENROLLED IN IMPAACT P1047

DESIGN: This is a follow up study of children enrolled in P1047 to determine the long term immunogenicity of quadrivalent HPV (QHPV) vaccine in HIV-1 infected children.

SAMPLE SIZE: 104 children and adolescents, who were enrolled into IMPAACT P1047, and who completed the scheduled vaccine doses for their designated arm, are eligible for this study. All subjects should be between 1 and 2 years of their last HPV vaccination.

POPULATION: This will be limited to subjects who were enrolled into IMPAACT P1047 and who completed the scheduled vaccine doses for their designated arm.

STRATIFICATION: Subjects participating in P1085 will remain in the stratification groups and treatment arms to which they were assigned during their participation in P1047.

REGIMEN: No study product will be given as part of this study.

STUDY DURATION: Subjects will be on study for a maximum of 208 weeks (4 years) after completing their vaccination schedule from P1047.

OBJECTIVES:

Primary Objective

1. To determine the HPV-type specific antibody levels at 2, 3.5, and 5 years after completion of the QHPV vaccine schedule for each of the arms in P1047 and compare them to published levels of QHPV-induced antibody levels present in age-similar children.
without HIV infection at these time intervals after QHPV vaccination.

Secondary Objectives

1. To compare the decline over the study interval in HPV type-specific antibody in subjects who received four doses of QHPV (Arm A) with those who received three doses of vaccine (Arm B) in P1047.

2. To determine the magnitude of HPV-specific antibody at different times after QHPV vaccination as a function of immune status (as defined by CD4 count and CD4%) and plasma HIV viral load.

3. To determine the persistence of HPV-specific CMI at 2, 3.5, and 5 years after completion of the QHPV schedule for each of the Arms in P1047.

4. To evaluate potential associations of HIV plasma RNA, lymphocyte immunophenotypes, HPV-specific memory B cell lymphocytes and HPV-specific CMI with the decay of anti-HPV antibody titers.

Hypotheses:

1. HPV type-specific antibodies will decline in both arms after completion of the specified QHPV vaccine schedule:

   1.1 Antibody levels will remain higher at equal intervals after vaccination in those who received 4 doses compared with those who received 3 doses of the QHPV.

   1.2 Antibody levels will be lower in HIV-infected children at all time points than in age-similar children without HIV infection.

2. There will be no appreciable changes in anti-HPV CMI from Study P1047 week 108 to years 2, 3.5, and 5 of the study in subjects who control HIV RNA load and maintain normal numbers of CD4 and B lymphocytes.

3. Subjects who fail or interrupt HAART will experience faster decay of anti-HPV antibodies and will lose anti-HPV CMI.
1.0 INTRODUCTION

1.1 Background

Vaccination to prevent cervical cancer - Cervical cancer is a leading cause of cancer-related morbidity and mortality among women worldwide (1). Human papilloma virus (HPV) is the primary cause of cervical cancer, and additionally is responsible for 40-90% of anal, vulvar, vaginal, penile and oropharyngeal cancers (2). The oncopgenic potential of HPV is type-specific, such that approximately 70% of cervical cancers are caused by HPV types 16 and 18 (3). HPV 16 and 18 are also the predominant types associated with anogenital and oropharyngeal cancers (2;4). In addition, HPV types 6 and 11 are associated with 90% of genital warts, and are rarely the cause of anogenital cancers (5).

The quadrivalent HPV vaccine (QHPV; Gardasil; Merck and Co.) that is licensed in the USA contains virus-like particles (VLPs) consisting of HPV L1 proteins from types 6, 11, 16 and 18 antigens (6) (7). In immunocompetent women these vaccines are 98-100% effective in preventing pre-cancerous cervical lesions caused by HPV types 16 and 18, such as cervical intra-epithelial neoplasia (CIN), and is also very effective in preventing vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia (8), and genital warts (9). QHPV elicits titers of type-specific neutralizing antibodies that are 60-100-fold higher than titers stimulated by natural infection (8;10); Levin et al; P1047 manuscript; in press, JAIDS).

A woman’s lifetime risk of acquiring HPV is over 80%, with most infections occurring within 3-4 years after the onset of sexual activity (6;8). Most of these infections are transient. However, persistence of HPV 16 and 18 is essential for the development of significant disease, including cervical intra-epithelial neoplasia 3 (CIN 3) and cancer (9;10). Many studies have shown several-fold higher prevalence of HPV and CIN 2/3 in HIV-infected women and men than in HIV- uninfected people (11). This is not the result of more frequent acquisition, which occurs with equal frequency among HIV- infected and HIV-uninfected females, but rather is explained by longer persistence of HPV infection (12). HPV infection also causes significant morbidity among HIV-infected males, who have a 7-fold increase in penile cancer and a 60-fold increase in anal cancer (13). HIV-infected males and
females also have high rates of genital warts, which are often recalcitrant to conventional therapies (14;15).

Two commercial HPV preventive vaccines (Gardasil; Merck and Co.; Cervarix; GlaxoSmithKline) have been developed and are FDA-approved. Both vaccines contain virus-like particles (VLP) of HPV types 16 and 18 that stimulate type-specific neutralizing antibodies, which are thought to prevent HPV infection (16;17). Gardasil also contains HPV types 6 and 11 VLPs (16). In immunocompetent women Gardasil is 98-100% effective in preventing pre-cancerous cervical lesions, such as CIN, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia, and is also very effective in preventing genital warts in men and women (16;18-22). Gardasil elicited titers of HPV type-specific neutralizing antibodies that were 60-100-fold higher than were stimulated by natural infection (16;18).

1.2 Rationale

**IMPAACT protocol that utilizes QHPV** - P1047 is a closed protocol that is investigating the safety and immunogenicity of QHPV in HIV-infected girls and boys, age 7 to <12 years of age. This study was a placebo-controlled trial that compared a recommended three dose schedule of QHPV in one study arm (Arm A) with an arm that received placebo (Arm B). At 96 weeks after study entry the QHPV recipients (Arm A) received a fourth dose of QHPV and were subsequently evaluated for evidence of an anamnestic antibody response. Also at 96 weeks the previous placebo recipients (Arm B) began the same three dose schedule of QHPV that was administered in Arm A. Thus, two different cohorts are currently available for future evaluation.

**Rationale for adding a follow-up study to P1047** – P1047 has thus far demonstrated that QHPV can be safely administered to HIV-infected boys and girls and will stimulate seroconversion in more than 95% of vaccinees. However, these antibody levels were 30-50% lower than those achieved in children without HIV infection (Levin et al; P1047 manuscript, in press, JAIDS; (23;24). The magnitude of the antibody response is an important outcome variable, since the titer of HPV-specific antibody at the site of infection (namely, genital mucosa and skin) is likely to be responsible for protection against acquiring infection with the HPV types present in QHPV, and the presence of these antibodies at genital mucocutaneous surfaces is largely explained by
transudation of HPV-specific antibody from serum to mucosal and other genital surfaces (25-28). Since levels of vaccine-induced antibodies decline with time after vaccination, it is uncertain how long vaccine-induced immunity will last. This concern is supported by some evidence that naturally acquired HPV-specific antibody might decline to a level that will permit re-infection in HIV uninfected patients (29). Persistence data for HPV-specific antibody will be available from 550 age-matched children that are being tested annually for 10 years after QHPV vaccination. Post-vaccine responses are published (23) and samples have been obtained for at least 4 years of this program (Merck protocol 018; A. Saah, personal communication). There is no antibody persistence information available from HIV-infected vaccinees of any age.

Less is known about the HPV-specific CMI generated by QHPV. In P1047, we showed that approximately 2/3 of the vaccine recipients developed ELISPOT responses to HPV 16, which is contained in the vaccine, but also to the related serotype 31, which is not in the vaccine. Cross protection against HPV types not included in the vaccine has been demonstrated in several HPV vaccine efficacy trials (30), but the mechanism of protection is not well understood. CMI responses are directed against smaller epitopes than antibody responses, and, therefore, the likelihood that CMI will recognize an area that is conserved across related HPV types is much greater than with humoral immunity. Recent studies have shown that the concentration of antigen-specific CD8+ T cells in the genital and intestinal sub mucosa correlate with protection against microbial pathogens (31;32). It is conceivable that a similar mechanism is operative in HPV infection. In addition, anamnestic antibody responses tend to be more vigorous when supported by CD4+ T help, and therefore might contribute to protection against acquiring HPV infection.

In summary, we seek to determine the long-term durability and kinetics of the vaccine-induced HPV-type-specific antibody and CMI responses in HIV-infected children that were, and are being, immunized in P1047. These subjects are a unique cohort that will allow us to approach this specific clinical issue.
2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.11 To determine the HPV-type specific antibody levels at 2, 3.5, and 5 years after completion of the QHPV vaccine schedule for each of the arms in P1047 and compare them to levels of QHPV-induced antibody levels present in age-similar children without HIV infection (published controls) at these time intervals after QHPV vaccination.

2.2 Secondary Objectives

2.21 To compare the decline over the study interval in HPV type-specific antibody in subjects who received four doses of QHPV (Arm A) with those who received three doses of vaccine (Arm B) in P1047.

2.22 To determine the magnitude of HPV-specific antibody at different times after QHPV vaccination as a function of immune status (as defined by CD4 count and CD4%) and plasma HIV viral load.

2.23 To determine the persistence of HPV-specific CMI at 2, 3.5, and 5 years after completion of the QHPV schedule for each of the arms in P1047.

2.24 To evaluate potential associations of HIV plasma RNA, lymphocyte immunophenotypes, HPV-specific memory B cell lymphocytes and HPV-specific CMI with the decay of anti-HPV antibody titers.

2.3 Hypotheses

2.31 HPV type-specific antibodies will decline in both Arms after completion of the specified QHPV vaccine schedule:

2.311 Antibody levels will remain higher at equal intervals after vaccination in those who received 4 doses compared with those who received 3 doses of the QHPV.

2.312 Antibody levels will be lower in HIV-infected children at all time points than in age-similar children without HIV infection.
2.32 There will be no appreciable changes in anti-HPV CMI from study week 108 to years 2, 3.5, and 5 of the study in subjects who control HIV RNA load and maintain normal numbers of CD4 and B lymphocytes.

2.33 Subjects who fail or interrupt HAART will experience faster decay of anti-HPV antibodies and will lose anti-HPV CMI.

3.0 STUDY DESIGN

P1085 is a follow up study from P1047 (Phase II Safety and Immunogenicity Study of Quadrivalent Human Papilloma Virus [types 6, 11, 16, 18] L1 Virus-like particle [VLP] vaccine (Gardasil®) in HIV-infected children ≥ 7 to < 12 years of age) to determine the long term immunogenicity of QHPV in HIV-infected children.

104 children and adolescents, who were enrolled into IMPAACT P1047, and who completed the scheduled vaccine doses for their designated arm, are eligible for this study. All subjects will be enrolled at between 1 and 2 years of their last HPV vaccination. No therapy will be given as part of this study. Interval history and blood samples for immunologic and virologic testing will be obtained at 2, 3.5, and 5 years after completion of the QHPV schedule for either arm of the P1047 study. This will permit comparison with published data obtained for up to 5 years after administration of QHPV to children without HIV infection.

It is anticipated that HPV type-specific antibodies will decline in both Arms after completion of the specified QHPV vaccine schedule and that antibody levels will remain higher at each testing interval after vaccination in those who received 4 doses compared with those who received 3 doses of the QHPV vaccine. Similarly, it is anticipated that antibody levels will be lower in HIV-infected children at all time points than in age-similar children without HIV infection.

3.1 Laboratory Evaluations

In addition to the evaluation of plasma HIV viral load, CD4% and CD4 count, HPV type 16-specific IFN-γ production and HPV type 16-specific IL-2 ELISPOT assay of peripheral blood mononuclear cells (PBMCs) will be determined. Specific responses to a related non-QHPV type, HPV-31, will also be tested and HPV-16-specific B and T cell memory and effector lymphocyte will be enumerated.
by flow cytometry. Luminex HPV-specific competitive and total IgG immunoassays and the enumeration of HPV-specific memory B cells in PBMCs in relation to total memory B cells will also be evaluated in this study.

The schedule of laboratory and clinical evaluations for this study is outlined in Appendix I “Schedule of Evaluations”.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 Previous enrollment in P1047
4.12 Completion of the P1047 scheduled vaccine doses for their designated arm.
4.13 Parent or legal guardian able and willing to provide signed informed consent
4.14 Subjects should be between 1 and 2 years following their last HPV vaccination.

4.2 Exclusion Criteria

4.21 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator’s opinion, would compromise the outcome of this study.
4.22 Administration of a γ-globulin-containing product within 90 days prior to enrollment.
4.23 Receipt of an additional dose of Merck HPV vaccine other than that administered for the P1047 study.
4.24 Receipt of GSK HPV vaccine.

4.3 Concomitant Medication Guidelines

There are no precautionary or disallowed medications in this study.

4.4 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving
final approval, sites will submit all required protocol registration
documents to the DAIDS Protocol Registration Office (DAIDS
PRO) at the Regulatory Compliance Center (RCC). The DAIDS
PRO will review the submitted protocol registration packet to
ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL NOT be
reviewed or approved by the DAIDS PRO, and sites will receive
an Initial Registration Notification when the DAIDS PRO receives
a complete registration packet. Receipt of an Initial Registration
Notification indicates successful completion of the protocol
registration process. Sites will not receive any additional
notifications from the DAIDS PRO for the initial protocol
registration. A copy of the Initial Registration Notification should
be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE
approval(s) for an amendment, sites should implement the
amendment immediately. Sites are required to submit an
amendment registration packet to the DAIDS PRO at the RCC.
The DAIDS PRO will review the submitted protocol registration
packet to ensure that all the required documents have been
received. Site-specific ICF(s) WILL NOT be reviewed and
approved by the DAIDS PRO and sites will receive an Amendment
Registration Notification when the DAIDS PRO receives a
complete registration packet. A copy of the Amendment
Registration Notification should be retained in the site's regulatory
files.

For additional information on the protocol registration process and
specific documents required for initial and amendment
registrations, refer to the current version of the DAIDS Protocol
Registration Manual.

4.5 Co-enrollment Procedures

Co-enrollment is permitted with any study that does not involve
administration of QHPV or addition of an immune suppressive
therapy or immune enhancing therapy or antibody-containing
blood products.
4.6 Subject Management

Subjects/guardians may be contacted by mail or telephone to remind them of their scheduled visits, given that there are only 3 of them in four years.

No study products are being tested as part of this prospective surveillance study. As such, adverse experiences are unlikely to be study-related, and will be managed according to the best clinical practice and the judgment of the site investigator. All deaths reported to the sites will be recorded and all significant adverse events reported at the interval clinic visits will be recorded.

4.7 Criteria for Study Discontinuation

4.71 The subject or parent/legal representative/guardian refuses further study participation or follow-up evaluations.
4.72 The subject is no longer followed at a domestic IMPAACT site and follow-up information can no longer be obtained.
4.73 The domestic IMPAACT site closes, and subject transfer is not possible.
4.74 The site principal investigator determines that further participation would be detrimental to the subject’s health or well-being.
4.75 The study is discontinued.
4.76 The subject fails to comply with the study requirements, so as to cause harm to him/herself or seriously interfere with the validity of the study results.

5.0 STUDY TREATMENT

No treatment or intervention will be provided as part of this study. Subjects will have received the QHPV as part of their previous enrollment in IMPAACT protocol P1047 “Phase II Safety and Immunogenicity Study of Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] L1 Virus-Like Particle (VLP) Vaccine (GARDASIL®) in HIV Infected Children ≥7 to <12 Years of Age.”

6.0 STATISTICAL CONSIDERATIONS

6.1 General Design Issues

P1085 is a follow-up study of P1047 (Phase II Safety and Immunogenicity Study of Quadrivalent Human Papilloma Virus [types 6, 11, 16, 18] L1 Virus-like particle [VLP] vaccine (Gardasil®) in HIV-Infected Children ≥7 to <12 years of age) to
determine the long term immunogenicity of QHPV in HIV-infected children. 130 children and adolescents were enrolled into P1047, and 126 of them received study vaccinations.

Approximately 111 subjects completed all scheduled vaccine doses (84 in Arm A, 27 in Arm B) in P1047; of these, 7 (5 in Arm A, 2 in Arm B) are from de-funded sites and will not participate in the P1085 study. Therefore, 104 subjects are eligible for this study. No therapy will be given as part of this study. Subjects participating in P1085 will remain in the stratification groups and treatment arms to which they were assigned during their participation in P1047. The purpose of stratifying subjects by immunologic history was to ensure adequate accrual across a range of immunologic capacity.

6.2 Outcome Measures

Primary Measures: HPV type-specific antibody at 2, 3.5, and 5 years after completion of the QHPV schedule for each of the arms in P1047. The power calculations are not provided because this will be a descriptive comparison between the HIV-1 infected subjects from P1085 and uninfected subjects who were accrued to another study. The manufacturer has committed to providing data on these uninfected subjects, and it will be of interest to compare the persistence of their response with that of the infected subjects in the current protocol. However, given that the data come from 2 different studies, no formal p-values will be calculated; thus, power calculations are not appropriate.

Secondary Endpoints and Response Variables:
- HPV-16 and 31 IFNγ and IL2 ELISPOT.
- HPV-16 B cell ELISPOT.
- HPV-16 and HPV-31 B and T cell memory and effector lymphocyte enumeration.

6.3 Randomization and Stratification

Subjects participating in P1085 will remain in the stratification groups and treatment arms to which they were assigned during their participation in P1047.

6.4 Sample Size and Accrual

Approximately 111 subjects completed all scheduled vaccine doses in P1047 (84 in Arm A, 27 in Arm B); of these, 7 (5 in Arm A, 2 in
Arm B) are from de-funded sites and will not participate in the P1085 study. Therefore, 104 subjects are eligible for this study. If we assume that 10% of subjects in P1047 will not agree to participate in the P1085 study, this would leave 71 subjects from Arm A and 22 from Arm B at the start of P1085. The P219C long-term follow-up study showed that the estimated lost-to-follow-up rate in perinatally HIV-1 infected subjects at the end of year 2, year 3.5, and 5 were 4.9%, 9.8% and 14.5%, respectively. Almost all P1085 participants are perinatally HIV-1 infected, so we assume that the lost to follow-up rate in P1085 at the end of year 2, year 3.5 and year 5 would be similar to P219C, at approximately 5%, 10% and 15%, respectively. Thus, the total lost to follow-up in P1085 would be 10% at the start of P1085, 15% at the end of year 2, 20% at the end of year 3.5, and 25% at the end of year 5.

It is assumed that the standard deviation of antibody level at years 2, 3.5, 5 after the last vaccination will be the same as for week 28 of P1047 and that the antibody level at years 2, 3.5, 5 will have a 15%, 30%, and 50% decline, respectively. The mean and standard deviation of \log_{10} antibody level at week 28 for serotypes 6, 11, 16, and 18 are (2.75, 0.55), (3.14, 0.43), (3.72, 0.50) and (2.96, 0.73) respectively. The potential antibody levels in Arm A (95% confidence interval) for serotypes 6, 11, 16, and 18 were calculated by using antilog (Figure 1-4), assuming the sample size to be 71 at the start of P1085, 67 at the end of year 1, 63 at the end of year 3 and 59 at the end of year 5.
Figure 1 Potential Antibody level (95% confidence interval) at 2, 3, 5, 5 years after the last vaccination, Serotype 6

Figure 2 Potential Antibody level (95% confidence interval) at 2, 3, 5, 5 years after the last vaccination, Serotype 11
The power to detect a 15%, 30%, or 50% decline of antibody levels from week 28 to a later time point was calculated, assuming that the data would be analyzed by paired t-tests. The number of pairs would be 67, 63, 59 between the week 28 of P1047 and the end of year 2, 3.5, 5 respectively. Statistical power for these tests increases as a function of the correlation between the two time points in question (Tables 1-3). We expect this
correlation to be relatively high, but have no definitive data on this. Thus, statistical power under a wide range of potential correlation coefficients ($\rho$) between the antibody levels at week 28 and later time points was calculated, with the correlation coefficients assumed to be 0.95, 0.9, 0.5 or 0. Table 2 shows that with $\rho=0.95$, a study sample of 63 subjects would provide at least 0.89 power to detect an antibody decline as small as 15% for serotype 6, 11 or, 16. The power to detect a 30% decline when $\rho \geq 0.9$ is at least 0.96 across serotypes, while the power to detect a 50% decline when $\rho=0.5$ is at least 0.90. In the unlikely, worst case scenario with $\rho=0$, the study would have power of at least 0.86 to detect a 50% decline across serotypes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Pairs</th>
<th>Serotype</th>
<th>Correlation Coefficient</th>
<th>15% Decline</th>
<th>30% Decline</th>
<th>50% Decline</th>
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<td>1</td>
</tr>
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<tr>
<td></td>
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Table 2 Persistence of QHPV antibody: Power to detect antibody decline over time given current data, number of pairs=63

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<th>Number of Pairs</th>
<th>Serotype</th>
<th>Correlation Coefficient</th>
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<th>30% Decline</th>
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Table 3 Persistence of QHPV antibody: Power to detect antibody decline over time given current data, number of pairs=59

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<th>Outcome</th>
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<th>Serotype</th>
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<th>30% Decline</th>
<th>50% Decline</th>
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The subjects in Arm A received four vaccinations, while those in Arm B received three. The statistical power to compare persistence of antibody levels between these groups has been calculated under the following assumptions:

1) A sample size of 71 subjects in Arm A and 22 in Arm B at the start of P1085, 67 subjects in Arm A and 21 subjects in Arm B at the end of year 2, 63 subjects in Arm A and 20 in Arm B at the end of year 3.5, 59 subjects in Arm A and 18 in Arm B at the end of year 5;

2) The data will be log transformed, such that the difference between groups is expressed as the ratio of their Geometric Mean Titers (GMT);

3) The standard deviation in both arms will be the same as the standard deviation derived from week 28 data; and

4) The data will be analyzed by means of a t-test.

Figures 5-8 show the results for each serotype, over a range of potential GMT ratios between groups at the end of year 3.5. Figures 9-12 show the results for each serotype, over a range of potential GMT ratios between groups at the end of year 5. At the end of year 3.5, the study would have power = 0.80 to detect significant differences between Arm A and Arm B if the true antibody levels in Arm A for serotype 6, 11, 16, and 18 were 2.24, 1.88, 2.1, 2.92 times the respective antibody levels in Arm B.
Figure 5 Power of Comparison between Arm A and Arm B
Serotype 6 at the end of 3.5 years

Figure 6 Power of Comparison between Arm A and Arm B
Serotype 11 at the end of 3.5 years
Figure 7 Power of Comparison between Arm A and Arm B
Serotype 16 at the end of 3.5 years

Figure 8 Power of Comparison between Arm A and Arm B
Serotype 18 at the end of 3.5 years
Figure 9: Power of Comparison between Arm A and Arm B
Serotype 6 at the end of year 5

Figure 10: Power of Comparison between Arm A and Arm B
Serotype 11 at the end of year 5
Figure 11 Power of Comparison between Arm A and Arm B
Serotype 16 at the end of year 5

Figure 12 Power of Comparison between Arm A and Arm B
Serotype 18 at the end of year 5
6.5 Monitoring

Clinical visits are scheduled at the end of year 2, 3.5, and 5 after the last vaccination of P1047. No toxicity reviews will be performed since no therapy will be given as part of this study.

6.6 Analyses

The paired t-test will be used to compare HPV type-specific antibody for each serotype between different time points after the last vaccination of P1047 for each study Arm. Geometric mean titers (GMTs) and 95% CIs for the GMTs will be presented at all time points at which serum samples are collected after the last vaccination of P1047.

T test will be used to compare HPV type-specific antibody for each type between Arm A and Arm B at each time point after the last vaccination of P1047. Linear mixed effects models will be used to estimate the rate of decline over time in antibody levels and to test whether the rate of decline differs significantly between treatment arms.

Spearman correlation analyses will be used to determine the association between the magnitude of HPV-specific antibody at different times after QHPV vaccination and the following: CD4 count, CD4% and plasma HIV viral load.

Descriptive analyses will estimate the persistence of HPV-specific CMI, bounded by 95% confidence intervals, at 2, 3.5, and 5 years after completion of the QHPV schedule for each of the arms in P1047.

Spearman correlations will examine the associations between changes from baseline at 2, 3.5, and 5 years after of the QHPV schedule and the following: HPV-specific B cell lymphocyte counts, lymphocyte phenotypic characteristics, and CMI.

7.0 EXPEDITED ADVERSE EVENT REPORTING

This study does not contain any treatment or intervention, thus no expedited adverse event (EAE) reporting is required. Every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed.
Any unanticipated problems will be reported to the DAIDS medical officer at the same time as the problems are reported to the responsible site IRBs overseeing the research according to pre-established procedures as required by 45 CFR 46.

8.0 HUMAN SUBJECTS

8.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendix II), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. Subjects will be asked to provide informed consent if they have reached an age at which this is permissible by local ethical guidelines. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB, local and state guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

8.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area.
available only to study staff and study monitors. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the Office for Human Research Protections (OHRP), the NIAID, the local IRBs, or Merck & Co., Inc.

8.3 Study Discontinuation

The study may be discontinued at any time by IMPAACT, the OHRP, the NIAID, the local IRB, Merck & Co., Inc., or other governmental agencies as part of their duties to ensure that research subjects are protected.

9.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

10.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.
11.0 REFERENCES


(7) Merck & Company Inc. Package insert for Gardasil (Human Papillomavirus Quadrivalent Vaccine, recombinant) revised Oct 2009


(21) Giuliano AR, Palefsky J. The efficacy of quadrivalent HPV (types 6/11/16/18) vaccine in reducing the incidence of HPV infection and HPV-related genital disease in young men. EUROGIN, Nice, France, November 10, 2008

(22) Palefsky J, Giuliano AR. Efficacy of the quadrivalent HPV vaccine against HPV 6/11/16/18-related genital infection in young men. UROGIN, Nice, France, November 13, 2008


# APPENDIX I

## SCHEDULE OF EVALUATIONS

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<th>Entry(^7)</th>
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<th>Year 5  (± 8 weeks)*</th>
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<td><strong>29 ml</strong></td>
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* Exceptions from these windows based on extenuating circumstances can be discussed with and may be agreed to by the Protocol Team.

**Footnotes:**

1. A targeted history will be obtained at each visit. The first visit will record: baseline diagnoses (including pregnancy, significant medical conditions, CDC HIV Clinical Stage, medications, and vaccinations within 2 weeks of the visit). Subsequent visits: record new diagnoses (including pregnancy, change in CDC HIV Clinical Stage, medications, and significant adverse events since the preceding study visit.)

2. Must be performed at DAIDS VQA-certified laboratory or a CLIA-certified laboratory. These tests may be omitted if this laboratory information is available from clinical care results obtained at this visit or within 1 month.

3. Lymphocyte subsets include CD4/CD8/CD19 counts and percentages. These tests must be performed at DAIDS VQA-certified laboratory or a CLIA-certified laboratory. These tests may be omitted if laboratory information is available from clinical care results obtained at this visit or within 1 month.

4. Assays performed on PBMCs will include HPV type 16- and 31-specific IFN-\(\gamma\), IL-2 and B cell ELISPOT assays; enumeration of HPV 16-specific effector and memory T and B cells; and Luminex competitive and total IgG HPV antibody immunoassays.

5. Serum will be stored for two years for potential retesting and evaluation by relevant new tests.

6. Total blood volumes may be 2-4 ml less if recent test results are used for lymphocyte subsets or plasma HIV RNA, such that additional blood does not have to be drawn.

7. Entry and Year 2 visit may be combined if the timing of the two visits coincides.

**NOTE:** For insufficient blood draws, priority of draw should be: immune assays (ELISPOTS and HPV antibody assays; followed by lymphocyte subsets; followed by HIV plasma RNA or DNA (if not available from chart abstraction – see footnote #2); followed by lymphocyte subsets (if not available from chart abstraction – see footnote #3).
APPENDIX II

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

IMPAACT P1085:
DURATION OF HUMAN PAPILLOMA VIRUS (HPV) TYPE-SPECIFIC ANTIBODY AFTER ADMINISTRATION OF QUADRIVALENT HPV VACCINE TO HIV-1 INFECTED CHILDREN PREVIOUSLY ENROLLED IN P1047
Version 1.0, dated May 5, 2010

SHORT TITLE FOR THE STUDY: Duration of HPV Antibody After HPV Vaccine

INTRODUCTION
You are / your child is being asked to take part in this research study because you were / your child was previously enrolled in another study, P1047 “Phase II Safety and Immunogenicity Study of Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] L1 Virus-Like Particle [VLP] Vaccine (GARDASIL®) in HIV-Infected Children ≥7 to < 12 Years of Age”, which looked at the use of a vaccine for Human Papilloma Virus (HPV) in HIV-infected children. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you become / your child becomes a part of this study, we want you to know about the study.

This is a consent form. It gives you / your child information about this study. The study staff will talk with you / your child about this information. You are / your child is free to ask questions about this study at any time. If you agree / your child agrees to take part in this study, you/your child will be asked to sign this consent form. You / your child will get a copy to keep.

WHY IS THIS STUDY BEING DONE?
This study is being done to evaluate how long the immune response from the HPV vaccine you / your child received persists. The immune response occurred after immunization and is what protects you/your child from HPV disease. You / your child received this vaccine as part of an earlier study (mentioned above). The vaccine is called Human Papillomavirus Vaccine (QHPV Vaccine, also known as GARDASIL®)

The study will check to see if the protective effects (called “antibodies”) produced by the vaccine have lasted, and for how long these effects will continue to last. You will not be given any medications or vaccines as part of this follow-up study.
WHAT DO I OR MY CHILD HAVE TO DO IN THIS STUDY?

Entry Visit, Years 2, 3.5 and 5 Visits

At the Entry visit, the study will be explained to you and you will be asked for your consent to participate. Depending on when you had your last HPV vaccination, the Year 2 visit may or may not be performed at the same time as the Entry visit.

At the Year 2 visit, you / your child will have a history taken that reviews recent significant illnesses, certain signs and symptoms of illness, and medications. There may be reasons why you are / your child is not eligible to take part in this study. The doctor or study staff will discuss these with you / your child.
You may be contacted by mail or telephone to remind you of your scheduled visits, given that there are only three visits in five years. These visits are expected to take approximately 45 minutes each.

At each of the three visits, your / your child’s recent medical history will be reviewed. Less than 2 tablespoons of blood will be drawn from a vein in your / your child’s arm for laboratory tests. These tests may include finding out the number of cells in the blood that fight HIV (known as CD4+ cells) and the amount of HIV virus in the blood (if any). The tests will include looking at your / your child’s blood to see if you have / your child has any antibodies (a protective part of the blood to fight infections) or cells that fight the HPV virus. Any tests that will be done as part of your / your child’s routine care (such as measuring CD4+ cells and HIV in the blood) at this or a recent visit will not be repeated, which will decrease the amount of blood taken.

OTHER INFORMATION
You / your child will be given the results of routine laboratory tests when they become available. Some of the research laboratory tests will not be shared with you or your child, since their value for medical care is still not clear. The information collected in this study may be used for other IMPAACT-approved HIV-related research.

Storage of Blood Samples
Some of your / your child’s blood will be stored (with protectors of identity) while you / your child participate in this study and while the samples are being studied. Samples will be held for 2 years after the last subject completes the study in order to repeat testing if necessary or to be re-tested if improved tests for evaluating the vaccine response become available. After the two year period, the samples will be destroyed.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Up to 104 children and adolescents who took part in the P1047 study will be eligible to take part in this study.

HOW LONG WILL I / MY CHILD BE IN THIS STUDY?
You / your child will be in this study for up to 4 years.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THIS STUDY EARLY?
The study doctor may need to take you / your child off the study early without your permission if:

- You are / your child is not able to attend the study visits as required by the study.
- The study is stopped or cancelled.

The study doctor may also need to take you / your child off the study without your / your child’s permission if:

- Continuing the study may be harmful to you / your child

WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site of injection, or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. A feeling of lightheadedness may also occur. There is no anticipated increased risk to pregnant women or to a fetus. Women who become pregnant while on study will remain on study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
You / your child will receive no known benefit from being in this study. Information learned from this study may help make future decisions about using the HPV vaccine in you / your child or other children who have HIV.

WHAT ABOUT CONFIDENTIALITY?
Efforts will be made to keep your / your child’s personal information confidential. We cannot guarantee absolute confidentiality. Any publication of this study will not use your / your child’s name or identify you / your child personally.

Your / your child’s records may be reviewed by the Office for Human Research Protections (OHRP), (insert name of site) IRB, the NIH, study staff, study monitors, local and national regulatory authorities, and drug companies (Merck & Co., Inc.) supporting this study. This is in accordance with the procedure from the original study with the HPV vaccine that you / your child participated in.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you / your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you / your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must
be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you / your child or your / your child’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you / your child as a participant in the research project under the following circumstances: possible child abuse and/or neglect or risk of harm to you, your child, or others.

WHAT ARE THE COSTS TO ME OR MY CHILD?
You / your child will not be expected to pay for any study related visits, or study procedures.

WHAT HAPPENS IF I AM / MY CHILD IS INJURED?
If you are / your child is injured as a result of being in this study, you / your child will be given immediate treatment for your/his/her injuries. The cost for this treatment will be charged to you or your insurance company or your child’s insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY / MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?
Taking part in this study is completely voluntary. You / your child may choose not to take part in this study or you / your child may stop participating in the study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are / your child is otherwise entitled.

We will tell you/your child about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you/your child want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE / MY CHILD HAS QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your / your child’s rights as a research subject, contact:
• name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
• telephone number of above
SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

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<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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