

Sponsor Protocol

Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies (LiVes LLC)

A Multicenter Study of the Pediatric HIV/AIDS Cohort Study (PHACS)

Protocol Number PH700



Photos are for illustrative purposes only. Any person depicted in the photo is a model.

Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies (LiVes LLC Study [Protocol PH700]), Version 1.4)

A Multicenter Substudy of the Pediatric HIV/AIDS Cohort Study (PHACS)

Protocol Number PH700

Sponsored by:

The National Cancer Institute (NCI) and The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Protocol Version 1.4, December 06, 2024

HLC IRB Approval Date: December 12, 2024

Effective Implementation Date: February 12, 2025

Protocol Co-chairs:	Anna-Barbara Moscicki, MD Denise L. Jacobson, PhD, MPH Tzy-Jyun Yao, PhD Howard D. Strickler, MD, MPH
Protocol Epidemiologist:	Denise L. Jacobson, PhD, MPH
Protocol Statistician:	Tzy-Jyun Yao, PhD
Multisite Principal Investigator:	Jennifer Jao, MD, MPH
Clinical Site Representatives:	Katherine Knapp, MD Elizabeth J. McFarland, MD Medea Gabriel, BSN Jamie Russell, MA, BSN Martha Cavallo, LPN, BSN
Community Task Force Representatives:	Latricia Conley Raiko Johnson, AASMA, CNA, BGS, AND Andrew Pulsipher
PHACS Program Director:	Liz Salomon, EdM
Director of the Data Management Center (DMC) at Frontier Science:	Sue Siminski, MS, MBA
Westat Project Director:	Tracy Wolbach, BA
DMC Project Manager:	Alexandria DiPerna, BS
Clinical Data Manager:	Haleigh Snyder, BS
Laboratory Data Manager:	Kevin Knowles, MA, PhD
Protocol Specialist:	Seun Ibironke, BS

Table of Contents

Protocol Team Roster	viii
List of Abbreviations	xi
Protocol Synopsis	xiv
Protocol Schema	xvii
1. Introduction	1
1.1 Study Background	1
1.2 Study Rationale	1
1.2.1 HPV Vaccines	1
1.2.2 Antibody Titer in HPV-Vaccinated Young Women Living with Perinatal HIV and Incidence of Abnormal Cervical Cytology/pap	2
1.2.3 Cervical Cancer Screening (CCS)	3
1.2.4 Cervical Cancer Screening in WLHIV	4
1.2.5 Promising New Strategies for CCS	5
2. Study Aims and Hypotheses	9
2.1 Aim 1	9
2.2 Aim 2a	9
2.3 Aim 2b	9
3. Study Design	10
3.1 Overall Study Design	10
3.1.1 Aim 1	10
3.1.2 Aim 2	10
3.2 General Design Considerations	11
3.3 Study Population	13
3.3.1 PHACS-Affiliated Protocols	13
3.3.2 Non-PHACS Affiliated Recruitment	15
3.4 Sample Size	15
3.5 Study Duration	16

Table of Contents (continued)

4.	Selection and Enrollment of Study Participants	17
4.1	Enrollment	17
4.2	Inclusion Criteria	17
4.3	Exclusion Criteria	17
4.4	Protocol Registration	18
4.5	Recruitment	18
4.6	Informed Consent	18
4.7	Co-enrollment	20
5.	Schedule of Study Evaluations, Description and Administration	21
5.1	Primary hrHPV at Testing 1 (or Testing 2, if necessary)	21
5.1.1	hrHPV-Positive at Testing 1 or Testing 2	21
5.1.2	PHS Testing 2: For Those hrHPV-Negative at Testing 1	22
5.1.3	hrHPV-Negative at PHS Testing 1 and 2	22
6.	Evaluations and Measures for Those Who Test Positive on PHS	23
6.1	Flow of Specimen Self-Collection Kits	23
6.2	HPV Immunization and Current ART Questionnaire	23
6.3	Reproductive Health and Tobacco Use Online Survey	23
6.4	Medical Data Abstraction	24
6.5	Urine Pregnancy Test at Baseline Colposcopy visit	24
6.6	Colposcopic Examinations at Baseline and Follow-Up	24
6.7	Collection of Cytology/pap and Samples for Triage Tests and Repository	24
6.8	Cervical Biopsy Specimens	24
6.9	Follow-Up Colposcopy Visits	25
6.9.1	Medical Record Abstraction in Follow-Up Years 1-3	25
7.	Evaluations and Measures for Those with Two Consecutive Negative Results from PHS	26
7.1	Annual Self-sampling for hrHPV Genotyping	26
7.1.1	Other Evaluations	26
8.	Data Collection and Site Monitoring	26
8.1	Data Records	26
8.2	Data Collection	27

Table of Contents (continued)

8.3	Data Quality Assurance	28
8.4	Clinical Site Monitoring and Record Availability	28
9.	Study Management	29
9.1	Data Management	29
9.2	Rolling Implementation and New Protocol Versions	29
9.3	Protocol Query Management	30
9.4	Long-Term Specimen Storage in the PHACS Repository	30
10.	Participant Management	31
10.1	Study Visit Management	31
10.2	Participant Compensation	32
10.3	Study Completion	32
10.4	Participant Discontinuation	32
11.	Adverse Event (AE) Reporting	34
12.	Study Impact and Safety Monitoring	35
12.1	Reporting Requirements	35
13.	Statistical/Analytic Considerations	36
13.1	Study Design	36
13.2	Statistical Analysis Plan	36
13.2.1	Baseline Characteristics	36
13.2.2	Aim 1	36
13.2.3	Aim 2a	37
13.2.4	Aim 2b	39
13.3	Power Calculations	39
13.3.1	Aim 1	39
13.3.2	Aim 2a and Aim 2b	39
13.4	Missing, Unused, and Spurious Data	40
13.5	Data Monitoring	40
14.	Human Subjects	41
14.1	Participant Confidentiality	41

Table of Contents (continued)

14.2	Certificate of Confidentiality	41
14.3	Risks and Benefits	42
14.3.1	Risks Associated with Participation in This Study	42
14.3.2	Benefits Associated with Participation in This Study	43
14.4	Institutional Review Board Review	43
14.5	Prisoner Participation	43
14.6	45 CFR § 160 and 164 Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule” Pursuant to the Health Insurance Portability and Accountability Act)	43
14.7	PHACS Repository Policies	43
14.8	Study Discontinuation	44
15.	Publication of Research Findings	45
16.	Biohazard Containment	45
	References	46
	Appendixes	
	Appendix I Schedule of Evaluations	57
	Appendix II Participating PHACS and HOPE Sites	62
	Tables	
Table 1.	Cervical cancer screening guidelines	4
Table 2.	Cross-sectional sensitivity, PPV, and percentage referred to colposcopy for four cervical cancer screening approaches for CIN 3+ or CIN 2 with concurrent HSIL	5
Table 3.	Comparison of performance of 12 HPV type methylation to established triage tests	7
Table 4.	Delineation of Research Visits and Standard of Care Visits	31
Table I-1.	Recruitment, Testing 1, and Testing 2	58
Table I-2.	Participants who Test hrHPV-Positive after Testing 1 or Testing 2	59
Table I-3.	Participants who Test hrHPV-Negative after Testing 2	61
	Figures	
Figure 1.	Antibody GMTs with 95 percent CIs according to HPV type, by dose and cohort	2

Table of Contents (continued)

Figure 2.	Risk of CIN 3 by HPV genotype and methylation status	6
Figure 3.	Internal validation study of methylation assay for detection of CIN 3	7
Figure 4.	Study Flow Diagram	12
Figure 5.	HPV Participant Flow Diagram	16

Protocol Team Roster

<p>Protocol Co-chair</p> <p>Anna-Barbara Moscicki, MD Professor of Pediatrics University of California - Los Angeles 10833 Le Conte Avenue 22 - 432 MD Los Angeles, CA 90095 Phone: (310) 206-6345 Email: amoscicki@mednet.ucla.edu</p>	<p>Protocol Co-chair</p> <p>Denise L. Jacobson, PhD, MPH Senior Research Scientist Department of Biostatistics Harvard T.H. Chan School of Public Health FXB Building, Room 609 651 Huntington Avenue Boston, MA 02115 Phone: (617) 432-3266 Email: jacobson@sdac.harvard.edu</p>
<p>Protocol Co-chair</p> <p>Tzy-Jyun Yao, PhD Senior Research Scientist Center for Biostatistics in AIDS Research Harvard T.H. Chan School of Public Health FXB Building, Room 605 665 Huntington Avenue Boston, MA 02115 Phone: (617) 432-0563 Email: tyao@sdac.harvard.edu</p>	<p>Protocol Co-chair</p> <p>Howard D. Strickler, MD, MPH Professor of Epidemiology Department of Epidemiology & Population Health Albert Einstein College of Medicine Jack and Pearl Resnick Campus 1300 Morris Park Avenue Belfer Building, Room 1312A Bronx, NY 10461 Phone: (718) 430-4055 Email: howard.strickler@einsteinmed.edu</p>
<p>Protocol Epidemiologist</p> <p>Denise Jacobson, PhD, MPH Senior Research Scientist Department of Biostatistics Harvard T.H. Chan School of Public Health FXB Building, Room 609 651 Huntington Avenue Boston, MA 02115 Phone: (617) 432-3266 Email: jacobson@sdac.harvard.edu</p>	<p>Protocol Statistician</p> <p>Tzy-Jyun Yao, PhD Senior Research Scientist Center for Biostatistics in AIDS Research Harvard T.H. Chan School of Public Health FXB Building, Room 605 665 Huntington Avenue Boston, MA 02115 Phone: (617) 432-0563 Email: tyao@sdac.harvard.edu</p>
<p>Multisite Principal Investigator</p> <p>Jennifer Jao, MD, MPH Associate Professor, Pediatrics Ann & Robert H. Lurie Children’s Hospital of Chicago 225 E. Chicago Avenue, Box 20 Chicago, IL 60611 Phone: (312) 227-4080 Email: jennifer.jao@northwestern.edu</p>	<p>Clinical Site Representative</p> <p>Katherine M. Knapp, MD, FAAP, AAHIVS Principal Investigator St. Jude Children’s Research Hospital 262 Danny Thomas Place Mail Stop 230 Memphis, TN 38105 Phone: (901) 595-4645 Email: katherine.knapp@stjude.org</p>

Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies (LiVes LLC Study [Protocol PH700])

<p>Clinical Site Representative Elizabeth J. McFarland, MD Principal Investigator Pediatrics Infectious Diseases, Box B055 Children’s Hospital Colorado 13123 E. 16th Avenue Aurora, CO 80045 Phone: (720) 777-1966 Email: betsy.mcfarland@cuanschutz.edu</p>	<p>Clinical Site Representative Medea Gabriel, BSN Pediatric Infectious Diseases Tulane University Health Sciences Center 1430 Tulane Avenue, #8408 New Orleans, LA 70112 Phone: (504) 988-6489 Email: mjones3@tulane.edu</p>
<p>Clinical Site Representative Jamie Russell, MA, BSN St. Jude Children’s Research Hospital 262 Danny Thomas Place Mail Stop 230 Memphis, TN 38105 Phone: (901) 595-8300 Email: jamie.russell-bell@stjude.org</p>	<p>Clinical Site Representative Martha Cavallo, LPN, BSN Bronx-Lebanon Hospital Center 1685 Morris Avenue, Suite 1G Bronx, NY 10457 Phone: (718) 960-1016 Email: mcavallo@bronxleb.org</p>
<p>Community Task Force Representative Laticia Conley Peers United Group (PUG) Chair c/o Westat, Inc. (Tracy Wolbach) 1600 Research Boulevard Rockville, MD 20850 Email: laticiaconley@gmail.com</p>	<p>Community Task Force Representative Raiko Johnson, AASMA, CNA, BGS, AND c/o Westat, Inc. (Tracy Wolbach) 1600 Research Boulevard Rockville, MD 20850 Email: rjohnson5107@gmail.com mailto:njcooper@texaschildrenshospital.org</p>
<p>Community Task Force Representative Andrew Pulsipher Family Consultant/Patient Navigator c/o Westat, Inc. (Tracy Wolbach) 1600 Research Boulevard Rockville, MD 20850 Email: andrewpulsipher@gmail.com</p>	<p>PHACS Program Director Liz Salomon, EdM Harvard T.H. Chan School of Public Health Department of Epidemiology 401 Park Drive Landmark Center, Floor 3 East (L3-045)</p>
<p>Director of the Data Management Center (DMC) at Frontier Science Sue Siminski, MS, MBA Frontier Science Foundation 4033 Maple Road Amherst, NY 14226 Phone: (716) 898-7278 Email: siminski@frontierscience.org</p>	<p>Westat Project Director Tracy Wolbach, BA Westat 1600 Research Boulevard Rockville, MD 20850 Phone: (240) 453-2658 Email: tracywolbach@westat.com</p>
<p>DMC Project Manager Alexandria DiPerna, BS Frontier Science Foundation 4033 Maple Road Amherst, NY 14226 Phone: (716) 834-0900 ext. 7266 Email: diperna@frontierscience.org</p>	<p>Clinical Data Manager Haleigh Snyder, BS Frontier Science Foundation 4033 Maple Road Amherst, NY 14226 Phone: (716) 834-0900 ext. 7381 Email: snyder@frontierscience.org</p>

Protocol Team Roster (continued)

Laboratory Data Manager	Protocol Specialist
<p>Kevin Knowles, MA, PhD Frontier Science Foundation 4033 Maple Road Amherst, NY 14226 Phone: (716) 834-0900 ext. 7238 Email: knowles@frontierscience.org</p>	<p>Seun Ibronke, BS Westat 1600 Research Boulevard Rockville, MD 20850 Email: seunibronke@westat.com</p>

List of Abbreviations

ACS	American Cancer Society
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AMP	Adolescent Master Protocol (PH200)
AMP Up	Adolescent Master Protocol for Participants 18 Years of Age and Older (PH300)
AMP Up Lite	Adolescent Master Protocol for Participants 18 Years of Age and Older – Lite (PH400)
ART	Antiretroviral Therapy
ASCCP	American Society for Colposcopy and Cervical Pathology
ASCUS	Atypical Squamous Cells of Undetermined Significance
cART	Combined Antiretroviral Therapies
CBC	Complete Blood Count
CC	Cervical Cancer
CCS	Cervical Cancer Screening
CD	Cluster of Differentiation
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CIN 2+	CIN 2+ throughout the protocol means CIN 2 and worse
CRFs	Case Report Forms
CVL	Cervicovaginal Lavage
DAIDS	Division of AIDS
DDE	Direct Data Entry
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
ECC	Endocervical Curettage
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EID	Effective Implementation Date
ELISA	Enzyme-Linked Immunosorbent Assay
ePRO	electronic patient-reported outcome
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GMT	Geometric Mean Titer

List of Abbreviations (continued)

H&E	Haematoxylin and Eosin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLC	Harvard Longwood Campus
HOPE	Health Outcomes around Pregnancy and Exposure to HIV/ARVs
HPV	Human Papillomavirus
hr	High-Risk
hrHPV	High-Risk Human Papillomavirus
HSIL	High-Grade Squamous Intraepithelial Lesions
HSP	Human Subjects Protection
HHS	Department of Health and Human Services
HTTPS	Hypertext Transfer Protocol Secure
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
LDMS	Laboratory Data Management System
LPC	Laboratory Processing Chart
LSIL	Low-Grade Squamous Intraepithelial Lesions
mL	Milliliter
MNPP	Manual of Network Policies and Procedures
MOP	Manual of Procedures
MSM	Men Who Have Sex with Men
NCI	The National Cancer Institute
NICHD	The <i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NPV	Negative Predictive Value
OHRP	Office for Human Research Protections
OSHA	Occupational Safety and Health Administration
PBMCs	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
pg	Picogram

List of Abbreviations (continued)

PHACS	Pediatric HIV/AIDS Cohort Study
PHEU	Perinatally HIV-Exposed but Uninfected
PHI	Protected Health Information
PHIV	Perinatally HIV-Infected
PHS	Primary high-risk HPV Screening
PI	Principal Investigator
PID	Participant Identification Number
PIN	Personal Identification Number
PPV	Positive Predictive Value
QNS	Query and Notification System
RA	Regulatory Affairs
RCM	Regulatory and Compliance Manager
RCT	Randomized Controlled Trial
RNI	Reportable New Information
SC	Site Coordinator
Se	Sensitivity
SES	Study Enrollment System
SID	Study Identification
SMARTT	Surveillance Monitoring for ART Toxicities
SOC	Standard of Care
Sp	Specificity
STIs	Sexually Transmitted Infections
UCLA	University of California – Los Angeles
USPSTF	U.S. Preventive Services Task Force
VLP	Virus-Like Particle
WHO	World Health Organization
WIHS	Women’s Interagency HIV Study
WLHIV	Women Living with HIV
WLPHIV	Women Living with Perinatal HIV

Protocol Synopsis

STUDY DESCRIPTION

A multi-centered follow-up study of the effectiveness of human papillomavirus (HPV) vaccine and examination of primary high-risk (hr) HPV screening (PHS) and reflex triage strategies among vaccinated and unvaccinated women living with HIV (WLHIV) who are currently or previously enrolled in PHACS-affiliated studies or non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics.

STUDY AIMS

- **Aim 1: To examine the effectiveness of HPV vaccine in WLHIV based on the following outcomes: 3-year cumulative risk of (i) vaccine-hrHPV types that persist 12 months or longer, and (ii) histologic (h) Cervical Intraepithelial Neoplasia (CIN) 2+.**

We hypothesize that HPV vaccination will be effective in reducing the risk of these outcomes, but the impact of vaccination will be lower in WLHIV than reported for the general population. Younger age at the time of vaccination will have greater effectiveness.

- **Aim 2a: To examine and compare the sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) to detect hCIN 2+ immediately or in 3 years in PHS-positive WLHIV using provider-collected specimens for the four reflex strategies: (i) cytology/pap, (ii) hrHPV extended genotyping, (iii) p16/Ki-67 dual-staining cytology/pap, and (iv) hrHPV/host methylation levels. We will also assess whether HPV vaccination modifies these performance characteristics.**

We hypothesize that cytology/pap and dual staining will have a poorer performance than methylation and genotyping to detect hCIN 2+ and these performance characteristics will be modified by HPV vaccine status.

- **Aim 2b: To examine the Se, Sp, PPV, and NPV in self-collected PHS+ samples for hCIN 2+ detection focusing on methylation and hrHPV genotyping.**

We hypothesize that methylation and high-risk genotyping will have strong performance characteristics in self-collected PHS positive specimens.

SAFETY MONITORING

- Routine team monitoring of any adverse impact of the study will rely on the PHACS Query and Notification System (QNS), a real-time web-based interactive reporting system.

SAMPLE SIZE

Approximately 810 WLHIV greater than or equal to 21 years of age, to less than or equal to 45 years of age currently or previously enrolled in PHACS-affiliated studies or non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics, will be tested for hrHPV using a Food and Drug Administration (FDA)-approved primary hrHPV screening test from self-collected specimens.

- Women testing hrHPV-positive (also called PHS-positive) initially will be asked to complete a baseline visit and up to three annual follow up clinic visits for colposcopy.
- Women testing hrHPV-negative at the first self-collection will be asked to participate in a second PHS test 12 months after the initial negative results. If hrHPV-positive, they will be asked to attend a baseline visit and up to three annual follow up clinic visits for colposcopy.
 - We expect that 520 women who screen hrHPV-positive from either the first or second screen and agree to the follow-up study (will complete a baseline and up to three annual clinical visits that include colposcopy.

Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies (LiVes LLC Study [Protocol PH700])

- Women who are PHS-negative on both tests will be mailed an annual self-sampling kit for research HPV genotyping for up to 3 additional years. We expect N=238 in this group.

STUDY ASSESSMENTS

Primary hrHPV Testing 1 and 2 (if necessary):

- Self-swab collection kits will be provided to participants, and
- Site Coordinator will:
 - Interview the participant to obtain current ART use and HPV vaccination history.
 - Perform medical chart abstraction for most recent CD4 count and HIV viral load, and HPV vaccination history.

Participants Positive for hrHPV (at Testing 1 or Testing 2): Baseline and follow-up colposcopy study visits during which the following procedures and evaluations will be conducted:

- Reproductive Health and Tobacco Use self-administered online survey;
- Site Coordinator re-interview to obtain current ART use and HPV Vaccination History;
- Perform medical chart abstraction for most recent CD4 count and HIV viral load, HPV vaccination history, and reproductive health.
- Standard colposcopic examination:
 - Documentation of standard colposcopic examination features
 - Visual inspection for vulvar, vaginal, and cervical lesions and warts
- Specimen collection:
 - Cervical biopsies of acetowhite areas based on ASCCP Colposcopy Guidelines (if indicated)
 - Routine cytology/pap
 - One unstained cytology/pap slide at baseline only
 - One cervical sample (endocervical/exocervical cells) for repository and biomarker evaluations
 - Cervical vaginal lavage with normal saline for repository
- Cervical biopsy specimen(s), if obtained:
 - A diagnostic read by the local pathology laboratory
 - Original histology/biopsy slide or an additional paraffin embedded section on a slide from each biopsy specimen to be sent to the Central Pathology Laboratory at UCLA for standardized research reading
- STI testing results if obtained as part of standard of care.

ENROLLMENT AND OUTCOME

- Women will be contacted and invited by the LiVes LLC site coordinator (SC) either by phone or in person. For those who agree and are eligible, consent will be obtained according to the standards of the single Institutional Review Board (sIRB) of record, the Harvard Longwood Campus (HLC) IRB, and local IRB policy, as applicable.
- Consented participants will be enrolled to the study through the Frontier Science Study Enrollment System (SES). Home sampling kits for hrHPV testing will be mailed to consented participants by the SC with instructions. Alternatively, participants can come to the clinic for self-collection and the SC will mail their samples to centralized laboratory. For those who collect samples at home, the participant will mail their collected sample to centralized laboratory for hrHPV testing. The local SC will be informed of the results by the UCLA study coordinator through secure communications. Those screened hrHPV-positive will be notified of their results by the SC and scheduled for an in-person baseline visit and up to three annual follow-up visits that include a colposcopy (and biopsy, where indicated). Outcomes are 3-year cumulative risk of (i) vaccine-HPV types that persist 12 months or longer, and (ii) histologic CIN 2+.
- If the PHS test is negative at Testing 1, participants will be asked to retest either in clinic or at home the following year with the same procedure as for Testing 1. If hrHPV-positive at Testing 2, they will be scheduled for a baseline and annual follow-up visits—the same as the colposcopy visits described above for hrHPV-positive.
- If hrHPV test is negative at Testing 2, the SC will mail participants a self-sample kit annually (starting the next year) for up to 3 years for research hrHPV testing to address Aim 1, but these will not be used for recruitment

Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies (LiVes LLC Study [Protocol PH700])

into the baseline and follow-up study. Results will not be shared with these participants, as they are research tests with no clinical implications. Participants will self-collect specimens in clinic or at home and send the specimen to the UCLA Department of Pediatrics.

DATA COLLECTION

Study data will be collected through hrHPV testing, colposcopic examination, interviews, surveys, medical abstraction, and PHACS-affiliated datasets.

Protocol Schema

Recruitment/Enrollment

- WLHIV aged 21 years up to and including 45 years old with an intact cervix currently or previously enrolled in PHACS-affiliated studies or non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics will be identified. Study staff will contact/approach potential participants and obtain informed consent.
- Eligible participants will be enrolled for primary hrHPV screening (PHS) using a self-collected sample. PHS testing will be done at a centralized laboratory.
- Participants who test positive for PHS will be scheduled for a baseline colposcopy examination which includes cytology/pap and biopsies, if indicated, repository specimens for biomarker testing, and will complete surveys/questionnaires.
- Participants negative for PHS will be asked to obtain another self-collected sample 1 year later. If positive, a baseline examination, as above, will be scheduled.
- Participants who are hrHPV-negative on the first and second testing will be asked to continue to obtain annual self-collected sample for research purposes only for the next 3 years.



Study Evaluations for Those with PHS Positive Results

- Standard colposcopic examination and specimen collection that include documentation of standard colposcopic features, visual inspection for lesions and warts, collection of routine cytology/pap, unstained cytology/pap slide, CVL, and endo/exocervical cells for biorepository, and cervical biopsy and histology/biopsy, when indicated.
- Administration of the Reproductive Health and Tobacco Use Online Survey and HPV Immunization and Current ART Questionnaire via interview by study staff.
- Cervical biopsy specimens obtained from the local pathology laboratory, namely a histology/biopsy slide from each biopsy specimen or a slice from the paraffin embedded tissue will be sent to the Central Pathology Laboratory at UCLA for standardized research reading.
 - If at the baseline or any follow-up colposcopy visit a participant is diagnosed with CIN 2 or worse on biopsy, the participant will be discontinued from the study and referred for SOC.
 - If the participant is found to have CIN 1 or less at baseline or follow-up colposcopy visits, the participant will be scheduled for a similar colposcopic examination annually until the end of study (2028).



Data for Analysis for Those with PHS Positive Results

- Study data collected through the questionnaire and online survey.
- Data from the standard colposcopic examination and specimen testing.
- Most recently documented CD4 count and HIV viral load, HPV vaccination history, all available previous cytology/pap and histology/biopsy results, and STI testing results if obtained at the colposcopic examination as part of standard of care.
- Medication history, CD4 counts, HIV viral load, tobacco use history, and types of contraceptive used.

1. Introduction

1.1 Study Background

Malignancies of the cervix are the fourth leading cause of cancer incidence and mortality in women worldwide with an estimated 500,000 new cases and over 300,000 deaths in 2018. Women living with HIV (WLHIV) are at particularly high risk.¹⁻⁷ While combination antiretroviral therapies (cART) has reduced the risk of human papillomavirus (HPV)-associated cancers in WLHIV, the incidence of HPV-associated malignancies is five- to six fold higher in this vulnerable group compared to women who are human immunodeficiency virus (HIV)-negative.⁵⁻⁷ These women represent a major part of the burden of Cervical Intraepithelial Neoplasia (CIN) 2+ in this population, even years following what appears to be successful treatment.^{8,9} The proposed study will focus on the two most important global strategies to reduce cervical cancer (CC) incidence and mortality, namely HPV vaccines and CC screening. This study will identify clinically relevant disease end points in HPV-vaccinated versus HPV-unvaccinated WLHIV and utilize these clinical data to establish optimal screening algorithms. We will achieve these goals by leveraging a unique resource, Pediatric HIV/AIDS Cohort Study (PHACS) and four affiliated studies: Surveillance Monitoring for ART Toxicities (SMARTT), which is a longitudinal study of WLHIV enrolled along with their HIV-exposed but uninfected offspring; Adolescent Master Protocol for Participants 18 Years of Age and Older (AMP Up), which remains by far the largest U.S.-based cohort of women living with perinatal HIV (WLP HIV); AMP Up Lite, which is a prospective cohort study for young adults with perinatal HIV infection; and Health Outcomes around Pregnancy and Exposure to HIV/ARVs (HOPE), which is enrolling WLHIV between ages 18 to 40 years old.

1.2 Study Rationale

1.2.1 HPV Vaccines

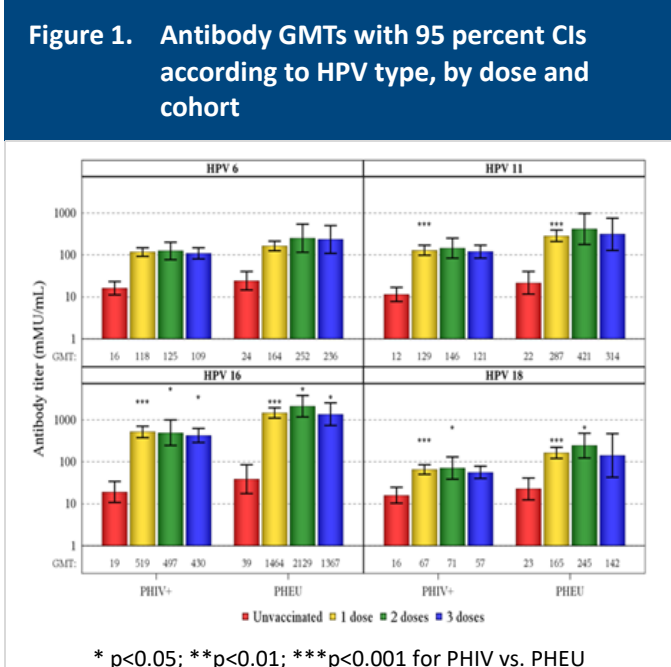
Although HPV vaccines are highly effective in the general population, their efficacy/ effectiveness in WLHIV is largely untested. HPV vaccine studies in WLHIV have, to date, almost exclusively focused on immunogenicity and safety, demonstrating that seroconversion rates and safety are similar to HIV uninfected women; whereas, antibody titers are lower in persons with HIV.¹⁰⁻¹⁵ More specifically, there is a paucity of effectiveness studies in WLHIV targeting clinically accepted HPV or disease end points, such as vaccine-type HPV persistence and CIN 2+. Of note, our prior study in adolescent and young WLP HIV in AMP Up found not only lower antibody titers but also a fivefold higher rate of low-grade abnormal cytology/pap in young WLHIV than among HIV-negative controls—including those vaccinated prior to their sexual debut (see Section 1.2.2 below).¹⁶ The majority of AMP Up WLHIV at that time were too young for development of CIN 2+ but are of age now and will be our target population in this study.

In an open-label one-arm study, McClymont et al.¹⁵ found a rate ratio (95% confidence interval [CI]) of 11.7 (2.6-52.1) for HPV type persistence in WLHIV vaccinated with quadrivalent (4vHPV) vaccine compared to rates in vaccinated HIV-negative published in the literature demonstrating reduced efficacy in WLHIV. The limitations noted were the design of comparing local HPV-vaccinated WLHIV with only summary values from referenced articles. In the only randomized controlled trial (RCT) of the 4vHPV vaccine to include women living with HIV, Wilkin et al.¹⁴ enrolled 575 persons

living with HIV aged ≥ 27 years to examine anal HPV persistence and anal high-grade squamous intraepithelial lesions (HSIL). The trial was halted based on futility showing no efficacy of the HPV vaccine for either persistence or HSIL. Hidalgo-Tenorio et al.¹⁷ conducted an RCT trial of 129 men who have sex with men (MSM) with HIV and found that the vaccine and placebo arms did not differ by HSIL or genital wart incidence over the 48 months of follow-up. Paleky et al.¹⁸ conducted a one-arm study of 4vHPV in 260 MSM with HIV, 18-26 years of age, and reported that none of the participants who were serologically naïve at baseline for 4vHPV types were found to develop low-grade squamous intraepithelial lesions (LSIL) or HSIL related to vaccine-HPV-types over 24 months. Overall, the limited current data among WLHIV are insufficient to make strong conclusions regarding efficacy/effectiveness of 4vHPV or other HPV vaccines. To address these gaps, the current study will compare vaccinated versus unvaccinated WLHIV with detailed hrHPV and histologic classification over 3 years of follow-up to examine whether the HPV vaccine is effective in preventing hrHPV persistence, an accepted definition used within the HPV vaccine literature,¹⁵ as well as histologic (h) CIN 2+ lesions.

1.2.2 Antibody Titer in HPV-Vaccinated Young Women Living with Perinatal HIV and Incidence of Abnormal Cervical Cytology/pap

Utilizing PHACS data, we measured HPV vaccine-type antibody levels from stored sera in 310 young persons with perinatal HIV (PHIV) and 148 youth who were perinatally HIV-exposed but uninfected (PHEU).^{16, 19, 20} Geometric mean titers (GMTs) were lower for all HPV vaccine types in the PHIV youth. However, GMT were similar whether participants received one, two, or three doses (Figure 1). Lack of association with dose remained true even when adjusting for age at vaccination—a known factor influencing GMT.²¹ For all four types, younger age and lower HIV viral load at first vaccine dose and fewer years from last vaccine dose to sample collection were each independently associated with higher GMT. Among the females, the cumulative prevalence of abnormal cervical cytology/pap (ASCUS+) in those vaccinated was almost 60 percent for WLPHIV and 4 percent for PHEU.¹⁶ Among the 56 WLPHIV and 7 PHEU who were sexually active and 4vHPV vaccinated, 33 WLPHIV and 1 PHEU had abnormal cervical cytology/pap with the majority (88%) being ASCUS/LSIL. No histology/biopsy was available.



When restricted to those who initiated vaccination prior to sexual debut, the Incidence Rate Ratio (IRR) was attenuated but WLPHIV continued to be at higher rate for abnormal cytology/pap (IRR=3.0, 95% CI 0.4 to 25.7). The number of vaccine doses, GMT, and number of sexual partners were not associated with abnormal cytology/pap. The data suggested abnormal cytology/pap was associated with low CD4, high viral

load, and lack of cART at first vaccination dose. The lack of observed vaccine effectiveness in the girls was alarming. It may be that the abnormal cytology/pap is due to non-vaccine-HPV-types, the lower titers are not protective, and/or the antibodies generated in WLP HIV are dysfunctional.²²⁻²⁵ WLP HIV are heavily antiretroviral therapy (ART)-experienced with often incomplete immune reconstitution.²⁵ Of note, WL HIV are vulnerable to hrHPV types (e.g., HPV 58) not found in current HPV vaccines.²⁶ It is also plausible that the hrHPV infections were acquired perinatally. Perinatal transmission of hrHPV has been well-documented; however, the vast majority are transient.²⁷⁻³³ Unfortunately, there are no large mother-infant studies of WL HIV. In a small study, our group detected hrHPV in the genitals of 30 percent of the PHIV girls aged 2-18 years who never reported sexual contact compared to 7 percent of HIV-negative girls,³⁴ suggesting that infants with HIV may experience persistent perinatally transmitted hrHPV infection after exposure during delivery³⁵ and their own immunosuppression. Including WLP HIV in studies, such as we propose, is clearly warranted.

1.2.3 Cervical Cancer Screening (CCS)

CCS remains one of the mainstays in reaching the World Health Organization's (WHO)'s goal to eliminate CC. The primary goal of CCS in the United States is to identify the precancers CIN graded as 2 or 3 (CIN 2, CIN 3), which if left untreated have a high risk for progression to cancer.³⁶ While most researchers believe that CIN 3 is the true precancer, because of the difficulty in distinguishing CIN 2 from CIN 3 objectively, most clinical algorithms use CIN 2 as a threshold for treatment, with the exception in women concerned about fertility.³⁶⁻³⁹ [Table 1](#) summarizes the United States Preventive Services Taskforce (USPSTF), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Cancer Society (ACS) recommendations for CCS in the general population. Each of the groups recommend primary hrHPV screening (PHS) as a preferred method due to its higher sensitivity and negative predictive value compared to cytology/pap.^{38,40,41} Worldwide, PHS is fast becoming the norm for CC screening, in part due to the declining specificity of cytology/pap in HPV-vaccinated women.⁴² One of the remaining hurdles to global implementation of PHS is its low positive predictive value (PPV), ranging from 15 to 28 percent,⁴³⁻⁴⁵ thus the need for cost-effective triage strategies to avoid unnecessary colposcopy procedures. For example, current Food and Drug Administration (FDA)-approved reflex strategies following a positive PHS include genotyping for hrHPV 16/18 and cytology/pap. Women positive for hrHPV 16/18 or who have atypical squamous cells of undetermined significance or more severe lesions (ASCUS+) are triaged to immediate colposcopy, whereas those with non-HPV 16/18 hrHPV that are cytologically normal are triaged to surveillance with screening in 1 year. A third triage technology recently approved by the FDA is intracellular dual-immunocytochemistry staining for p16 and Ki-67 (CINtec® PLUS Cytology/pap, Roche),⁴⁶ which indicates cell cycle deregulation, a hallmark of transforming hrHPV infections.⁴⁷ Several studies show that triage using dual staining has a higher specificity and PPV than cytology/pap alone for detection of CIN 2+, especially in young women.⁴⁸⁻⁵² To date, ASCCP has yet to incorporate dual staining to its management guidelines pending further data analysis of its performance.

	Recommendation	Age to screen (years)	Alternative**
ACS 2020¹	PHS* q 5 years	25-65	Cotesting q 5 y or Cytology/pap q 3 y
USPSTF²/ACOG/ASCCP	Cytology/pap q 3 years PHS q 5 years	21-29 30-65	As above

* Must be FDA-approved test: Roche Cobas, BD Onclarity and Abbott Alinity

** Alternative only if primary HPV limited access

¹ American Cancer Society

² United States Preventive Services Taskforce guidelines 2018

1.2.4 Cervical Cancer Screening in WLHIV

As with hrHPV-associated cancers, rates of hrHPV infections and their associated abnormal cytology/pap are elevated in WLHIV, making efficient CCS strategies a challenge.^{1-7, 53} Rates of hrHPV infections range between 30 percent and 70 percent, and rates of abnormal cytology/pap range from 24 percent to 51 percent.⁵⁴⁻⁶² WLP HIV have equally high rates of hrHPV and abnormal cytology/pap as women who acquired HIV horizontally.^{1, 56-58} Drs. Moscicki and Strickler are active members of a working group for the U.S. Department of Health and Human Services (HHS) that develops guidelines for CCS and triage of abnormal cytology/pap for WLHIV (<https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new>). Recommendations differ from the general population in several ways including screening starting at 21 years (vs. 25 years per ACS), shorter intervals (ranging from 1 to 3 years vs. 5 years), and referral of low-grade (L) SIL regardless of age. Currently, cytology/pap alone (without hrHPV testing) is recommended up to 29 years of age, and cotesting or cytology/pap alone is recommended in women over 30 years of age. The low sensitivity of cytology/pap necessitates referral based on mild abnormalities as a threshold. Sadly, the large number of WLHIV unnecessarily referred to colposcopy leads to multiple medical and psychological complications.⁵⁹⁻⁶⁴ Unfortunately, PHS is not addressed in the guidelines based on lack of studies to guide recommendations. While there are concerns regarding the high rates of hrHPV among these women, little data are available on the performance of the triage tests. Most recently, our research group showed that PHS with hrHPV 16/18 genotyping in adult WLHIV greatly reduced colposcopy rates compared to cytology/pap alone or cotesting (24% vs. 32% vs. 40%, respectively) with no loss in sensitivity.⁶⁵ Testing for P16/Ki67 also provided encouraging results. Triage in HPV-vaccinated WLHIV populations may have unique caveats as hrHPV 16 appears to play less of a role in HSIL in WLHIV than the general population and WLHIV are more likely to have hrHPV types 11, 18, 33, 51, 52, 53, 58, and 61, and multiple hrHPV types.⁶⁶

Primary hrHPV Screening in WLHIV. Dr. Strickler’s group was one of the first to publish the performance of PHS in WLHIV on detection of CIN 2+.⁶⁵ They enrolled 865 WLHIV (323 from the Women’s Interagency HIV Study (WIHS) and 542 from WIHS-affiliated colposcopy clinics). All participants underwent cytology/pap and hrHPV testing (Roche, Cobas), including hrHPV 16/18 genotyping, and a subsample of women had p16/K67 dual stain. WLHIV who tested hrHPV-positive or had cytologic ASCUS+ underwent colposcopy, as did a random 21 percent of WLHIV who were

hrHPV-negative. The mean age was 46 years, median CD4 was 592 cells/ μ L, and 95 percent used cART. The sensitivity (Se), PPV, and immediate colposcopy referral (%) for cervical cancer screening method is shown in [Table 2](#). Current standard cotesting resulted in 29 percent of colposcopy referrals. PHS alone had the highest referral rate (35%), but with hrHPV 16/18 genotyping, referrals were reduced to 9 percent with little loss in sensitivity. p16/Ki-67 immunochemistry had the highest PPV, 20 percent, but 13 percent specimen inadequacy. These data support the utility of PHS with reflex hrHPV 16/18 genotyping. As this study had a median age over 40 years, these findings cannot be generalized to young women, as their hrHPV prevalence rates are two to three times higher than in these older participants. Our planned study in younger WLHIV will confirm the value of PHS and would add data on p16/Ki-67 dual staining, as well as hrHPV extended genotyping and hrHPV/host genome methylation. Dr. Strickler’s group reported an association between hrHPV methylation and precancer in WLHIV, but this observation has not been tested for CCS triage.⁶⁷ Our proposed study will test various algorithms using combinations of each of these methods to identify efficient triage for hrHPV-positive WLHIV.

Screening strategy	Cross-sectional indication for colposcopy	Sensitivity (95% CI)	PPV (95% CI)	% Colposcopy referral
hrHPV cotesting	HPV16/18 or other hrHPV+ and ASCUS or LSIL +	91% (75%, 97%)	12% (8%, 16%)	29%
Primary HPV screening	Any hrHPV+	87% (71%, 95%)	9% (6%, 13%)	35%
PHS genotype	HPV 16/18+	84% (68%, 93%)	13% (9%, 18%)	9%
p16/Ki-67	p16/Ki-67+	82% (60%, 93%)	20% (13%, 30%)	15%

1.2.5 Promising New Strategies for CCS

1.2.5.1 Self-Collection

There is general agreement that hrHPV deoxyribonucleic acid (DNA) testing using self-collected cervical/vaginal specimens yields similar results to samples collected during a gynecologic exam and benefits from a higher rate of acceptability.^{43, 68} As a result, there is great interest in the use of self-sampling for CCS because it bypasses the need for trained healthcare providers and a gynecologic exam, and is applicable to even limited resource settings in the United States and internationally. Several countries, including Sweden and the Netherlands, now offer women the choice to use self-collection versus a provider visit for CCS. The samples can be easily shipped to a central testing facility. This project will take advantage of the PHACS-affiliated studies where women are already experienced in collecting intravaginal self-sampling for hrHPV, including mailing in specimens when convenient (see Section 6.1).

1.2.5.2 hrHPV Genotyping

There has been recent interest in extending genotyping beyond 16/18. A study by DeMarco et al.⁷³ showed that hrHPV 31, 33, 35, 52, and 58 have lower risk for CIN 2+ than 16, 18, and 45, but substantially higher risk for CIN 2+ than hrHPV 39, 51, 56, 59, and 68, which would assist in differentiating risk among the non-16/18 hrHPV.

1.2.5.3 hrHPV and Host DNA Methylation

Promising recent data in the general population and in WLHIV have shown strong differences in hrHPV DNA methylation at CpG sites of the viral capsid genes L1 and L2 as well as several human CpG sites between women with and without CIN 2+.⁷⁴⁻⁸⁴ One of the barriers associated with viral methylation is the inclusion of all important methylation CpG sites for all high-risk types in a single assay. A recent study reported on multi-type hrHPV methylation (16/18/31/33/35/39/45/51/52/56/58/59) demonstrating the feasibility of using methylation as a triage for hrHPV-positive women.⁸⁵ Data remain very limited in WLHIV.⁸³ Additional data are needed to better determine the potential use of this approach for reflex triage following a positive PHS test in WLHIV. Unlike cytology/pap as a reflex triage test, methylation does not require morphologic assessment and is therefore suitable for self-collected samples, circumventing the need for a clinical visit.

Dr. Wentzensen, our collaborator from the National Cancer Institute, co-led a study with Dr. Burk at Einstein School of Medicine to examine combined multi-hrHPV type methylation.⁸⁵ One of the challenges of hrHPV methylation is making certain that the CpG changes are relevant to all of the carcinogenic hrHPV types, especially when used in WLHIV. Dr. Wentzensen and colleagues showed strong correlation between CIN 3 and methylation for hrHPV types 16, 18, 31, and 45.^{74,86} In a recent publication, the group examined the feasibility of performing methylation on 12 hrHPV to triage hrHPV-positive women⁸⁵ through a nested case-control study of 30 women with CIN 3/adenocarcinoma in situ and 30 controls with hrHPV but without disease. Controls were selected based on a single hrHPV type infection for hrHPV types (16/18/31/33/35/39/45/51/52/56/58/59). Next-generation bisulfite sequencing was performed on CpG sites within the L1 and L2 genes. Methylation CpG sites were identified that were strongly associated with CIN 3/adenocarcinoma in situ (AIS) for all 12 types (ORs ranged from 4.76 to 23 with the majority of p values <0.001). **Figure 2** shows the elevated risk of CIN 3 by methylation status of 12 hrHPV genotypes. They then compared differences in triage tests (listed in **Table 3**) for Se (Se fixed at 80% for methylation), specificity (Sp), and PPV and negative predictive value (NPV). The risk of CIN 3/AIS was highest in women testing positive on the 12 type hrHPV DNA methylation test and lowest among those positive for either ASCUS+ cytology/pap or hrHPV16/18. CIN 3/AIS risk in the methylation negatives was similar to cytology/pap and hrHPV 16/18 negative.

Figure 2. Risk of CIN 3 by HPV genotype and methylation status

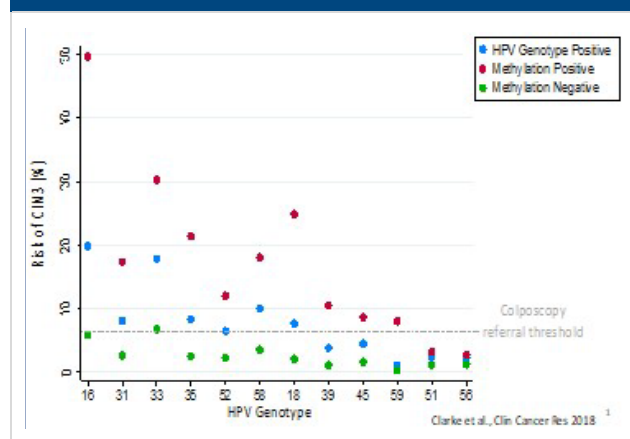


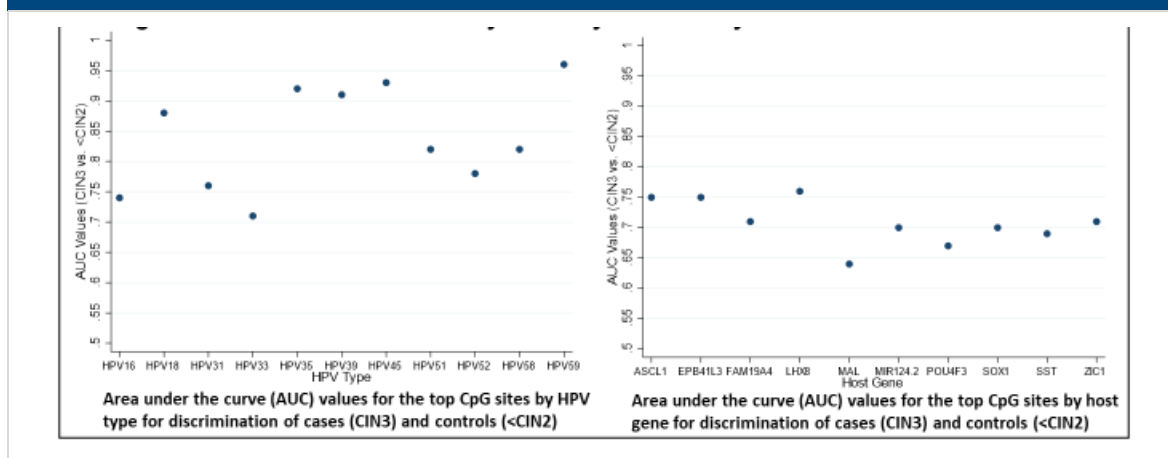
Table 3. Comparison of performance of 12 HPV type methylation to established triage tests

	Cytology/pap	HPV16/18	Cytology/pap and HPV16/18	Methylation
Threshold	ASCUS+	Either 16 or 18 positive	ASCUS+ or 16 or 18 positive	Sensitivity fixed at 80%
Positivity	48.7%	30.8%	63.7%	38.5%
Sensitivity	76.6%	56.7%	89.9%	80.0%
Specificity	54.1%	71.8%	38.8%	65.6%
PPV	14.3%	16.8%	12.8%	18.9%
1-NPV	4.2%	5.7%	2.5%	3.0%

Source: Clarke et al, Clin Cancer Res 2018

In an internal validation ([Figure 3](#)) study including approximately 250 cases (CIN 3) and 300 controls (<CIN 2), the methylation assay achieved good discrimination for detection of CIN 3, with several sites across most host genes achieving AUCs ≥ 0.70 . For viral methylation, the assay achieved good discrimination for detection of CIN 3, with more than 100 CpG sites across all hrHPV types achieving AUCs ≥ 0.75 and several sites achieving AUCs ≥ 0.85 . In summary, this study provides important evidence that host and hrHPV DNA methylation may have strong potential as a triage test for women hrHPV-positive. Strengths include a lower rate of positivity compared to other triage tests, resulting in fewer unnecessary referrals to colposcopy. Risks of CIN 3+ associated with a methylation-negative test fell below the current ASCCP threshold set (4.1%) for colposcopy referral, demonstrating safety of a negative test.³⁹ Methylation assays are especially attractive since they could be performed on self-collected samples, negating the need for a clinic visit.

Figure 3. Internal validation study of methylation assay for detection of CIN 3



In summary, understanding vaccine effectiveness is critical to designing appropriate CCS strategies for WLHIV. For example, new screening strategies are moving toward PHS, which has high sensitivity but low PPV in the general population, requiring triage tests to increase specificity and PPV. Given that rates of hrHPV detection are two- to threefold higher in WLHIV, the performance characteristics of these triage strategies to detect hCIN 2+ are likely to behave differently and will

be critical to study in WLHIV. As there are few studies comparing triage strategies in HPV-vaccinated and unvaccinated WLHIV, PHS is currently not recommended in the United States for WLHIV. We have a unique opportunity to examine vaccine effectiveness in WLHIV by partnering with PHACS, the largest U.S.-based prospective cohort of WLP HIV, a largely understudied population, augmented with a large cohort of women who acquired HIV through other modes of transmission. In addition to vaccine effectiveness, our study design also provides the opportunity to examine CC screening strategies and the impact of HPV vaccination.

2. Study Aims and Hypotheses

LiVes LLC (PH700) is a multi-centered follow-up study to determine the effectiveness of human papillomavirus (HPV) vaccine in women living with HIV (WLHIV) and to assess primary high-risk (hr)HPV screening (PHS) and reflex triage strategies among vaccinated and unvaccinated WLHIV who are currently or previously enrolled in PHACS-affiliated studies or non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics.

2.1 Aim 1

To examine the effectiveness of HPV vaccine in WLHIV based on the following outcomes: 3-year cumulative risk of (i) vaccine-hrHPV types that persist 12 months or longer, and (ii) histologic (h) CIN 2+ (CIN 2+ throughout the protocol means “CIN 2 and worse”).

Hypothesis:

We hypothesize that HPV vaccination will be effective in reducing the risk of these outcomes, but the impact of vaccination will be lower in WLHIV than reported for the general population. Younger age at the time of vaccination will have greater effectiveness.

2.2 Aim 2a

To examine and compare the sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) to detect hCIN 2+ immediately or in 3 years in PHS-positive WLHIV using provider-collected specimens for the four reflex strategies: (i) cytology/pap, (ii) hrHPV extended genotyping, (iii) p16/Ki-67 dual-staining cytology/pap, and (iv) hrHPV/host methylation levels. We will also assess whether HPV vaccination modifies these performance characteristics.

Hypothesis:

We hypothesize that cytology/pap and dual staining will have a poorer performance than methylation and genotyping to detect hCIN 2+ and these performance characteristics will be modified by HPV vaccine status.

2.3 Aim 2b

To examine the Se, Sp, PPV, and NPV in self-collected PHS-positive samples for hCIN 2+ detection focusing on methylation and hrHPV genotyping.

Hypothesis:

We hypothesize that methylation and hrHPV genotyping will have strong performance characteristics in self-collected PHS positive specimens.

3. Study Design

3.1 Overall Study Design

3.1.1 Aim 1

Aim 1 will determine the 3-year cumulative risk of (i) vaccine-HPV types that persist 12 months or longer, and (ii) hCIN 2+. We will implement an investigation of HPV vaccine effectiveness in WLHIV, comparing all vaccinated and unvaccinated WLHIV. Our objective is to determine to what extent HPV vaccine works in WLHIV to assist in the development of cervical cancer prevention strategies in this vulnerable population. WLHIV currently or previously enrolled in PHACS-affiliated studies **or** non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics will be recruited, all of which include those with non-perinatally or perinatally acquired transmission. To ensure an adequate number of outcomes and considering the timing of vaccine availability (approved in 2007), we plan to enroll women who are at least 21 years of age and less than or equal to 45 years of age. Collectively, participants recruited from these four complementary studies will provide a wide distribution of age groups when our outcomes, hrHPV persistence and CIN 2+, peak. Moreover, we will have a relatively even distribution of women who are HPV-vaccinated and unvaccinated. However, we expect younger woman to have a higher rate of vaccination. Consented WLHIV will be screened using an FDA-approved test for PHS (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), and those positive (PHS-positive) will be scheduled to attend a baseline visit and annual follow up clinic visits for questionnaires/surveys, colposcopy, sample collection, and biopsy if indicated.

Those PHS-negative will be asked to participate in a second PHS screen the following year and, if PHS-positive, will also be asked to attend a baseline visit and annual follow-up clinic visits for colposcopy, sample collection, and biopsy if indicated. Women who are PHS-negative on both screens will be mailed an annual self-sampling kit for research hrHPV genotyping for 3 additional years. Outcomes for Aim 1 include detection of 12 months persistence of vaccine-hrHPV types (all enrolled) or histologic (h) CIN 2+ cumulatively over 3 years (in those with colposcopic exam). For estimating the cumulative risk of CIN 2+, we assume that women with two consecutive hrHPV-negative results will not develop CIN 2+ by 3 years after baseline based on previous studies.³⁹ They will thus be classified as \leq CIN 1.

3.1.2 Aim 2

Aim 2a will determine the Se/Sp and PPV and NPV baseline assay test results using provider-collected specimens for detection of hCIN 2+ immediately or in 3 years in PHS-positive WLHIV.

Aim 2b will determine the Se/Sp/PPV and NPV baseline assay test results using self-collected specimens for host/hrHPV methylation and hrHPV genotyping for hCIN 2+ in PHS-positive WLHIV.

As accurate screening and diagnosis is critical to the worldwide goal of cervical cancer elimination, we have incorporated examination of triage strategies for PHS—now the preferred approach worldwide. As previously discussed, PHS in which a hrHPV test is used as the initial screening assay has high Se but low PPV for CIN 2+, requiring an additional triage test. The current study design will assess and compare the performance of four reflex triage tests for the detection of CIN 2+ for

hrHPV-positive women, including the standard Centers for Disease Control and Prevention (CDC)-recommended screening tests (cytology/pap and/or genotyping for hrHPV 16/18) as well as additional cutting-edge and experimental screening methods. As described for Aim 1, all PHS-positive WLHIV will be invited for a baseline visit for colposcopy and biopsy (as indicated based on acetowhitening results) and will continue to be followed annually for up to 3 years. For Aim 2a, samples will be collected at the baseline colposcopy visit for the four triage tests: (i) hrHPV 16/18 genotyping as well as extended genotyping, (ii) cytology/pap, (iii) dual staining for p16/Ki67, and (iv) host/hrHPV DNA methylation. Both extended genotyping and methylation assays are not currently FDA-approved, although both are considered promising. PHS has not been adopted for WLHIV because of the paucity of relevant data in this vulnerable population, and because the optimal algorithms for reflex testing in WLHIV have not been determined. Our design will examine the performance characteristics of these assays in detecting CIN 2+ over a 3-year period. Aim 2b will use the residual self-sample from the first positive screening PHS to examine the performance of the two assays not requiring cervical cell morphology, (i) extended hrHPV genotyping and (ii) host/hrHPV methylation, making this approach attractive since it will avoid a clinic visit for the collection of triage tests, which is now the norm.

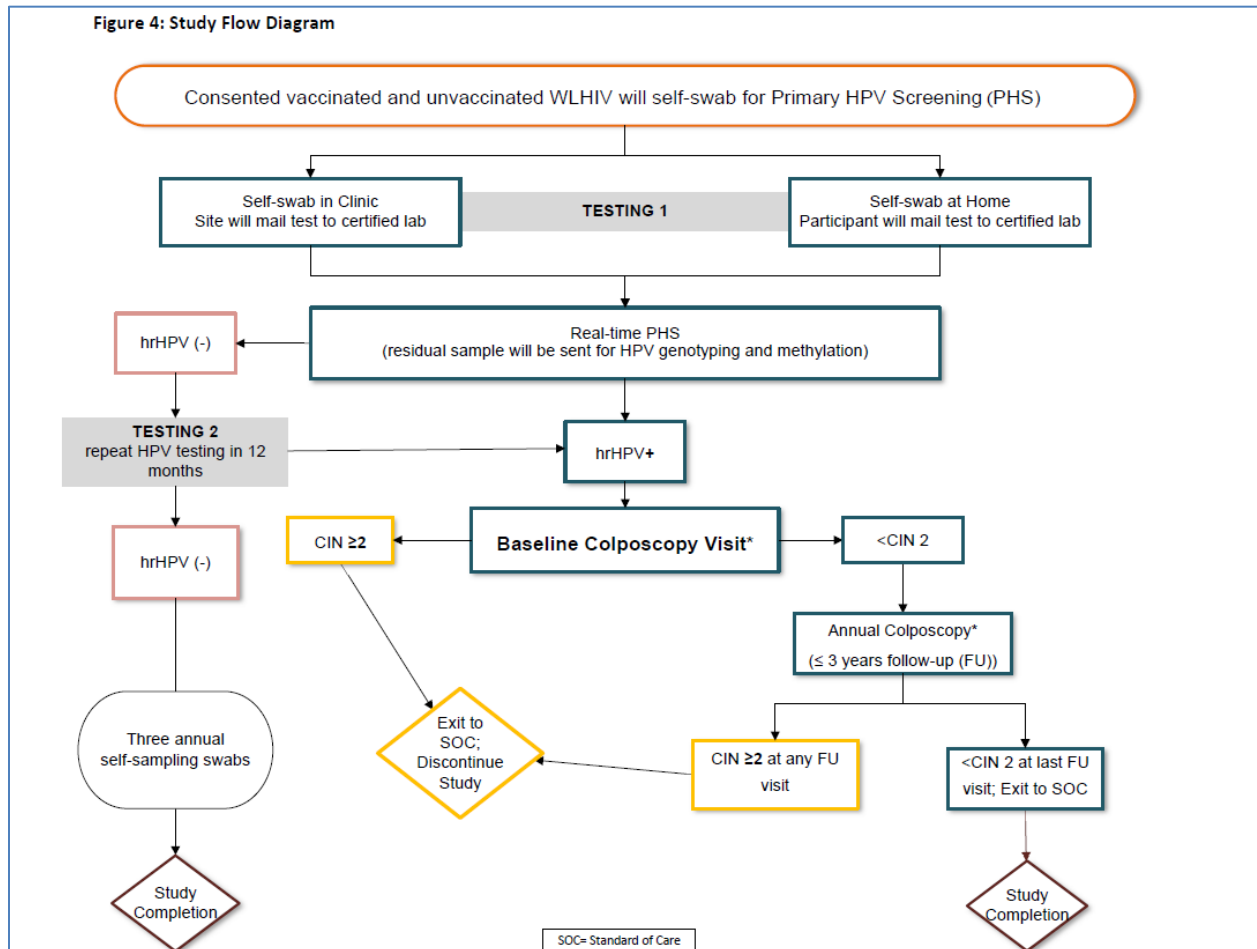
3.2 General Design Considerations

Figure 4 shows the broad design of recruitment and follow-up, and **Figure 5** (see Section 3.4) includes the estimated number of vaccinated and unvaccinated by hrHPV status. Over 3 years of follow-up, the study is designed to maximize the detection of hrHPV persistence by hrHPV genotyping, and CIN 2+ by performing annual colposcopy examinations in PHS-positive women. We chose CIN 2+ since CIN 2+ is currently used as the treatment threshold. Women with CIN 2+ at any visit will be referred for treatment per standard of care (SOC) and will be considered to have completed the study. Women with \leq CIN 1 will be followed annually with colposcopy (and biopsy, if indicated), research sample collection, medical chart abstraction since the last visit, and survey/questionnaire completion. The study is also designed to minimize false negative results of a single PHS by repeat testing in 1 year if initially PHS-negative. For Aim 1, to maximize observation time to detect persistent hrHPV, all PHS-negative WLHIV will continue to provide an annual self-sample for hrHPV genotyping for research testing over the 3 years after the initial screening (total of 4 observations), but those with two consecutive PHS-negative results (Testing 1 and Testing 2) will not go to colposcopy, as the NPV for CIN 2+ over 5 years after two sequential negative tests is close to 100 percent.⁸⁷ For Aim 2a and 2b, only PHS-positive women will be considered for analysis, since the high sensitivity of PHS is well established. Follow-up of these women will determine the performances of the provider-collected four triage tests and residual self-collected sample two triage tests for determining baseline, as well as cumulative CIN 2+. A 3-year window was chosen since this is the currently recommended CCS interval for WLHIV with normal test results. Women with hrHPV persistence at the last visit and abnormal cytology/pap (atypical squamous cells of undetermined significance [ASCUS]+) will also be referred for SOC treatment. Our design will also enable us to examine whether HPV vaccination status impacts triage strategies.

Although all WLHIV enrolled in the study will either be participants who are currently or previously enrolled in PHACS-affiliated studies **or** non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics, we will obtain an informed consent to participate in this study. As shown in **Figure 4**, home self-sampled cervicovaginal specimens will be used for initial hrHPV testing to reduce

participant inconvenience and enhance participation.⁸⁸ Self-collected specimens have been shown to provide similar results to samples collected by a clinician during a gynecologic examination using a validated and FDA-approved PHS test,⁸⁹ and several countries have now adopted self-collection as a choice for screening.

Figure 4. Study Flow Diagram



3.3 Study Population

3.3.1 PHACS-Affiliated Protocols

This study will enroll WLHIV who are currently or previously enrolled in PHACS-affiliated studies **or** non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics. Nine PHACS sites were chosen based on their current participant volume and willingness to participate.

- The current PHACS grant will run through July 2025 (P01 HD103133; Principal Investigators (PIs) Williams, Chadwick, Jao, Hernandez-Diaz), and includes the SMARTT, AMP Up, AMP Up Lite studies.
- HOPE was given their initial award starting September 2020 through February 2026 (1R01HD101351-01; PIs Williams, Chadwick, Kacanek, Powis).

3.3.1.1 SMARTT

Beginning in 2007, the PHACS SMARTT study began enrolling pregnant WLHIV at 22 U.S.-based sites. Mothers and their PHEU children are followed longitudinally to study the health of the mothers in pregnancy and the children with perinatal exposure to HIV and antiretroviral drugs. Each mother attends scheduled in-person visits (along with their child) at delivery and 1, 3, 5, 7, 9, 11, 13, 15, and 17 years of age when data are collected on physical, behavioral, and mental health. Serum, plasma, peripheral blood mononuclear cells (PBMCs) and a hair sample are collected for the PHACS Repository. Among the selected nine sites in AMP Up, seven are also SMARTT sites. There are currently 2,404 biological mothers with HIV on the study, of whom 1,128 are from the seven SMARTT sites engaged in this substudy, and 776 of these women are 40 years of age or younger. We estimate that 50 percent have received at least a single HPV vaccine dose—younger women having higher rates (90%, mostly with v9hrHPV) than older women (20%, mostly with v4hrHPV). Of the 776 women 40 years of age or younger, the median age is 34 years (IQR 30, 37), 73 percent identify as Black, 20 percent as White, and 18 percent report Hispanic ethnicity. Mean CD4 count during pregnancy among these participants was 589 cell/mm³, and 31 percent were receiving cART with an integrase inhibitor/entry inhibitor/fusion inhibitor (II/EI/FI), 38 percent with a protease inhibitor (PI), 15 percent with a non-nucleoside reverse transcriptase inhibitor (NNRTI), 2 percent none, and the remaining were other or missing.

3.3.1.2 AMP Up

The PHACS AMP Up Study is a multicenter study designed to evaluate long-term effects of PHIV infection and ART on numerous health and behavioral domains. Starting in 2007, PHACS initially enrolled children with perinatally acquired HIV (PHIV) and PHEU aged 7-16 years into the Adolescent Master Protocol (AMP), and in 2014, AMP Up opened for enrollment for ≥ 18-year-old persons living with PHIV or PHEU with a modified protocol to accommodate adolescents and young adults. PHEU are not included in the proposed study. There are currently 350 WLP HIV in AMP Up across 15 sites in the United States, including Puerto Rico. Approximately 90 percent have been HPV-vaccinated and the majority (90%) with the nonavalent vaccine (9vhrHPV). Participants in AMP Up have in-person visits every 3 years with annual chart abstraction and online self-administered questionnaires. AMP Up has resulted in a rich biorepository including serum, plasma, peripheral blood monocytes, oral swabs and washes, self-collected vaginal specimens, and urine. Of

note, AMP Up has an 89 percent retention rate since 2014, and many AMP Up participants regularly participate in affiliated studies. From the nine clinical recruitment sites for this study, we have 237 active WLP HIV. Their median age is 25 (IQR 23, 30) years. Based on self-report, 21 percent report Hispanic ethnicity, 71 percent identify as Black, 21 percent as White, and 8 percent as other racial/ethnic identities. The median CD4 count among WLP HIV in AMP Up is 577 cells/mm³ (IQR 284-821). When ARV regimens are grouped hierarchically, 63 percent are receiving cART with an II/EI/FI, 15 percent cART with PI, 12 percent cART with NNRTI, 6 percent other antiretroviral (ARV), and 4 percent no ARV.

3.3.1.3 AMP Up Lite

The PHACS AMP Up Lite study is a prospective cohort study designed to define the impact of HIV ART on young adults with PHIV as they transition into adulthood. It enrolls young adults living with perinatal HIV at or beyond their 18th birthday. Approximately 500 PHIV young adults will be enrolled in the study. The entry visit includes: a) clinical assessments: height, weight, and blood pressure measurements; b) interviewer-administered medical history questionnaire; c) online survey on demographics, healthcare access and utilization, transition to adult HIV care, depression, health-related quality of life, social support, relationships, self-efficacy, HIV-related stigma, reproductive history, sexual behavior, substance use, ART adherence, fracture history, and self-reported hearing issues; and d) chart abstraction of medical diagnoses, antiretroviral therapies, immunizations, CD4, viral load, HIV resistance testing, complete blood count (CBC) profile, chemistry panel, lipid profile, glucose, pregnancy and pregnancy outcomes, results of sexually transmitted infection (STI) testing, and abnormal cytology/pap and histology/biopsy in the 12 months prior to entry, history of acquired immunodeficiency syndrome (AIDS)-defining illness and CDC classification, and mental health diagnoses. Serum, plasma, and PBMCs are collected for the PHACS Repository. At the annual follow-up visits, participants complete an online survey of demographics, height and weight, healthcare access and utilization, transition to adult HIV care, depression, health-related quality of life, social support, relationships, self-efficacy, HIV-related stigma, reproductive history, sexual behavior, substance use, ART adherence, interval fractures, and self-reported hearing issues. Chart abstraction at annual visits includes those mentioned above for the entry visit. At Year 5 only, there is collection of repository specimens: serum, plasma, and PBMCs. From 2017 until April of 2023, 320 participants living with PHIV have been enrolled in AMP Up Lite. The retention rate is 97 percent at 48 months and 96 percent at 60 months. At enrollment, the median age was 25 with 63 percent female; 65 percent self-identify as Black or African American, 25 percent as White, and 22 percent as Hispanic. At the most recent visit, the median age was 29 for males and 28 for females, and the ARV regimens were 70 percent combination cART with integrase strand transfer inhibitor (INSTI)/EI/FI, 10 percent cART with PI, 10 percent cART with NNRTI, 3 percent other ARV, 3 percent no ARV, and 5 percent missing information. Twenty percent of females have ever been pregnant. Among those still on study, the median CD4 count was 532 cells/mm³, and 41 percent had an HIV viral load of ≤ 75 copies/mL.

3.3.1.4 HOPE

The PHACS-affiliated study HOPE is a longitudinal observational study designed to evaluate the health and well-being of WLHIV of reproductive age. HOPE is independent, but affiliated with PHACS, and is enrolling 18-to-45-year old WLHIV who are nulliparous, pregnant, postpartum, or

parous but nonpregnant from 12 PHACS clinical sites. That target sample size is 1,630. The enrollment started in April 2022, and by June 1, 2023, 297 WLHIV were enrolled. For the 297 WLHIV, the median age is 30 (IQR 25, 35) years, 71 percent Black, 25 percent White, and 29 percent Hispanic ethnicity. The last available median CD4 count was 679 (IQR 428, 919) cell/mm³ and median log₁₀ viral load scale was 1.30 (IQR 1.30, 2.16) copies/mL. Serum, plasma, PBMCs, vaginal swabs for microbiome, metabolomics, and STI testing; rectal swab for microbiome; and hair, saliva, and oral swab are collected for the PHACS and HOPE repository. We note that 82 (27.6%) of the 297 enrolled WLHIV in HOPE were not co-enrolled in any other PHACS studies, and thus, WLHIV in these clinical sites could be additional resources for this study as well.

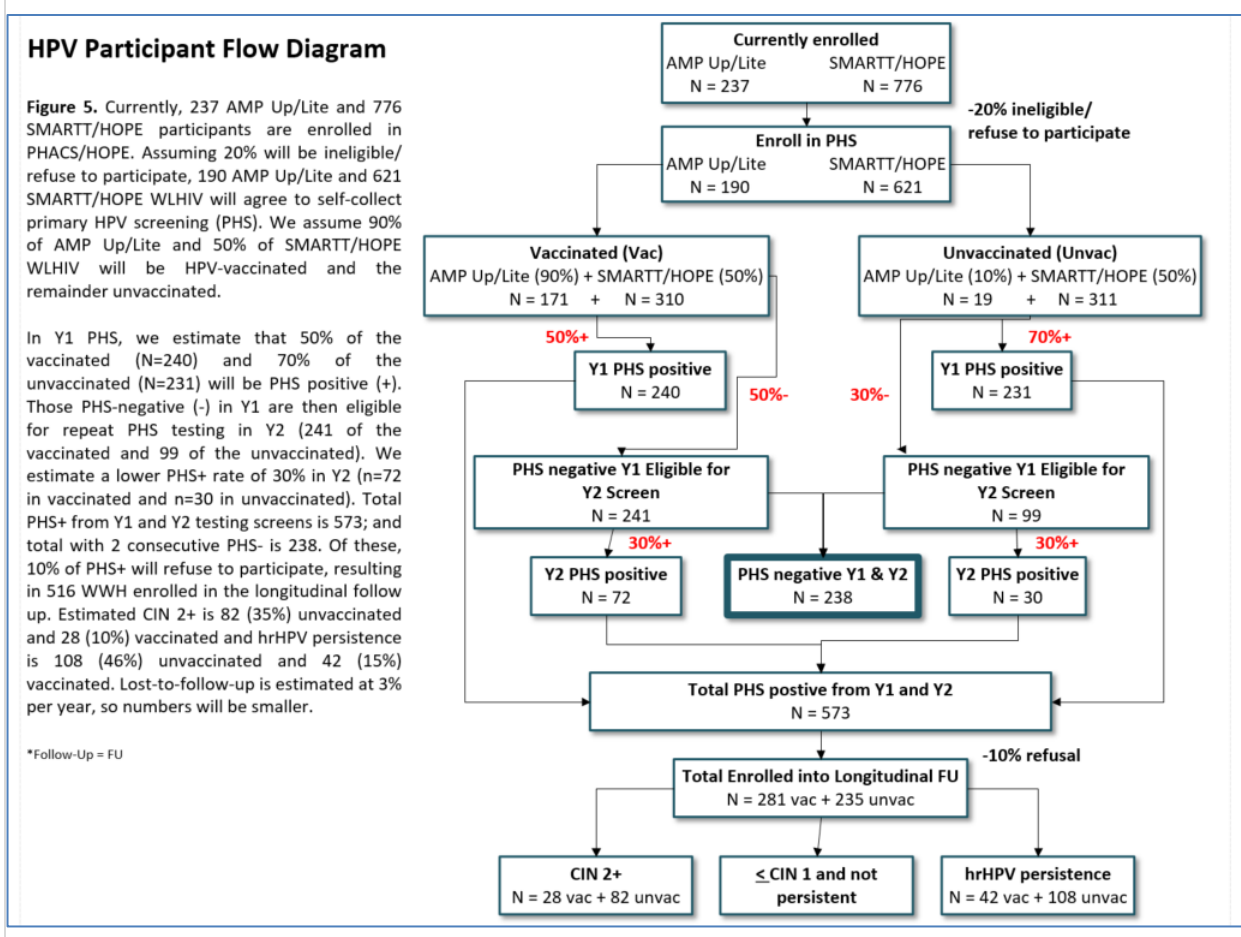
3.3.2 Non-PHACS Affiliated Recruitment

As the current PHACS P01 grant contract will end July 31, 2025, we are expanding the recruitment pool to include WLHIV who are known to the current LiVes LLC Sites, and the sites' affiliated clinics.

3.4 Sample Size

We expect that roughly 621 WLHIV from SMARTT or HOPE and 190 WLP HIV from AMP Up or AMP Up Lite ([Figure 5](#)) will go through screening for hrHPV (based on 20% refusal/ineligible estimates). As our initial estimates have changed because of the end of PHACS, we expanded our inclusion criteria so that we believe our estimates will remain the same. The figure has not been altered to estimate the numbers we expect. We use the assumed 3-year cumulative prevalence-incidence for each outcome to calculate the minimal effect size between 481 vaccinated and 330 unvaccinated WLHIV. In preliminary findings in AMP Up (see Section 3.3.3), 33 percent had a 3-year cumulative persistence of any hrHPV type. About 90 percent of these women were vaccinated. We thus assume 50 percent and 30 percent 3-year cumulative prevalence-incidence of persistence hrHPV for unvaccinated and vaccinated WLHIV, respectively. As illustrated in Figure 5, there will be about 281 vaccinated and 235 unvaccinated PHS positive WLHIV who will continue into the follow-up study.

Figure 5. HPV Participant Flow Diagram



3.5 Study Duration

Recruitment and enrollment are expected to occur over a 24-month period from the date that the last participating site completes protocol registration, as specified in Section 4.4. The study is expected to be completed within 5 years. The study visits to be completed by each follow-up participant are expected to last between 90-120 minutes, including questionnaire and survey administration, colposcopic examination (with biopsy, if indicated), and cervical specimen collection. Cervical specimen collection will be done during the time of colposcopy and should take no more than 2 minutes of additional time.

4. Selection and Enrollment of Study Participants

4.1 Enrollment

Potential participants can be WLHIV who are currently or previously enrolled in PHACS-affiliated studies **or** non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics. Enrollment will remain open until the targeted number of participants is enrolled or until enrollment is closed by the Protocol Team.

When a participant is eligible for the study and informed consent has been obtained, the site will use the SES at Frontier Science to enter participant and eligibility information. Participants currently or previously enrolled in one or more PHACS-affiliated studies (e.g., SMARTT, AMP Up, AMP Up Lite, and/or HOPE) will continue to use their PHACS and/or HOPE participant identification number (PID). New non-PHACS-affiliated participants will receive a new PID.

Once a participant is confirmed as eligible and enrolled, the SES will generate a study identification number (SID). In this study, the SID will serve as the participant's protocol-specific personal identification number (PIN) that will be used as the participant identifier in web-based assessments.

4.2 Inclusion Criteria

To be considered eligible for enrollment, an individual must meet the criteria listed below:

- At least 21 years of age and less than or equal to 45 years of age;
- WLHIV regardless of mode of transmission or HPV vaccination status;
- Currently or previously enrolled in PHACS-affiliated studies **or** non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics;
- Willing to participate and able to provide informed consent;
- Willing to grant access to other PHACS and/or HOPE data, if applicable; and
- Willing to provide access to medical records.

Women with a PHS-positive test (either at PHS Testing 1 or 2) by the centralized laboratory (see Sections 5.1.1 and 5.1.2) will be scheduled for baseline colposcopic examination. Women with a history of treated CIN 2+ who are no longer under active surveillance colposcopy per participant report will be included because of the high rate of CIN 2+ recurrence. These women represent a major part of the burden of CIN 2+ in this high-risk population, even in the years following what appears to be successful treatment.¹⁰⁻¹¹

4.3 Exclusion Criteria

To be considered eligible for enrollment, an individual must not meet any of the criteria listed below:

- Currently known to be pregnant via self-report at hrHPV screening for initial consent;

- Special consideration: Women who are not pregnant and enrolled but later test positive on urine pregnancy test at the baseline colposcopy visit will be asked to defer their colposcopy until after 6 weeks following the end of the pregnancy. However, pregnancy during follow-up will be allowed, and guidelines for endocervical curettage (ECC) and treatment will be followed.³⁹
- Women known to have active CIN 2 or greater, undergoing active surveillance with colposcopy (per participant report);
- Women with known bleeding disorders;
- Women unable to consent for themselves; and
- Women with a hysterectomy with removal of the cervix will be excluded from the study and, if such a procedure is conducted during the participant’s study enrollment, the individual will be censored from analysis at the last visit prior to the hysterectomy and taken off-study.

4.4 Protocol Registration

Prior to implementation of this study, the Harvard Longwood Campus Institutional Review Board (HLC IRB) will approve the study protocol, including template informed consent forms (ICFs) and participant-facing documents. Subsequently, the local IRBs at participating sites will cede review of this study to the HLC IRB through the execution of a reliance agreement. All site-specific participant-facing materials, including ICF addendums (to incorporate local IRB requirements), fact sheets, and recruitment materials, must then be reviewed and approved by the HLC IRB. Finally, sites must receive regulatory approval for protocol registration approval from Westat Regulatory Affairs (RA). Confirmation of protocol registration must occur before any participant is enrolled in the protocol. Original, approved regulatory documents must be maintained at the site. This study will follow the PHACS procedures for protocol registration, which are outlined in the PHACS Manual of Network Policies and Procedures (MNPP). The MNPP chapter pertaining to protocol registration can also be found on the PHACS website (<https://my.phacsstudy.org>).

4.5 Recruitment

Following the achievement of single IRB reliance and approval to enroll in the study, the site coordinator (SC) will contact the potential participant either by phone or in person to inform them about this study. Study-specific details, including the information to be collected and the evaluations and assessments required, will be discussed. If the participant chooses, they can have the approved script sent to them by email. For those who agree to participate, proper informed consent will be obtained according to the standards of the HLC IRB and local IRBs, as applicable, as per Section 4.6 below. If the participant initially refuses to take part in the study, the SC will ask if they can be contacted in the future to reconsider enrollment.

4.6 Informed Consent

The site’s designated study staff member will discuss details about participation in this study with eligible participants who indicate an interest in participating, as stated in Section 4.5. This discussion can occur in person while the participant is in clinic for a SOC appointment or another PHACS-affiliated/HOPE study visit, or by phone/video conference call.

Once pre-screening eligibility is determined, study details, including self-sampling, follow-up if found hrHPV-positive at either first or second HPV self-collection testing, and risks and benefits, the information and specimens to be collected, and assessments to be completed, will be discussed with the potential participant, and all questions will be answered during the informed consent process. Informed consent will be obtained prior to any study-related medical abstraction or evaluations are performed. Designated study staff will initiate the informed consent process utilizing ICFs that have been reviewed and approved by the HLC IRB. Consents will only be available in English or Spanish.

The informed consent process may occur in person using a paper ICF at the clinical site if participants are at the clinic for another purpose (e.g., routine care or other study visit), or remotely through telephone/video conference call or by electronic ICF (as available). A copy of the signed ICF will be provided to the participant regardless of the method of obtaining consent. When necessary, re-consenting may occur when there are protocol modifications requiring re-consent or when the participant is no longer affiliated with the local clinical site.

If consenting over the phone or via video conference, or online (if available), the consenting process may include verification of comprehension and will require participants to acknowledge that they have read and agree to the consent form by initialing specific consenting questions, and by signing at the end of the consent form. Verification of identification during the consent process will be confirmed if either consenting remotely or in person. Details are in the PH700 MOP.

A witness may be utilized during the consent process in the following circumstances:

1. When consenting individuals who may be illiterate/low-literate (persons who have decision-making capacity, but who cannot read/write/see/talk; these participants can indicate their consent by "making their mark" on the consent form, if appropriate); and
2. If/when a witness is used, the witness will sign the consent form.

A witness will not be used during consent beyond this scenario. As such, the witness signature line on the consent form will remain blank in those scenarios.

When a witness is used, the witness must be literate and must understand what is being communicated to the participant in the informed consent. Ideally the witness should be an impartial third party, someone not connected with/to the research (e.g. not be the person obtaining consent), impartial to participant and study team, if possible/feasible (e.g. not a family member).

The PH700 Protocol Team will work with the clinical sites and the HLC IRB to ensure that the remote informed consent process is developed in accordance with sites' local IRB requirements. If the online informed consent should occur, clinical site staff will be available for phone consultation to address questions or concerns. Participants will always be offered the option of coming to the clinic to consent or re-consent in person. Clinical site staff will monitor whether the mental capacity of a participant changes throughout the course of the study. Each site employs psychology staff that can advise when a participant's competence to give initial or continuing consent is in question, and sites will contact the HLC IRB and/or their local IRB for guidance.

4.7 Co-enrollment

Participants in this study may be currently or previously enrolled in PHACS-affiliated studies **or** non-PHACS-affiliated participants recruited from LiVes LLC-affiliated clinics

Enrollment of participants who are in this study into other studies (with or without similar goals/data collection as this study) is at the discretion of the Protocol Co-Chairs and the clinical site PI. The clinical site PI must take into account any issues that enrollment in the additional study may require, and which may compromise the participant's ability to fulfill the requirements of this study.

Sites must query the Protocol Team through the QNS for permission to co-enroll participants. The Protocol Team will provide either a "blanket" one-time approval or case-by-case permission for co-enrollment.

5. Schedule of Study Evaluations, Description and Administration

The evaluations and assessments that will be performed as part of this study and their administration are described below. Refer to Chapter 6, Evaluations and Measures for Those Who Test Positive on PHS, for details on the study visits and/or time points at which these will be performed.

5.1 Primary hrHPV at Testing 1 (or Testing 2, if necessary)

After the participant's consent and enrollment, the next steps are to:

- Obtain self-collected vaginal swab for hrHPV testing from the participant (at home or in the clinic);
- Coordinator or designee to:
 - Conduct phone/in-person interview for HPV vaccination history, current ART use, and age of first vaginal intercourse; and
 - Perform medical chart abstraction for most recent CD4 count, most recent HIV viral load, and complete HPV vaccination history.

5.1.1 hrHPV-Positive at Testing 1 or Testing 2

5.1.1.1 Baseline Colposcopy Visit and Annual Colposcopy Follow-Up Visits 1, 2, and 3 (if applicable) for hrHPV-Positive

The baseline colposcopy visit assessment will include the following:

- Urine pregnancy test (if not documented within the last 2 weeks)
- Reproductive Health and Tobacco Use Online Survey
- Medical chart abstraction for prior cervical health issues (cytology/pap, histology/biopsy and treatment, if applicable)
- Medical chart abstraction for most recent CD4 count and HIV viral load, and HPV vaccination history since the last visit/chart abstraction, and STI testing results if obtained as part of standard of care
- Collection of HPV vaccine history and current ART use (participant-reported via interview)
- Standard colposcopy examination with biopsy per ASCCP guidelines, if indicated
- Routine cytology/pap for local lab
- Unstained cytology/pap slide to be mailed to NIH for dual staining
- Endocervical and exocervical sample for biomarkers and repository
- Cervical vaginal lavage for repository

- Histology/biopsy reading by local lab and release of slide or new section sent to the University of California – Los Angeles (UCLA) for central read

The annual colposcopy visit assessments will include all of the above with the exception of the unstained cytology/pap slide and urine pregnancy testing.

5.1.2 PHS Testing 2: For Those hrHPV-Negative at Testing 1

The PHS Testing 2 for those that are hrHPV-negative at Testing 1 will consist of the following:

- Contact participant to confirm continued interest in the study and contact/address information
- Obtain re-consent (if needed)
- Self-collected vaginal swab obtained for Year 2 (Testing 2) (at home or in the clinic)
- Phone/in-person interview for HPV vaccination history and current ART use
- Medical chart abstraction for most recent CD4 count and HIV viral load, and HPV vaccination history since the last visit

5.1.2.1 hrHPV-Positive at Testing 2

5.1.2.1.1 Baseline and Annual Follow Up Colposcopy Visit

For participants whose self-collected swab was hrHPV-positive at Testing 2, the participant will follow the Baseline Colposcopy and Follow-up visits as described in Section 5.1.1.1 above.

5.1.3 hrHPV-Negative at PHS Testing 1 and 2

After a participant is confirmed to be hrHPV-negative at PHS Testing 1 and 2, the next steps are:

- Self-collected sample obtained annually at hrHPV-negative follow-up visits 1-3 for research only (at home or in the clinic); therefore, no results will be provided to the participants
- Phone/in-person interview for HPV vaccination history and current ART use
- Medical chart abstraction for most recent CD4 count and HIV viral load, and HPV vaccination history since the last visit.

6. Evaluations and Measures for Those Who Test Positive on PHS

This is a follow-up study that requires up to four in-person study visits. It is preferable for the colposcopy and baseline study assessments to be scheduled within 60 days following the participant's notification of the positive hrHPV test result. However, as it is known that scheduling specialty care can be difficult, the colposcopy and baseline study assessments may occur outside of the 60 day window, if dependent on scheduling. An extended window does not impact data/specimen fidelity; it is meant to minimize disruption to and burden on participants. If/when this occurs, it will be documented with a note to file in the participant's record. The situation may arise for each annual colposcopy exam as well, and therefore, if the follow-up colposcopy cannot be completed within 12 months +/- 60 days of the previous colposcopy due to scheduling issues, a note to file will be documented in the participant's record. If the colposcopy cannot be completed within 90 days of the target date, query via the QNS. Arrangements should be made so that study visit evaluations, such as the colposcopic examination, cytology/pap, and histology/biopsy, can be done at a time other than the participant's full menses. All research specimens are to be processed at the clinical sites' local processing laboratory, entered in the laboratory data management system (LDMS), and stored until shipment to the PHACS Repository. Specimens will be shipped from the PHACS Repository for central testing. See the PH700 Laboratory Processing Chart (LPC) and Manual of Procedures (MOP) for details.

6.1 Flow of Specimen Self-Collection Kits

Clinical study sites will prepare home sampling (specimen collection) kits so that they are participant-specific. The kits will include the manufacturer's detailed instructions for self-collection. The sites will decide how to provide the kits to participants (e.g., mail, in-person clinic visit, or drop-off). Details can be found in the PH700 MOP.

6.2 HPV Immunization and Current ART Questionnaire

This brief questionnaire will be administered by clinical study site staff as an interview either in person or by phone. Questions includes history of HPV vaccination, the types and dates of the vaccination, and current antiretroviral medications. Documentation will be requested, if available.

6.3 Reproductive Health and Tobacco Use Online Survey

The participant will be provided an online survey link to complete questions on sexual/reproductive behavior and tobacco use. The survey aims to collect the participants' histories of smoking, recent sexual behaviors, last menstrual period, tampon use, douching practices, last vaginal intercourse, recent intravaginal medications, antibiotic use, and contraception use. Two surveys will be administered: one at baseline visit and another at all of the follow-up colposcopy visits.

6.4 Medical Data Abstraction

Medical chart abstraction will be for the most recent CD4 count and viral load prior to the colposcopy visit and all prior cervical cancer screening tests and cervical histology/biopsy results, when available. Data will be collected on HPV vaccine history through chart abstraction, documentation from the participant, and/or self-report. Attempts will be made to verify HPV vaccine dates, including accessing state registries or obtaining data from outside clinics. If unavailable, self-reported history will be acceptable, obtained via interview. STI testing results will be collected if obtained at colposcopy examination as part of standard of care.

6.5 Urine Pregnancy Test at Baseline Colposcopy visit

Participants will have a pregnancy test at the clinic if no test was done within 2 weeks (and documentation available) before the colposcopic exam. If pregnant at the Baseline visit, the participant will not be seen as part of the study that day but will be asked to reschedule the visit after the pregnancy ends. The initial hrHPV-positive test will be valid for the rescheduled colposcopy. The participant will not need to be retested.

6.6 Colposcopic Examinations at Baseline and Follow-Up

All colposcopists will undergo standardized protocol training for examinations and sample collection. Eight of the sites already participate in a PHACS hrHPV substudy with trained colposcopists. All efforts will be made to engage colposcopists already trained by PHACS to support this project. The examination will begin with documentation of standard colposcopic examination features. The colposcopist will perform a visual inspection for vulvar, vaginal, and cervical lesions and warts. Collection for cytology/pap and research triage tests will be performed first, followed by the colposcopic examination with acetic acid and biopsies to be obtained based on colposcopy standards⁹⁰ with a minimum of two (up to 4) biopsies directed at regions of acetowhitening. If no acetowhitening is seen, it is at the discretion of the provider to obtain a random biopsy at the squamocolumnar junction. Results from the standard colposcopic examination will be shared with participants per good clinical practices and clinical site study staff will provide referrals if follow-up care is warranted outside of the study algorithm (see **Figure 4**). Attempts will be made to schedule the colposcopy visits when the participant is not having their full menses. If unscheduled bleeding and/or light menses occurs and is minor, the exam will continue.

6.7 Collection of Cytology/pap and Samples for Triage Tests and Repository

See the PH700 LPC and MOP for details. A second unstained slide will be made from the same liquid cytology/pap as the routine standard of care slide. The unstained cytology/pap will be sent to the NIH for dual staining.

6.8 Cervical Biopsy Specimens

Biopsies will be sent to the local laboratory for processing and clinical diagnosis. p16 staining for the histologic CIN 2 lesions is standard at all laboratories. Histology/biopsy slides will be released and sent to UCLA for a centralized read blinded to the local pathologist read. Consent to send histology/biopsy slide(s) will be obtained using the clinical site's institutional release form, if

needed. If requested by the site, slides will be returned to the site after standardized research reading is completed.

In the case where after ceding review to the HLC IRB the local IRB does not approve of releasing the slides to UCLA, a second slide will be made from the same paraffin block and sent to UCLA. Diagnosis from the local pathology laboratory will be obtained. Results from the UCLA pathology lab will be shared with the local pathology lab and case report forms (CRFs) sent to Frontier Science. If discrepant, this will be communicated to the local pathology lab, and it will be recommended that the original slide be re-reviewed. The diagnosis at UCLA will be considered as the study end point. In the case of a CIN 2 or 3 diagnosis by the local laboratory and a discrepant diagnosis of CIN 1 or less by the UCLA laboratory, continuation in the study will be shared decision-making between the local colposcopist and the clinical site PI/study team.

6.9 Follow-Up Colposcopy Visits

Annual visits will include the health questionnaire, HPV vaccine interim history, the colposcopy exam, and collection of samples, as above. Those with histologically confirmed CIN 2+ diagnosed at any visit will be referred for SOC treatment and considered to have completed the study. In the case of a CIN 2 or 3 diagnosis by the local laboratory and a discrepant diagnosis of CIN 1 or less by the UCLA laboratory, continuation in the study will be shared decision-making between the local colposcopist and the site PI/study team. In the case of CIN 2, 3 by the UCLA centralized pathologist and CIN 1 by the local laboratory, the participant will be considered as completed and referred back to SOC. If no consensus is reached, the participant will be referred for local follow-up and study participation considered complete.

Follow-up visits to ascertain 1-, 2-, and 3- year risk of CIN 2+ will align with the current ASCCP risk-based management guidelines.³⁹ CIN 1 or less will be followed at 12-month intervals up to 3 years.³⁹

6.9.1 Medical Record Abstraction in Follow-Up Years 1-3

Medical record abstraction from PHACS-affiliated studies, and/or from the electronic medical record, in follow-up visits in Years 1-3 will include (since the previous study visit):

- CD4 count, HIV viral load, and HPV vaccination history;
- All available **interim** cervical cancer screening test results, cytology/pap, histology/biopsy results, and treatments not obtained as part of the research study; and
- STI testing results if obtained at the colposcopy examination as part of standard of care.

7. Evaluations and Measures for Those with Two Consecutive Negative Results from PHS

7.1 Annual Self-sampling for hrHPV Genotyping

For WLHIV with a hrHPV-negative result on PHS Testing 1 and 2, annual self-sampling kits for hrHPV genotyping, as described above, will be mailed to participants (or collected in clinic) at the following time points: hrHPV-negative follow-up visits 1, 2 and 3. As described for PHS, the self-collected vaginal samples will be mailed directly to UCLA for hrHPV genotyping. As these are research tests and will be batched, we will not inform participants of the results because it is not clinically manageable, but results will be used for Aim 1 outcomes (vaccine-type persistence).

7.1.1 Other Evaluations

In addition to the request for self-sampling for hrHPV genotyping as described above, the coordinator or designee will also conduct phone/in-person interview for HPV vaccination history and current ART use since the previous contact with the participant and perform medical chart abstraction for most recent CD4 count and HIV viral load, and HPV vaccination since the previous contact.

8. Data Collection and Site Monitoring

8.1 Data Records

For medical record reviews and other non-web-based data collection, hard-copy CRFs will be made available for download from the Frontier Science PHACS portal. Whenever possible, sites are encouraged to complete CRFs electronically, including those that are used as source documents, and can also be completed electronically through direct data entry (DDE) into the electronic data capture (EDC) system. Specimens will be managed, labeled, and tracked through the LDMS. The EDC systems and LDMS have built-in basic error checking capability, so that minor errors can be resolved at the site before data are transmitted to the PHACS Central Database.

Participants must not be identified by name on any CRFs, web-based assessments, laboratory specimens, clinical evaluation results, or laboratory results that are part of the research records. Participants are to be identified by the PID and SID/PIN numbers assigned by PHACS. PID and SID/PIN numbers and study research records, such as source documents, will be stored separately at the site.

The online survey will be administered using a secure cloud-based commercial electronic patient-reported outcome (ePRO) tool that is specifically used for creating web-based data collection instruments. The online surveys can be completed on any device on which the internet can be accessed, including a smartphone. Skip patterns will be programmed into the survey, and questions can be skipped by participants if they choose. Questions will not be accompanied by sound except where necessary per the design of the survey.

The online survey data collected using the commercial ePRO tool will be transferred using Hypertext Transfer Protocol Secure (HTTPS) connections that adhere to the FDA guidelines for

secure EDC. The collected data will be stored on the secure cloud server on which the ePRO tool resides and will be transferred to the PHACS Central Database at Frontier Science. Access to the server will be highly restrictive and limited to a small number of technical and project staff who have been authorized by PHACS leadership to have access.

8.2 Data Collection

Data collection will be conducted according to the Schedule of Evaluations in **Appendix I**. Study visit windows for participants testing hrHPV-positive at Testing 1 will vary from the visit windows for participants testing hrHPV-positive at Testing 2 and for those screening hrHPV-negative at both Screenings 1 and 2. Completion of online surveys and medical record abstractions should be conducted as close to the target data collection time point as possible.

According to Human Subjects Protection (HSP) guidelines, a participant may voluntarily decline any specific protocol assessment or specimen collection during a study visit, and any such missed assessments will not be considered a protocol deviation/reportable new information (RNI). We will operate under this practice, and thus, voluntary participant refusal of any research activities does not require HLC IRB notification. The site should document the participant's decline of a specific protocol assessment or specimen collection in the participant's study record, as needed, and on the appropriate CRF.

Each scheduled study visit has a variety of assessments to be conducted. The window for completion of all study-related baseline activities, including the colposcopy examination with sample collection, the questionnaire, and online surveys (if applicable), is 60 days once the participant is notified of the PHS-positive result. It is preferable for the colposcopy and baseline study assessments to be scheduled within 60 days following the participant's notification of the positive test result. However, as it is known that scheduling specialty care can be difficult, the colposcopy and baseline study assessments may occur outside of the 60-day window, if dependent on scheduling. An extended window does not impact data/specimen fidelity; it is meant to minimize disruption to and burden on participants. If/when this occurs, it will be documented with a note to file in the participant's record. The situation may arise for each annual colposcopy exam as well, and therefore, if the follow-up colposcopy cannot be completed within 12 months +/- 60 days of the previous colposcopy due to scheduling issues, a note to file will be documented in the participant's record. If the colposcopy cannot be completed within 90 days of the target date, query via the QNS.

If the participant is unable to have a visit conducted within the visit window, or unable to complete all visit assessments within their specific required timeframe according to the type of assessment, the clinical site should consult the guidelines within the PH700 MOP. Every effort should be made by the site staff to follow the HLC IRB-approved protocol and MOP. If this is not possible, the instance and reasons should be escalated to the PH700 Protocol Team through the QNS, and the HLC IRB may need to be informed via the PHACS Regulatory and Compliance Manager (RCM) or designee. Additionally, the site should document the occurrence in the participant's study record, as needed, and the appropriate CRF.

All data reported in the database must have corresponding source documentation on file at the clinical site to substantiate all submitted data, unless the CRFs are completed by DDE by the site

staff or participant and no other source documents are available. Instructions about recording study data on the CRFs and the entry of data into the computerized database will be provided to study staff by Frontier Science.

8.3 Data Quality Assurance

Investigators receiving Federal funding must adhere to the Code of Federal Regulations (CFR) to protect research participants and produce reliable study information. Sites participating in research sponsored by the National Cancer Institute (NCI) must have an internal quality assurance plan that will identify problems and correct errors in research study records.

8.4 Clinical Site Monitoring and Record Availability

Clinical site monitoring to ensure protocol and regulatory compliance will be conducted by Westat, Inc. at each participating LiVes LLC site.

The site investigator will make study documents (e.g., ICFs, CRFs) and pertinent hospital or clinic records readily available for inspection by the HLC IRB (as the single IRB) and local IRB, the National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), and the site monitors acting on behalf of the NCI. Site monitors will verify that proper study consent documents are collected, that data collected matches source documents, and that regulatory compliance is maintained.

Note: Participating sites are responsible for specifying these individuals and the PHACS investigators as recipients of private health information in the individual's authorization required under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.

9. Study Management

9.1 Data Management

This study will follow PHACS standards and recommended guidelines for data management. Frontier Science will provide clinical site staff with instructions concerning the collection and recording of study data, including the use of the LDMS and how to access and use the online surveys. The clinical data will be entered into an electronic case report form (eCRF) using an EDC. Each site is responsible for keying the data in a timely fashion according to standards set by the PHACS Network. The EDC system has built-in basic error checking capability so that minor errors can be resolved at the site. The data entered will then be exported to the PHACS Central Database where additional checking and processing will take place. Data will be checked for completeness, accuracy, and consistency. Data errors found during the automatic processing and loading of the data will be communicated to sites via daily update reports. Additional data checks will be performed by the study data manager and communicated via an interactive query mechanism integrated within the EDC system.

The LDMS will be used to manage, label, and track specimens collected in the PHACS Network. The LDMS has built-in basic error checking capability so that minor errors can be resolved at the laboratory before data are transmitted to the PHACS Central Database.

It is the responsibility of Frontier Science to ensure the completeness, quality, and integrity of clinical and laboratory data collected for PHACS-affiliated studies. This role extends from protocol development to generation of the final study databases.

9.2 Rolling Implementation and New Protocol Versions

As this study will be implemented across multiple clinical sites, implementation of the study will occur on a rolling basis as each site becomes ready. Furthermore, deployment of surveys, study assessment tools, and other study-related activities may occur on a rolling basis depending on their availability and readiness. It is acknowledged that rolling implementation is no fault of the sites.

The introduction of a new protocol version may result in a period of delay between HLC IRB approval and functional rollout of the new protocol version to sites in order to allow time for operational changes to be made. In addition, data collection instruments may need to be modified as a result of the approved new protocol and may not be available immediately upon receipt of HLC IRB approval. The Protocol Team will ensure that all infrastructure-based operational components required for initiating implementation of the new protocol version (including the enrollment system's eligibility checklist and the new data collection instruments) have been aligned with the updated protocol version and are completed. The date this is done is the effective implementation date (EID). Sites should not enroll or follow participants under the new protocol version prior to the EID.

9.3 Protocol Query Management

For the integrity of the study and the welfare of the participants, it is important for the clinical site staff to have immediate access to the research team. Queries for this protocol should be sent to the Protocol Team using the PHACS QNS, accessible via the PHACS website (<https://phacsstudy.org>). The Protocol Chairs or designee will respond to queries within 2 business days after receipt. Queries are automatically archived by the PHACS webmaster. Queries deemed relevant to all sites will be posted as frequently asked questions (FAQs) on the PHACS website, where they will be available to all sites for future reference. The categories of queries and the appropriate team member for responding are as follows:

- Protocol violations or adverse participant, staff, or community experiences related to the protocol should be reported to the Protocol Team via the QNS and to the local IRB as stipulated in their guidance.
- Study management issues requiring clarification should be reported via the QNS and managed by the Protocol Specialist with the help of the Protocol Chairs and/or Frontier Science, if necessary.
- Participant management issues that fall outside the protocol parameters should be reported via the QNS and managed by the Protocol Chairs or designee.

9.4 Long-Term Specimen Storage in the PHACS Repository

Research liquid cytology/pap and cervicovaginal lavage (CVL) that remain after study-specific testing is completed will continue to be stored in the PHACS Repository for future use.

10. Participant Management

10.1 Study Visit Management

Participation in this study requires a maximum of four in-person visits for participants who are PHS-positive on the screening test using self-collected sample (Testing 1). See Table 4 for what is considered standard of care billable versus research funded visits.

Visit	Research/paid by the study	Colposcopy and pathology billable per standard of care (SOC) guidelines, if possible ^{1,2}
Baseline Colposcopy	X	
Follow-Up #1 Colposcopy	^	If abnormal histology/biopsy or cytology/pap from previous study colposcopy visit or if current colposcopy is abnormal requiring biopsy^^
Follow-Up #2 Colposcopy	^	If abnormal histology/biopsy or cytology/pap from previous study colposcopy visit or if current colposcopy is abnormal requiring biopsy^^
Follow-Up #3 Colposcopy	^	If abnormal histology/biopsy or cytology/pap from previous study colposcopy visit or if current colposcopy is abnormal requiring biopsy^^

¹ If not possible, the study will cover the cost

² All routine cytology/pap collected during study colposcopy visits is considered standard cervical cancer screening and thus not covered by the research study.

^ If no abnormalities, the follow-up research colposcopies will be covered by the study

^^ If participant has CIN 2 or greater at any research visit, they will be discontinued from the study and referred for standard of care follow-up not covered by the study.

For PHS-negative participants, they will be contacted the following year for a second self-sample collection (Testing 2). If PHS-positive, the participant will be scheduled for baseline and up to three follow-up colposcopy visits. If negative, participant will be scheduled for three additional annual self-collections for research hrHPV testing. Re-consenting may be needed prior to data/sample collection.

The window for completion of all study-related baseline activities, including the colposcopic examination with sample collection, the interview, and online survey, is 60 days once the participant is notified of a hrHPV-positive test. This is a study that requires up to four in-person study visits. Follow-up examinations should be scheduled within 12 months +/- 60 days of previous colposcopy.

It is preferable for the colposcopy and baseline study assessments to be scheduled within 60 days following the participant's notification of the positive test result. However, as it is known that scheduling specialty care can be difficult, the colposcopy and baseline study assessments may occur outside of the 60 day window, if dependent on scheduling. An extended window does not impact data/specimen fidelity; it is meant to minimize disruption to and burden on participants. If/when this occurs, it will be documented with a note to file in the participant's record. The situation may arise for each annual colposcopy exam as well, and therefore, if the follow-up colposcopy cannot be completed within 12 months +/- 60 days of the previous colposcopy due to scheduling issues, a

note to file will be documented in the participant's record. If the colposcopy cannot be completed within 90 days of the target date, query via the QNS.

From time to time a study participant may not be able to complete a visit or a required assessment within the window specified by the schedules of evaluations. If this is the case, a site may seek approval from the Protocol co-Chairs to conduct the visit or have the participant complete assessments beyond the designated window, so long as the extension of the window does not impact data/specimen fidelity.

According to HSP guidelines, a participant may voluntarily decline any specific protocol assessment or specimen collection during a study visit, and any such missed assessments will not be considered a protocol deviation. Thus, voluntary participant refusal of any research activities does not require HLC IRB notification. The site should document the participant's decline of a specific protocol assessment or specimen collection in the participant's file and on the appropriate CRF.

10.2 Participant Compensation

As approved by the HLC IRB, study participants will receive \$25 remuneration for obtaining each of the self-collected samples, and the remuneration for baseline and each annual colposcopy follow-up visit session will be determined by the local site. Local IRBs may designate the need for additional remuneration or reimbursement as deemed appropriate in the site-specific consent addendum.

10.3 Study Completion

Participants who tested hrHPV-positive at Testing 1 or 2 will be considered having completed the study after:

1. Completion of 3 follow-up colposcopy visits; or
2. A colposcopy result was found to be CIN 2 or greater at any time during the study (the participant would be discontinued from the study and referred to their provider for SOC); or
3. The end of study.

Participants who had two consecutive hrHPV-negative results from Testing 1 and 2, they would be considered having completed the study after:

1. Completing three additional self-collected research swabs sent to UCLA; or
2. The end of study.

10.4 Participant Discontinuation

The Protocol Team will monitor the rate and reasons for discontinuing follow-up. Participants will be discontinued from the study if any of the following occurs:

- The participant withdraws permission;

- The participant fails to comply with the study requirements so as to cause harm to self or seriously interfere with the validity of the study results, and the clinical site PI believes that compliance is unlikely to improve;
- The clinical site PI determines that further participation would be detrimental to the participant's health or well-being;
- The study is stopped by a governmental agency, including the NCI, NIH, or HHS;
- The study must be stopped for administrative reasons;
- The clinical site is terminated for significant participant safety concerns, study integrity, poor performance issues, or lack of funding; or
- The HLC IRB decides to withdraw approval for the study due to participant safety concerns.

Sites may also discontinue participants according to PHACS Policy for Missed In-Person Study Visits or Data Collection Intervals, Declaring Participants Lost to Follow Up, and Participants Re-Joining Studies. When participants discontinue study participation, contact information will be requested in order to be able to notify participants of important findings or to request participation in future evaluations. Relevant participant management information can be found on the PHACS Manual of Network Policies and Procedures (MNPP) webpage, as well as in the LiVes LLC MOP.

11. Adverse Event (AE) Reporting

This study is not a therapeutic study, and no medications are being prescribed as part of this study. Participants enrolled in this study may develop common conditions requiring treatment during the course of the study period. Study personnel will assist the participants in receiving care as appropriate to their roles at their sites. The participants may experience adverse events associated with HIV infection, antiretroviral therapy exposure, or other medications that they may be taking in the course of their clinical care. Site investigators are encouraged to use the FDA MedWatch system to report any events possibly associated with medications clinically prescribed for the participant.

All clinical sites have psychologists, social workers, or other clinical staff qualified to address a situation if a participant becomes distressed during or after completing the colposcopies, online surveys, or interviews. Participants will be offered further support, evaluation, and referrals, as needed. The PHACS Emergency Procedures is in place at all sites to provide guidance regarding research-related or clinical signs of distress during participants' research visits. Resources for mental health support will be provided to all participants, as appropriate. Colposcopy and biopsy will be performed by certified nurse practitioners in colposcopy or board-certified gynecologists to assure any complications that occurred because of biopsy will be immediately addressed or if the occurrence is after the patient is released, the provider will be available to address clinical symptoms.

Participation in this study poses no greater harm or discomfort to research participants that they would otherwise experience during a colposcopic examination during regular clinical care. See Chapter 11 for information on possible negative study impact events and their reporting.

12. Study Impact and Safety Monitoring

Participant or staff-associated negative study impact events will be evaluated according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0, December 2004; Clarification, August 2009). Events will be monitored by the Protocol Team, NIH program officials, and local IRB panels.

Reporting of participant- or staff-associated negative study impact events to the Protocol Team and NIH program officials will result in the examination of study procedures as necessary to address concerns about participant management, enrollment, recruitment, adequacy of staff training, and/or to modify study procedures.

12.1 Reporting Requirements

Negative study impact events involving study participants or staff are to be reported to the Protocol Team through the QNS. “Impact events” include clinical events described in the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events (Version 1.0, December 2004; Clarification, August 2009) and/or other negative impact events for study participants or their parents/guardians. Examples include but are not limited to:

- Visible distress or other injury resulting from the research encounter; and
- Inadvertent or unintended disclosure of the HIV status of a participant who might be unaware of their HIV status.

Study impact events of a Grade 2 or greater that have a possible association with study procedures must be documented in the participant’s research record and reported to the Protocol Team via the QNS system within 48 hours of awareness. Grade 2 or greater impact events should be monitored by clinical site staff at least weekly until the event resolves to \leq Grade 1. Each follow-up evaluation is to be reported to the Protocol Team via the QNS and documented in the participant’s research record. Incidents must also be reported to the HLC IRB and the local IRB, as applicable, according to procedures and requirements of the home institution.

Any event that is unexpected, related to the research, and/or adds/increases risks to participants or others will be reported to the HLC IRB as an RNI. Any event that is deemed to have negatively impacted a participant to a more than minimal extent and is related to the study activity must be reported to the PHACS RCM by the study site through the PHACS QNS. Reportable events could involve study participants and/or staff members. All RNIs will be communicated with the IRB according to their policy. All reportable events will be reported to the HLC IRB within 5 business days.

13. Statistical/Analytic Considerations

13.1 Study Design

This study is designed to compare unvaccinated to vaccinated WLHIV participants on 3-year cumulative risk of HPV vaccine-type persistence and CIN 2+ from the date of the self-collected vaginal swab for HPV testing, to evaluate the Se, Sp, PPV, and NPV of four reflex strategies to detect CIN 2+ immediately or within 3 years among PHS-positive WLHIV, and to evaluate performance characteristics of self-collected PHS for two of the reflex tests (methylation and hrHPV genotyping). All PHS-positive participants at the screening tests will have a maximum of four in-person colposcopy visits (baseline and up to three follow-up visits).

For Aim 1, we will continue to monitor those with two consecutive negative hrHPV results, as the results will be used for the HPV vaccine-type persistence outcome. We will continue to have the SC send them self-sampling materials for hrHPV genotyping annually to be performed at UCLA. As these are research tests and will be batched, we will not inform participants of the results.

13.2 Statistical Analysis Plan

13.2.1 Baseline Characteristics

We will describe baseline characteristics (e.g., sociodemographic, clinical) of women enrolled in PHS by vaccination status and hrHPV positivity using the median (interquartile range) for continuous and N (%) for categorical variables. For those enrolled in the annual colposcopic exam, we will use ASCUS+ as the cutoff for positive cytology/pap; dual stain will be according to the manufacturer's cutoff. Methylation will be according to the NIH-recommended cutoff values. We define three hierarchical hrHPV genotype groups: (1) 16, 18; (2) 31, 33, 35, 45, 52, 58; and (3) 39, 51, 56, 59, 68.⁷³ We will define positivity in hrHPV genotyping by each genotype in groups (1) or (2) separately and then combined.

13.2.2 Aim 1

Examine the effectiveness of HPV vaccine based on the following outcomes: 3-year cumulative risk of (i) vaccine-HPV types that persist 12 months or longer, and (ii) histologic (h) CIN 2+ for all enrollees "Persistence" will be defined as at least two consecutive positive tests for a specific HPV genotype that occurs at any time over follow-up, which starts at the first hrHPV screening test. All enrollees will be included in Aim 1, those who tested hrHPV-positive at Testing 1 or 2 and those who tested hrHPV-negative at both screening tests. First, we will look at persistence of each of the seven vaccine-hrHPV types (16, 18, 31, 33, 45, 52, 58) separately. Next, we will look at persistence of any of the seven hrHPV types, restricting to those who received G9. We expect that the majority of HPV-vaccinated women received G9 since those ≤ 36 years old in 2024 would have been ≤ 26 years old in 2014 when G9 was approved. WLHIV who only had HPV types measured at one time point will miss the persistence endpoint. We will check whether this missing is informative. For both HPV persistence and CIN 2+, it is difficult to determine whether the detection of disease after baseline was undiagnosed prevalent disease or incident disease after baseline PHS. Therefore, we will estimate the 3-year cumulative risk of each outcome separately using the prevalence-incidence survival model developed by Egemen et al., and Cheung et al.,⁹¹⁻⁹² which can include covariates such

as vaccination status (no vaccine, V4HPV, V9HPV), age at vaccination (if vaccinated), and other potential confounders such as baseline age and reported sexual onset date. Number of vaccine doses will be adjusted for if data are available. We will also look for effect modification of vaccination status by perinatal vs non-perinatal HIV using an interaction term. For hrHPV persistence, we will use the first time point of the consecutive hrHPV-positive measures at the time of disease. If no persistent hrHPV-positive results are detected by the end of follow-up, the participant will be censored at the last follow-up time regardless of the outcome of the last test. A sensitivity analysis will be performed treating those without consecutive hrHPV-positive results, but the last follow-up is positive as persistent at the last time point. For estimating the cumulative risk of CIN 2+, we assume that women with two consecutive hrHPV-negative results will not develop CIN 2+ by 3 years after baseline based on previous studies.³⁹ They will thus be classified as \leq CIN 1.

13.2.3 Aim 2a

Examine and compare the Se, Sp, PPV, and NPV to detect hCIN 2+ immediately and in 3 years in PHS-positive WLHIV using four reflex strategies: (i) cytology/pap, (ii) HPV extended genotyping, (iii) p16/Ki-67 dual-staining cytology/pap, and (iv) HPV/host methylation levels. All consenting women with hrHPV-positive results that undergo colposcopy will have the four assays tested using provider-collected samples at baseline. Two separate analyses will be performed based on timing of the CIN 2+ outcome: (1) the immediate colposcopic examination outcome at baseline, and (2) the cumulative detections of CIN 2+ by the end of 3 years (3-year cumulative cases). We will estimate and compare between HPV vaccination status Se, Sp, PPV, and NPV with 95 percent CIs of each individual assay at baseline on the CIN 2+ outcome at baseline and then separately for the cumulative cases by 3 years. To compare the performance among the four individual assays, we will evaluate relative Se, Sp, PPV, and NPV as described below.⁹³ For WLHIV who haven't developed CIN 2+ but are lost to follow-up or the study has closed to follow up before 3 years of colposcopy after baseline, the true disease status by the end of 3 years will be missing. To assess the performance of the diagnosis tests based on biomarkers, we will assume CIN 2+ has not developed at 3 years. Sensitivity analyses will be conducted assuming all these censored WLHIV developed CIN 2+. We have focused on a 3-year interval since current cervical cancer screening guidelines recommend 3-year intervals for WLHIV compared to the general population, which is 5 year intervals. Cases identified after baseline include development of new incident CIN 2+ and lesions that may have been missed at baseline (e.g., misdirected biopsy or lesion not yet visible by colposcopy). Annual visits will allow us to identify women who may need closer surveillance than 3 years.

Relative Se or Sp. For each comparison between two triage tests, there will be two records per person, one for each test type. A log binomial model for the chance of a positive test result will be fit to compare the performance between two tests, using generalized estimating equation (GEE) to account for the correlation between two different test results in the same participant. Specifying the log link allows for direct estimation of the relative true positive (Se) and false positive rate (FPR = 1 - Sp).

$$\log P(\text{test is positive}) = \beta_0 + \beta_1 (\text{CIN2+ present}) + \beta_2 \text{Test2} + \beta_3 (\text{CIN 2+ present}) \times \text{Test2}$$

Interpretation of the parameters:

- FPR for test 1 = $\exp(\beta_0)$
- FPR for test 2 = $\exp(\beta_0 + \beta_2)$
- Se for test 1 = $\exp(\beta_0 + \beta_1)$
- Se for test 2 = $\exp(\beta_0 + \beta_1 + \beta_2 + \beta_3)$

Therefore,

- Relative FPR of test 2 to test 1 = $\exp(\beta_2)$
- Relative Se = $\exp(\beta_2 + \beta_3)$.

Note that since all WLHIV in follow-up will have colposcopy results (gold standard) regardless of triage test results, we can model the chance of a negative test result in a similar way to compare the true negative (Sp) and false negative (1-Se) between two tests.

Relative PPV or NPV. Similarly, we can simultaneously estimate PPV and NPV for a given assay or combination test by modelling the probability of “agreement” between test and histology/biopsy outcome (i.e., whether or not the assay is positive in the presence of CIN 2+ and negative in the absence of CIN 2+), compared between tests:

$$\log P(\text{agreement}) = \alpha_0 + \alpha_1 (\text{test is negative}) + \alpha_2 \text{Test2} + \alpha_3 (\text{test is negative}) \times \text{Test2}.$$

Interpretation of the parameters:

- PPV of test 1 = $\exp(\alpha_0)$
- PPV of test 2 = $\exp(\alpha_0 + \alpha_2)$
- NPV of test 1 = $\exp(\alpha_0 + \alpha_1)$
- NPV of test 2 = $\exp(\alpha_0 + \alpha_1 + \alpha_2 + \alpha_3)$
- Relative PPV of test 2 to test 1 = $\exp(\alpha_2)$
- Relative NPV = $\exp(\alpha_2 + \alpha_3)$

The above models can be extended to include other covariates and interaction terms with test type⁹³⁻⁹⁴ to assess the impact of factors such as HPV vaccination (unvaccinated, vaccine V4HPV, vaccine V9HPV), CD4 counts, or viral loads on these indexes for any given test pair. Similarly, we will assess the impact of vaccination on the association between a test result and the cumulative 3-year cases of CIN 2+ by including the test result at baseline, vaccination status, and an interaction term between them as covariates, separately for each of the two assays compared. HPV genotyping results will be included as a three-category variable based on the hierarchical groups defined above. The impact of PHIV status will also be examined separately by including PHIV status and an interaction term between test results and PHIV status. Se and (1-Sp) of all triage tests, including the four individual tests and tests with reasonable combinations of the individual test results, will be plotted in a scatter plot of Se versus 1-Sp to display the performances of all tests for an informal comparison.⁹⁵

13.2.4 Aim 2b

Examine the Se, Sp, PPV, and NPV in self-collected PHS-positive samples for CIN 2+ detection, focusing on methylation and HPV genotyping. We will calculate the Se, Sp, PPV, and NPV of each test on CIN 2+ with 95 percent CIs, as described above, using the residual sample from the baseline self-collected specimens of WLHIV with hrHPV-positive. As mentioned, having triage strategies that do not require an additional visit before colposcopy triage would be optimal. The Se and (1-Sp) of these two tests will be included in the above-mentioned scatter plot of the tests from provider-collected samples for informal comparison.

13.3 Power Calculations

13.3.1 Aim 1

As illustrated in **Figure 5**, we anticipate that there will be about 481 vaccinated and 330 unvaccinated WLHIV participating in the PHS screening. In preliminary findings in AMP Up (see Section 3.3.3), 33 percent had a 3-year cumulative persistence of any hrHPV type. About 90 percent of these women were vaccinated. We thus assume 50 percent and 30 percent 3-year cumulative prevalence-incidence of persistence hrHPV for unvaccinated and vaccinated WLHIV, respectively. Based on the younger age of our population, we estimate a relatively high rate of CIN 2+ compared to older women. Ranges of CIN 2+ vary greatly (6% to 40%)⁹⁶⁻¹⁰⁰ with highest rates found in countries with low CCS rates. In a study of adolescents who acquired HIV horizontally, 22 percent of LSIL progressed to HSIL over 3 years, reflecting a rate of 9 percent.⁴ In a study of WLHIV in India with normal cytology/pap at baseline, there was a cumulative CIN 2+ incidence of 11 percent for those with HPV 16, 13 percent with HPV18, and 5.4 percent with other hrHPV types per person year.¹⁰⁰ Rates of CIN 2+ due to non-vaccine types in vaccinated and unvaccinated are likely similar.⁹⁶ We anticipate 10 percent cumulative prevalence-incidence of CIN2+ by 3 years for vaccinated WLHIV and 18 percent for unvaccinated WLHIV. With these expected prevalences, assuming an alpha of 0.05 and 80 percent power, using the test for a ratio of two proportions, we can detect a ratio of 0.80 (i.e., 40% for vaccinated WLHIV) or lower for persistent hrHPV, and a ratio of 0.61 (i.e., 11% for vaccinated WLHIV) or lower for CIN 2+.

13.3.2 Aim 2a and Aim 2b

As illustrated in **Figure 5**, we assume 312 of the 481 vaccinated and 261 of the 330 unvaccinated WLHIV will be PHS-positive with two rounds of screening. It is realistic to expect that we will have 516 hrHPV + women (281 vaccinated and 235 unvaccinated) eligible for follow-up colposcopy follow-up samples. Se for all triage methods in this study is relatively high, and thus the focus of improvement is on Sp or PPV and the power calculation is based on Sp. For WLHIV with PHS-positive, we anticipate 5 percent baseline prevalence and 15 percent 3-year cumulative incidence of CIN 2+ for vaccinated and 30 percent and 43 percent, respectively, for unvaccinated WLHIV with PHS-positive. Then the baseline prevalence and cumulative prevalence for the combined study group will be 16 percent and 28 percent; that is, 84 percent and 72 percent without CIN 2+, respectively. Assuming these as the true prevalence, we will be able to estimate Sp for any of the triage tests with the width of a 95 percent CI $\leq 10\%$ for the combined sample and $\leq 18\%$ for estimates by vaccination status. We will be able to estimate the difference in Sp between vaccinated and unvaccinated WLHIV with the width of a 95 percent CI $\leq 20\%$. For comparison between two

tests in Aim 2a, using a two-sided McNemar test for Se or Sp¹⁰¹ with a significance level of 0.05 and 80 percent of power, and assuming 30 percent of discordant rate between two assays, the minimum detectable difference in Sp is 7.5 percent (8.2%) at baseline (3 years) based on a sample size of 516 women. We note that power does not vary with the actual Sp but only the difference between specificities. All power analyses were done in PASS 15.0.4.¹⁰²

13.4 Missing, Unused, and Spurious Data

Every effort in data collection will be made to ensure that the amount of missing data is kept to a minimum, as missing data complicates the statistical analyses or results in biased parameter estimates.

When data for covariates are missing, the extent and pattern of missing data will first be assessed. If data are missing for only a few cases, then data analysis will be conducted only on study participants with complete data. However, when such a strategy would result in loss of data from a substantial proportion of participants (such as greater than 10%), or if the outcomes for those with and without missing covariates are very different, then missing indicator categories can be used for categorical variables.

13.5 Data Monitoring

No interim efficacy analyses are planned for this observational study. Routine monitoring, which will be performed by the Protocol Team, will include the following: accrual, study status/progress, and data and specimen timeliness and completeness.

14. Human Subjects

This study will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and 45 CFR § 46. It is the judgment of the Protocol Team that this protocol belongs in Category One Research under 45 CFR § 46 Subpart D: Research not involving greater than minimal risk. The judgment is premised on the definition of minimal risk that is found in 45 CFR § 46.102 (i):

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

14.1 Participant Confidentiality

Participants currently or previously enrolled in one or more PHACS-affiliated studies (e.g., SMARTT, AMP Up, AMP Up Lite, and/or HOPE) will continue to use their PHACS and/or HOPE participant identification number (PID). New non-PHACS-affiliated participants will receive a new PID. A unique SID/PIN number will be assigned by the SES when the participant is successfully enrolled into the study. The PID and SID/PIN numbers will be used for identification purposes on all laboratory specimens, evaluation forms, online surveys, and reports retained in the research records and generated by the PHACS database. A list linking the participant names with the PID and SID/PIN numbers will be securely stored at the clinical site under double locks, separate from all other research records. All research records will be stored in a secured area in locked files.

All study staff members at the clinical sites are required to sign nondisclosure forms pledging to hold research information in confidence. All off-site LiVes LLC investigators and collaborators are required to sign data use agreements pledging not to seek the identity of study participants.

Study staff will work with participants to record contact information, which may also include the names and contact information of people (friends, family, or others) who may always know the whereabouts of participants. Establishing this list is a voluntary exercise and, if used in the event that contact is lost with a participant, only a previously agreed-to level of information will be disclosed. When contact is reestablished with participants who were lost, willingness to continue study participation will be first ascertained.

14.2 Certificate of Confidentiality

As an NIH-funded project using identifiable, sensitive information, PHACS is automatically issued a Certificate of Confidentiality from the U.S. HHS. With this certificate in place, the PHACS researchers cannot be forced to turn over identifying information about a study participant in any Federal, state, or local criminal, administrative, legislative, or other proceedings. This certificate does not prevent a study participant from volunteering to turn over their research information, nor does it prevent researchers from providing research-related information to others when requested by the study participant or when required by law such as in cases of suspected or actual harm to or by the study participant.

The site investigator will make study documents (e.g., ICFs, CRFs) and pertinent records available for inspection by the HLC IRB, local IRB, the Westat site monitors, the NCI, the OHRP, or the sponsor's designee for confirmation of the study data.

14.3 Risks and Benefits

14.3.1 Risks Associated with Participation in This Study

14.3.1.1 Risk Category: Research Not Involving Greater than Minimal Risk (45 CFR § 46.404)

Participation in this study poses no more harms or discomforts to research participants than they may experience in normal daily life, routine medical care, or during a colposcopic examination. Risks from routine medical procedures include the following:

- The colposcopic examination may elicit feelings of fear and anxiety in some study participants. Routine SOC regarding the management of discomfort will be implemented during the examination.
- The biopsy, if done, may cause discomfort, pain, and some bleeding in the area of collection.
- The information that participants provide during the online survey will not be shared with medical providers without their permission, unless there is serious risk of self-harm or harm to others as specified in the consent and local IRB/ethics committee requirement. This includes information about sexual behavior and substance use.

Breach of confidentiality is always a risk however, many steps will be taken to protect study data/specimens, including securely storing data and specimens in partnership with Frontier Science (the Data Management Center for this study), only permitting approved research study team members to have access to data/specimens, and participants will never be directly identified in any report of the study results. With respect to specifically minimizing the risk of an online survey data breach, tips to protect privacy while filling out online surveys will be shared, and we will monitor the data closely throughout the study.

14.3.1.2 Inadvertent or Unintended Disclosure of HIV Status

The study staff will take precautions to prevent inadvertent disclosure of HIV infection status to the participants in this study who may not know their own HIV status. Participants may also be exposed to the clinical area and waiting rooms where HIV material is displayed. This may raise their awareness of the issue of HIV status for themselves or others.

Awareness of and sensitivity to issues about disclosure of a participant's HIV status extends to all study staff. Protocol-specific training of study staff will address the issue of HIV disclosure and the measures that should be taken to prevent inadvertent or unintended disclosure of a participant's HIV status.

14.3.1.3 Reproductive Health and Tobacco Use Online Survey

Information on the reproductive health and tobacco use reported by participants in the confidential online survey will not be disclosed to the LiVes LLC site study staff or to the clinicians responsible

for their healthcare, unless there is serious risk of self-harm or harm to others as specified in the consent and local IRB/ethics committee requirement. This includes information about sexual behavior.

14.3.2 Benefits Associated with Participation in This Study

Although no clear benefit is expected for participants enrolled in this study, participants who are determined to have HSIL will receive referrals for further care outside of the study. Site study staff will provide participants and their caregivers with assistance to identify resources and facilitate access to care and evaluation as appropriate. However, PHACS will not provide any payment for further care received outside of this study.

14.4 Institutional Review Board Review

All participating sites will rely on the HLC IRB as their single Institutional Review Board (sIRB) of record.

Prior to initiation of study implementation, participating sites will sign Reliance Agreements detailing the roles and responsibilities of the HLC IRB in relation to participating sites. The HLC IRB and the PHACS RCM will retain copies of all Reliance Agreements and communications and facilitate the process of obtaining HLC IRB approval for this protocol, ICFs, and any other participant-facing documents (e.g., fact sheets, recruitment materials, assessment surveys/interviews). The HLC IRB Reliance Agreement Specialist and the PHACS RCM will maintain consistent and regular communications to ensure that participating sites are in compliance with the requirements of the HLC IRB.

14.5 Prisoner Participation

PHACS and the NCI have concluded that this protocol does NOT meet Federal requirements governing prisoner participation in human subjects research and should NOT be considered by the HLC or local IRBs for the recruitment of prisoners. Participants who become prisoners after enrollment may not be seen for research visits as long as they are considered prisoners.

14.6 45 CFR § 160 and 164 Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule” Pursuant to the Health Insurance Portability and Accountability Act)

Each site is responsible for adherence to their individual institution’s HIPAA policies and procedures.

14.7 PHACS Repository Policies

It is not expected that PHI will be needed to create and operate the PHACS Repository. In addition, since biologic specimens, in and of themselves, do not constitute PHI under 45 CFR § 164.501, the Privacy Rule will not apply to the creation of the PHACS Repository. It will be sufficient to seek informed consent from individuals, as required by 45 CFR § 46.116, to have their specimens included in the PHACS Repository. The PHACS Repository Policy and samples of the ICFs for the PHACS Repository can be found in the PHACS MNPP. Consent for collection of repository specimens

is included within the sample study ICF. Participants may participate in this study without agreeing to the long-term storage of their specimens in the PHACS Repository for future testing not necessarily related to the primary aims of this study.

14.8 Study Discontinuation

This study may be discontinued at any time by the NICHD or NCI.

15. Publication of Research Findings

Publication of the results of this study will be governed by PHACS policies as outlined in the PHACS Publication Policy (available on the PHACS website). Any presentation, abstract, or manuscript will be made available for review by the study sponsor prior to submission.

Participant summaries of findings will be developed and provided directly to the clinical sites to allow them to submit for local IRB review prior to distribution to participants, as applicable.

16. 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 (CDC). These procedures can be found at <https://www.cdc.gov>.

All study specimens will be transported in accordance with Federal and local laws, and in compliance with Occupational Safety and Health Administration (OSHA) blood-borne pathogens standards. *This policy includes the samples being transported by ground to the local laboratory.* Compliance will be achieved by education of personnel involved with packaging and transporting specimens.

All infectious specimens must be shipped as Diagnostic Specimens according to current International Air Transport Association (IATA) Shipping Guidelines for Infectious Substances Class/Div. 6.2. Refer to individual carrier guidelines (e.g., FedEx, Airborne Express) for specific instructions.

References

1. Brogly SB, Watts DH, Ylitalo N, Franco EL, Seage GR, 3rd, Oleske J, Eagle M, Van Dyke R. Reproductive health of adolescent girls perinatally infected with HIV. *Am J Public Health*. 2007;97(6):1047-52. Epub 2007/04/28. doi: 10.2105/ajph.2005.071910. PMID: 17463385; PMCID: PMC1874205.
2. Frisch M, Glimelius B, van den Brule AJ, Wohlfahrt J, Meijer CJ, Walboomers JM, Goldman S, Svensson C, Adami HO, Melbye M. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med*. 1997;337(19):1350-8. doi: 10.1056/nejm199711063371904. PMID: 9358129.
3. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA*. 2001;285(13):1736-45. doi: 10.1001/jama.285.13.1736. PMID: 11277828.
4. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu J, Fahrat S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. *J Infect Dis*. 2004;190(8):1413-21. Epub 2004/09/21. doi: 10.1086/424466. PMID: 15378433.
5. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. *Archives of internal medicine*. 2010;170(15):1337-45. doi: 10.1001/archinternmed.2010.253. PMID: 20696958; PMCID: PMC2921231.
6. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst*. 2009;101(16):1120-30. Epub 2009/08/04. doi: 10.1093/jnci/djp205. PMID: 19648510; PMCID: PMC2728745.
7. Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol*. 2009;10(12):1152-9. Epub 2009/10/13. doi: 10.1016/s1470-2045(09)70282-7. PMID: 19818686.
8. Massad LS, Fazzari MJ, Anastos K, Klein RS, Minkoff H, Jamieson DJ, Duerr A, Celentano D, Gange S, Cu-Uvin S, Young M, Watts DH, Levine AM, Schuman P, Harris TG, Strickler HD. Outcomes after treatment of cervical intraepithelial neoplasia among women with HIV. *J Low Genit Tract Dis*. 2007;11(2):90-7. doi: 10.1097/01.lgt.0000245038.06977.a7. PMID: 17415113.
9. Reimers LL, Sotardi S, Daniel D, Chiu LG, Van Arsdale A, Wieland DL, Leider JM, Xue X, Strickler HD, Garry DJ, Goldberg GL, Einstein MH. Outcomes after an excisional procedure for cervical intraepithelial neoplasia in HIV-infected women. *Gynecol Oncol*. 2010;119(1):92-7. doi: 10.1016/j.ygyno.2010.06.012. PMID: 20605046; PMCID: PMC3089021.
10. Levin MJ, Moscicki AB, Song LY, Fenton T, Meyer WA, 3rd, Read JS, Handelsman EL, Nowak B, Sattler CA, Saah A, Radley DR, Esser MT, Weinberg A. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*. 2010;55(2):197-204. doi: 10.1097/QAI.0b013e3181de8d26. PMID: 20574412; PMCID: PMC3033215.
11. Toft L, Tolstrup M, Müller M, Sehr P, Bonde J, Storgaard M, Østergaard L, Søggaard OS. Comparison of the immunogenicity of Cervarix® and Gardasil® human papillomavirus vaccines for oncogenic non-vaccine serotypes HPV-31, HPV-33, and HPV-45 in HIV-infected

- adults. *Hum Vaccin Immunother.* 2014;10(5):1147-54. Epub 2014/02/19. doi: 10.4161/hv.27925. PMID: 24553190; PMCID: PMC4896591.
12. Kojic EM, Kang M, Cespedes MS, Umbleja T, Godfrey C, Allen RT, Firnhaber C, Grinsztejn B, Palefsky JM, Webster-Cyriaque JY, Saah A, Aberg JA, Cu-Uvin S. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis.* 2014;59(1):127-35. Epub 2014/04/09. doi: 10.1093/cid/ciu238. PMID: 24723284; PMCID: PMC4305143.
 13. Money DM, Moses E, Blitz S, Vandriel SM, Lipsky N, Walmsley SL, Loutfy M, Trottier S, Smaill F, Yudin MH, Klein M, Harris M, Cohen J, Wobeser W, Bitnun A, Lapointe N, Samson L, Brophy J, Karatzios C, Ogilvie G, Coutlée F, Raboud J. HIV viral suppression results in higher antibody responses in HIV-positive women vaccinated with the quadrivalent human papillomavirus vaccine. *Vaccine.* 2016;34(40):4799-806. Epub 2016/08/17. doi: 10.1016/j.vaccine.2016.08.016. PMID: 27544584.
 14. Wilkin TJ, Chen H, Cespedes MS, Leon-Cruz JT, Godfrey C, Chiao EY, Bastow B, Webster-Cyriaque J, Feng Q, Dragavon J, Coombs RW, Presti RM, Saah A, Cranston RD. A randomized, placebo-controlled trial of the quadrivalent human papillomavirus vaccine in human immunodeficiency virus-infected adults aged 27 years or older: AIDS Clinical Trials Group Protocol A5298. *Clin Infect Dis.* 2018;67(9):1339-46. doi: 10.1093/cid/ciy274. PMID: 29659751; PMCID: PMC6186857.
 15. McClymont E, Lee M, Raboud J, Coutlée F, Walmsley S, Lipsky N, Loutfy M, Trottier S, Smaill F, Klein MB, Harris M, Cohen J, Yudin MH, Wobeser W, Money D, CTN 236 HPV in HIV Study Team. The efficacy of the quadrivalent human papillomavirus vaccine in girls and women living with human immunodeficiency virus. *Clin Infect Dis.* 2019;68(5):788-94. doi: 10.1093/cid/ciy575. PMID: 29985988.
 16. Moscicki AB, Karalius B, Tassiopoulos K, Yao TJ, Jacobson DL, Patel K, Purswani M, Seage GR. Human papillomavirus antibody levels and quadrivalent vaccine clinical effectiveness in perinatally human immunodeficiency virus-infected and exposed, uninfected youth. *Clin Infect Dis.* 2019;69(7):1183-91. Epub 2019/03/31. doi: 10.1093/cid/ciy1040. PMID: 30927547.
 17. Hidalgo-Tenorio C, Pasquau J, Omar-Mohamed M, Sampedro A, López-Ruz MA, López Hidalgo J, Ramírez-Taboada J. Effectiveness of the quadrivalent HPV vaccine in preventing anal \geq HSILs in a Spanish population of HIV+ MSM aged > 26 Years. *Viruses.* 2021;13(2). doi: 10.3390/v13020144. PMID: 33498165; PMCID: PMC7908967.
 18. Palefsky JM, Lensing SY, Belzer M, Lee J, Gaur AH, Mayer K, Futterman D, Stier EA, Paul ME, Chiao EY, Reirden D, Goldstone SE, Tirado M, Cachay ER, Barroso LF, Da Costa M, Darragh TM, Rudy BJ, Wilson CM, Kahn JA. High prevalence of anal high-grade squamous intraepithelial lesions, and prevention through human papillomavirus vaccination, in young men who have sex with men living with human immunodeficiency virus. *Clin Infect Dis.* 2021;73(8):1388-96. doi: 10.1093/cid/ciab434. PMID: 33991185; PMCID: PMC8528397.
 19. Dias D, Van Doren J, Schlottmann S, Kelly S, Puchalski D, Ruiz W, Boerckel P, Kessler J, Antonello JM, Green T, Brown M, Smith J, Chirmule N, Barr E, Jansen KU, Esser MT. Optimization and validation of a multiplexed luminex assay to quantify antibodies to neutralizing epitopes on human papillomaviruses 6, 11, 16, and 18. *Clin Diagn Lab Immunol.* 2005;12(8):959-69. doi: 10.1128/cdli.12.8.959-969.2005. PMID: 16085914; PMCID: PMC1182182.

20. Opalka D, Lachman CE, MacMullen SA, Jansen KU, Smith JF, Chirmule N, Esser MT. Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11, 16, and 18 by a multiplexed luminex assay. *Clin Diagn Lab Immunol.* 2003;10(1):108-15. doi: 10.1128/cdli.10.1.108-115.2003. PMID: 12522048; PMCID: PMC145272.
21. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, Puchalski D, Giacoletti KE, Singhs HL, Lukac S, Alvarez FB, Barr E. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: A randomized controlled trial. *Pediatr Infect Dis J.* 2007;26(3):201-9. doi: 10.1097/01.inf.0000253970.29190.5a. PMID: 17484215.
22. Gunn BM, Alter G. Modulating antibody functionality in infectious disease and vaccination. *Trends in molecular medicine.* 2016;22(11):969-82. Epub 2016/10/21. doi: 10.1016/j.molmed.2016.09.002. PMID: 27756530.
23. Westra J, van Assen S, Wilting KR, Land J, Horst G, de Haan A, Bijl M. Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clinical and experimental immunology.* 2014;178(1):40-7. doi: 10.1111/cei.12390. PMID: 24889761; PMCID: PMC4360192.
24. Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, Nene BM, Esmay PO, Joshi S, Poli UR, Jivarajani P, Verma Y, Zomawia E, Siddiqi M, Shastri SS, Jayant K, Malvi SG, Lucas E, Michel A, Butt J, Vijayamma JM, Sankaran S, Kannan TP, Varghese R, Divate U, Thomas S, Joshi G, Willhauck-Fleckenstein M, Waterboer T, Muller M, Sehr P, Hingmire S, Kriplani A, Mishra G, Pimple S, Jadhav R, Sauvaget C, Tommasino M, Pillai MR. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. *Lancet Oncol.* 2016;17(1):67-77. Epub 2015/12/15. doi: 10.1016/s1470-2045(15)00414-3. PMID: 26652797; PMCID: PMC5357737.
25. Krogstad P, Patel K, Karalius B, Hazra R, Abzug MJ, Oleske J, Seage GR, Williams PL, Borkowsky W, Wiznia A, Pinto J, Van Dyke RB, Pediatric HIV/AIDS Cohort Study, IMPAACT 219C, and NICHD International Site Development Initiative (NISDI) Investigators. Incomplete immune reconstitution despite virologic suppression in HIV-1 infected children and adolescents. *AIDS.* 2015;29(6):683-93. doi: 10.1097/QAD.0000000000000598. PMID: 25849832; PMCID: PMC4391276.
26. Clifford GM, Tully S, Franceschi S. Carcinogenicity of human papillomavirus (HPV) types in HIV-positive women: A meta-analysis from HPV infection to cervical cancer. *Clin Infect Dis.* 2017;64(9):1228-35. doi: 10.1093/cid/cix135. PMID: 28199532; PMCID: PMC5399941.
27. Niyibizi J, Rodier C, Wassef M, Trottier H. Risk factors for the development and severity of juvenile-onset recurrent respiratory papillomatosis: A systematic review. *Int J Pediatr Otorhinolaryngol.* 2014;78(2):186-97. Epub 2013/12/26. doi: 10.1016/j.ijporl.2013.11.036. PMID: 24367938.
28. Rintala MA, Grenman SE, Jarvenkyla ME, Syrjanen KJ, Syrjanen SM. High-risk types of human papillomavirus (HPV) DNA in oral and genital mucosa of infants during their first 3 years of life: Experience from the Finnish HPV Family Study. *Clin Infect Dis.* 2005;41(12):1728-33. doi: 10.1086/498114. PMID: 16288396.

29. Smith EM, Parker MA, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Evidence for vertical transmission of HPV from mothers to infants. *Infect Dis Obstet Gynecol*. 2010;2010:326369. Epub 2010/03/20. doi: 10.1155/2010/326369. PMID: 20300545; PMCID: PMC2838362.
30. Medeiros LR, Ethur AB, Hilgert JB, Zanini RR, Berwanger O, Bozzetti MC, Mylius LC. Vertical transmission of the human papillomavirus: A systematic quantitative review. *Cad Saude Publica*. 2005;21(4):1006-15. Epub 2005/07/16. doi: 10.1590/s0102-311x2005000400003. PMID: 16021238.
31. Castellsague X, Drudis T, Canadas MP, Gonce A, Ros R, Perez JM, Quintana MJ, Munoz J, Albero G, de Sanjose S, Bosch FX. Human Papillomavirus (HPV) infection in pregnant women and mother-to-child transmission of genital HPV genotypes: a prospective study in Spain. *BMC Infect Dis*. 2009;9:74. doi: 10.1186/1471-2334-9-74. PMID: 19473489; PMCID: PMC2696457.
32. Rintala MA, Grenman SE, Puranen MH, Isolauri E, Ekblad U, Kero PO, Syrjanen SM. Transmission of high-risk human papillomavirus (HPV) between parents and infant: A prospective study of HPV in families in Finland. *Journal of clinical microbiology*. 2005;43(1):376-81. Epub 2005/01/07. doi: 10.1128/jcm.43.1.376-381.2005. PMID: 15634997; PMCID: PMC540188.
33. Unger ER, Fajman NN, Maloney EM, Onyekwuluje J, Swan DC, Howard L, Beck-Sague CM, Sawyer MK, Girardet RG, Sautter RL, Hammerschlag MR, Black CM. Anogenital human papillomavirus in sexually abused and nonabused children: A multicenter study. *Pediatrics*. 2011;128(3):e658-65. Epub 2011/08/17. doi: 10.1542/peds.2010-2247. PMID: 21844060.
34. Moscicki AB, Puga A, Farhat S, Ma Y. Human papillomavirus infections in nonsexually active perinatally HIV infected children. *AIDS Patient Care STDS*. 2014;28(2):66-70. doi: 10.1089/apc.2013.0313. PMID: 24460009; PMCID: PMC3926149.
35. Meyrelles ARI, Siqueira JD, Hofer CB, Costa TP, Azevedo AP, Guimarães BV, Seuánez HN, Soares MA, Almeida G, Soares EA, Machado ES. HIV/HPV co-infection during pregnancy in southeastern Brazil: Prevalence, HPV types, cytological abnormalities and risk factors. *Gynecol Oncol*. 2013;128(1):107-12. Epub 2012/10/09. doi: 10.1016/j.ygyno.2012.10.003. PMID: 23063764.
36. Waxman AG, Chelmow D, Darragh TM, Lawson H, Moscicki AB. Revised terminology for cervical histopathology and its implications for management of high-grade squamous intraepithelial lesions of the cervix. *Obstet Gynecol*. 2012;120(6):1465-71. doi: 10.1097/aog.0b013e31827001d5. PMID: 23168774; PMCID: PMC4054813.
37. Kyrgiou M, Mitra A, Arbyn M, Stasinou SM, Martin-Hirsch P, Bennett P, Paraskevaidis E. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: Systematic review and meta-analysis. *BMJ*. 2014;349:g6192. doi: 10.1136/bmj.g6192. PMID: 25352501; PMCID: PMC4212006.
38. Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, Guerra CE, Oeffinger KC, Shih YT, Walter LC, Kim JJ, Andrews KS, DeSantis CE, Fedewa SA, Manassaram-Baptiste D, Saslow D, Wender RC, Smith RA. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020;70(5):321-46. Epub 2020/07/30. doi: 10.3322/caac.21628. PMID: 32729638.
39. Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, Huh WK, Kim JJ, Moscicki AB, Nayar R, Saraiya M, Sawaya GF, Wentzensen N, Schiffman M, 2019 ASCCP Risk-Based

- Management Consensus Guidelines Committee. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Low Genit Tract Dis.* 2020;24(2):102-31. doi: 10.1097/lgt.0000000000000525. PMID: 32243307; PMCID: PMC7147428.
40. Centers for Disease Control and Prevention. Cancers associated with human papillomavirus, United States—2012–2016. USCS Data Brief, no 10. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services, 2019. Available from: <https://www.cdc.gov/cancer/uscs/about/data-briefs/no10-hpv-assoc-cancers-unitedstates-2012-2016.htm>. Accessed: 2023/09/06.
 41. Monsonego J, Cox JT, Behrens C, Sandri M, Franco EL, Yap PS, Huh W. Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: Data from the ATHENA trial. *Gynecol Oncol.* 2015;137(1):47-54. Epub 2015/02/11. doi: 10.1016/j.ygyno.2015.01.551. PMID: 25667973.
 42. Teoh D, Nam G, Aase DA, Russell R, Melton GB, Kulasingam S, Vogel RI. Test performance of cervical cytology among adults with vs without human papillomavirus vaccination. *JAMA Netw Open.* 2022;5(5):e2214020. doi: 10.1001/jamanetworkopen.2022.14020. PMID: 35612854; PMCID: PMC9133945.
 43. El-Zein M, Bouten S, Louvanto K, Gilbert L, Gotlieb WH, Hemmings R, Behr MA, Franco EL. Predictive value of HPV testing in self-collected and clinician-collected samples compared with cytology in detecting high-grade cervical lesions. *Cancer Epidemiol Biomarkers Prev.* 2019;28(7):1134-40. Epub 2019/04/25. doi: 10.1158/1055-9965.Epi-18-1338. PMID: 31015201.
 44. Wang J, Du Y, Dong J, Zhou Y, Wang P, Zhang X, Chen Y, He P. Clinical significance of genotyping for human papillomavirus (HPV) 16 18/45 combined with cytology in cervical exfoliated cells in HPV oncogenic mRNA-positive women. *Gynecol Oncol.* 2019;153(1):34-40. Epub 2019/01/12. doi: 10.1016/j.ygyno.2018.12.028. PMID: 30630629.
 45. Chatzistamatiou K, Moysiadis T, Angelis E, Kaufmann A, Skenderi A, Jansen-Duerr P, Lekka I, Kilintzis V, Angelidou S, Katsiki E, Hagemann I, Tsertanidou A, Koch I, Boecher O, Soutschek E, Maglaveras N, Agorastos T. Diagnostic accuracy of high-risk HPV DNA genotyping for primary cervical cancer screening and triage of HPV-positive women, compared to cytology: preliminary results of the PIPAVIR study. *Arch Gynecol Obstet.* 2017;295(5):1247-57. Epub 2017/03/25. doi: 10.1007/s00404-017-4324-x. PMID: 28337594.
 46. Cuschieri K, Ronco G, Lorincz A, Smith L, Ogilvie G, Mirabello L, Carozzi F, Cubie H, Wentzensen N, Snijders P, Arbyn M, Monsonego J, Franceschi S. Eurogin roadmap 2017: Triage strategies for the management of HPV-positive women in cervical screening programs. *Int J Cancer.* 2018;143(4):735-45. Epub 2018/01/18. doi: 10.1002/ijc.31261. PMID: 29341110.
 47. Yu L, Fei L, Liu X, Pi X, Wang L, Chen S. Application of p16/Ki-67 dual-staining cytology in cervical cancers. *J Cancer.* 2019;10(12):2654-60. doi: 10.7150/jca.32743. PMID: 31258773; PMCID: PMC6584925.
 48. Wentzensen N, Fetterman B, Castle PE, Schiffman M, Wood SN, Stiemerling E, Tokugawa D, Bodelon C, Poitras N, Lorey T, Kinney W. p16/Ki-67 dual stain cytology for detection of cervical precancer in HPV-positive women. *J Natl Cancer Inst.* 2015;107(12):d1v257. doi: 10.1093/jnci/d1v257. PMID: 26376685; PMCID: PMC4675094.

49. Ebisch RM, van der Horst J, Hermsen M, Rijstenberg LL, Vedder JE, Bulten J, Bosgraaf RP, Verhoef VM, Heideman DA, Snijders PJ, Meijer CJ, van Kemenade FJ, Massuger LF, Melchers WJ, Bekkers RL, Siebers AG. Evaluation of p16/Ki-67 dual-stained cytology as triage test for high-risk human papillomavirus-positive women. *Mod Pathol*. 2017;30(7):1021-31. Epub 2017/03/17. doi: 10.1038/modpathol.2017.16. PMID: 28304400.
50. Ovestad IT, Dalen I, Hansen E, Loge JL, Dybdahl BM, Dirdal MB, Moltu P, Berland JM. Clinical value of fully automated p16/Ki-67 dual staining in the triage of HPV-positive women in the Norwegian Cervical Cancer Screening Program. *Cancer Cytopathol*. 2017;125(4):283-91. Epub 2016/12/05. doi: 10.1002/cncy.21807. PMID: 27918650.
51. Areán-Cuns C, Mercado-Gutiérrez M, Paniello-Alastruey I, Mallor-Giménez F, Córdoba-Iturriagagoitia A, Lozano-Escario M, Santamaria-Martínez M. Dual staining for p16/Ki67 is a more specific test than cytology for triage of HPV-positive women. *Virchows Arch*. 2018;473(5):599-606. Epub 2018/08/09. doi: 10.1007/s00428-018-2432-z. PMID: 30094492.
52. Pirtea L, Secosan C, Margan M, Moleriu L, Balint O, Grigoras D, Sas I, Horhat F, Jianu A, Ilina R. p16/Ki-67 dual staining has a better accuracy than human papillomavirus (HPV) testing in women with abnormal cytology under 30 years old. *Bosn J Basic Med Sci*. 2019;19(4):336-41. doi: 10.17305/bjbm.2018.3560. PMID: 29924960; PMCID: PMC6868483.
53. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: Risk factors and differences, by phylogenetic type. *J Infect Dis*. 2004;190(1):37-45. Epub 2004/06/08. doi: 10.1086/421467. PMID: 15195241.
54. Moscicki AB, Ellenberg JH, Vermund SH, Holland CA, Darragh T, Crowley-Nowick PA, Levin L, Wilson CM. Prevalence of and risks for cervical human papillomavirus infection and squamous intraepithelial lesions in adolescent girls: Impact of infection with human immunodeficiency virus. *Arch Pediatr Adolesc Med*. 2000;154(2):127-34. doi: 10.1001/archpedi.154.2.127. PMID: 10665598.
55. Delmas MC, Larsen C, van Benthem B, Hamers FF, Bergeron C, Poveda JD, Anzén B, van den Hoek A, Meier F, Peña JM, Savonius H, Sperandeo D, Suligoj B, Vernazza P, Brunet JB. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. *European Study Group on Natural History of HIV Infection in Women. AIDS*. 2000;14(12):1775-84. doi: 10.1097/00002030-200008180-00013. PMID: 10985315.
56. Ananworanich J, Prasitsuebsai W, Kerr SJ, Hansudewechakul R, Teeratakulpisarn N, Saisawat K, Ramautarsing R, Achalapong J, Pussadee K, Keadpuksa S, Mackay T, Pankam T, Rodbamrung P, Petdachai W, Chokeyhaibulkit K, Sohn AH, Phanuphak N. Cervical cytological abnormalities and HPV infection in perinatally HIV-infected adolescents. *J Virus Erad*. 2015;1(1):30-7. PMID: 26005716; PMCID: PMC4439002.
57. Adler DH, Wallace M, Bennie T, Mrubata M, Abar B, Meiring TL, Williamson AL, Bekker LG. Cervical dysplasia and high-risk human papillomavirus infections among HIV-infected and HIV-uninfected adolescent females in South Africa. *Infect Dis Obstet Gynecol*. 2014;2014:498048. Epub 2014/11/13. doi: 10.1155/2014/498048. PMID: 25389377; PMCID: PMC4217359.
58. Sohn AH, Kerr SJ, Hansudewechakul R, Gatechompol S, Chokeyhaibulkit K, Dang HLD, Tran DNH, Achalapong J, Teeratakulpisarn N, Chalermchockcharoenkit A, Thamkhantho M,

- Pankam T, Singtoroj T, Termrungruanglert W, Chaithongwongwatthana S, Phanuphak N. Risk factors for human papillomavirus infection and abnormal cervical cytology among perinatally human immunodeficiency virus-infected and uninfected Asian youth. *Clin Infect Dis*. 2018;67(4):606-13. doi: 10.1093/cid/ciy144. PMID: 29617952.
59. Lehtovirta P, Finne P, Nieminen P, Skogberg K, Savonius H, Paavonen J, Heikinheimo O. Prevalence and risk factors of squamous intraepithelial lesions of the cervix among HIV-infected women - a long-term follow-up study in a low-prevalence population. *Int J STD AIDS*. 2006;17(12):831-4. doi: 10.1258/095646206779307649. PMID: 17212861.
60. Micheletti AM, Dutra Vde F, Murta EF, Paschoini MC, Silva-Vergara ML, Barbosa e Silva G, Adad SJ. Cervicovaginal cytological abnormalities in patients with human immunodeficiency virus infection, in relation to disease stage, CD4 cell count and viral load. *Diagn Cytopathol*. 2009;37(3):164-9. doi: 10.1002/dc.20892. PMID: 19170167.
61. McKenzie KP, Rogers RK, Njoroge JW, John-Stewart G, Richardson BA, Mugo NR, De Vuyst H, Pamnani RN, Rana FS, Warui D, Chung MH. Cervical squamous intraepithelial lesions among HIV-positive women on antiretroviral therapy in Kenya. *Curr HIV Res*. 2011;9(3):180-5. doi: 10.2174/157016211795945214. PMID: 21585334.
62. Atashili J, Adimora AA, Ndumbe PM, Ikomey GM, Rinas AC, Myers E, Eron J, Smith JS, Miller WC. High prevalence of cervical squamous intraepithelial lesions in women on antiretroviral therapy in Cameroon: Is targeted screening feasible? *Cancer Epidemiol*. 2012;36(3):263-9. Epub 2011/11/01. doi: 10.1016/j.canep.2011.10.003. PMID: 22047636; PMCID: PMC3288586.
63. Kola-Palmer S, Walsh JC. Correlates of psychological distress immediately following colposcopy. *Psychooncology*. 2015;24(7):819-24. Epub 2015/01/12. doi: 10.1002/pon.3738. PMID: 25581290.
64. Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PP, Mustafa RA, Schünemann H, Paraskeva E, Arbyn M. Cytology versus HPV testing for cervical cancer screening in the general population. *Cochrane Database Syst Rev*. 2017;8(8):Cd008587. doi: 10.1002/14651858.CD008587.pub2. PMID: 28796882; PMCID: PMC6483676.
65. Strickler HD, Keller MJ, Hessol NA, Eltoun IE, Einstein MH, Castle PE, Massad LS, Flowers L, Rahangdale L, Atrio JM, Ramirez C, Minkoff H, Adimora AA, Ofotokun I, Colie C, Huchko MJ, Fischl M, Wright R, D'Souza G, Leider J, Diaz O, Sanchez-Keeland L, Shrestha S, Xie X, Xue X, Anastos K, Palefsky JM, Burk RD. Primary HPV and molecular cervical cancer screening in US women living with HIV. *Clin Infect Dis*. 2020. doi: 10.1093/cid/ciaa1317. PMID: 32881999.
66. Clifford GM, Gonçalves MA, Franceschi S. Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS*. 2006;20(18):2337-44. doi: 10.1097/01.aids.0000253361.63578.14. PMID: 17117020.
67. Gradissimo A, Lam J, Attonito JD, Palefsky J, Massad LS, Xie X, Eltoun IE, Rahangdale L, Fischl MA, Anastos K, Minkoff H, Xue X, D'Souza G, Flowers LC, Colie C, Shrestha S, Hessol NA, Strickler HD, Burk RD. Methylation of high-risk human papillomavirus genomes are associated with cervical precancer in HIV-positive women. *Cancer Epidemiol Biomarkers Prev*. 2018;27(12):1407-15. Epub 2018/09/20. doi: 10.1158/1055-9965.Epi-17-1051. PMID: 30237251; PMCID: PMC6279505.
68. Andersson S, Belkic K, Mints M, Ostensson E. Acceptance of self-sampling among long-term cervical screening non-attenders with HPV-positive results: Promising opportunity for

- specific cancer education. *J Cancer Educ.* 2019. doi: 10.1007/s13187-019-01608-0. PMID: 31522376.
69. Madzima TR, Vahabi M, Lofters A. Emerging role of HPV self-sampling in cervical cancer screening for hard-to-reach women: Focused literature review. *Can Fam Physician.* 2017;63(8):597-601. PMID: 28807952; PMCID: PMC5555324.
70. Nelson EJ, Maynard BR, Loux T, Fatla J, Gordon R, Arnold LD. The acceptability of self-sampled screening for HPV DNA: A systematic review and meta-analysis. *Sex Transm Infect.* 2017;93(1):56-61. Epub 2017/01/20. doi: 10.1136/sextrans-2016-052609. PMID: 28100761.
71. Chao YS, Clark M, Ford C. HPV self-sampling for primary cervical cancer screening: A review of diagnostic test accuracy and clinical evidence. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK532211>. Accessed: 2023/09/06.
72. Arbyn M, Verdoodt F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, Minozzi S, Bellisario C, Banzi R, Zhao FH, Hillemanns P, Anttila A. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol.* 2014;15(2):172-83. Epub 2014/01/14. doi: 10.1016/S1470-2045(13)70570-9. PMID: 24433684.
73. Demarco M, Hyun N, Carter-Pokras O, Raine-Bennett TR, Cheung L, Chen X, Hammer A, Campos N, Kinney W, Gage JC, Befano B, Perkins RB, He X, Dallal C, Chen J, Poitras N, Mayrand MH, Coutlee F, Burk RD, Lorey T, Castle PE, Wentzensen N, Schiffman M. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. *EClinicalMedicine.* 2020;22:100293. Epub 2020/04/25. doi: 10.1016/j.eclinm.2020.100293. PMID: 32510043; PMCID: PMC7264956.
74. Wentzensen N, Sun C, Ghosh A, Kinney W, Mirabello L, Wacholder S, Shaber R, LaMere B, Clarke M, Lorincz AT, Castle PE, Schiffman M, Burk RD. Methylation of HPV18, HPV31, and HPV45 genomes and cervical intraepithelial neoplasia grade 3. *J Natl Cancer Inst.* 2012;104(22):1738-49. Epub 2012/10/23. doi: 10.1093/jnci/djs425. PMID: 23093560; PMCID: PMC3571257.
75. Mirabello L, Schiffman M, Ghosh A, Rodriguez AC, Vasiljevic N, Wentzensen N, Herrero R, Hildesheim A, Wacholder S, Scibior-Bentkowska D, Burk RD, Lorincz AT. Elevated methylation of HPV16 DNA is associated with the development of high grade cervical intraepithelial neoplasia. *Int J Cancer.* 2013;132(6):1412-22. Epub 2012/08/20. doi: 10.1002/ijc.27750. PMID: 22847263; PMCID: PMC3493709.
76. Vasiljević N, Scibior-Bentkowska D, Brentnall A, Cuzick J, Lorincz A. A comparison of methylation levels in HPV18, HPV31 and HPV33 genomes reveals similar associations with cervical precancers. *J Clin Virol.* 2014;59(3):161-6. Epub 2014/01/08. doi: 10.1016/j.jcv.2013.12.014. PMID: 24468012; PMCID: PMC3969303.
77. Vasiljević N, Scibior-Bentkowska D, Brentnall AR, Cuzick J, Lorincz AT. Credentialing of DNA methylation assays for human genes as diagnostic biomarkers of cervical intraepithelial neoplasia in high-risk HPV positive women. *Gynecol Oncol.* 2014;132(3):709-14. Epub 2014/02/06. doi: 10.1016/j.ygyno.2014.02.001. PMID: 24508839; PMCID: PMC3989115.
78. Brentnall AR, Vasiljevic N, Scibior-Bentkowska D, Cadman L, Austin J, Cuzick J, Lorincz AT. HPV33 DNA methylation measurement improves cervical pre-cancer risk estimation of an

- HPV16, HPV18, HPV31 and \textit{EPB41L3} methylation classifier. *Cancer Biomark*. 2015;15(5):669-75. doi: 10.3233/cbm-150507. PMID: 26406956.
79. Frimer M, Sun C, McAndrew T, Smith B, Harari A, Chen Z, Mirabello L, Wentzensen N, Goldberg GL, Rodriguez AC, Schiffman M, Burk RD. HPV16 CpG methyl-haplotypes are associated with cervix precancer and cancer in the Guanacaste natural history study. *Gynecol Oncol*. 2015;138(1):94-100. Epub 2015/05/19. doi: 10.1016/j.ygyno.2015.05.001. PMID: 26001326; PMCID: PMC4867226.
 80. Mirabello L, Frimer M, Harari A, McAndrew T, Smith B, Chen Z, Wentzensen N, Wacholder S, Castle PE, Raine-Bennett T, Schiffman M, Burk RD. HPV16 methyl-haplotypes determined by a novel next-generation sequencing method are associated with cervical precancer. *Int J Cancer*. 2015;136(4):E146-53. Epub 2014/09/03. doi: 10.1002/ijc.29119. PMID: 25081507; PMCID: PMC4262737.
 81. Lorincz AT, Brentnall AR, Scibior-Bentkowska D, Reuter C, Banwait R, Cadman L, Austin J, Cuzick J, Vasiljević N. Validation of a DNA methylation HPV triage classifier in a screening sample. *Int J Cancer*. 2016;138(11):2745-51. Epub 2016/02/08. doi: 10.1002/ijc.30008. PMID: 26790008; PMCID: PMC4832297.
 82. Schmitz M, Eichelkraut K, Schmidt D, Zeiser I, Hilal Z, Tettenborn Z, Hansel A, Ikenberg H. Performance of a DNA methylation marker panel using liquid-based cervical scrapes to detect cervical cancer and its precancerous stages. *BMC Cancer*. 2018;18(1):1197. doi: 10.1186/s12885-018-5125-8. PMID: 30509219; PMCID: PMC6276155.
 83. Kremer WW, Steenbergen R, Heideman D, Kenter GG, Meijer C. The use of host cell DNA methylation analysis in the detection and management of women with advanced cervical intraepithelial neoplasia: A review. *BJOG*. 2021;128(3):504-14. Epub 2020/08/09. doi: 10.1111/1471-0528.16395. PMID: 32619334; PMCID: PMC7818489.
 84. Verhoef L, Bleeker MCG, Polman N, Steenbergen RDM, Meijer C, Melchers WJG, Bekkers RL, Molijn AC, Quint WG, van Kemenade FJ, Berkhof J, Heideman DAM. Performance of DNA methylation analysis of ASCL1, LHX8, ST6GALNAC5, GHSR, ZIC1 and SST for the triage of HPV-positive women: Results from a Dutch primary HPV-based screening cohort. *Int J Cancer*. 2022;150(3):440-9. Epub 2021/10/13. doi: 10.1002/ijc.33820. PMID: 34558659; PMCID: PMC9293097.
 85. Clarke MA, Gradissimo A, Schiffman M, Lam J, Sollecito CC, Fetterman B, Lorey T, Poitras N, Raine-Bennett TR, Castle PE, Wentzensen N, Burk RD. Human papillomavirus DNA methylation as a biomarker for cervical precancer: Consistency across 12 genotypes and potential impact on management of HPV-positive women. *Clin Cancer Res*. 2018;24(9):2194-202. Epub 2018/02/02. doi: 10.1158/1078-0432.CCR-17-3251. PMID: 29420222; PMCID: PMC5932258.
 86. Clarke MA, Luhn P, Gage JC, Bodelon C, Dunn ST, Walker J, Zuna R, Hewitt S, Killian JK, Yan L, Miller A, Schiffman M, Wentzensen N. Discovery and validation of candidate host DNA methylation markers for detection of cervical precancer and cancer. *Int J Cancer*. 2017;141(4):701-10. Epub 2017/05/26. doi: 10.1002/ijc.30781. PMID: 28500655; PMCID: PMC6774256.
 87. Harris TG, Burk RD, Palefsky JM, Massad LS, Bang JY, Anastos K, Minkoff H, Hall CB, Bacon MC, Levine AM, Watts DH, Silverberg MJ, Xue X, Melnick SL, Strickler HD. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human

- papillomavirus test results. *JAMA*. 2005;293(12):1471-6. doi: 10.1001/jama.293.12.1471. PMID: 15784870.
88. Yeh PT, Kennedy CE, de Vuyst H, Narasimhan M. Self-sampling for human papillomavirus (HPV) testing: A systematic review and meta-analysis. *BMJ Glob Health*. 2019;4(3):e001351. Epub 2019/05/14. doi: 10.1136/bmjgh-2018-001351. PMID: 31179035; PMCID: PMC6529022.
89. Polman NJ, Ebisch RMF, Heideman DAM, Melchers WJG, Bekkers RLM, Molijn AC, Meijer CJLM, Quint WGV, Snijders PJF, Massuger LFAG, van Kemenade FJ, Berkhof J. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: A randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol*. 2019;20(2):229-38. Epub 2019/01/15. doi: 10.1016/S1470-2045(18)30763-0. PMID: 30658933.
90. Wentzensen N, Massad LS, Mayeaux EJ, Jr., Khan MJ, Waxman AG, Einstein MH, Conageski C, Schiffman MH, Gold MA, Apgar BS, Chelmow D, Choma KK, Darragh TM, Gage JC, Garcia FAR, Guido RS, Jeronimo JA, Liu A, Mathews CA, Mitchell MM, Moscicki AB, Novetsky AP, Papasozomenos T, Perkins RB, Silver MI, Smith KM, Stier EA, Tedeschi CA, Werner CL, Huh WK. Evidence-based consensus recommendations for colposcopy practice for cervical cancer prevention in the United States. *J Low Genit Tract Dis*. 2017;21(4):216-22. doi: 10.1097/lgt.0000000000000322. PMID: 28953109.
91. Egemen D, Cheung LC, Chen X, Demarco M, Perkins RB, Kinney W, Poitras N, Befano B, Locke A, Guido RS, Wisner AL, Gage JC, Katki HA, Wentzensen N, Castle PE, Schiffman M, Lorey TS. Risk estimates supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis*. 2020;24(2):132-43. doi: 10.1097/lgt.0000000000000529. PMID: 32243308; PMCID: PMC7147417.
92. Cheung LC, Pan Q, Hyun N, Schiffman M, Fetterman B, Castle PE, Lorey T, Katki HA. Mixture models for undiagnosed prevalent disease and interval-censored incident disease: applications to a cohort assembled from electronic health records. *Stat Med*. 2017 Sep 30;36(22):3583-3595. Epub 2017/06/28. doi: 10.1002/sim.7380. PMID: 28660629; PMCID: PMC5583012.
93. Pepe MS, Alonzo TA. Comparing disease screening tests when true disease status is ascertained only for screen positives. *Biostatistics*. 2001;2(3):249-60. doi: 10.1093/biostatistics/2.3.249. PMID: 12933537.
94. Joshi S, Muwonge R, Kulkarni V, Mandolkar M, Lucas E, Pujari S, Sankaranarayanan R, Basu P. Can we increase the cervical cancer screening interval with an HPV test for women living with HIV? Results of a cohort study from Maharashtra, India. *Int J Cancer*. 2022. Epub 2022/07/19. doi: 10.1002/ijc.34221. PMID: 35852007.
95. Stoler MH, Baker E, Boyle S, Aslam S, Ridder R, Huh WK, Wright TC, Jr. Approaches to triage optimization in HPV primary screening: Extended genotyping and p16/Ki-67 dual-stained cytology-Retrospective insights from ATHENA. *Int J Cancer*. 2020;146(9):2599-607. Epub 2019/10/06. doi: 10.1002/ijc.32669. PMID: 31490545; PMCID: PMC7078939.
96. McClymont E, Coutlée F, Lee M, Albert A, Raboud J, Walmsley S, Lipsky N, Loutfy M, Trottier S, Smaill F, Klein MB, Yudin MH, Harris M, Wobeser W, Bitnun A, Samson L, Money D, CTN 236 HPV in HIV Study Team. Brief report: Persistence of non-vaccine oncogenic HPV genotypes in

- quadrivalent HPV-vaccinated women living with HIV. *J Acquir Immune Defic Syndr*. 2020;83(3):230-4. doi: 10.1097/qai.0000000000002258. PMID: 31917750.
97. Mogtomo ML, Malieugoue LC, Djiengang C, Wankam M, Moune A, Ngane AN. Incidence of cervical disease associated to HPV in human immunodeficiency infected women under highly active antiretroviral therapy. *Infect Agent Cancer*. 2009;4:9. doi: 10.1186/1750-9378-4-9. PMID: 19493339; PMCID: PMC2701409.
98. Sahasrabuddhe VV, Bhosale RA, Joshi SN, Kavatkar AN, Nagwanshi CA, Kelkar RS, Jenkins CA, Shepherd BE, Sahay S, Risbud AR, Vermund SH, Mehendale SM. Prevalence and predictors of colposcopic-histopathologically confirmed cervical intraepithelial neoplasia in HIV-infected women in India. *PLoS One*. 2010;5(1):e8634. Epub 2010/01/08. doi: 10.1371/journal.pone.0008634. PMID: 20072610; PMCID: PMC2798747.
99. de Andrade AC, Luz PM, Velasque L, Veloso VG, Moreira RI, Russomano F, Chicarino-Coelho J, Pires E, Levi JE, Grinsztejn B, Friedman RK. Factors associated with colposcopy-histopathology confirmed cervical intraepithelial neoplasia among HIV-infected women from Rio De Janeiro, Brazil. *PLoS One*. 2011;6(3):e18297. Epub 2011/03/30. doi: 10.1371/journal.pone.0018297. PMID: 21479179; PMCID: PMC3068170.
100. Joshi S, Muwonge R, Kulkarni V, Deodhar K, Mandolkar M, Lucas E, Sankaranarayanan R. Incidence of cervical intraepithelial neoplasia in women infected with human immunodeficiency virus (HIV) with no evidence of disease at baseline: Results of a prospective cohort study with up to 6.4 years of follow-up from India. *Int J Cancer*. 2019;144(5):1082-91. Epub 2018/11/20. doi: 10.1002/ijc.31826. PMID: 30132840.
101. Li J, Fine J. On sample size for sensitivity and specificity in prospective diagnostic accuracy studies. *Stat Med*. 2004;23(16):2537-50. doi: 10.1002/sim.1836. PMID: 15287083.
102. PASS 15 Power Analysis and Sample Size Software. Kaysville, UT: NCSS, LLC; 2017. Available from: <http://ncss.com/software/pass>. Accessed: 2023/09/06.

Appendix I Schedule of Evaluations

This study requires up to four visits. For those PHS-positive at screening, study-related activities must be completed within a 60-day window from when the participant is notified of test results.

- If PHS-positive at Testing 1, the participant will have four in-person visits, baseline and up to three follow-up visits, completing the evaluations below.
- If PHS-negative at Testing 1, but PHS-positive 12 months later at Testing 2 (10-14 months of the Testing 1 of self-collected swab), the participant will have up to three in-person visits, baseline and up to two follow-up visits, completing the evaluations below.
- If PHS-negative at both Testing 1 and Testing 2, the site staff will provide self-swab research hrHPV test kits at up to three additional years (Years 3, 4, and 5) to be mailed to the UCLA lab. This window is within 1 year +/- 60 days from previous self-collected swab.

Arrangements should be made so that study visit evaluations such as the colposcopic examination and specimen collection can be done as part of a SOC visit. All research specimens are to be processed at the clinical sites' local processing laboratory, entered in LDMS if applicable, and stored until shipment to the PHACS Repository. Specimens will be shipped from the PHACS Repository for central testing. See the PH700 LPC and MOP for details.

As it is known that scheduling specialty care can be difficult, the colposcopy and baseline study assessments may occur outside of the 60 day window, if dependent on scheduling. An extended window does not impact data/specimen fidelity; it is meant to minimize disruption to and burden on participants. If/when this occurs, it will be documented with a note to file in the participant's record. The situation may arise for each annual colposcopy exam as well, and therefore, if the follow-up colposcopy cannot be completed within +/- 60 days of the previous colposcopy due to scheduling issues, a note to file will be documented in the participant's record. If the colposcopy cannot be completed within 90 days of the target date, query via the QNS.

**Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies
(LiVes LLC Study [Protocol PH700])**

Table I-1. Recruitment, Testing 1, and Testing 2

Study Time Point/Visit			
	Enrollment and Instructions for Testing 1 ¹	Testing 1 (Collection date)	Testing 2 ³
Visit Window	No window between recruitment, consenting/enrollment, and Testing 1		10-14 months of Testing 1 self-collection date
Study Assessment			
Review and confirm the Inclusion/Exclusion Criteria	X		
Confirm eligibility for HPV self-testing			X
Obtain a signed Informed Consent Form	X		X ⁴
Provide self-collection kit/swab to participant	X ⁵		X
Administer HPV Immunization and Current ART Questionnaire	X ^{5,6}		X ^{6,7}
Participant self-collection of swab		X ²	X ²
Medical Chart Abstraction			
Most recent CD4 count and HIV viral load	X ⁵		X ⁷
HPV Vaccination History	X ⁵		X ⁷

¹ Consenting and Enrollment and Testing 1 and may happen on the same day if the participant is consented in clinic (during a visit for another study or at a standard of care (SOC) visit).

- Recruitment and/or consenting may also occur remotely by telephone or video conference.

² The self-collection swab should be mailed by the site and the participant to the certified lab, preferably, within 24 hours of collection, but ultimately no later than 96 hours (4 calendar days) of collection. If greater than 96 hours, refer to the PH700 LPC and MOP for further information on how to manage specimen collection and shipment.

³ Testing 2 only occurs if the results from the Testing 1 self-collected swab were hrHPV-Negative.

⁴ If either the main consent template or the site-specific consent addendum changed since previous signing, or single IRB or local IRB requires re-consenting, the participant must be re-consented prior to visit assessments taking place.

⁵ No study activities may occur until the signed consent is received by the study team.

⁶ Via phone or in-person interview.

⁷ Collect data since the last study visit/contact.

**Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies
(LiVes LLC Study [Protocol PH700])**

Table I-2. Participants who Test hrHPV-Positive after Testing 1 or Testing 2

Study Time Point/Visit		
	Baseline (BL) ¹	Annual Colposcopy Follow-up 1, 2, 3 ^{1,2}
Visit Window	Within 60 days of participant HPV-Positive (+) notification	Within 1 year +/- 60 days of previous colposcopy
Study Assessment		
Review and confirm the Inclusion/Exclusion Criteria		X (Confirm)
Administer HPV Immunization and Current ART Questionnaire	X ^{3,4}	X ⁴
Administer the Reproductive Health and Tobacco Use Online Survey	X ⁵	X ⁵
Colposcopy Visits for hrHPV-Positive		
Urine pregnancy test ⁶	X ⁷	
Standard colposcopic examination	X	X
If applicable ⁸ , cervical biopsies of acetowhite areas	X ⁹	X ⁹
Routine cytology/pap for local lab	X	X
Cervical vaginal lavage with normal saline for repository	X	X
One cervical sample (endo/exocervical cells) for biomarker and repository evaluations	X	X
Unstained cytology/pap slide to be mailed to NIH for dual staining	X	
Medical Chart Abstraction		
All available previous cervical cancer screening test results, cytology/pap, histology/biopsy results, and treatment	X	
All available interim cervical cancer screening test results, cytology/pap, histology/biopsy results, and treatments not obtained as part of the research study		X ⁴

**Real-world Effectiveness of HPV Vaccine in Women Living with HIV and Its Impact on Cervical Cancer Screening Accuracies
(LiVes LLC Study [Protocol PH700])**

Most recent CD4 count and HIV viral load	X ⁴	X ⁴
HPV vaccination history	X ⁴	X ⁴
STI testing results if obtained at colposcopy as part of standard of care	X	X

¹ If either the main consent template or the site-specific consent addendum changed since previous signing or single IRB or local IRB requires re-consenting, the participant must be re-consented prior to visit assessments taking place.

² Depending on when the participant is enrolled, participants will have up to 3 annual follow-up visits during this 5-year grant period.

³ Via phone or in-person interview.

⁴ Collect data since the last study visit.

⁵ A separate survey link is available for the baseline and follow-up online surveys.

⁶ In clinic **BEFORE** the colposcopic examination (If not documented within the last 2 weeks).

⁷ If the participant is pregnant, they will not be seen as part of the study that day. The participant will be asked to reschedule their visit after their pregnancy ends.

⁸ Based on ASCCP Colposcopy Guidelines (2-3 acetowhite areas).

⁹ The cervical biopsy should include:

- Diagnostic read by the local pathology laboratory; and
- Original histology/biopsy slide or an additional paraffin embedded section on a slide from each biopsy specimen to be sent to the Central Pathology Laboratory at UCLA for standardized research reading. Refer to the PH700 LPC and MOP for further information on specimen collection.

Table I-3. Participants who Test hrHPV-Negative after Testing 2

Study Time Point/Visit	
Visit Window	Annual Follow-up 1, 2, 3 ¹
	Within 1 year +/-60 days of previous self-collected swab
Study Assessment	
Review and confirm the Inclusion/Exclusion Criteria	X
Provide self-collection kit/swab ² to participant to complete at home or in the clinic	X
Administer HPV Immunization and Current ART Questionnaire ³	X ⁴
Medical Chart Abstraction	
Most recent CD4 count and HIV viral load	X ⁴
HPV vaccination history	X ⁴

¹ If either the main consent template or the site-specific consent addendum changed since previous signing or single IRB or local IRB requires re-consenting, the participant must be re-consented prior to visit assessments taking place.

² Research swab self-collection kit, not the same collection kit from Testing 1 and 2; mailed to UCLA by SC or by participant. Refer to the PH700 LPC and MOP for further information on specimen collection.

³ Via phone or in-person interview.

⁴ Collect data since the last study visit.

Appendix II Participating PHACS and HOPE Sites

The following are PHACS sites eligible to participate in this protocol:

Site Number	Site Name and Location	SMARTT (PH100)	AMP Up (PH300)	AMP Up Lite (PH400)	HOPE
2	Boston Children’s Hospital – Boston, MA		X		
7	St. Jude Children’s Research Hospital – Memphis, TN	X	X		X
9	University of Colorado, Denver – Denver, CO	X	X		X
13	Bronx-Lebanon Hospital – Bronx, NY	X	X	X	X
18	University of Miami – Miami, FL	X	X		X
19	Baylor College of Medicine, Texas Children’s Hospital – Houston, TX	X	X	X	X
20	Tulane University – New Orleans, LA	X	X		X
23	Jacobi Medical Center – Bronx, NY		X		
24	Lurie Children’s Hospital – Chicago, IL	X	X		X