SUMMARY OF CHANGES

A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT)

Version 5.0

NCI Protocol #: AMC-099
Local Protocol #: AMC-099

NCI Version Date: 07AUG2023
Protocol Date: 07AUG2023

I. Scientific and Substantive Changes:

#	Section	Comments
1.	6.5 9.9 Appendix I	Women diagnosed with invasive carcinoma will complete a one-year follow-up visit in lieu of completing all visits as specified in the calendar of protocol version 4.

II. Administrative and Editorial Changes:

#	Section	Comments
2.	Global	The protocol was updated to version 5.0, and the date was updated to 07AUG2023.
3.	Protocol Roster	Contact information were updated. Jeanette Lee was replaced as Protocol Statistician by Himanshu Joshi and Mayuri Jain. In addition, the address for Elizabeth Stier, protocol co-chair, was updated.
4.	Protocol Roster	The AMC ODMC contact email address was updated to reflect the protocol-specific email alias.
5.	Site roster	The site roster has been updated to reflect all participating sites and the site's principal investigator.
6.	2.3	Added language to clarify that the screening eligibility include participants 25 years or older, known to be living with HIV and willing and able to provide informed consent. In addition, language was added to clarify only eligible women were randomized to study vaccine.

7.	3.1 3.2	Added clarification to the section titles that the criteria outlined are for randomization.
8.	4.1 4.2	Added language to include CTEP's template language for an investigator's CTEP registration and site registration. This added a new section, section 4.0 Registration Procedures.
9.	6.6	Added Merck's requirement to report all study drug exposures during pregnancy or lactation to Merck GPV. In addition, language was added to clarify that the reporting for pregnancy outcome is made within Advantage eClinical.
10.	7.0 7.2 7.3 7.6	Adverse event text has been revised to reflect the guidance from Merck regarding reporting procedures for exchange of adverse event information.
11.	7.5	Added language to clarify that Grade 1 or 2 adverse events that do not lead to premature discontinuation of study vaccine (or placebo) do not need to be reported in Advantage eClinical but must be reported in the participant's study records.
12.	7.8	Language was added to clarify that the reporting for pregnancy outcome is made within Advantage eClinical.
13.	8.4	Added guidance from Merck regarding reporting of study drug defects.
14.	9.4 Appendix I	The window was revised in protocol amendment v4.0 but a sentence in section 9.4 and the Appendix I still needed to be revised. The text has been revised to accurately state that Week 26 evaluations should take place with a +/- 4 weeks window.
15.	10.5.5	To maintain consistency with the timepoints for the stored HPV serology, week 78 was added as a timepoint for log-transformed antibody titer reports.
16.	Appendix II	Mentions of the specific assay used (previously Roche Linear Array) was removed as it is no longer available.
17.	Appendix IV	The Data and Safety Monitoring Plan (DSMP) was updated to reflect version 9.0 of the DSMP.
18.	Appendix V	To maintain consistency across guidance documents, vulvar specimens were included in the parenthesis for histology specimens.

AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL #099:

A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT)

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT03284866
Regulatory Status:	Pursuant to national requirements for each participating site
Pharmaceutical Support Provided by:	Merck & Co. Gardasil 9 (9-valent Human Papillomavirus, Recombinant Vaccine, NSC 784724)
Protocol Chair:	Carla Chibwesha, MD, MSc
Protocol Co-Chair:	Timothy Wilkin, MD, MPH Elizabeth Stier, MD

Version 5.0, 07AUG2023
NCI Version Date 07AUG2023

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site_____, agree to conduct and follow this protocol: **AMC Protocol #099 – A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT) (Version 5.0, 07AUG2023),** as written according to AMC, NCI, and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (DD/MMM/YYYY)

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ABBREVIATIONS

ACSR	AIDS and Cancer Specimen Resource
Advantage eClinical	Advantage eClinical Internet and Data Entry System
AE	Adverse event
AERS	Adverse Event Reporting System
AIDS	Acquired immune deficiency syndrome
AIS	Adenocarcinoma in situ
AMC	AIDS Malignancy Consortium
CDC	Centers for Disease Control and Prevention
CDUS	Clinical Data Update System
CIN	Cervical intraepithelial neoplasia
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Treatment and Evaluation Program
CTMS	Clinical Trials Monitoring System
DARF	Investigational Agent Accountability Record Form
DHHS	Department of Health and Human Services
FDA	Food and drug administration
FFPE	Formalin-fixed paraffin-embedded
HGAIN	High-grade anal intraepithelial neoplasia
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hrHPV	High risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesions
IEC	Independent ethics committee
IND	Investigational new drug
LCM	Laser capture microdissection

LEEP	Loop electrosurgical excisional procedure
LSIL	Low-grade squamous intraepithelial lesions
MOP	Manual of procedures
NCI	National cancer institute
ODMC	Operations and Data Management Center
OHRP	Office of human research protection
PCR	Polymerase chain reaction
PIO	Protocol Information Office
SAE	Serious adverse event
SPEER	Specific protocol exceptions to expedited reporting
STI	Sexually transmitted infection
VAIN	Vaginal intraepithelial neoplasia
VIA	Visual inspection with acetic acid
VIN	Vulvar intraepithelial neoplasia

PROTOCOL ROSTER

AMC Protocol #099

A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT)

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SITE ROSTER

AMC Protocol #099

A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT)

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PROTOCOL SYNOPSIS

Title:	A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT)
Phase of Study:	Phase III
Participating Institutions:	This protocol will be open to all AMC international member sites.
Accrual Target:	536 participants
Population:	HIV-infected females 25 and older, currently receiving antiretroviral therapy for at least 6 months with no prior history of cervical, vulvar, or vaginal cancer. Participants must be HPV-positive by GeneXpert hrHPV assay with HPV16, 18/45, or 31/33/35/52/58 detected. Participants must not have had a hysterectomy, prior treatment for cervical HSIL or prior HPV vaccination.
Regimen:	Potential participants will be tested for cervical human papillomavirus (HPV) infection (GeneXpert hrHPV assay and HPV DNA PCR) and undergo cervical colposcopy. If eligible, the participant will be randomized to receive either the 9-valent HPV vaccine or saline placebo. Participants will return 4 and 26 weeks later to complete the vaccination (or placebo) series. At week 4, participants will have HPV testing, cervical colposcopy, and undergo cryotherapy or loop electrosurgical excisional procedure (LEEP) as appropriate. Participants undergoing cervical cryotherapy will have cervical biopsies obtained just prior to the treatment. Participants will be followed with HPV testing (GeneXpert and HPV DNA PCR) at week 26, 52, 78, and 104, as well as with cytology and cervical colposcopy with biopsies at week 26, 52, and 104.
Duration:	Participants will be followed for 2 years following randomization.
Primary Objective:	To determine if HPV vaccination reduces the occurrence of cervical HSIL among HIV-infected women participating in an HPV test-and-treat strategy for cervical cancer prevention.

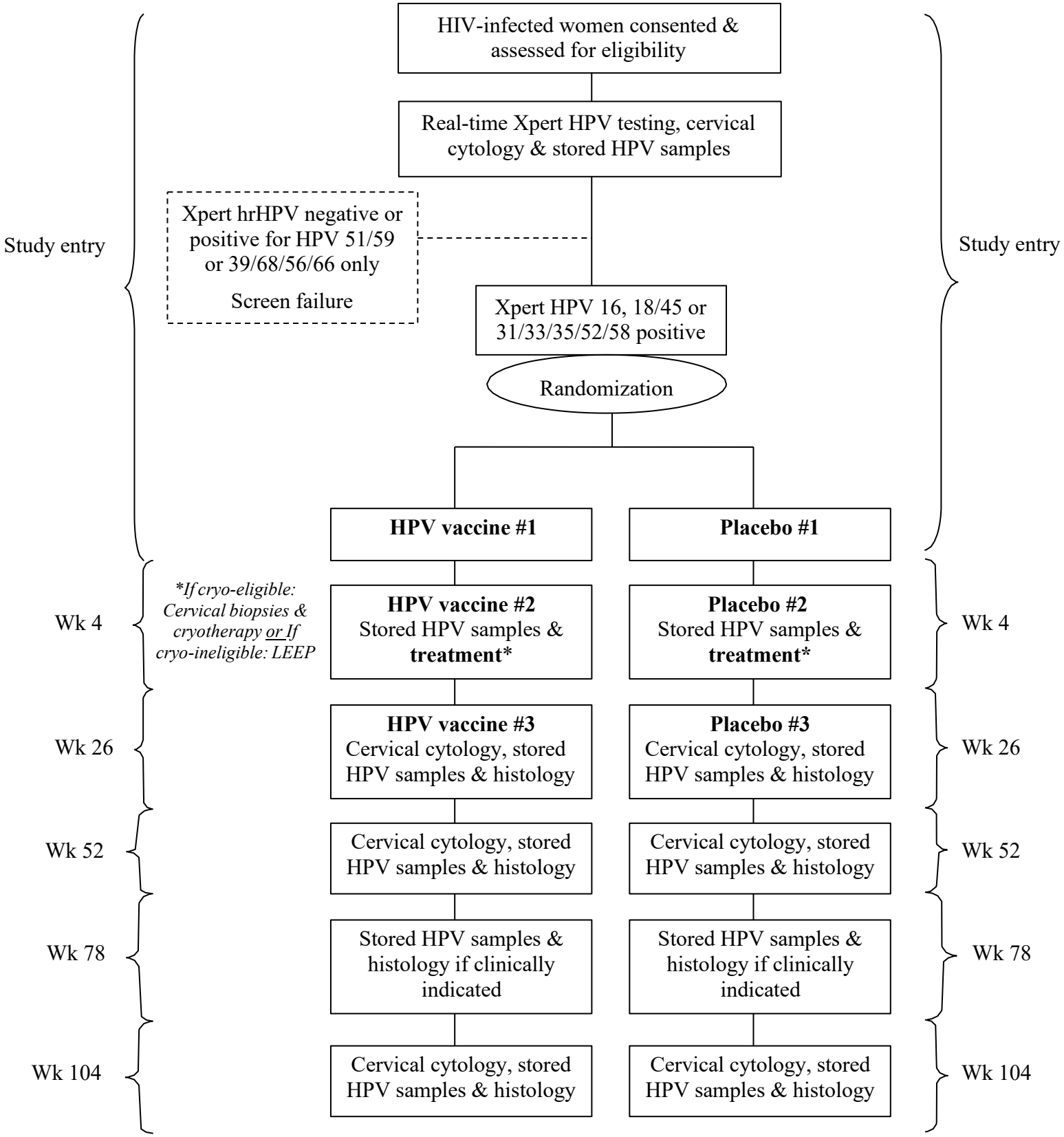
Secondary Objectives:

- To describe occurrence of cervical HSIL from week 52 to week 104.
- To examine the predictors of sustained absence of cervical HSIL through week 104 and clearance of HPV infections after cervical treatment, including: baseline types and quantity of HPV, presence of HSIL at baseline, cryotherapy vs. LEEP, CD4+ cell count, plasma HIV-1 RNA, ART use, age, sexual behavior, and vaccination use.
- To compare, between study arms, incident cervical vaccine type HPV infections and cervical cytology results.
- To describe prevalent and incident vulvar HSIL or cancer in this population.

Exploratory Objectives:

- To determine if HPV vaccination alters the HPV type distribution for cervical and vulvar HSIL.
- To conduct HPV strain variant analysis of cervical and vulvar HSIL specimens.
- To establish a tissue microarray library of cervical specimens for biomarker analysis and discovery.
- To describe the prevalence and hrHPV type distribution in the anus and its relationship to persistent cervical HPV infection and incident cervical or vulvar HSIL.
- To conduct exploratory analysis of vaccine-induced antibody titers, incident HSIL, and confirmed vaccine type infections.

PROTOCOL SCHEMA



1 OBJECTIVES

1.1 Hypothesis

HPV vaccination reduces the occurrence of cervical HSIL among HIV-infected women participating in an HPV test-and-treat strategy for cervical cancer prevention (i.e., women treated for hrHPV).

1.2 Primary Objective

To determine if HPV vaccination reduces the occurrence of cervical HSIL among HIV-infected women participating in an HPV test-and-treat strategy for cervical cancer prevention.

1.3 Secondary Objectives

1.3.1 To describe occurrence of cervical HSIL from week 52 to week 104.

1.3.2 To examine the predictors of sustained absence of cervical HSIL through week 104 and clearance of HPV infections after cervical treatment, including: baseline types and quantity of HPV, presence of HSIL at baseline, cryotherapy vs. LEEP, CD4+ cell count, plasma HIV-1 RNA, ART use, age, sexual behavior, and vaccination use.

1.3.3 To compare, between study arms, incident cervical vaccine type HPV infections and cervical cytology results.

1.3.4 To describe prevalent and incident vulvar HSIL or cancer in this population.

1.4 Exploratory Objectives

1.4.1 To determine if HPV vaccination alters the HPV type distribution for cervical and vulvar HSIL.

1.4.2 To conduct HPV strain variant analysis of cervical and vulvar HSIL specimens.

1.4.3 To establish a tissue microarray library of cervical specimens for biomarker analysis and discovery.

1.4.4 To describe the prevalence and hrHPV type distribution in the anus and its relationship to persistent cervical HPV infection and incident cervical or vulvar HSIL.

1.4.5 To conduct exploratory analysis of vaccine-induced antibody titers, incident HSIL, and confirmed vaccine type infections.

2 BACKGROUND

2.1 Study Disease

Cervical cancer remains the second most common cancer among women worldwide, and more than 85% of the global burden of this disease occurs in the developing world. It is well documented that HIV-infected women are at higher risk of HPV infection, with rates as high as 45% - 90%.[1-3] Despite being preventable, cytologic abnormalities, pre-invasive cervical disease (HSIL), and invasive cervical cancer also occur more frequently in HIV-infected women.[2,4]

Recurrence of HSIL after cervical treatments is quite common among HIV-infected women. Recent data from a randomized controlled trial of LEEP vs. cryotherapy for cervical HSIL in HIV-infected women in Johannesburg found that 27% had recurrent HSIL in the cryotherapy group and 19% in the LEEP group, p=.21.[38] A recent Kenyan study also found that 19% of women treated with cryotherapy for a positive VIA had HSIL on follow-up colposcopy.[39]

The AIDS Clinical Trials Group A5282 trial randomized HIV-infected women with high risk HPV infection with no cervical lesions or cervical lesions appropriate for cryotherapy to immediate cryotherapy or a cytology-based strategy. Through 2.5 years of follow-up, 25% of women randomized to cryotherapy developed cervical HSIL by cytology.[40]

The HPV test-and-treat strategy is a promising prevention option that allows same day screening and treatment. GeneXpert machines are becoming widely available in resource-constrained settings and make this strategy feasible in many settings. The 9-valent HPV (9vHPV) vaccine may improve the long-term outcomes for women entering this strategy by providing broad protection against new hrHPV infections and improving the response to treatments of HPV types in cervical HSIL present prior to vaccination.

2.1.1 HPV vaccination in the context of SIL treatment

Joura and colleagues studied (HIV-uninfected) women receiving excisional cervical treatments while participating in clinical studies of the quadrivalent HPV vaccine. In their combined retrospective evaluation of the two Phase III HPV vaccine trials, 587 vaccines and 763 placebo recipients underwent treatments of the cervix.[5] Women who had received the quadrivalent HPV vaccine had a 46.2% lower risk of subsequent HPV disease (95% CI: 22.5-63.2%) and a 64.9% lower risk of cervical HSIL as compared to women who had received placebo (95%CI: 20.1-86.3%). Interestingly, the observed effect was not restricted to infection or SIL caused by vaccine types. A retrospective, non-randomized study from Korea compared the recurrence of cervical HSIL in 360 HIV-uninfected women who had vaccination just after LEEP (n=360) compared to a group that did not get vaccinated (n=377). Cervical HSIL was observed in 9 vaccinated women (2.5%) vs. 27 (7.2%) unvaccinated women (HR 2.8, 95% CI: 1.3-6.0).[6] Hildesheim and colleagues reported on data from a randomized clinical trial of the bivalent HPV vaccine.[7] They found no evidence that HPV vaccination improved responses to LEEP. However, the number of HSIL recurrences post-LEEP was very low (<1% per year and only 4 events total between arms).

Swedish and colleagues conducted a retrospective chart review of HIV-uninfected men who have sex with men who were diagnosed with high-grade anal HSIL. They showed a trend towards a lower risk for recurrent or persistent HGAIN after undergoing ablative treatment of HSIL among men who had been previously vaccinated (HR 0.5, 95% CI: 0.3 – 1.0).[8]

These data suggest that HPV vaccination may improve outcomes of treatment of HSIL. HPV infects the epithelium through micro-abrasions in the epithelium.[9] HPV antibodies induced by HPV vaccination, when present in high titers, prevent infection by binding the virus and preventing interaction with the acellular basement membrane.[10] At lower antibody titers, this interaction is not blocked. Lower antibody titers block the interaction of the HPV virion and the basal epithelial cells thereby preventing infection by a second mechanism.[11] This provides a mechanism for vaccine protection even when antibody titers have fallen to low levels.

Persistence of hrHPV after LEEP is a major risk factor for recurrence of cervical HSIL. LEEP may clear HPV infection of the cervix but will not clear HPV infections at other sites in the genital tract (i.e. vagina or vulva) that may lead to re-infection of the healing cervix. Women are also at risk for re-infection from their sexual partners. We hypothesize that HPV antibodies induced by HPV vaccination present in the cervical area after LEEP will protect the healing epithelium from re-infection with HPV by the two mechanisms discussed above. Existing data suggest that antibodies are detectable one week after vaccination.[12,13]

Of note, we are performing cervical treatments (cryotherapy or LEEP) 4 weeks after the first vaccination. This is being done to delay the time that cervical HSIL is being untreated and to minimize the time from randomization to the baseline histologic assessment. In a prior trial of HPV vaccination, the antibody titer 1 month after the first vaccine appeared similar or even greater than that observed at 2 months after vaccination.[13]

2.2 Study Agents

2.2.1 Gardasil 9

Gardasil (quadrivalent HPV vaccine consisting of recombinant L1 particles for types 6, 11, 16, and 18) has been shown to prevent cervical, vaginal, anal, and external genital lesions caused by the vaccine types.[14] However, it does not hasten clearance of prevalent HPV infections.[15] It also does not prevent or treat lesions caused by ongoing infection with the vaccine types.[16,17]

The safety and immunogenicity of HPV vaccination in HIV-infected populations has been established in several trials, but there are no data on efficacy.[18,19] The 9-valent HPV vaccine (9vHPV) is a new FDA-approved vaccine that includes vaccine-like particles for HPV types 31, 33, 45, 52, 58, in addition to types 6, 11, 16, and 18. In a phase 3 trial of 9vHPV in 14,204 females age 16-26, 9vHPV led to a 96.7 percent reduction (95% CI: 80.9-99.8%) in the combined incidence of high- grade cervical/vulvar/vaginal disease caused by HPV types 31, 33, 45, 52, 58 (1 case in the group that received 9vHPV vs. 30 cases in the group that received the quadrivalent HPV vaccine).[20] The study also found a 96.0% efficacy (95% CI: 94.4-

97.2%) against six-month persistent HPV infection with HPV types 31, 33, 45, 52, 58 (35 cases in the group that received V503 vs. 810 cases in the group that received the quadrivalent HPV vaccine). See the Merck website for the most recent package insert.

Current guidelines from the Advisory Committee on Immunization Practices/Centers for Disease Control recommend deferring HPV vaccination during pregnancy, although the vaccines have not been associated causally with adverse outcomes of pregnancy or adverse events in the developing fetus. These guidelines allow for vaccination of breastfeeding women.[36]

2.3 Study Design and Rationale

The HPV test-and-treat strategy is a promising cervical cancer prevention approach. This was evaluated in a 3-arm study comparing hrHPV testing, VIA (visual inspection of the cervix after a wash of acetic acid without the aid of a colposcope) and a control arm of delayed evaluation in a large clinical trial of South African women.[21] Women aged 35-65 received a test for hrHPV (hc2, Digene) and VIA at baseline. Women with hrHPV detected in the hrHPV group and VIA abnormalities in the VIA group underwent cervical cryotherapy. The HPV-test-and-treat strategy was the most effective at preventing HSIL. The HPV-based approach appeared to work particularly well among HIV-infected women.[22] Among approximately 300 HIV-infected women randomized to the HPV arm, 3.1% developed HSIL through 3 years of follow-up compared to 14.9% the HIV-infected women randomized to the control arm ($p<0.001$). Nearly all HSIL developed among women infected with hrHPV at baseline. These results suggest that an HPV test-and-treat strategy is efficacious in HIV-infected women and should be considered as a cervical cancer prevention strategy. ACTG A5282 is an ongoing randomized clinical trial that is comparing the efficacy of an HPV test-and-treat strategy as compared to a cytology-based approach in HIV-infected women. The study completed accrual in June 2014. Study follow-up concludes December 2016.

2.3.1 GeneXpert HPV Assay

The Cepheid Xpert HPV Assay (Xpert hrHPV) is a new, qualitative, real-time polymerase chain reaction (PCR) assay for the detection of hrHPV DNA. The assay is formatted in a single-use GeneXpert Test cartridge and is run on the Cepheid GeneXpert® System, a multi-analyte, random access, molecular-diagnostic platform ranging in capacity from 1 to 80 test processing modules. Importantly, a single hrHPV DNA test can be completed in one hour, permitting same-day screening, diagnosis, and treatment which reduces the potential loss to follow-up in lower-resource settings and permits decentralized, clinic-based (vs. lab-based) testing. It uses ThinPrep (CytoLyt) media and yields five separate results: (a) HPV16, (b) HPV18/45, (c) P3-HPV 31/33/35/52/58, (d) P4-HPV51/59, (e) P5-HPV39/68/56/66. Xpert was compared to two validated hrHPV tests, cobas4800 (cobas, Roche Molecular Diagnostics) and hc2, and to histologic outcomes using specimens from colposcopic referral populations at seven clinical sites in the U.S. ($n = 697$).[23] Xpert was equally sensitive for HSIL ($n = 141$) as cobas (90.8% vs. 90.8%), and more sensitive than hc2 (90.8% vs. 81.6%, $p = 0.004$). Xpert was more specific than cobas (42.6% vs. 39.6%, $p = 0.02$) and less specific than hc2 (42.6%

vs. 47.7%, p < 0.001). hrHPV detection by the Xpert demonstrated excellent clinical performance for identifying women with HSIL that was comparable to currently available clinically-validated tests.

Investigators tested stored samples from VICAR-1, a study comparing three cervical cancer screening tests in HIV-infected women from Johannesburg.[37] Of the 1,161 results available, 720 (62%) were positive by Xpert and 711 (61%) were positive by hc2. The Cohen's kappa statistic was 0.78 (95% CI: 0.74-0.82) indicating substantial agreement. The sensitivity for HSIL on biopsy was 88% (95% CI: 84%-93%) for Xpert and 92% (95% CI: 87%-96%) for hc2, not statistically different (McNemar's p=0.5). The specificity and negative and positive predictive values of Xpert for HSIL were 48% (45%-52%), 91% (88%-95%), and 40% (36%-44%), respectively. The positive predictive value for HPV16 was markedly higher than those of the other HPV results (71% vs. 34% to 44%). HPV16, HPV18/45, and HPV 31/33/35/52/58 were all independently associated with the presence of HSIL (p<0.01 for each); HPV51/59 and HPV39/68/56/66 were not associated with HSIL.

One limitation of an HPV test-and-treat strategy is that the specificity for HSIL is relatively low. This means that many women are treated who do not have cervical HSIL. The VICAR-1 data suggest that HPV51/59 and HPV39/68/56/66 were not predictive of HSIL. However, the specificity of Xpert for cervical HSIL can be increased from 48% to 60% by ignoring HPV51/59 and HPV39/68/56/66 results. This increases the positive predictive value from 40% to 44%.

2.3.2 Study design

This is a randomized, double-blind, placebo-controlled trial.

Screening: Participants will provide informed consent and be assessed for eligibility. Participants should continue in screening if they are 25 years or older, known to be living with HIV and willing and able to provide informed consent. Participants will undergo a speculum examination for collection of specimens for HPV testing and cervical cytology. Xpert HPV testing will be performed in real-time at the clinical research site, and aliquots will be stored for future research. VIA/colposcopy will be performed to assess for cryotherapy eligibility. In order to reduce the risk that women with invasive cervical cancer are enrolled into the trial, the cervix will be examined for lesions suspicious for cancer. If lesions suspicious for cancer are found, then randomization should be delayed and cervical biopsies should be obtained. These participants will be eligible for randomization if the biopsies do not show invasive cancer.

- If hrHPV negative, then the participant is ineligible for the study.
- If hrHPV positive with only HPV 51/59 or HPV 39/68/56/66 detected, then the participant is ineligible for the study.
- If hrHPV positive with HPV16, HPV 18/45, or HPV31/33/35/52/58 detected, women are eligible for randomization.

An anal swab will also be performed for future testing by HPV DNA PCR. The anal swab must be collected prior to or during the randomization visit. Blood will

be drawn for CD4+ cell count and plasma HIV-1 RNA testing.

Randomization: Women who meet eligibility criteria for randomization (see Sections 3.2 and 3.3) will be randomized to study vaccine (9vHPV or saline placebo). Randomization will be stratified by treatment type chosen at baseline (i.e., cryotherapy vs. LEEP), by presence of HPV 16 at baseline, and study site.

All participants will return 4 and 26 weeks later to complete the vaccination (or placebo) series.

The 4-week visit will also include VIA/colposcopy, during which women will be re-assessed for cryotherapy eligibility. Women will be deemed eligible to undergo cryotherapy if they have (1) no visible cervical lesions 2) any visible lesions are located entirely on the ectocervix and that are no more than 2-3 mm into the endocervical canal, and (3) visible lesions cover < 75% of the cervix, and (4) all visible lesions are deemed appropriate for cryotherapy by the treating provider.

- If cryo-eligible (no lesions seen or lesions suitable for cryotherapy), then two cervical biopsies will be performed followed by immediate cryotherapy.
- If extensive lesions are seen (i.e. cryo-ineligible lesions), then LEEP should be performed with histologic analysis of the LEEP specimen.

Note: All study participants will be treated (using either cryotherapy or LEEP) for a cervical hrHPV infection. Although not standard of care across sub-Saharan Africa, this HPV test-and-treat approach is evidence-based and supported by current World Health Organization guidelines.[24]

Long-term follow up

Women will be followed for two years following randomization. Women will be seen every 26 weeks for hrHPV testing through week 104. Women will undergo cervical cytology and colposcopy with directed biopsies at week 26, week 52, and week 104. Colposcopy at week 78 will be performed as clinically indicated based on cytology results and clinical examination (i.e., cervical lesions seen during the gynecological exam concerning for HSIL or cancer). An anal swab will also be collected at weeks 52 and 104 for future testing for HPV DNA PCR.

At each colposcopy, the vulva will be carefully examined for the presence of vulvar HSIL. Vulvar lesions suspicious for HSIL will be biopsied. The management of vulvar HSIL will be determined by the local investigator.

If invasive cervical cancer is found at any stage of follow up during the study, the participant will be referred for gynecological follow up per standard of care in the country. The protocol team will consult with the treating provider to optimize the management of all cases of invasive cancer. If cervical HSIL is found in follow-up, management will be at the discretion of the treating provider.

2.4 Correlative Studies

2.4.1 To determine if HPV vaccination alters the HPV type distribution for cervical and vulvar HSIL

The COVENANT trial's long-term follow-up (104 weeks) creates the opportunity to better characterize viral and cellular factors associated with HPV infection and histological abnormalities in HIV-infected women.

Laser capture microdissection can be used to enhance molecular analyses as it allows investigators to examine genomic, proteomic, and immunohistochemical characteristics within specific cell populations.[25,26] It is well established that HIV-infected women are more likely than their uninfected counterparts to have multiple, concurrent HPV infections.[27] Conventional, whole tissue section PCR does not characterize how individual HPV types relate to specific histologic abnormalities within the section.[28]

For this sub-study, we will utilize conventional whole tissue section PCR on all cervical and vulvar HSIL lesions. If multiple HPV types are found, we will then perform HPV DNA PCR testing of microdissected cervical and vulvar tissue specimens to map the distribution of specific HPV types within histological sections from cervical or vulvar biopsies. Tissues specimen will be obtained during follow-up as described above. Formalin-fixed paraffin-embedded (FFPE) biopsies will be sectioned for laser capture microdissection (LCM) and a portion of the tissue then processed for HPV DNA PCR. All available FFPE specimens (including baseline HSIL specimens) will be included in the analysis.

2.4.2 To conduct HPV strain variant analysis of cervical and vulvar HSIL

HPV vaccination should prevent HSIL due to new vaccine-type HPV infections but may be less efficacious for recurrence (or persistence) of HSIL present at baseline. For this sub-study, we will determine the HPV strain variants for cases in which the same HPV type was observed in HSIL at baseline and in follow-up. The analysis will involve sequencing the HPV E6 gene in FFPE specimens to identify strain variants. This will allow us to distinguish whether incident HSIL lesions are resulting from infection with the strain found in HSIL at baseline as opposed to a new strain.

2.4.3 To establish a tissue microarray library of cervical specimens for biomarker analysis and discovery

Molecular biomarkers with higher sensitivity and specificity than current-generation HPV DNA, mRNA, and oncoprotein tests are urgently needed to simplify triage and improve diagnosis of pre-invasive and invasive cervical cancer. Immunohistochemical biomarkers such as p16 (INK4a) and Ki-67 have been demonstrated to correlate with severity of cytological and histological abnormalities in HIV-negative women.[29-31] Furthermore, cellular biomarkers may be useful in the triage of an abnormal cervical screen, identifying women at highest risk of progression to invasive cancer.[32] COVENANT creates a unique opportunity to further delineate molecular biomarkers associated with HPV infection, LSIL, HSIL, and invasive cancer specimens among HIV-infected women. We will also investigate whether biomarker expression is associated with persistence of HSIL after treatment with cryotherapy or LEEP.

As described above, FFPE cervical biopsies will be sectioned for LCM. A second portion of the microdissected tissue will be used to create a tissue microarray library

consisting of normal, HPV-infected, LSIL, HSIL, and invasive cancer specimens for biomarker analysis and discovery. Any future studies using these specimens will need to receive separate approval by NCI and CTEP.

2.4.4 To describe the prevalence and hrHPV type distribution in the anus and its relationship to persistent cervical HPV infection and incident cervical or vulvar HSIL

We will collect anal swabs from women participating in the trial. These swabs will be collected at baseline, week 52, and week 104, and will characterize the hrHPV type distribution of anal HPV infection in this population. We will evaluate the concordance between anal and cervical HPV types. We also will evaluate the relationship between anal infections and incident cervical HPV infections that persist for two or more study visits.

2.4.5 Exploratory analysis of vaccine-induced antibody titers, incident HSIL, and confirmed vaccine type infections

We will examine women with cervical or vulvar HSIL in the vaccine group caused by vaccine types. We will explore the antibody titers for the vaccine type found in the HSIL in these women as compared to those without HSIL caused by that type.

3 PARTICIPANT SELECTION

A rostered AMC investigator must document that each protocol participant meets all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

3.1 Eligibility Criteria for Randomization

3.1.1 HIV-1 infection, documented by one of the following any time prior to study entry: Any licensed rapid HIV test.

- HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit. And confirmed by one of the following:
- Licensed western blot.
- Second antibody test by a method other than the initial rapid HIV and/or E/CIA.
- HIV-1 antigen.
- Plasma HIV-1 RNA viral load.
- Documentation of receipt of antiretroviral therapy.

Note: The term "licensed" refers to a kit that has been certified or licensed by an oversight body within the participating country and validated internally.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

3.1.2 HPV positive by the GeneXpert hrHPV assay with HPV16, HPV 18/45, or HPV31/33/35/52/58 detected.

Note: Participants who are hrHPV positive with only HPV51/59 or HPV 39/68/56/66 detected are not eligible.

3.1.3 Age $\geq$ 25 years.

Note: Most guidelines do not include women younger than 30 years of age in HPV-based testing strategies. The age limit of 25 was selected given the accelerated HPV disease progression among HIV-infected women.

3.1.4 Receipt of ART for at least 180 days prior to randomization.

3.1.5 Participants of childbearing potential, defined as a sexually mature woman who: (1) has not undergone a hysterectomy or bilateral oophorectomy or (2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months), must have a negative urine or serum pregnancy test within 3 weeks prior to enrollment and agree to use an effective form of contraception (e.g., barrier contraception or hormonal contraception), delaying pregnancy for at least 12 months and ideally for the

duration of the study.

Note: We anticipate that young women of child-bearing potential who would otherwise be eligible for inclusion may not wish to delay pregnancy for a 2-year period. We therefore request that those willing to participate delay pregnancy for at least 12 months, while receiving the 9vHPV vaccine (or placebo) through the primary endpoint at Week 52. We acknowledge that study evaluations during the follow-up period would be impacted by pregnancy, but do not believe that this will be a common enough occurrence to affect the statistical power.

Note: Breastfeeding women are eligible for the trial if meeting all other entry criteria.

3.1.6 If the participant is of childbearing potential, she should be at least 3 months postpartum.

3.1.7 Karnofsky score ≥70% (see Appendix III).

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria for Randomization

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally, the presence of any of the following conditions will exclude a participant from study enrollment:

3.2.1 Current STI requiring treatment (women may participate after adequate treatment, at the discretion of the treating provider).

3.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Gardasil or Gardasil 9.

3.2.3 Uncontrolled intercurrent illness that would limit compliance with study requirements.

3.2.4 Prior hysterectomy with removal of the cervix.

3.2.5 Prior treatment for cervical HSIL.

Note: Cervical scarring that occurs after treatment with cryotherapy or LEEP may impact future visual evaluation of the cervix, making VIA or colposcopy more challenging.

3.2.6 Prior history of cervical, vulvar, or vaginal cancer.

3.2.7 Cervical, vulvar, or vaginal lesions suspicious for cancer based on clinical appearance (e.g. necrotic, ulcerated, and/or fungating masses), unless biopsies show no invasive cancer.

3.2.8 Known bleeding diathesis.

3.2.9 Prior HPV vaccination.

3.2.10 Current or planned use of anticoagulants other than aspirin or non-steroidal anti-inflammatory agents.

3.2.11 Documentation of WHO Clinical Stage 3 or 4 condition within 6 months of entry.

3.2.12 CD4 count <200 cells/mm^3 within 6 months of entry.

Note: This refers to any CD4 obtained for routine care. Documentation of CD4 is not required prior to entry.

3.3 Number of Participants to be Enrolled

3.3.1 Proposed sample size

This study will enroll 536 participants.

3.3.2 Accrual rate

Approximately 30 participants per month.

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types:

IVR: MD, DO, or international equivalent,

NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),

AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;

Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and

Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents (Table 4-A):

Table 4-A: Required Registration Documents

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

Abbreviations: A: Associate; AB: Associate Basic; AP: Associate Plus; CV: Curriculum Vitae; FDA: Food and Drug Administration; GCP: Good Clinical Practice; IVR: Investigator; NCI: National Cancer Institute; NPIVR: Non-Physician Investigator

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

Addition to a site roster,

Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,

Act as the site-protocol Principal Investigator (PI) on the IRB approval, and

Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at **https://ctep.cancer.gov/InvestigatorResources/default.htm**. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

Each site must complete a protocol-specific registration packet, including an AMC DTL using the provided AMC template or local equivalent. The CI is required to review and sign the DTL prior to the site receiving an approved site registration status and enrolling participants to the study. The AMC DTL template is provided in the protocol registration packet for this protocol, located on the AMC Operations web site at https://amcoperations.com/. Any individual at the enrolling site on a participating roster may initiate the site DTL. Instructions on completing the DTL are embedded in the AMC DTL template.

The AMC DTL must be updated contemporaneously as personnel are added or removed and/or study roles and delegated tasks change. Changes must be approved by the CI, and documented by his/her initials and date, before they are implemented.

4.3 Participant Enrollment Procedures

Sites must have this protocol approved by their Independent Ethics Committee (IEC) and be registered for study participation with the AMC Operations and Data Management Center (ODMC) before they may enroll participants.

4.3.1 Registration for screening

After an informed consent form has been signed by the participant, the participant must be registered for screening (AMC-099, Screening Segment) on-line via Advantage eClinical. After successful registration into screening, the participant will receive an eleven-digit participant ID and will then enter the screening process (Screening and Pre-entry visits).

4.3.2 Enrollment

After the screening evaluations have been obtained and the participant is determined to be eligible, the participating site will complete the protocol-specific eligibility checklist and enroll the participant into AMC-099 Randomization Segment (on-line via Advantage eClinical). Enrollment should occur no more than 1 week prior to the first vaccination (enrollment 1 day prior to or on the day of vaccination is strongly encouraged). Once the eligibility checklist is submitted, a system generated confirmation email will be sent to the enroller upon successful completion of the participant enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amipm@emmes.com or via phone at 001-301-251-1161) for further instructions.

Participants must be enrolled into AMC-099 Randomization Segment to receive the treatment assignment. Enrollment is required prior to receiving the first vaccination.

5 TREATMENT PLAN

5.1 Agent Administration

Protocol agents will be administered on an outpatient basis. Reported adverse events and potential risks for the 9-valent HPV vaccine are described in Section 6.

5.1.1 Regimen

9-valent HPV recombinant vaccine, 0.5 mL or placebo will be administered as three separate 0.5 mL doses according to the visit schedule.

5.1.2 Study product administration

9-valent HPV recombinant vaccine, or placebo, intramuscularly in the deltoid region of the upper arm or the higher anterolateral area of the thigh. The vaccine, or placebo, will be administered in the clinic by study personnel using aseptic technique during preparation and administration.

Preparation of 9vHPV vials

- One vial of 9vHPV will be used to prepare this dose. Prior to injection, the pharmacist or designee will shake the vaccine vial well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.
- 9vHPV vaccine should not be diluted or mixed with other vaccines.
- After thorough agitation, 9vHPV vaccine will be a white, cloudy liquid. Do not use the product if particulates are present or if it appears discolored.
- Using aseptic technique, the pharmacist or designee must withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe.
- Once drawn into the syringe, the vaccine should be kept cold (2° to 8°C) until it is ready to be administered to the participant. Use promptly.

Note: Refer to the manual of procedures (MOP) for instructions regarding transportation of study product.

- The syringe should be labeled as "9-valent HPV Vaccine or Placebo." The syringe should also be labeled with the date/time product was withdrawn from the refrigerated vial into the syringe.
- All used vaccines should be discarded appropriately.

Preparation of 9vHPV pre-filled syringes

- Shake well before use.
- Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe.
- Discard syringe after use.

Preparation of saline placebo

- Using aseptic technique, the pharmacist or designee must withdraw 0.5-mL of Sodium Chloride for Injection, 0.9% using a sterile needle and syringe.
- Once drawn into the syringe, the placebo should be kept cold (2° to 8° C) until it is ready to be administered to the participant. Use promptly.

Note: Refer to the MOP for instructions regarding transportation of study product.

- The syringe should be labeled as "9-valent HPV Vaccine or Placebo.. The syringe should also be labeled with the date/time product was withdrawn from the refrigerated vial into the syringe.

Study product administration

- 9vHPV or saline placebo will be administered as 0.5 mL doses according to the visit schedule.
- The participant should be seated or lying down while receiving the vaccine.
- The vaccine (or placebo) will be administered intramuscularly in the deltoid region of the upper arm or the higher anterolateral area of the thigh in the clinic by study personnel using aseptic technique during preparation and administration.
- All injections should preferably be given in the deltoid region and in the non- dominant arm, however if this is not feasible, the dominant arm may be used.
- The vaccine must not be injected intravascularly, subcutaneously, or intradermally.
- Vaccination should be deferred at the discretion of the site investigator if the participant is febrile or acutely ill.
- Following each vaccination, clinic staff will observe the participant for 15 minutes.
- The participant should be shielded from seeing the vaccine or placebo to mask treatment assignment. See MOP for details.

5.1.3 Expected adverse events

Please refer to the FDA-approved package insert for a comprehensive list of AEs. This package insert is available at www.gardasil9.com and by request from the AMC ODMC.

Local reactions include pain, swelling, erythema, itching and bruising. Systemic reactions include syncope, fever, nausea and vomiting, dizziness, fatigue, headache, and chills. Other rare, but serious side effects reported with this vaccine that may be associated with this vaccine include hypersensitivity reactions.

Because vaccine recipients may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes (either sitting or lying down) after administration is recommended. Syncope, sometimes associated with tonic-clonic

movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

5.2 Study Vaccine Preparation

Gardasil 9 should be administered as soon as possible after being removed from refrigeration. Gardasil 9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8° and 25° C) does not exceed 72 hours. Cumulative multiple excursions between 0° and 2° C are also permitted as long as the total time between 0° and 2° C does not exceed 72 hours. These are not, however, recommended for storage.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), HPV vaccination may continue until week 26.

5.4 Duration of Follow Up

2 years after randomization.

5.5 Criteria for Discontinuation of Vaccine or Removal from Study

Premature 9vHPV (or placebo) Discontinuation

- Request by participant to terminate treatment.
- Treatment-related AEs as discussed in Section 6.
- Clinical reasons believed life-threatening by the site investigator, even if not addressed in Section 6.

Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- At the discretion of the NCI, IRB/EC, industry supporter, FDA, Office for Human Research Protections (OHRP), investigator, or other country-specific government agencies as part of their duties to ensure that research participants are protected.

5.6 Concomitant Medications

To avoid adverse events (AEs) caused by drug interactions, sites must refer to the most recent package inserts for the study vaccine and concomitant agents whenever a concomitant medication is initiated or a dose is changed.

Sites must also refer to the most recent study product's package insert to access additional current information on prohibited and precautionary medications.

Prohibited medications include:

- Investigational treatments of cervical HSIL or other HPV disease.

- HPV vaccines other than study provided vaccines.

Note: If a prohibited medication is taken after completion of all HPV vaccination visits, contact the Protocol Chair(s) first to discuss premature discontinuation.

Precautionary medications include:

- Systemic antineoplastic or immunomodulatory treatment.
- Systemic corticosteroids (of greater than 14 days duration).
- Investigational vaccines, interleukins, interferons, growth factors, or IVIG.
- Anticoagulants other than nonsteroidal anti-inflammatory agents and aspirin.
    - Please note that participants on such anticoagulants should not undergo cervical biopsies or LEEP treatment. Please consult the protocol team to discuss the management of such participants.

Site staff must contact the Protocol Chair(s) for guidance if a participant requires a precautionary medication within 14 days prior to a study vaccine visit.

Antiretroviral therapy will follow local site guidelines and will not be provided by the study. All concomitant medications, including changes to ongoing medications, must be reported in the source documents. Concomitant medications include prescription medications only. The following concomitant medications must be reported in Advantage eClinical: changes to the antiretroviral regimen; medications that are causally related to serious adverse events; and prohibited/precautionary medications.

6 DOSE MODIFICATIONS AND CLINICAL MANAGEMENT OF PROCEDURAL COMPLICATIONS

6.1 Injection Site Reactions

For injection reactions judged to be severe, the protocol team should be notified within 24 hours and further vaccines should not be given to that participant prior to consultation with protocol co-chairs.

For injection reactions judged to be life-threatening, the protocol team should be notified within 24 hours and no additional vaccinations shall be given to that participant.

The protocol team should be contacted within 24 hours for any Grade 3 or 4 reactions (e.g., injection site reactions, elevated temperatures following vaccination that occur at any point during study participation) thought definitely, possibly, or probably related to vaccination. Further vaccines should not be given to that participant prior to consultation with the protocol chairs.

6.2 Other Adverse Events

The following guidelines should be used for the management of AEs that are felt to be at least possibly related to vaccines:

- Grade 1 or 2 Toxicity/AE
  Participants who develop a Grade 1 or 2 AE may continue study vaccine. If a participant experiencing Grade 1 or 2 AEs chooses to permanently discontinue study treatment or study participation, please record the AE in Advantage eClinical.
- Grade 3 or 4 Toxicity/AE
  Participants who develop a Grade 3 or 4 AE that is at least possibly related to vaccine should be reevaluated for that toxicity until the AE returns to Grade ≤2. The study vaccine may be given at the discretion of the site investigator. If the same Grade 3 or 4 AE recurs and is considered by the investigator to be possibly, probably, or definitely related to the study vaccine, the study vaccine must be permanently discontinued. If, in the investigator's opinion, the AE has NOT been caused by the study vaccine or if the event is an asymptomatic laboratory abnormality, study treatment may continue.

For instructions regarding participants experiencing Grade 3 or 4 AEs that are at least possibly related to vaccine and that result in premature discontinuation of study vaccine or study participation, see Sections 4.5 and 8.9. These participants should be followed weekly until resolution of the AE

6.3 Grade 3 or Higher Procedural Complications

If the site investigator considers a Grade 3 or higher event to be related to the study procedure(s), it is left to the discretion of site investigator to determine whether the procedure(s) should be repeated at future visits.

6.4 Cryotherapy- and LEEP-Related Complications

Vaginal Bleeding

Bleeding post cervical biopsy will first be controlled with direct pressure using a dry swab. If this is not sufficient, then a swab with Monsel's solution will be applied to stop the bleeding.

When postoperative bleeding occurs, it usually appears 4-6 days after treatment and often from the posterior lip of cervix. This bleeding can usually be controlled in the clinic by fulguration, applying Monsel's paste, or using a silver nitrate applicator stick. Rarely, placement of a suture at the bleeding site is necessary. The risk of postoperative infection is very small and can likely be reduced even more by delaying surgical treatment until any woman with a likely diagnosis of pelvic inflammatory disease, cervicitis, vaginal trichomoniasis, or bacterial vaginosis has been adequately treated and recovered.

Vaginal Infection

The chance of postoperative infection is lessened by (1) only performing cryotherapy or LEEP when there is no evidence of bacterial STIs and (2) advising women to abstain from vaginal intercourse for 6 weeks post procedure.

In addition, participants are to be advised of the symptoms of infection and encouraged to return to the clinic if the symptoms occur. If a participant presents postoperatively with a malodorous discharge, it should be cultured if possible and empirical treatment prescribed with antibiotics that are effective for pelvic inflammatory disease.

6.5 Other Diseases/Conditions

Invasive Cervical, Vaginal, or Vulvar Cancer

Each clinical research site conducting COVENANT will develop its own plan for the clinical management of invasive cervical, vaginal, or vulvar cancer. Plans will be submitted to the COVENANT protocol team for review prior to the enrollment of women at the site.

Women diagnosed with invasive cancer should be followed for 12 months by telephone or in-person visits to characterize cancer stage and initial treatment outcomes. No additional samples should be collected. These participants will receive additional treatments as indicated in the site-specific clinical management plan.

Other Gynecological Conditions

Cervical polyps, vulvar HSIL, vaginal HSIL, and vulvovaginal warts will be managed according to local standard of care.

6.6 Pregnancy

Participants who become pregnant after study entry will continue to be followed on study. These participants will come into the clinic to complete study evaluations as per the schedule in Section 8.0 but will not undergo study vaccination, LEEP, cryotherapy, or cervical biopsy until 6 weeks after the pregnancy is completed. If there is suspicion of invasive cancer, clinical management is left to the discretion of the site investigator.

The pregnancy will be initially reported as an adverse event as required by NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and

DCP INDs and IDEs. Pregnancy outcome for the participant and the infant will be reported within Advantage eClinical as required once outcomes are known.

Women who are breastfeeding may continue in the study and undergo all scheduled evaluations.

All reports of Study Drug exposure during pregnancy or lactation, whether associated with an AE or not, must be reported to Merck GPV in accordance with the timelines and contact information for an SAE. Principal Investigator shall follow pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy shall be forwarded to Merck GPV by AMC ODMC.

Sites are strongly encouraged to register the pregnancy with The Antiretroviral Pregnancy Registry as soon as the site becomes aware of it. More information is available at www.apregistry.com.

6.7 Dose Delays and Visit Schedule Modifications

In the event of dose delay at week 4, the week 26 visit should occur 22 weeks after the actual date of the week 4 dose. In the event of dose delay at week 26, the week 52 visit should occur 26 weeks after the week 26 dose is administered.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting **in addition** to routine reporting (via Advantage eClinical). All adverse event reporting will be conducted via Advantage eClinical for this protocol. Institution and Principal Investigator shall fully comply with all of their respective reporting obligations to the applicable regulatory authorities with respect to any AE, SAE or SUSAR that arises from the study.

The CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 5.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Version 5.0 of CTCAE.

7.1 Adverse event list for Gardasil 9

The most common (≥10%) local and systemic adverse reactions in females 16 through 26 years of age were injection-site pain (89.9%), injections-site swelling (40.0%), injection-site erythema (34.0%), and headache (14.6%).

The most common (≥10%) local and systemic reactions in girls 9 through 15 years of age were injection-site pain (89.3%), injections-site swelling (47.6%), injection-site erythema (34.1%), and headache (11.4%).

Other expected but less common (<10%) injection site reactions include injection site pruritus, mass, or hematoma. Other less common (<10%) systemic systems include fever, nausea, emesis, dizziness, and flu-like symptoms. Syncope has been reported after vaccination. There have been rare reports of allergic reactions to the vaccine.

7.2 Classification of AEs by Severity and Relationship to Study Drug Administration

7.2.1 "Adverse Event" or "AE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

7.2.2 Serious Adverse Event (SAE): "Serious Adverse Event" or "SAE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious".

7.2.3 "Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

7.2.4 Life-threatening Adverse Event: Any AE that places the participant or participant, in view of the Investigator, at immediate risk of death from the reaction.

Hospitalization: hospitalization for serious AE reporting purposes is defined as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the AE and should ONLY be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. (e.g., a hospital visit where a patient is admitted for observation or minor treatment such as, hydration and released in less than 24 hours). Prolongation of hospitalization is defined as an extension of current hospitalization equal to or greater than 24 hours.

Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

7.2.5 Toxicity: Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion, the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes. The CTCAE continues to use the term 'toxicity' because of familiarity.

7.2.6 Attribution: The determination of whether an AE is related to a medical treatment or procedure. Attribution categories:

Definite – The AE is clearly related to the investigational agent.

Probable – The AE is likely related to the investigational agent.

Possible – The AE may be related to the investigational agent.

Unlikely – The AE is doubtfully related to the investigational agent.

Unrelated – The AE is clearly NOT related to the investigational agent.

7.3 Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction, Potential Incident Reporting

Emmes on behalf of the Principal Investigator, henceforth referred to as "Institution" shall forward to Merck's Global Pharmacovigilance ("Merck GPV") group, any SAE or SUSAR, including, but not limited to, all initial and follow-up information involving any study subject in the study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format) within two (2) business days of but not longer than three (3) calendar days of receipt of the information. This information shall be transmitted to Merck GPV using the contact information provided below or such other modified contact

information as provided by Merck in writing. All information shall be transmitted in the English language and contain the reporter's name and the study subject identifier code. SUSAR information will be reported unblinded if the Study Drug has been blinded in the study. Randomization codes for all other SAEs will be provided to Merck GPV at end of study if the Study Drug has been blinded in the Study.

SAE reports and any other relevant safety information are to be forwarded to Merck GPV facsimile number: 215-661-6229, or toll-free fax 1-800-547-5552. Merck will confirm receipt of the report within one (1) business day. If confirmation is not received within one (1) business day, Principal Investigator/Institution will contact Merck to determine if the original report needs to be re-sent. Principal Investigator/Institution will maintain a record of the confirmation.

7.4 Expedited Adverse Event Reporting

7.4.1 Expedited AE reporting for this study must use Advantage eClinical. The reporting procedures to be followed are presented in this section and will align with the principles for SAE reporting in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 6.3.3).

A 24-hour notification is to be made to the AMC ODMC by telephone at 001-301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into Advantage eClinical by the original submitter at the site.

7.4.2 Advantage eClinical is programmed for automatic electronic distribution of SAE reports to the following individuals: the AMC ODMC, AMC Medical Monitor, Protocol Chairs, and the Principal Investigator at the institution.

7.4.3 Expedited Reporting Guidelines

Investigators must report ALL SAEs (as defined in Section 6.2.3) that occur from enrollment through 30 days following treatment discontinuation to the AMC and IECs as required. The investigator's initial report to the AMC will be made using the Adverse Event form in Advantage eClinical within 24 hours of awareness of the event, followed by a completed SAE form as soon as possible, and in no more than 5 calendar days of awareness.

After 30 days following treatment discontinuation, SAEs will only be reported in the SAE form if determined by the investigator to have an attribution to the investigational agent of possible, probable, or definite.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions – Disease Progression"**. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes

suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

7.5 Routine Adverse Event Reporting

All grade 3, 4, and 5 adverse events **must** be reported in routine study data submissions. **Grade 1 or 2 adverse events leading to premature discontinuation of study vaccination (or placebo) must be reported in Advantage eClinical. If the Grade 1 or 2 adverse event does not lead to premature discontinuation of study vaccination (or placebo), it should not be reported in Advantage eClinical but must be reported in the participant's study record.**

Participants who develop a Grade 1 or 2 AE may continue study vaccine.

All adverse events must be reported in the participant's study record. A study investigator must document his/her assessment of each adverse event.

7.6 Non-Serious Events of Interest

Merck may define certain Non-Serious Events of Interest. If any Non-Serious Events of Interest are defined, Merck will provide such information in writing to Principal Investigator at the time of Protocol approval, execution of this Agreement or anytime thereafter. Reporting of any defined Non-Serious Events of Interest will be handled in the same manner as SAEs unless mutually agreed otherwise in writing by the parties.

7.7 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.8 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting within Advantage eClinical unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 6.1.

8.1 Gardasil 9

Gardasil 9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

8.1.1 Cervical, vulvar, vaginal, and anal cancer caused by Human papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58.

8.1.2 Genital warts (condyloma acuminate) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

8.1.3 Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)

8.1.4 Cervical intraepithelial neoplasia (CIN) grade 1

8.1.5 Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3

8.1.6 Vaginal intraepithelial neoplasia (VAIN) grades 1, 2, and 3

Dosage: Administer Gardasil 9 intramuscularly as a 0.5 mL dose at the following schedule: 0, 1 month, 6 months.

Storage requirements: Gardasil is supplied in vials and pre-filled syringes. Store refrigerated at 2° to 8° C (36° to 46° F). Do not freeze. Protect from light.

Formula: Each 0.5 mL dose of Gardasil 9 contains:

30 mcg	HPV Type 6 L1 protein
40 mcg	HPV Type 11 L1 protein
60 mcg	HPV Type 16 L1 protein
40 mcg	HPV Type 18 L1 protein
20 mcg	HPV Type 31 L1 protein
20 mcg	HPV Type 33 L1 protein
20 mcg	HPV Type 45 L1 protein
20 mcg	HPV Type 52 L1 protein
20 mcg	HPV Type 58 L1 protein
500 mcg	Aluminum (provided as AAHS)
9.56 mg	Sodium chloride
0.78 mg	L-histidine
50 mcg	Polysorbate 80
35 mcg	Sodium borate

<7 mcg	Yeast protein
	Water for injection

8.2 Placebo

Sodium Chloride for Injection, 0.9%. This will be acquired locally by participating sites. See the approved package insert for complete information.

8.3 Pharmacy: Study Vaccine Supply, Distribution, and Accountability

8.3.1 Study vaccine acquisition

Participating sites are to refer to the study MOP located on the AMC ODMC web site (www.AIDSCancer.org) for drug ordering information.

8.3.2 Study vaccine accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Investigational Agent Accountability Record Form (DARF) (available on the CTEP home page (http://ctep.cancer.gov) or by contacting the Pharmaceutical Management Branch at PMBAfterHours@mail.nih.gov). The DARF documents the drug delivery date to the site, inventory at the site, use by each study participant, and disposal of the drug (if applicable). A separate DARF is required for each protocol using the same agent. The investigator will ensure that the drugs are used only in accordance with this protocol.

Additional instructions regarding drug accountability will be provided in the study MOP.

8.3.3 Study vaccine transfers

Vaccine may not be transferred from one participant to another participant, from one center to another center, or from one protocol to another protocol.

8.4 Study Drug Defects

In the event Principal Investigator or Institution becomes aware of a defect or possible defect in the Study Drug provided (or placebo provided by Merck being tested or used as a reference in the Study), Institution and Principal Investigator agree to notify Merck within one (1) business day of first becoming aware of the defect or possible defect.

9 CLINICAL AND LABORATORY EVALUATIONS

Schedules shown in the Study Calendar below are provided in Appendix I. Please see the Manual of Procedures for more about timing of visits conducted outside of protocol-defined windows.

9.1 Screening/Baseline Evaluations

Baseline evaluations are to be conducted within 45 days prior to the first vaccination, unless otherwise specified below.

9.1.1 Informed consent discussion including optional donation of left-over specimens to ACSR.

9.1.2 Demographics and medical history, including history of AIDS defining illnesses, prior HPV-related anogenital disease such as cervical, vaginal, vulvar or anal SIL or condyloma.

9.1.3 Medication history, including date of first ART use and current ART regimen.

9.1.4 Height and weight, targeted physical exam, and vital signs (blood pressure, pulse, temperature).

9.1.5 Urine pregnancy test (if participant is of childbearing potential)

9.1.6 Vulvar exam with biopsies of lesions suspicious for HSIL.

9.1.7 Speculum examination with collection of cervical specimens for HPV testing and cervical cytology. Xpert HPV testing will be performed in real-time at the clinical research site, and aliquots will be stored for future research.

9.1.8 Colposcopy will be performed to assess the cervix for lesions suspicious for cancer. If lesions suspicious for cancer are found, then randomization should be delayed and cervical biopsies should be obtained. These participants will be eligible for randomization if the biopsies do not show invasive cancer.

The colposcopist should decide on cervical treatment should the participant be randomized. Women are eligible for cryotherapy if no lesions are seen, or if cryotherapy-eligible lesions are seen. Cryotherapy-eligible lesions are those that occupy less than 75% of the circumference, and lesions that do not extend into the cervical canal.

9.1.9 Assessment of eligibility by a CTEP-registered investigator.

9.1.10 Anal swab for HPV testing.

9.2 Randomization/Entry (May be done on the same day as screening and up to 45 days after screening)

9.2.1 Assessment of interim medical history including adverse events and concomitant medications.

9.2.2 Targeted physical exam and vital signs.

9.2.3 The participants should be assessed for all eligibility criteria. If eligible, then participants should be randomized via Advantage eClinical.

9.2.4 Blood draw for CD4+ T-cell count, plasma HIV-1 RNA, and stored HPV serology.

9.2.5 Anal swab for HPV testing, unless the anal swab was collected at screening.

9.2.6 Administration of 9vHPV or placebo.

9.2.7 Baseline questionnaire.

9.3 Week 4 Evaluations (+4 weeks)

The week 4 evaluations should take place within +4 weeks of the scheduled date.

9.3.1 Assessment of interim medical history including adverse events and concomitant medications.

9.3.2 Targeted physical exam and vital signs.

9.3.3 Urine pregnancy test (if participant is of childbearing potential)

9.3.4 Speculum exam with collection of a cervical specimen for stored testing for HPV.

9.3.5 Cervical colposcopy to assess eligibility for cryotherapy vs. LEEP.

9.3.6 If cryotherapy, perform at least 2 cervical biopsies followed by immediate cryotherapy. The biopsies should be sent for histologic assessment.

9.3.7 If LEEP, perform LEEP without obtaining pre-LEEP biopsy. LEEP specimen should be sent for histologic assessment.

9.3.8 Administration of 9vHPV or placebo.

9.4 Week 26 Evaluations (+/- 4 weeks)

The week 26 evaluations should take place within +/- 4 weeks of the scheduled date. The visit must occur at least 12 weeks after the week 4 9vHPV or placebo administration and at least 20 weeks after the 1st dose.

9.4.1 Assessment of interim medical history including adverse events and concomitant medications.

9.4.2 Targeted physical exam and vital signs.

9.4.3 Urine pregnancy test (if participant is of childbearing potential)

9.4.4 Vulvar exam with biopsies of lesions suspicious for HSIL.

9.4.5 Speculum exam with collection of cervical specimens for stored testing for HPV and cervical cytology.

9.4.6 Cervical colposcopy with biopsy of visible lesions. If no lesions are seen, then 2 random cervical biopsies should be obtained.

9.4.7 Blood draw for stored HPV serology.

9.4.8 Administration of 9vHPV or placebo.

9.5 Week 52 Evaluations (+/- 3 weeks)

The week 52 evaluations should take place within +/- 3 weeks of the scheduled date.

9.5.1 Assessment of interim medical history including adverse events and concomitant medications.

9.5.2 Targeted physical exam and vital signs.

9.5.3 Urine pregnancy test (if participant is of childbearing potential)

9.5.4 Vulvar exam with biopsies of lesions suspicious for HSIL.

9.5.5 Speculum exam with collection of cervical specimens for stored testing for HPV and cervical cytology.

9.5.6 Cervical colposcopy with biopsy of visible lesions. If no lesions are seen, then 2 random cervical biopsies should be obtained.

9.5.7 Anal swab for HPV testing.

9.5.8 Blood draw for stored HPV serology.

9.5.9 Follow-up questionnaire.

9.6 Week 78 Evaluations (+/- 3 weeks)

The week 78 evaluations should take place within +/- 3 weeks of the scheduled date.

9.6.1 Assessment of interim medical history including adverse events and concomitant medications.

9.6.2 Targeted physical exam and vital signs.

9.6.3 Urine pregnancy test (if participant is of childbearing potential)

9.6.4 Speculum exam with collection of a cervical specimen for stored testing for HPV.

9.6.5 Optional cervical colposcopy with biopsy of visible lesions. This should be done if week 52 cervical cytology shows ASC-H or HSIL, but no HSIL was found on histology, or if there is suspicion for undiagnosed HSIL.

9.6.6 Blood draw for stored HPV serology.

9.7 Week 104 Evaluations (+/- 3 weeks)

The week 104 evaluations should take place within +/- 3 weeks of the scheduled date.

9.7.1 Assessment of interim medical history including adverse events and concomitant medications.

9.7.2 Targeted physical exam and vital signs.

9.7.3 Urine pregnancy test (if participant is of childbearing potential)

9.7.4 Vulvar exam with biopsies of lesions suspicious for HSIL.

9.7.5 Speculum exam with collection of cervical specimens for stored testing for HPV and cervical cytology.

9.7.6 Cervical colposcopy with biopsy of visible lesions. If no lesions are seen, then 2 random cervical biopsies should be obtained.

9.7.7 Anal swab for HPV testing.

9.7.8 Blood draw for stored HPV serology.

9.7.9 Follow-up questionnaire.

9.8 HSIL Treatment (week 26 or later)

Participants diagnosed with HSIL on cervical histology at week 26 or later should return for LEEP treatment of cervical HSIL, preferably within 6 weeks from the date of the biopsy. A urine pregnancy test should be performed prior to the procedure. The local provider should contact the protocol team if he or she feels that an alternative treatment is indicated (e.g. cone biopsy or hysterectomy).

9.9 Early Discontinuation Evaluations

Participants who withdraw consent should be taken off study without further evaluations.

Participants who discontinue the study prior to the week 4 visit should be taken off study without further evaluations.

Participants who discontinue the study less than 8 weeks after the week 4 visit should be taken off study without further evaluations.

Otherwise, participants should undergo week 104 evaluations unless it has been less than 8 weeks since their last cervical biopsy. If withdrawing less than 8 weeks after the last cervical biopsy, then no further evaluations should be performed.

If a participant is diagnosed with invasive cancer, no additional samples should be collected. The participant should be followed for 12 months by telephone of in-person visit to characterize cancer stage and initial treatment outcomes. The participant will receive additional treatment as indicated in the site's clinical management plan.

10 STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

10.1.1 Primary endpoint

Cervical HSIL or invasive cervical cancer diagnosed after the week 4 visit through week 52 post-randomization.

Note: cervical histology will be obtained at week 4 from all participants. HSIL detected on these samples will not be counted as endpoints. We expect 45% of participants to have HSIL detected at week 4. The primary endpoint is a combination of new HSIL detection, recurrent HSIL, and persistent HSIL, or a diagnosis of invasive cervical cancer.

The primary analysis population will include all randomized participants who receive at least one study vaccine injection and have histologic results at week 26 or week 52. Confirmatory analyses will be performed on the per-protocol population, which includes all randomized study participants who received all 3 study vaccinations, underwent cervical treatment (cryotherapy or LEEP at week 4), and had histology results from week 26 and/or 52. Confirmatory analyses that control for differences in baseline CD4 count and plasma HIV-1 RNA will also be performed. For each arm (vaccine and placebo), the event rate will be estimated using its point estimate and 95% Poisson confidence intervals. Poisson regression analyses will be used to compare the two arms with respect to event rate. In addition, time to event from week 4 to 52 will be described using the Kaplan-Meier method for each arm, and the two arms will be compared with respect to time to event using the log-rank test. Follow-up time will end at week 26 for those participants who do not return for week 52 or do not have evaluable histology specimens at week 52.

10.1.2 Secondary endpoints

To describe occurrence of cervical HSIL from week 52 to week 104

- Cervical HSIL diagnosed after the week 52 visit through week 104 post- randomization

To examine the predictors of sustained absence of cervical HSIL through week 104 and clearance of HPV infections after cervical treatment, including: baseline types and quantity of HPV, presence of HSIL at baseline, cryotherapy vs. LEEP, CD4+ cell count, plasma HIV-1 RNA, ART use, age, sexual behavior, and vaccination use

- Cervical HSIL diagnosed after the week 4 visit through week 104, HPV DNA PCR, hrHPV testing by Xpert

To compare, between study arms, incident cervical vaccine type HPV infections and cervical cytology results.

- HPV DNA PCR, cervical cytology

To describe prevalent and incident vulvar HSIL or cancer in this population

- Vulvar HSIL or cancer

10.2 Sample Size/Accrual Rate

The primary endpoint for this study is the Poisson event rate between week 4 and week 52 post-randomization defined as the number of events divided by the cumulative follow-time from week 4 through week 52. The sample size estimation is based on testing that the ratio of the event rate for the HPV vaccine group (9 per 100 person-years= λ_T) to the event rate for the placebo group (18 per 100 person-years = λ_C) = 0.50. With a one-sided significance level of 0.10 and power of 0.90, 496 participants (evenly divided between the two arms) are needed for this study (calculated using the EaST commercial software package).[35] Since the follow-up period to observe this endpoint is from week 4 to 52, the follow-up duration for each participant is expected to be 0.92 years (48 weeks/52 weeks). Assuming that 7.5% of women drop out prior to 52 weeks, 536 women will be enrolled in the study.

Events include HSIL detection (new, recurrent, or persistent) or diagnosis of invasive cervical cancer. Follow-up duration for each participant will start at week 4 and end at the time an event occurs or at 52 weeks if the participant is event-free.

10.3 Stratification Factors

Randomization will be stratified by treatment type chosen at baseline (i.e., cryotherapy vs. LEEP), by presence of HPV 16 at baseline, and study site. The study will use a stratified, random permuted block randomization scheme.

10.4 Analysis of Secondary Endpoints

10.4.1 To describe occurrence of cervical HSIL from week 52 to week 104

The event rate for each arm from week 52 to week 104 for women who are event-free at 52 weeks will be estimated using its point estimate and 95% Poisson confidence interval. Poisson regression will be used to compare the two groups with respect to the event rate from week 52 to 104.

10.4.2 To examine the predictors of sustained absence of cervical HSIL through week 104 and clearance of HPV infections after cervical treatment, including: baseline types and quantity of HPV, presence of HSIL at baseline, cryotherapy vs. LEEP, CD4+ cell count, plasma HIV-1 RNA, ART use, age, sexual behavior, and vaccination use

Poisson regression analyses will be used to determine if factors such as CD4+ cell count, plasma HIV-1 RNA, ART use, age, baseline HPV types, sexual behavior, and vaccine use are associated with of sustained absence of cervical HSIL and clearance of HPV infections after cryotherapy or LEEP. These analyses will also control for use of LEEP or cryotherapy.

10.4.3 To compare, between study arms, incident cervical vaccine type HPV infections and cervical cytology results

The proportions of women who acquire vaccine specific HPV types (6, 11, 16, 18, 31, 33, 45, 52, 58) will be estimated among women without detection for each type at baseline using type specific HPV DNA PCR. We will only consider persistent

HPV infections (i.e. infections present at 2 consecutive timepoints). Vaccine and placebo participants will be compared with respect to these proportions using the chi-square test corrected for continuity. The proportion of women with abnormal cervical cytology at baseline, week 26, 52, and 104 will be reported and compared between arms.

10.4.4 To describe prevalent and incident vulvar HSIL or cancer in this population

The prevalence of vulvar HSIL or cancer at baseline will be estimated using the binomial proportion and its 95% confidence interval. The proportion of women who acquire vulvar HSIL among those negative for vulvar HSIL at baseline for both intervention arms will be estimated as a binomial proportion for both groups. The chi-square test corrected for continuity will be used to compare arms with respect to the proportions who acquire vulvar HSIL during the study. Logistic regression analyses will be used to evaluate associations of vulvar HSIL acquisition with clinical and demographic factors and arm.

10.5 Analysis of Exploratory Endpoints

10.5.1 To determine if HPV vaccination alters the HPV type distribution for cervical and vulvar HSIL

We will characterize the HPV type distribution in baseline histology specimens and compare this to the types observed among incident cervical and vulvar HSIL lesions. Specifically, we will compare the number and proportion of vaccine-type and non-vaccine type lesions between arms. This analysis will help us understand whether observed protection from vaccination is restricted to lesions caused by vaccine types.

We will test the hypothesis that HPV vaccination will reduce the proportion of HSIL caused by vaccine types. We expect approximately 60 cases of HSIL in the placebo group compared 30 in the control group to be diagnosed after week 4. We expect approximately 90% of HSIL to be related to vaccine types in the absence of vaccination. This sample size yields 80% power to show a reduction in the proportion of HSIL caused by vaccine types among vaccine recipients of 90% vs. 63%.

10.5.2 To conduct HPV strain variant analysis of cervical and vulvar HSIL specimens

For study participants who have the same HPV type in HSIL specimens at baseline and follow-up timepoints, sequencing will be performed to determine whether or not HSIL is caused by an identical HPV strain. We will use all available pairs of baseline and follow-up HSIL caused by the same HPV type. We will report the proportion of these pairs with the same HPV strain in both treatment arms.

Additionally, we will report the rates of HSIL caused by new vaccine type infections. We will compare the two study groups using a chi-square test. This will be a descriptive analysis only as we do not have sufficient data on which to power this analysis.

10.5.3 To establish a tissue microarray library of cervical specimens for biomarker analysis and discovery

There is no pre-specified statistical analysis plan for this objective. Any future studies using these specimens will need to receive separate approval by NCI and CTEP.

10.5.4 To describe the prevalence and hrHPV type distribution in the anus and its relationship to persistent cervical HPV infection

At each time point, we will estimate the prevalence of hrHPV types in the anus. For each study arm, time point and hrHPV type, we will use McNemar's chi-square test to compare the prevalence of that type in the anus and cervix. For each hrHPV type, chi-square analyses will be used to compare the two HPV vaccination groups with respect to the distribution of that type in the (anus, cervix): (+,+), (+,-), (-,+), and (- ,-). We will report the proportion of incident cervical infections that were preceded by anal detection of the same type.

10.5.5 Exploratory analysis of vaccine-induced antibody titers, incident HSIL, and confirmed vaccine type infections

We will examine women with cervical or vulvar HSIL in the vaccine group caused by vaccine types. We will explore the antibody titers for the vaccine type found in the HSIL in these women as compared to those without HSIL caused by that type.

We will report log-transformed antibody titers at baseline, week 26, week 52, week 78, and week 104. We will test the hypothesis that HSIL caused by vaccine types will be associated with a lower vaccine-induce antibody titers. Given an estimated 15 events and 30 controls, we have 80% power to show a 0.55 log10 difference in titers assuming a standard deviation of 0.6 log10.[18] We will also perform a similar analysis of vaccine titers between those with incident vaccine type HPV infections that persist for 2 or more study visits and those that do not.

10.6 Futility and Efficacy Halting Rules

There will be a single interim efficacy review when 50% of the study participants have completed week 52 of follow-up. The Lan and DeMets spending function will be used with the O'Brien-Fleming boundaries based on a one-sided test at the overall 0.10 significance level. At the final test, an overall one-sided alpha level of 0.10 and 90% power will be maintained. The boundaries and operating characteristics for the planned analyses are found in the table below. The DSMB will be informed of the results of the interim analysis. Consideration will be given to halting the study if the efficacy or futility boundary is crossed during the interim analysis.

Analysis	Information fraction	Reject H_0 (Efficacy) Bound Z	Overall α spent	Reject H_1 (Futility) Bound Z	Overall β spent
1 (Interim)	0.50	$Z > 2.054$	0.020	$Z < -0.203$	0.020
2 (Final)	1.00	$Z > 1.316$	0.100	$Z \leq 1.316$	0.100

11 ROLE OF DATA MANAGEMENT

11.1 CRF Instructions

Access to the internet data entry system for this study, Advantage eClinical , and instructions for recording of study data on CRFs will be provided by the AMC ODMC at **www.AIDSCancer.org**. Participating institutions are responsible for submitting data and/or data forms via Advantage eClinical in accordance with the AMC Data Entry Guide and specific form instructions, within the timelines specified by the AMC's Standards of Procedure for Site Performance Measures.

11.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix IV, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

11.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (**http://ctep.cancer.gov/reporting/cdus.html**).

The AMC ODMC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 National Regulatory Review, IEC Approval, and Informed Consent

The principles of Independent Ethics Committee (IEC) approval and informed consent described in the Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46) must be followed. IEC approval of the protocol and the informed consent form must be given in writing. The AMC will ensure that all participating centers, as required by the applicable regulatory requirements in each country in which the trial will be conducted, will submit any required applications to the appropriate authorities for review, acceptance, and/or permission to begin the trial. Any notification/submission should be dated and contain sufficient information to identify the protocol (ICH E6). Documentation of this authorization will be collected by the AMC before each center will be activated to enroll participants.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IEC, which specifically approves the protocol and informed consent, before participant enrollment. The IEC must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IEC must review the research project at least once every 365 days during the duration of the project. Continuing approval of the project must also be given in writing and provided to the AMC ODMC.

Records of all study review and approval documents must be kept on file by the Investigator and are participant to inspection during or after completion of the study. AEs must be reported to the IEC according to local procedures. The IEC should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IEC, including a list of all reports and documents submitted.

Written informed consent will be obtained from the participant. The nature and the significance of the risks associated with the study must be explained to the participant. The informed consent will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, all risks of the investigational agent(s) and/or study participation as listed in the model informed consent form, and all other elements of informed consent as required by regulation. A copy of the consent form will be given to the participant to keep.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and national laws and regulations governing the confidentiality and disclosure of health information.

12.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. All amendments require approval by the IEC of the treating institution. A copy of the written approval of the IEC, and the national regulatory authority for clinical trials (as applicable) must be sent to the ODMC.

12.3 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino		+		=	
Not Hispanic or Latino	536	+	0	=	536
Ethnic Category: Total of all participants	536	+	0	=	536
Racial Category					
American Indian or Alaskan Native		+		=	
Asian		+		=	
Black or African American	536	+	0	=	536
Native Hawaiian or other Pacific Islander		+		=	
White		+		=	
Racial Category: Total of all participants	536	+	0	=	536
	(A1 = A2)		(B1 = B2)		(C1 = C2)

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APPENDIX I: SCHEDULE OF EVALUATIONS

	Screening/ Baseline	Randomization/ Entry	Wk 4	Wk 26 (+/- 4 weeks)	Wk 52	Wk 78	Wk 104
Informed consent	X						
Demographics	X						
Medical history	X						
Concurrent medication review	X	X	X	X	X	X	X
Interim medical history and adverse event evaluation[1]		X	X	X	X	X	X
Targeted physical exam and vital signs (BP, HR, temp)	X	X	X	X	X	X	X
Height/Weight	X						
Urine pregnancy test (if participant of childbearing potential)	X		X	X	X	X	X
Assessment of eligibility	X	X					
Randomization		X					
Questionnaire		X			X		X
Vulvar examination +/- biopsy[2]	X			X	X		X
Real-time GeneXpert HPV	X						
Stored cervical HPV testing	X		X	X	X	X	X
Cervical cytology	X			X	X		X
Cervical colposcopy +/- biopsy	X[3]		X[4]	X[4]	X[4]	If indicated by cytology	X[4]
Cryotherapy or LEEP			X				
LEEP treatment of HSIL				As needed			
CD4 count, HIV-1 RNA viral load		X					
Stored HPV serology		X		X	X	X	X
Stored anal HPV testing[5]	X	X			X		X
9-valent HPV vaccine or placebo		X	X	X			

1. If the participant is diagnosed with invasive cancer, no additional samples should be collected and the participant should be followed for 12 months (phone or in-person visit) to characterize cancer stage and initial treatment outcome.
2. Biopsy only required if there is suspicion of HSIL
3. Biopsy to be performed if suspicious for cancer
4. Biopsy required of potentially cancerous areas. If none, two random biopsies to be collected.
5. The anal swab must be collected once, prior to treatment either during screening or at the randomization visit.

APPENDIX II: LABORATORY TESTING

Test and Sample	Primary Testing Lab	Screening/ Baseline	Randomization/ Entry	Wk 4	Wk 26	Wk 52	Wk 78	Wk 104
Cervical cytology Conventional glass slide prepared using cytobroom	Local lab with a subset of slides reviewed centrally	X			X	X		X
Real-time Gene Xpert HPV Cervical swab into 20 mL vial of Thinprep,	Study site using Gene Xpert	X						
Gene Xpert HPV on stored specimens Cervical swab into 20 mL vial of Thinprep,	Central lab			X	X	X	X	X
Cervical HPV DNA PCR Will use aliquot of Thinprep from Xpert test	Central lab	X		X	X	X	X	X
Anal HPV DNA PCR Anal swab into 20 mL vial of Thinprep,	Central lab	X	X			X		X
CD4 count Venipuncture sample in an EDTA tube	Local lab		X					
HIV-1 RNA PCR Venipuncture sample in an EDTA tube	Local lab		X					
HPV serology Venipuncture sample in plain tube processed for stored sera	Merck lab using competitive Luminex immunoassay[34]		X		X	X	X	X
Cervical histology Tischler punch biopsy specimen or LEEP specimen into 10% Formalin	Local lab with a subset of specimens reviewed centrally			X	X	X		X
Vulvar histology Keyes punch biopsy specimen into 10% Formalin	Local lab with a subset of specimens reviewed centrally	X			X	X		X
Whole tissue section PCR and laser capture microdissection of cervical biopsies FFPE tissue sections	Central lab			X	X	X		X
Whole tissue section PCR and laser capture microdissection of vulvar biopsies FFPE tissue sections	Central lab	X			X	X		X
Biomarker assessment of cervical tissue microarray library FFPE tissue sections	Central lab			X	X	X		X

APPENDIX III: PERFORMANCE STATUS SCALES

Karnofsky Performance Scale		ECOG Performance Status Scale	
Percent	**Description**	**Grade**	**Description**
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX IV: AMC DATA AND SAFETY MONITORING PLAN

(Version 9.0 October 6, 2020)

Introduction

The AIDS Malignancy Consortium (AMC) Data and Safety Monitoring Plan (DSMP) outlines the measures employed by the group to monitor the safety of participants and ensure the data validity and integrity for all clinical trials it conducts. This includes methods to: 1) monitor the progress of trials and the safety of participants; 2) comply with regulatory requirements for adverse event (AE) reporting; 3) processes for trial termination or temporary suspension and major modifications; and 4) plans for ensuring data accuracy and protocol compliance. As the AMC conducts protocols of varying research phase, region of conduct (which may include trials conducted in the U.S., international sites, or both), IND Sponsor (AMC Investigator, CTEP, or industry-sponsored) and clinical data entry system use, this plan addresses broad processes applying to the range of trial designs and requirements. Refer to the individual AMC protocol to identify the applicable study characteristics for the relevant requirements described in this plan.

Monitoring the Progress of Trials and the Safety of Participants

Routine and Expedited AE reporting

All AMC protocols that collect safety data adhere to the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm), as applicable to the clinical protocol. AEs are to be recorded in the source documents, assessed by a CI for the AE reporting criteria, and promptly reported in the clinical data entry system as required by each protocol. For AMC trials conducted under a CTEP IND and AMC trials conducted within the U.S.US, all AEs that meet the NCI's expedited reporting requirements are reported to the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application, either directly or through integration with Medidata Rave where this system is employed for AMC protocols. Use of this system ensures notification to the protocol chair and Investigational Drug Branch (IDB) at CTEP, as required for trials conducted under a CTEP IND, and a uniform expedited reporting and safety review process for AMC domestic trials. The system may also be programmed to include Sponsor notification as required for trials with industry support. Alternate process for expedited AE reporting to the AMC protocol chairs and AMC Operations and Data Management Center (ODMC) within the clinical data entry system (AdvantageEDC or Advantage eClinical only) may be defined in the protocol for select trials (international studies and The ANCHOR Study).

All serious adverse events (SAEs) received by the AMC ODMC will be reviewed by the AMC medical monitor at the AMC ODMC for consideration of individual participant safety, safe trial conduct, data reporting quality for AE term selection, and appropriate application of the regulatory criteria for seriousness, expectedness, and relatedness to the investigational therapy. If alternate procedures are followed for SAE review, the process for adequate medical monitoring will be defined in the AMC protocol and the Transfer of Regulatory Obligations (TORO) with the Sponsor. AMC medical monitor review includes review of the CTEP-AERS report before CTEP

submission for IDB review (if applicable), or review of the SAE report in the data entry system for trials not using CTEP-AERS for expedited reporting. The IND Sponsor or its designee will issue the determination as to whether the AE requires IND safety reporting to FDA as a serious and unexpected suspected adverse drug reaction (SUSAR). For protocols not conducted under an IND, in the event of disagreement between the reporting physician and the AMC medical monitor regarding the relationship of the AE to the investigational agent(s) (i.e., determination of whether the attribution is unrelated or unlikely, or possible, probable, or definite), the AMC medical monitor will provide the final determination of the relationship. IND safety reporting to FDA is performed by CTEP for trials conducted under a CTEP IND; IND safety reporting is performed by the Sponsor or Sponsor's designee (AMC ODMC or other party defined in the study agreement or TORO) for IND studies sponsored by AMC Investigators or industry sponsors.

Expedited Reporting to the Institutional Review Board (IRB)

The requirements for IRB review will be identified in the protocol section on ethical and regulatory obligations. All AMC trials initiated before September 1, 2020 and all international sites for all AMC studies are subject to local IRB review; only U.S.US sites are subject to the NCI requirement to use a single IRB for protocols initiated on or after September 1, 2020. For trials subject to local IRB review, the site principal Investigator is responsible for ensuring that expedited AE reports for its trial participants and any unanticipated problems that affect the local institution only are submitted to the local IRB of the reporting institution, per the local IRB's requirements for such reporting. For studies reviewed by the single IRB, the protocol chair will render a determination as to whether a SAE or other problem constitutes a trial-wide unanticipated problem that requires reporting to that IRB, in accordance with its standards of procedure.

To comply with Investigator notification requirements for IND studies under 21 CFR 312.32 and 312.55, IND safety reports from all trials the AMC conducts and reports from external sponsors investigating the same agents are made available to all Investigators upon receipt from the Sponsor or its designee, either via the password-protected section of the AMC Operations web site (AMC trials subject to local IRB review only) or the CTSU website (U.S.US trials subject to single IRB review/CTEP IND agents). The site CI responsible for the applicable AMC protocol(s) is responsible for reviewing any IND safety reports received and documenting submission to the IRB of record (if required by local policy) within the timeline defined by the Clinical Trials Monitoring Branch (CTMB) audit guidelines.

Procedures for Monitoring Trial Progress and Pharmacovigilance

For trials using AdvantageEDC or Advantage eClinical for clinical data entry, the AMC ODMC provides on demand tabular listings of all reported AEs and SAEs on a participant level to the protocol chair and co-chair(s) for review via the password-protected section of the AMC Operations web site, www.AIDScancer.org. For trials using OPEN and Medidata Rave for clinical data collection, data listing will be made available using that system. Summary reports of AEs by frequency and relationship to the investigational agent(s) are provided to all AMC Investigators and their staff. It is the responsibility of each site to provide trial-specific AE listings to their respective IRB, if required by its policies. For blinded studies, the AE and SAE listings are reviewed and tabulated without treatment assignment.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the protocol chair and also by the appropriate Scientific Working Group (SWG) during scheduled conference calls (monthly SWG calls and as required, protocol-specific monitoring conference calls). Summary accrual, summary AE, and individual SAE reports are provided to SWG leadership and protocol chairs to monitor participant safety during these monthly calls.

The AMC medical monitor reviews listings of all reported AEs on a quarterly basis for assuring compliance with the protocol requirements for AE reporting and the identification of any safety concerns (individual AE or increased frequency/severity of expected AEs) for the agents under investigation. Findings from these reviews are communicated to the protocol chairs and all AMC Investigators, and posted to the AMC Operations web site.

Data and Safety Monitoring Board Review (DSMB) Review

The AMC has formed an independent Data and Safety Monitoring Board (DSMB) for AMC trials and for the ANCHOR Study. As required by NCI policy, the AMC requires DSMB review for all Phase III randomized trials. All other clinical trials that the AMC initiates will be reviewed by the AMC ODMC and AMC Statistical Center during protocol development to issue a recommendation as to whether the study requires DSMB oversight, which will require the approval of the AMC Executive Committee. This determination will be based on the phase of the study, experimental design, risk posed by the investigational approach, extent of data available on the safety of an investigational agent, risk posed by the natural course of the health condition under research, and the categories of vulnerable populations involved. The involvement of a DSMB in reviewing an AMC protocol will be identified in each clinical protocol as approved by CTEP and, as applicable, required by the IRB of record.

Regarding the composition of the AMC DSMB, voting members usually include physicians, statisticians, an ethicist, and a patient advocate. All voting members have no other affiliation to the AMC and are appointed by the AMC Executive Committee with the approval of the OHAM Director. Nonvoting members are the AMC group statistician, the protocol statistician, an AMC ODMC staff member, two representatives (normally a clinician or statistician) from CTEP, and the grant program directors from the NCI Office of HIV and AIDS Malignancy (OHAM).

The DSMB reviews all applicable AMC studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all trials under review are prepared by the AMC group statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB charter. This report addresses specific toxicity issues and any other concerns about the conduct of the trial, as defined by the protocol plan for DSMB review. The report may contain information for the DSMB to render determinations for participant safety, early trial termination, results reporting, or continuing accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB chair to the AMC group chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required

modification; stop) must be included in the document. The group chair or designee is then responsible for notifying the protocol chair and relevant SWG chair before the recommendations of the DSMB are carried out. In the unlikely event that the protocol chair does not concur with the DSMB, then the OHAM program directors and the NCI division director or designee must be informed of the reason for the disagreement. The protocol chair, relevant SWG chair, group chair, DSMB chair, and NCI division director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a protocol amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, the DSMB's recommendations are provided to all AMC Investigators and staff. It is each site principal Investigator's responsibility for conveying this information to its local IRB as relevant for its protocol participation. For trials reviewed by a single IRB, the AMC ODMC will support notification to the IRB as required per its procedures.

Cohort Trial Reviews Not Subject to DSMB Review

For Phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met based on a review of all safety data for the protocol-defined evaluation period. If applicable for Phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage Phase II trial, is based on meeting criteria stated in the protocol, and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met.

Plans for Assuring Compliance with Requirements Regarding AE Reporting

The protocol chair, AMC group chair, and the AMC ODMC share responsibility in assuring that participating Investigators comply with applicable regulatory and protocol requirements for AE reporting. The AMC site principal Investigator certifies compliance with NCI and FDA requirements for trial conduct by signing the site subaward agreement for the grant and the AMC Adherence Statement for site membership; clinical Investigators also certify compliance in completing the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP Investigator registration, and also for AMC IND studies sponsored by AMC Investigators or industry sponsors. Protocol compliance with AE identification, assessment and reporting requirements is assessed by the AMC ODMC using several methods: 1) programmed system checks and messages to instruct the site to complete routine and/or expedited reporting when certain criteria are reported in the clinical data entry system; 2) programmed data reports provided to the protocol chairs that identify reports requiring expedited AE reporting; 3) remote review of data entry or data reports to ensure compliance with protocol and NCI AE reporting requirements; 4) AMC medical monitor review described in the section above; and, 5) routine site audits by reviewing the site's source documentation.

The clinical data entry systems used for AMC studies include the Oncology Patient Enrollment Network, OPEN for enrollment, and Medidata Rave for clinical data entry for enrolled participants; trials activated before September 1, 2020 or that involve only AMC international sites may be reported in AdvantageEDC/Advantage eClinical, a web-based data entry and enrollment system. These data entry systems are programmed to notify the site Investigator, protocol chair, AMC medical monitor, and AMC ODMC via email in the event that a site reports an AE that meets

expedited reporting criteria to NCI and/or FDA. Additional reporting conditions may be programmed depending on the Sponsor reporting requirements of a given protocol (e.g., adverse events of special interest [AESI]). If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC medical monitor review reported AEs on a routine basis to identify AEs reported by sites that require expedited reporting. The protocol chair, AMC SWG chairs, AMC group chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

For studies monitored by CTEP using the Data Mapping Utility (DMU), cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. For trials monitored by the NCI's Clinical Data Update System (CDUS), AE information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), AE information is transmitted electronically to NCI every two weeks.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that temporary or permanent suspension of a trial, or major modification to the protocol is under consideration, the protocol chair will convene the AMC ODMC, AMC Statistical Center, and SWG chair by conference call to discuss the options. Suspension actions will also be reviewed by the AMC Executive Committee for program oversight and direct communication of the action with the OHAM program directors. For Phase III trials, closure decisions are typically rendered by the AMC DSMB; if the trial in question is under AMC DSMB oversight but rendered by the AMC Investigators, the AMC DSMB will be notified of the suspension and the reason. For Phase I and II trials, the protocol chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO), with copy to OHAM Directors, when studies are temporarily or permanently closed. In the event of major trial modification, CTEP must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC clinical site staff into the applicable clinical data entry system for the trial. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. Submitted data entry forms are reviewed for compliance with the protocol and data entry instructions according to the AMC ODMC's standards for data quality processes. AMC ODMC staff routinely interacts with site staff to resolve any data submission problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventative action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site

does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option to implement remedial action(s) for the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site Investigators or staff members.

APPENDIX V: CENTRAL PATHOLOGY REVIEW PATHOLOGY REVIEW

On a quarterly basis throughout the study, sites will be requested to ship all histology specimens (vulvar specimens, cervical biopsies and LEEP specimens) and 25% of cytology specimens to a central laboratory in South Africa for an external quality assurance review.

Sites will be notified when and which specimens should be submitted for central review. Preferably, the actual slide used to determine the interpretation will be submitted to the central laboratory. If this is not possible because of local regulations, then a new slide should be sectioned from the tissue block and submitted to the central laboratory.

HANDLING OF SPECIMENS

Specimens should be submitted to the following address:

Johann Schneider, MMed Anat Path
Division of Anatomical Pathology
National Health Laboratory Service
10th Floor Green Avenue, Room 52
Tygerberg Hospital
Tygerberg
7535 South Africa

RECORD OF SPECIMENS

This study will track specimens via GlobalTrace^{SM}, a component of the AMC Advantage eClinical system. The GlobalTrace shipment manifest must accompany all specimen shipments. See the MOP for instructions on the use of GlobalTrace.

APPENDIX VI: BASELINE QUESTIONNAIRE

General Site Information	
Subject ID	____ _____-_____- _____
Administered By	
Date of Administration (DDMMYYYY)	

Thank you for agreeing to speak with me today.

I will be asking some questions about your health, as well as some personal questions -- if you feel uncomfortable answering any question or want to stop at any time, just let me know.

Sociodemographic Questions		
1	How many years of schooling have you completed?	_____years
2	Which best describes your marital status?	1☐ Never married 2☐ Married/cohabitating 3☐ Divorced/separated 4☐ Widowed
3	Do you work for pay on a regular basis?	1☐ Yes 2☐ No
4	How to you usually pay for your healthcare?	1☐ Government/public funding 2☐ Private insurance 3☐ Self pay, out of pocket

Health Behavioral Questions		
5	Have you used tobacco (smoked or smokeless), chew or snuff at least 100 times in your life? *If no, skip to question 7*	1☐ Yes 2☐ No
6	Have you used tobacco (smoked or smokeless), chew or snuff in the past month?	1☐ Yes 2☐ No
7	Have you ever had a cervical cancer screening test (e.g., a Pap smear or VIA) prior to being in this study?	1☐ Yes 2☐ No

The next few questions will ask sex you may have had in the past. Let's review some of the words so that we agree what we are talking about: Vaginal sex is when a man puts his penis in a woman's vagina.		
8	Have you ever had vaginal sex in your life? *If no or choose not to answer, skip to question 17*	1☐ Yes 2☐ No 3☐ Choose not to answer
9	How many men have you had vaginal sex with in your life?	1☐ 1 man 2☐ 2-5 men 3☐ 6-10 men 4☐ 11-50 men 5☐ > 50 men 6☐ Choose not to answer
10	Have you had vaginal sex in the past 12 months? *If no or choose not to answer, skip to question 17*	1☐ Yes 2☐ No 3☐ Choose not to answer
11	How many men have you had vaginal sex with in the past 12 months?	1☐ 1 man 2☐ 2-5 men 3☐ 6-10 men 4☐ 11-50 men 5☐ > 50 men 6☐ Choose not to answer
12	Have you had a new sex partner in the last 12 months?	1☐ Yes 2☐ No 3☐ Choose not to answer
13	Did you use a condom the last time you had vaginal sex?	1☐ Yes 2☐ No 3☐ Don't know 4☐ Choose not to answer

14	How often do you use condoms for vaginal sex?	1☐ Often 2☐ Sometimes 3☐ Rarely 4☐ Never 5☐ Don't know 6☐ Choose not to answer
15	Do you have a main/primary/steady partner? *If no, skip to 17*	1☐ Yes 2☐ No 3☐ Choose not to answer
16	Was your main/primary/steady partner circumcised?	1☐ Yes 2☐ No 3☐ Choose not to answer
17	Anal sex is when a man puts his penis into a women's rectum or anus. Have you ever had anal sex in your life? *If no or choose not to answer, skip to question 22*	1☐ Yes 2☐ No 3☐ Choose not to answer
18	How many men have you had anal sex with in your life?	1☐ 1 man 2☐ 2-5 men 3☐ 6-10 men 4☐ >10 men 5☐ Choose not to answer
19	Have you had anal sex in the past 12 months?	1☐ Yes 2☐ No 3☐ Choose not to answer
20	Did you use a condom the last time you had anal sex?	1☐ Yes 2☐ No 3☐ Don't know 4☐ Choose not to answer

21	How often do you use condoms for anal sex?	1☐ Often 2☐ Sometimes 3☐ Rarely 4☐ Never 5☐ Don't know 6☐ Choose not to answer
22	Has someone ever put their mouth or tongue on your genitals in your life? *If no or choose not to answer, then end*	1☐ Yes 2☐ No 3☐ Choose not to answer
23	With how many people have you done this in your life?	1☐ 1 person 2☐ 2-5 people 3☐ 6-10 people 4☐ > 10 people 5☐ Choose not to answer
24	Has someone ever put their mouth or tongue on your genitals in the last 12 months?	1☐ Yes 2☐ No 3☐ Choose not to answer

To be signed by the person administering this questionnaire:

Signature: _____ Date: _____

APPENDIX VII: FOLLOW-UP QUESTIONNAIRE

General Site Information	
Subject ID	_____-_____- _____
Week #	Week 52 Week 104
Administered By	
Date of Administration (DDMMMYYYY)	

Thank you for agreeing to speak with me today.

I will be asking some questions about your health, as well as some personal questions -- if you feel uncomfortable answering any question or want to stop at any time, just let me know.

Health Behavioral Questions		
1	Have you used tobacco (smoked or smokeless), chew or snuff at least 100 times in your life? *If no, skip to question 3*	1☐ Yes 2☐ No
2	Have you used tobacco (smoked or smokeless), chew or snuff in the past month?	1☐ Yes 2☐ No
The next few questions will ask about sex you may have had in the last 12 months. Let's review some of the words so that we agree what we are talking about: Vaginal sex is when a man puts his penis in a woman's vagina		
3	Have you had vaginal sex in the past 12 months? *If no or choose not to answer, skip to question 10*	1☐ Yes 2☐ No 3☐ Choose not to answer
4	How many men have you had vaginal sex with in the past 12 months?	1☐ 1 man 2☐ 2-5 men 3☐ 6-10 men 4☐ 11-50 men 5☐ > 50 men 6☐ Choose not to answer

5	Have you had a new sex partner in the last 12 months?	1☐ Yes 2☐ No 3☐ Choose not to answer
6	Did you use a condom the last time you had vaginal sex?	1☐ Yes 2☐ No 3☐ Don't know 4☐ Choose not to answer
7	How often do you use condoms for vaginal sex?	1☐ Often 2☐ Sometimes 3☐ Rarely 4☐ Never 5☐ Don't know 6☐ Choose not to answer
8	Do you have a main/primary/steady partner? *If no, skip to 10*	1☐ Yes 2☐ No 3☐ Choose not to answer
9	Was your main/primary/steady partner circumcised?	1☐ Yes 2☐ No 3☐ Choose not to answer
10	Anal sex is when a man puts his penis into a women's rectum or anus. Have you ever had anal sex in the past 12 months? *If no or choose not to answer, skip to question 13*	1☐ Yes 2☐ No 3☐ Choose not to answer
11	Did you use a condom the last time you had anal sex?	1☐ Yes 2☐ No 3☐ Don't know 4☐ Choose not to answer

12	How often do you use condoms for anal sex?	1☐ Often 2☐ Sometimes 3☐ Rarely 4☐ Never 5☐ Don't know 6☐ Choose not to answer
13	Has someone ever put their mouth or tongue on your genitals in the last 12 months?	1☐ Yes 2☐ No 3☐ Choose not to answer

To be signed by the person administering this questionnaire:

Signature: _____ Date: _____