AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL #084:

Screening HIV-Infected Women for Anal Cancer Precursors

A Multi-Center Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT01946139
Regulatory Status:	Exempt from IDE requirements [21 CFR 812.2(c)]
Specimen analysis and support by:	Gen-Probe, Inc. Arbor Vita Corp. and QIAGEN Sciences, LLC
Protocol Chair:	Elizabeth Chiao, MD
Protocol Co-chair:	Elizabeth Stier, MD

Version 6.0

21 March 2018

NCI Version Date: 21 March 2018

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **Screening HIV-Infected Women for Anal Cancer Precursors (Version 6.0, 21MAR2018),** as written according to AMC, NCI and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations are permitted.

_____ _____

Signature Date (mm/dd/yyyy)

TABLE OF CONTENTS

ABBREVIATIONS

ACSR	AIDS Cancer Specimen Resource
CTEP-AERS	CTEP Adverse Event Reporting System
AdvantageEDC^{SM}	AMC Internet Data Entry System
AE	Adverse Event
AIN	Anal intraepithelial neoplasia
AMC	AIDS Malignancy Consortium
ANC	Absolute neutrophil count
ASC-H	Atypical squamous cells, cannot exclude HSIL
ASC-US	Atypical squamous cells of undetermined significance
cART	Combination antiretroviral therapy
CDC	Centers for Disease Control
CDUS	Clinical Data Update System
CIN	Cervical intraepithelial neoplasia
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DHHS	Department of Health and Human Services
DSMB	Data Safety and Monitoring Board
ELISA	Enzyme linked immunosorbent assay
FDA	Food and Drug Administration
GEE	Generalized estimating equations
HAART	Highly-active antiretroviral therapy
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	High-risk
HRA	High resolution anoscopy
HSIL	High-grade squamous intraepithelial lesion(s)

IRB	Institutional review board
IVIG	Intravenous immunoglobulin
LSIL	Low-grade squamous intraepithelial lesion(s)
Ml	Milliliter
MSM	Men who have sex with men
NCI	National Cancer Institute
NILM	Negative for intraepithelial lesion or malignancy
OHAM	Office of HIV and AIDS Malignancy
OHRP	Office for Human Research Protections
ODMC	Operations and Data Management Center
PBMC	Peripheral blood mononuclear cell
PIO	Protocol Information Office
SAE	Serious adverse event
SCCA	Squamous cell carcinoma of the anus
SN	Sensitivity
SP	Specificity
STI	Sexually transmitted infection
TCA	Trichloroacetic acid ablation
VaIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia

SITES PARTICIPATING IN THE STUDY

This protocol will be open to all interested AMC institutions approved by the AMC HPV Working Group. The approval will be based on the capacity to perform high resolution anoscopy (HRA).

PROTOCOL ROSTER

AMC #084

Screening HIV-Infected Women for Anal Cancer Precursors

Protocol Chair:
Elizabeth Chiao, MD, MPH
Assistant Professor of Medicine
Baylor College of Medicine
2002 Holcombe Blvd
Houston, TX 77030
Phone: (713) 794-8666
Fax: (713) 748-7359
Email: echiao@bcm.edu

Protocol Co-chair:
Elizabeth Stier, MD
Associate Professor, Obstetrics and Gynecology
Boston Medical Center
85 E. Concord St
Boston, MA 02118
Phone: (617) 414-5101
Fax: (617) 414-7300
Email: elizabeth.stier@bmc.org

AMC Biorepository:
Sylvia Silver, DA
GW Biorepository
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu

Statistician:
Jeannette Y. Lee, PhD
AMC Statistical Center
University of Arkansas for Medical Sciences
4301 W. Markham, #781
Little Rock, AR 72205-7199
Phone: (501) 526-6712
Fax: (501) 526-6729
Email: jylee@uams.edu

Operations & Data Management:
AMC Operations & Data Management Center
The EMMES Corporation
401 N. Washington St., Suite700
Rockville, MD 20850
Phone: (301) 251-1161
Fax: (240) 238-2842
Email: amcpm@emmes.com

PROTOCOL SYNOPSIS

AMC-084: Screening HIV-Infected Women for Anal Cancer Precursors

DESIGN:	Prospective cohort study
DURATION:	Up to 2 years
SAMPLE SIZE:	300
POPULATION:	HIV-positive females 18 and older without previously diagnosed high-grade intraepithelial lesions (HSIL) of the anus or anal cancer
REGIMEN:	All participants will undergo anal cancer screening with anal cytology and several different anal HPV testing modalities every 6 months for up to 2 years while on study. All participants will undergo High Resolution Anoscopy (HRA) evaluations at baseline/Visit 1, Month 12/Visit 3, and Month 24/Visit 5. Standard screening procedures involving HRA for all abnormal anal cytology tests will also be performed for the interim visits. If diagnosed with HSIL (as defined by HSIL diagnosed on *any* anal biopsy) at any scheduled study visit, participants will discontinue the study early.
PRIMARY OBJECTIVES:	1) To determine the sensitivity and specificity of HPV testing using different methods of detection, including HPV Hybrid Capture 2 (HC2), HPV mRNA assays (APTIMA) and Arbor Vita OncoE6 HPV test and whether they improve the screening performance of routine anal cytology for the detection of anal HSIL when measured against the gold standard, biopsy-proven HSIL. 2) To determine the prevalence and risk factors for prevalent HSIL in HIV-positive women. 3) To determine incidence and risk factors associated with HSIL and anal HPV over 2 years among HIV positive women undergoing semi-annual anal evaluations.
EXPLORATORY OBJECTIVES:	1) To evaluate the acceptability of anal cancer screening among HIV-positive women. 2) To collect data on quality of life and health care costs (including non-direct health care costs and time costs) for an economic evaluation of the cost-effectiveness of anal cancer screening strategies in HIV-positive women.

PROTOCOL SCHEMA

Visit 0: Pre-Entry (Screening)

- Informed consent for study participation and ACSR donation
- Document HIV diagnosis, medical and medication history
- Urine pregnancy test
- Collect ANC and platelet count if not done for routine care ≤ 120 days prior to enrollment

Visit 1: Enrollment (Baseline)

- Baseline Questionnaire at visit
- Targeted physical and anogenital exam, medical record and medication review
- Collect CD4 count/percentage and HIV viral load if results not available from routine care ≤ 120 days prior
- Collect 2 cervical/vaginal specimens (1 for local cytology, then 1 in ThinPrep for central HPV testing)
- Collect 3 Anal Swabs (1 for local cytology, then 1 in ThinPrep for central HPV testing, and 1 swab placed in a lysis tube provided by ArborVita).
- HRA with minimum of 2 biopsies (up to 6 directed biopsies of areas suspicious for AIN; random biopsies if fewer than 2 directed biopsies are taken)
- Blood for ACSR donation (optional; 2 yellow top tubes if consent given; can be collected during subsequent visits)
- Post-Procedure Questionnaire via phone call within 1-5 weeks after visit
- Send cervical and anal ThinPrep specimens to AMC Biorepository within 4 weeks of collection

Visit 2 (Month 6) AND Visit 4 (Month 18) Follow Up (-14 / +160 days)

- Follow-up Questionnaire at visit
- Targeted physical and anogenital exam, medical record and medication review
- 3 Anal Swabs (1 for local cytology, then 1 in ThinPrep for central HPV testing, and 1 swab placed in a lysis tube provided by ArborVita)
- Send anal ThinPrep specimens to AMC Biorepository within 4 weeks of collection

Visit 3 (Month 12) AND Visit 5 (Month 24) Follow Up (-14 days / +160 days)

- Follow-up Questionnaire at visit
- Targeted physical and anogenital exam, medical record and medication review
- Collect CD4 count/percentage and HIV viral load if results not available from routine care ≤ 120 days prior for Visit 5 only
- Collect 2 Cervical Swabs (1 for local cytology, then 1 in ThinPrep for central HPV testing)
- Collect 3 Anal Swabs (1 for local cytology, then 1 in ThinPrep for central HPV testing, and 1 swab placed in a lysis tube provided by ArborVita)
- HRA with minimum of 2 biopsies (up to 6 directed biopsies of areas suspicious for AIN; random biopsies if fewer than 2 directed biopsies are taken)
- Post-procedure Questionnaire via Phone Call within 1-5 weeks after visit
- Send cervical and anal ThinPrep specimens to AMC Biorepository within 4 weeks of collection

Cytology and Histology Slide Submission Requirements

- **Quality Control:** Submit all baseline anal histology slides collected from the first six months after enrollment of the first study participant at a given study site. These slides should be batch shipped to the AMC Biorepository as soon as possible 6 months (no more than 9 months) after enrollment of the first study participant at each study site.
- **Central Pathology Review:** All anal histology slides from Visits 1-5 that were not submitted for quality control must be submitted for central review. All slides may be batched for submission to the AMC Biorepository every 6 months after the first subject's enrollment at that site.

1.0 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Anal cancer rates among HIV-positive women in the cART era

Anal cancer rates in HIV-positive individuals have continued to increase over the past decade despite the widespread use of combination antiretroviral therapy (cART).[1-3] The highest risks appear to be among HIV-positive men who have sex with men (MSM);[4] however, HIV-positive women are also at increased risk for anal cancer, with an incidence rate of approximately 10-29 per 100,000 person-years.[5,6] Chaturvedi et al [4] reported that the incidence of anal cancer among HIV-positive women in the U.S. has increased in the post-cART era from 0 between 1980 and 1989 to approximately 11 per 100,000 in the years between 1996 and 2004. In addition, our research demonstrated that in the cART era, the incidence of squamous cell carcinoma of the anus (SCCA) increased significantly among women and the disease increased most rapidly among African Americans.[7] Thus SCCA remains a growing problem for HIV-positive women, who in the United States are primarily African American (67%) and Latina (13%).

1.1.2 Anal HPV, AIN, and anal carcinoma

SCCA shares biologic similarities with cervical cancer, including detectable precancerous lesions and high-risk (HR) human papillomavirus (HPV) infection. HPV has been detected in 99% of cervical cancers and 80 to 90% of anal cancers, with HPV types 16 or 18 detected in about 70% of cervical and 80% of anal cancers.[8] It is likely that the pathogenesis of anal cancer is similar to that of cervical cancer: that is, anal HPV infection, in conjunction with other yet to be determined factors, leads to the development of anal high-grade squamous intraepithelial lesions (HSIL), a likely precursor to anal cancer.[9,10] It also has been shown that the rate of progression from anal dysplasia to invasive SCCA is high. Among immuno-competent individuals, the rate of progression from anal intraepithelial neoplasia (AIN) to invasive SCCA has been reported as approximately 10% over a median time of 5 years.[11,12] In a recent study of HIV-positive MSMs, 7% of 156 individuals who had HSIL of the anus developed invasive cancer over a median period of 8.6 months. The authors noted that all of the individuals diagnosed with invasive cancer had previously refused therapy for anal dysplasia.[13] Because of the high rate of progression from high-grade anal intraepithelial neoplasia (AIN 2,3) or HSIL[14] to invasive SCCA, the significant morbidity and mortality associated with SCCA, and because SCCA shares many biologic properties with cervical cancer, several research and practice groups have recommended anal cancer prevention strategies for both HIV-positive men and women.[15]

1.1.3 Anal Cancer Screening Guidelines

There is no consensus regarding the optimal anal cancer screening strategy among HIV-positive individuals, particularly HIV-positive women. Prior to the introduction of cervical cytology screening programs, the incidence of cervical cancer in the U.S. was 40-50/100,000. Largely due to the success of cervical cytology screening, in which high-grade cervical squamous intracellular lesions

(HSIL), or cervical intraepithelial neoplasia (CIN)[14] is detected and treated before progression to cancer occurs, the incidence of cervical cancer has declined to 8-10/100,000. Indeed, screening with cervical cytology is considered to be one of the most successful cancer prevention programs.[16] Because of the increased incidence of anal cancer, the significant morbidity and mortality associate with SCCA, and because of the biologic similarities between cervical and anal cancer, anal cancer screening programs have been proposed for both HIV-positive men and women in the U.S.[17]

However, little data are available to determine its effectiveness. The New York State guidelines for primary care of HIV-positive individuals recommend screening HIV-positive MSM and women with a history of CIN and condyloma yearly with anal cytology tests.[15] In contrast, the Department of Health and Human Services (DHHS) guidelines for the prevention and treatment of opportunistic infections among HIV-positive individuals states "… studies of screening and treatment programs for AIN 2 or 3 should not be implemented before definitive recommendations for anal cytology screening can be made."[18] Others have questioned the availability of resources needed to implement anal cancer screening among HIV-positive women.[19] Although studies have shown anal cytology testing to be cost-effective among HIV-positive MSM,[20,21] no such studies using female-specific cancer screening data have been conducted among HIV-positive women, the target population of the current study.

1.1.4 Anal cancer cytology test characteristics for HIV-positive women

The reported sensitivity (SN) and specificity (SP) of anal cytology is highly variable, and is impacted by the type of population sampled.[22,23] Several studies have adequately evaluated the effectiveness of anal cytology testing by comparing the SN and SP of the test to histology from high-resolution anoscopy (HRA) directed biopsy in HIV-positive men. The SNs ranged from 69% to 93%, and the SPs ranged from 32% to 59%.[22,24] More recent studies have also shown that the SN and SP of anal cytology are dependent on the type of population screened, likely due to the variability in disease prevalence rates. Berry et al[23] found that in HIV-positive men the SN of abnormal cytology to detect high-grade anal neoplasia was 87% and in HIV-negative MSM it was 55%. Other studies have shown that among HIV-positive individuals the SN and SP of anal cytology is dependent on the percentage of anal canal involvement.[22] Anatomic differences, as well as lesion size and infection with multiple HR HPV types have been hypothesized to cause SN and SP differences. These parameters differ between HIV-positive MSM and women, thus, extrapolation of anal cytology test characteristics from HIV-positive men to HIV-positive women is likely invalid. Of note, the target sensitivity, specificity, positive predictive and negative predictive values lie well within the performance characteristics of many other well-established and widely recommended cancer screening modalities, including cervical cytology and mammography.[25,26] Determining the screening test performance characteristics in HIV-positive women is necessary.

1.1.5 Anal HPV and anal intraepithelial neoplasia prevalence among HIV-positive women

Few studies have reported estimates of anal HPV and anal cytology prevalence, and fewer have reported anal histology results.[27,28,29] Despite the data on cervical HPV infection and cervical disease in HIV-positive women and data on anal HPV, cytologic abnormalities, and histologic abnormalities among HIV-positive men, there are limited data on anal HPV infection and disease among HIV-positive women. There have only been 4 studies describing the prevalence of HPV infection and anal infection among HIV-positive women.[27-30] In these studies the rates of anal HPV varied dramatically from 16%-90% and the prevalence of anal cytologic abnormalities varied from 17%-39%. The variance in HPV prevalence is likely due to differences in the type of test performed and possibly the transport medium of the test. There are even less data reported regarding anal histologic diagnoses. Among those studies where HRA and biopsy were performed,[27-28] histology results were only available in a small percentage of their population. Additionally, only one longitudinal study has been published describing incidence of anal HPV infection, and the cohort for this study was recruited in the pre-cART/early cART era.[31] Therefore, further comprehensive studies in the cART era are needed to determine more precise estimates of factors impacting anal HPV infection, cytologic abnormalities, and anal histologic diagnoses.

There are no data evaluating the screening test characteristics of U.S. Food and Drug Administration (FDA) -approved and experimental HR HPV testing for anal cancer screening among HIV-positive women. Among HIV-positive MSM, it has been shown that HPV testing adds little information to anal cytologic testing because of the very high prevalence of anal HR HPV prevalence (in most populations > 90%).[32] However, it appears that HIV-positive women may have a lower rate of anal HR HPV infection; therefore, HR HPV testing may improve the SN and SP of anal cytology. There have been no studies evaluating HR HPV test characteristics among HIV-positive women, using either the FDA-approved Hybrid Capture 2 (HC2) test (Qiagen Corporation, Gaithersburg, MD), the APTIMA HPV test (GenProbe Corp, San Diego, CA), or the OncoE6™ test (Arbor Vita, Fremont, CA), a test that is currently in development.

1.1.6 Hybrid Capture2 (HC2) HPV test

In 2005 the FDA approved the use of HC2, a high-risk HPV DNA probe, as an adjunct to cervical cytology screening for women aged 30 years and over. HC2 detects 13 of the HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The benefits of adding HC2 testing include: 1) having a sensitive and readily reproducible measure of the risk of disease and 2) having a high negative predictive value with a single test. The combination of the HC2 assay and cytology is also used in the triage of women with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results, with an SN of 99.2% (95% confidence interval (CI): 97.4-100%) and an SP of 87.3% (95% CI: 84.2-90.4%) to detect CIN2 or worse.[33]

1.1.7 APTIMA HPV Test

The APTIMA HPV test detects messenger RNA (mRNA) for HPV proteins E6/E7 in 14 oncogenic HPV types. Of all experimental HPV tests, the ATPIMA test has

recently received FDA approval for cervical HPV testing based on studies that have shown the APTIMA test to significantly improve the specificity of detecting CIN2+, thereby decreasing the number of "false positive" HPV tests compared to HC2. The test may be more predictive than the detection of HPV DNA alone because upregulation of mRNA from the oncogene region of the HPV genome (E6 and E7) likely predicts which HPV infections are more likely to persist and progress to a high-grade lesion and cancer. The performance characteristics of APTIMA HPV were compared with HC2 for the detection of CIN2+ in specimens collected from women referred for colposcopy because of abnormal cytology. APTIMA HPV had an SN of 95.2% and an SP of 42.2%, compared with HC2, which had an SN of 99.6% and an SP of 28.4% when used without concurrent cytology.[34]

1.1.8 ArborVita OncoE6™ HPV test

The Arbor Vita Onco***E6***™ Cervical Test (E6 Test) is an immunochromatographic test applying the lateral flow format ("strip test," conceptually similar to over-the-counter pregnancy tests) to detect elevated levels of the HPV E6 oncoprotein from a cervical cytology specimen. As now demonstrated from the outcome of a clinical study[1] performed in China, the Onco***E6***™ Cervical Test seems to have the potential to preferentially detect those women with actively transforming HPV infection among the much bigger group of women with clinically irrelevant HPV infection.

The Onco***E6***™ Cervical Test detects E6 oncoproteins of HPV types 16 and 18 on two distinct test lines ("oncoprotein typing") though monoclonal antibodies (mAb) specific to the targeted E6 oncoproteins, using a capture mAb / E6 / detector mAb sandwich principle. The E6 Test can be performed from a "dry" cervical polyester tipped (Dacron) swab, or from PreservCyt solution. The E6 Test can be performed and interpreted upon short training by anyone having none to very basic laboratory skills. Briefly, the cervical specimen is subjected to a simple two step lysis procedure, followed by a short centrifugation for lysate clearance. An aliquot of this lysate is allowed to run up the strip driven by capillary forces, and if E6 oncoprotein was present in the sample, a capture mAb / E6 / detector mAb complex will be formed at the HPV16 and/or HPV18 test lines, respectively. The run up step is followed by a wash step and a development step, and then by visual inspection of the outcome. The time from sample collection to result is approx. 2.5 hours. The appearance of a control line on the strip assures proper function of the reagents, and a positive control (mixture of recombinant HPV 16 and 18 E6 protein) is part of the Onco***E6***™ Cervical Test kits.[37]

1.1.9 Assay analytic performance

The manufacturers of each of the three study devices will be providing support for the investigation in the form of assay performance at the manufacturers' central laboratories.

The devices will be used for specimen testing according to the performance standards for cervical evaluation outlined in the manufacturer's device labeling and other published standards of performance.[35,36,37,38] Each of these tests will be run on at least a monthly basis.[47] The companies will report assay results to the AMC on a monthly basis for the first 6 months of the trial, which will be closely

monitored by the protocol co-chairs to determine if the sampling methods provide sufficient materials. The protocol will be amended if the stated sampling method does not consistently provide adequate material for testing.

1.1.10 Cost-effectiveness analysis

While clinical and epidemiologic studies are important steps in determining the utility of anal cytology testing among women, they provide no information on clinical benefits (life expectancy and quality-adjusted life expectancy), costs (measured in dollars), and cost-effectiveness of different anal cancer screening strategies for HIV-positive women. Only three papers were identified describing cost-effectiveness analyses of screening for anal cancer.[20,39,40] Using age-specific HIV incidence as the only female specific data, Czoski-Murray and colleagues[40] provided the only cost-effectiveness analysis of anal cancer screening in HIV-positive women. All other parameters were informed by data collected to populate the MSM screening model. A more realistic model would incorporate data from anal cancer screening in HIV-positive women. To address this very important knowledge gap, the data from this study will be used in a future economic analysis to assess the most cost-effective anal cancer screening approach for HIV-positive women.

1.1.11 Background summary

Determining the operating characteristics of commercially approved and soon-to-be-approved HPV tests for anal use is necessary to inform anal cancer screening strategies for HIV-positive women.

In addition, carefully constructed cost-effectiveness studies with accurate transition point estimates are necessary for evaluating the utility of and the best strategies for anal cancer screening among HIV-positive women.

1.2 Rationale

The current state of anal cancer screening recommendations is similar to the state of cervical cancer screening recommendations in the 1960s, prior to the era of evidence-based medicine. Although screening for anal cancer among HIV-positive individuals has been endorsed by experts and promulgated by some guidelines, the available information has critical gaps that we will be able to address in our study:

1) Anal cytology and HPV test characteristics: What are the screening test characteristics of anal cytology and commercially available or soon-to-be commercially available HPV tests in HIV-positive women using HRA and biopsy as the gold standard?
2) Anal HSIL in HIV-positive women: What is the prevalence of histologically-verified anal HSIL? What is the incidence of anal HSIL and HPV infection?
3) Predictors of anal HPV and HSIL in HIV-positive women: Does cervical HPV, behavioral, and/or immunologic characteristics, such as cART adherence and nadir CD4 count risk identify women at risk for anal HPV and HSIL?
4) Poor documentation of Cost-effectiveness: What is the cost-effectiveness of anal cancer screening strategies in the U.S. for HIV-positive women?

By concurrently evaluating HPV tests along with anal cytology and comparing those results with high resolution anoscopy with directed biopsy, we will be able to ascertain the performance characteristics of anal cytology and HPV tests for the detection of HSIL. In addition, we will be able to determine the prevalence, incidence, and risk factors for HPV and HSIL from the longitudinal follow-up cohort study. The information gained from this study is crucial for the development of appropriate guidelines to screen for HSIL of the anus in HIV-positive women.

1.3 Study Design

We propose a multi-site, 2-year longitudinal cohort study of 300 HIV-positive women who will be evaluated at 6-month intervals. This cohort study will be the first to provide important information regarding the test characteristics, epidemiology, and natural history of anal HPV infection and HSIL among a cohort of HIV-positive women undergoing semi-annual anal evaluations.

2.0 HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypotheses

2.1.1 Anal HPV testing with HC2, APTIMA, or Arbor Vita OncoE6 HPV Test will improve the performance, including the SN and SP of anal cytology testing among HIV-positive women when measured against the gold standard, biopsy-proven HSIL.

2.1.2 Anal HSIL and anal HPV infection are associated with risk factors including cervical HPV, behavioral, and immunologic characteristics, such as plasma HIV RNA, current CD4 and nadir CD4 counts.

2.2 Primary Objectives

2.2.1 To determine the sensitivity and specificity of HPV testing using different methods of detection, including HPV Hybrid Capture 2 (HC2), HPV mRNA assays (APTIMA) and Arbor Vita OncoE6 HPV assay and whether they improve the screening performance of routine anal cytology for the detection of anal HSIL when measured against the gold standard, biopsy-proven HSIL.

2.2.2 To determine the prevalence and risk factors for prevalent HSIL in HIV-positive women.

2.2.3 To determine incidence and risk factors associated with anal HSIL and HPV over 2 years among HIV positive women undergoing semi-annual anal evaluations.

2.3 Exploratory Objectives

2.3.1 To evaluate the acceptability of anal cancer screening among HIV-positive women.

2.3.2 To collect data on quality of life and health care costs (including non-direct health care costs and time costs) for an economic evaluation of the cost-effectiveness of anal cancer screening strategies in HIV-positive women.

3.0 PARTICIPANT SELECTION

3.1 Inclusion Criteria

3.1.1 Women age 18 and older. “Women” is defined as persons documented as female at birth. Younger women are not included as anal cancer is a disease of adults.

3.1.2 HIV positive. HIV-1 infection, as documented by any federally approved, licensed HIV rapid test performed in conjunction with screening (or ELISA, test kit, and confirmed by Western blot or other approved test). Alternatively, this documentation may include a record demonstrating that another physician has documented the participant's HIV status based on either: 1) approved diagnostic tests, or 2) the referring physician's written record that HIV infection was documented, with supporting information on the participant's relevant medical history and/or current management of HIV infection.

3.1.3 Karnofsky performance status ≥ 70%.

3.1.4 Absolute neutrophil count ≥ 750 cells/mm^3 within 120 days of study entry.

3.1.5 Platelet count ≥ 75,000 cells/mm^3 within 120 days of study entry.

3.2 Exclusion Criteria

3.2.1 Current or history of anal or peri-anal carcinoma.

3.2.2 History of anal HSIL cytology or histology; or anal cytology result with “ASCUS, cannot exclude HSIL.”

3.2.3 Known permanent or irreversible bleeding disorder, or any illness that, in the opinion of the clinical investigator, would contraindicate any biopsy of the anal canal.

3.2.4 For women able to conceive, evidence of pregnancy by a positive urinary pregnancy test within 72 hours prior to study entry. Pregnant women are excluded from enrollment in this study because of concerns about performing HRA during pregnancy.

3.2.5 Serious medical or psychiatric illness that in the opinion of the site Investigator will interfere with the ability of the participant to give informed consent or adhere to the protocol.

3.2.6 Ongoing use of anticoagulant therapy other than aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs (NSAIDS).

3.2.7 Inability to provide informed consent.

3.2.8 Treatment of anal and/or perianal HPV associated disease (i.e., condyloma or low-grade AIN) within 4 months of study entry.

3.3 Number of Study Participants to be Enrolled

3.3.1 Proposed sample size

This study will enroll 300 participants.

3.3.2 Accrual rate

Approximately 20 participants per month.

3.4 Study Enrollment Procedures

Sites must have this protocol approved by the reviewing Institutional Review Board (IRB) and be registered for study participation with the AMC Operations and Data Management Center (ODMC) before they may enroll participants.

3.4.1 Enrollment

After the participant has signed informed consent, screening evaluations have been performed, and the participant is determined to be eligible, the participating site will complete the protocol-specific eligibility checklist and enroll the participant into AMC-084 (on-line via AdvantageEDC^{SM}). Enrollment should occur no more than 1 week prior to Visit 1 (enrollment 1 day prior to or on the day of Visit 1 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 amcpm@emmes.com or via phone at 301-251-1161) for further instructions.

Participants must be enrolled into AMC-084 prior to initiating the study.

3.4.2 Screen failure

If a participant does not meet the eligibility criteria or refuses to take part in the study, a tracking sheet will be maintained locally on the number of participants eligible, approached, and enrolled (no PHI will be included).

4.0 CLINICAL AND LABORATORY EVALUATIONS

4.1 Schedule of Evaluations

Participants in the study will follow schedule of evaluations found in Appendix I, Schedule of Evaluations.

4.2 Timing of Evaluations

4.2.1 Screening

Screening evaluations must occur prior to the participant starting any study procedures.

The screening and enrollment visit may be combined if the requisite laboratory results are available through routine clinical care.

In addition to data being collected on participants who enroll into the study, demographic data and reasons for screening failures (that are available) will be captured in a screening log.

4.2.2 On-study evaluations

Evaluations must occur after participant registration. Study visits must be scheduled on the weeks indicated in the Schedule of Evaluations (Appendix I) from -14 days to +160 days for visits 2-5 for the duration of the participant's participation. For visit 1, all study evaluations should be completed within 50 days before the enrollment visit.

4.3 Special Instructions and Definitions of Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. All data requested by the study should be recorded in the source documents. All stated evaluations will be entered on the appropriate case report form (CRF) via the AdvantageEDC^{SM} Internet Data Entry System unless otherwise specified. Quality assurance of data should follow the standards prescribed by the AMC.

4.3.1 Medical/medication history

Medical history

- CDC HIV risk categories and history of AIDS defining conditions
- History of treatment for HSIL of the cervix (CIN2,3) or cervical cancer
- History of treatment for HSIL of the vulva (VIN2,3) or vulvar cancer
- History of prior anal cancer screening with cytology or HRA
- History of pelvic radiation
- History of splenectomy
- Presence of chronic hepatitis B or C
- Year of HIV diagnosis
- Nadir CD4 count (if known)
- Allergies to any medications, including lidocaine, shellfish, or contrast agents
- Previous history of AIDS-defining opportunistic infection
- Listing of other past medical history
- Topical or surgical treatment of HPV-related disease

- History of prior cervical cytologies or biopsies in the past 2 years, and most severe prior cervical cytology and biopsy results (if available)
- History of prior anal cytologies or anal biopsies
- History of systemic cytotoxic chemotherapy and/or radiation (other than pelvic radiation)

A medication history must be present in source documents, including:

- Current and past ART regimens
- Actual or estimated start date of each agent that is part of the current cART therapy
- History of any prescription medications, immune modulating herbal supplements, and over the counter medication taken within 14 days of study entry
- History of HPV vaccination

4.3.2 Concomitant medications/antiretroviral medication modifications

Concomitant medications

Use of any systemic antineoplastic or immunomodulatory treatment, systemic corticosteroids, investigational vaccines, interleukins, interferons, growth factors, or intravenous immunoglobulin (IVIG) should be documented in the CRFs.

Any prescription medications that are not listed above that have been initiated since the last report should be documented in the source documents only. If the participant receives any dose of a HPV vaccine while on study, this must be documented in the source and reported in the CRFs.

Antiretroviral medications

Any modifications to antiretroviral medications since the last report will be entered on the CRFs. Modifications would include more than 14 consecutive days of missed antiretroviral medications. Modifications do not include change in current antiretroviral medication dose or formulations.

4.3.3 Nadir CD4+ cell count

The participant's prior nadir CD4+ cell count (absolute value and date) should be documented, when possible, with a copy of the nadir CD4+ cell count report and entered on the CRF. If this documentation is not available, then participant recollection will suffice. For participants who do not know the exact nadir value and for whom there is no source documentation, then recall of the categorical nadir (e.g., < 50, < 100, < 200, 200-500, ≥ 500 cells/mm^3) will suffice. If unknown, then the category of "unknown" will suffice.

4.3.4 Clinical assessments

Targeted physical exam

This should be documented in the source documents only. A targeted physical examination is to include vital signs (temperature, pulse, and blood pressure) and assessment of Karnofsky Performance Status (KPS) (Appendix II). The rest of the

targeted exam is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit.

The vulvar and perianal area will be examined for signs of HPV-related lesions. The presence or absence of vulvar/perianal condyloma will be recorded on the CRFs. Anal cytology and digital anal/rectal exam (DARE) are performed at each study visit. HRA with biopsy of visible disease (in the anal canal or perianus) (or at least 2 random sites from 2 different quadrants, if no disease is visible) will be performed to assess anal HPV-associated disease at visits 1, 3, and 5. Exception: If the participant is pregnant at visits 3 or 5, the HRA with biopsy will be deferred.

The participant will have a cervical/vaginal speculum exam with cervical/vaginal cytology (for visit 1, the participant will need a specimen if not available from within the past 42 days) and HPV collected annually beginning with the initial assessment (Visit 1).

4.3.5 Research staff administered questionnaires

A member of the research staff will administer a questionnaire to the study participant at each study visit to determine her smoking status, recent sexual history, as well as questions to assess quality of life, acceptability of the procedure, ascertain costs to the participant associated with anal cancer screening. The estimated time to complete this questionnaire is 20 minutes. The questionnaire includes the EQ-5D-5L for quality of life,[41] PHQ-4 for anxiety and depression,[42] the faces rating scale,[43] medication adherence,[44] acceptability of screening procedures,[45] sexual behaviors,[29] and personal health care cost information.[46] as well as adapted questions on self reported HIV medication adherence[46] and women's experience with colposcopy.[46] The baseline questionnaire (Appendix XIII) is administered at visit 1. The follow-up questionnaire (an abbreviated version of the baseline questionnaire) is administered at each subsequent visit (see Appendix XV).

4.3.6 Telephone follow-up questionnaire

The telephone follow-up questionnaire (Appendix XIV) may be conducted as a study visit if preferred by study staff or study participant. Each study participant will be contacted by the research coordinator/study nurse 1-5 weeks after each HRA procedure to:

- Administer a brief questionnaire assessing perceptions/acceptability of the HRA; and,
- Review the results from the HRA (cytology and biopsies).

4.3.7 Clinical and laboratory evaluations (See Appendix I for timing of evaluations)

- Anal cytology (See Appendix III, Anal Sampling Procedures)
- Anal HPV studies (See Appendix III and VII, HPV Specimen Collection and Shipping)
- Cervical cytology (See Appendix V, Cervical Sampling Procedures)
- Cervical HPV studies (See Appendix V and VI)
- Digital anal/rectal exam (DARE)

- High resolution anoscopy (HRA) with biopsy (See Appendix IV)
- Blood collection for donation to the AIDS and Cancer Specimen Resource (ACSR) (two 8.5 ml yellow top tubes at ANY VISIT if the participant consents to donation)
- Laboratory test results from within 120 days of enrollment include the following:
    - Absolute neutrophil count
    - Platelet count
    - HIV viral load: Viral load studies will be performed using an assay with a limit of detection of 75 copies/ml or less (visits 1 and 5 only)
    - T cells: CD4 counts and percentages will be quantified (visits 1 and 5 only).
- Pregnancy test for women who can conceive: Pregnancy test (urine HCG) will be performed (and results obtained) within 72 hours of the enrollment visit, at Visit 3 (12 months), and at Visit 5 (24 months)

4.3.8 Evaluations during pregnancy

Any participant who becomes pregnant while on study will remain on study, and resume normal procedures once the pregnancy resolves. While pregnant, the HRA procedures may be omitted due to discomfort to the participant and an absence of data on the effect of these procedures on a developing fetus. Anal cytology sampling procedures may be omitted at the preference of the participant and the provider, and cervical cytology procedures may still be performed if required for the participant's medical care. Participants will resume all visits and procedures after resolution of the pregnancy. Any visits or procedures that are missed for this reason should be reported as missed visits and/or forms in AdvantageEDC, as appropriate.

4.4 Pathology Review

4.4.1 Initial pathology reading:

The specimens will first be sent to the local site's pathology department for processing and pathology interpretation. Each cytology and histology specimen will be assigned a unique accession number in the GlobalTrace^{SM} specimen tracking system for data reporting purposes and for subsequent consensus pathology assessments.

Anal and cervical cytology specimens will be assigned a reading according to the current Bethesda System terminology:

- Negative for intraepithelial lesion or malignancy (NILM)
- Atypical squamous cells of undetermined significance (ASC-US)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Atypical squamous cells, cannot exclude HSIL (ASC-H)
- Atypical glandular cells (AGC)
- Cancer, specify squamous cell or adenocarcinoma

Anal histology specimens will be assigned a reading as per the CAP-ASCCP LAST Project terminology

- Benign/Reactive: squamous metaplasia; etc
- LSIL (condyloma OR AIN1)
- HSIL (AIN2, AIN2/3, or AIN3)
- Cancer, specify squamous cell or adenocarcinoma

Cytology and histology readings from the local cytopathology laboratories will be reported in the appropriate CRF in AdvantageEDC[SM].

4.5 Consensus Pathology Review

All anal histology slides taken during Visits 1-5 will be submitted to the AMC Biorepository for central pathology review. See Appendix VI for details.

4.6 Follow-up for Abnormal Results

Clinical management for all study participants will be based on the local pathology interpretation. However, if the consensus pathology review is significantly different from the local pathology review, that information will be communicated to the clinical site to aid in patient management.

Anal

- If the anal cytology shows HSIL or ASC-H and no corresponding anal or perianal HSIL was found on HRA, then the participant should undergo another HRA in 3-6 months.
- Further evaluation and/or treatment recommendations will be made according to HRA findings (See Appendix IX for recommendations regarding further evaluation and/or treatment).

Cervical

- Participants with abnormal cervical cytology should be referred for colposcopy as per ASCCP management guidelines (See Appendix IX).

STUDY VISITS: (i.e., 6 month visits) participants will remain on schedule for data collection regardless of any interval visits for HRA, colposcopy, or treatment procedures (e.g., for symptomatic condyloma or HSIL of the cervix, CIN2, 3).

Results from any abnormal follow-up and any interval treatment procedures will be recorded in the CRF at the subsequent scheduled study visit.

4.7 Early Study Discontinuation Procedures

An Early Discontinuation form will be completed for all early study discontinuations to document the reason for early discontinuation.

5.0 CRITERIA FOR DISCONTINUATION

5.1 Early Study Discontinuation

- Diagnosis of histologic HSIL on any anal biopsy or cancer of the anus by either the local pathologists or the central pathology review at any time (including the enrollment visit). Only participants with benign or LSIL diagnoses on ALL anal biopsies at each visit will be allowed to continue in the study. Participants who have only cytologic HSIL diagnoses are permitted to continue on study as long as histology results do not show HSIL.
- Request by participant to withdraw from the study.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- The participant is judged by the Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the AMC, IRB, Office for Human Research Protections (OHRP), or NCI.
- Clinical reasons believed life-threatening by the investigator.

6.0 ADVERSE EVENT REPORTING

Adverse event (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 routine reporting (via AdvantageEDC^{SM}).

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.

6.1 Expected Adverse Events Related to the Study Procedures

Anal cytology collection, HRA, and anal biopsy

- Participants will likely experience pressure and urgency to defecate during the anal cytology collection and HRA. Participants may experience discomfort during the injection of local anesthetic (if used). There may be mild to moderate intra- and post-procedural pain for up to 2 weeks. Participants sometimes require pain medication post-procedure. Rarely, this pain can be severe or last longer than 2 weeks.
- Mild bleeding and discharge is relatively common after the procedure and may occur up to 2 weeks after the biopsy is taken. Rarely, there can be severe bleeding occurring 1-2 weeks post-procedure that is severe enough to prompt an evaluation at the emergency room.
- There is a slight risk (<1%) of infection or abscess post-procedure requiring antibiotics.

6.2 Classification of Adverse Events by Severity and Relationship

6.2.1 Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

6.2.2 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.

6.2.3 Serious Adverse Event (SAE): Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect.

6.2.4 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.

6.2.5 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.

6.2.6 Unexpected Adverse Event: Any AE that is not listed in available sources including the package insert, the Investigator's Brochure, or the protocol.

6.2.7 CTEP Adverse Event Reporting System (CTEP-AERS): An electronic system for expedited submission of AE reports.

6.2.8 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.

6.3 Routine AE Reporting

All adverse events (AEs) of Grade 3 or greater severity that are possibly, probably, or definitely attributed to the study procedures will be recorded on the Adverse Event Form in AdvantageEDC^{SM}. Only adverse events of Grade 3 or greater severity are required for safety monitoring and study analysis. Adverse Event Forms will not be required for Grade 1 and 2 AEs; these events will only require recording in source documents. Participants withdrawn from the study due to AEs will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided.

7.0 STATISTICAL CONSIDERATIONS

7.1 Sample Size

The primary objective of the study is to evaluate the sensitivity and specificity of the following methods for the detection of HSIL of the anus (as determined by consensus pathology): anal cytology, HPV hybrid capture 2, HPV mRNA assays (APTIMA) and Arbor Vita OncoE6 HPV test. Note that throughout this section, HSIL (of the anus) is defined as the local or consensus pathology interpretation of any anal biopsy. At the initial visit, all women will undergo an HRA-directed biopsy to determine if they have HSIL. Since HRA is considered the "gold standard," the findings on HRA will determine whether a woman is classified as having HSIL or not. HSIL may be under-diagnosed due to operator error, thus the diagnosis of HSIL will be based on the procurement of at least 2 biopsies during HRA. HSIL will be thus be defined as having the diagnosis determined by either local pathologist or the consensus pathology on *any* anal biopsy at a given visit. Based on previous reports,[41] it is anticipated that approximately 10% of women will have HSIL. The prevalence of HRA-proven HSIL can be estimated with a 95% confidence interval of +/- 3.3%.

For each of the methods of detection, the null hypothesis that the sensitivity is 50% can be tested against the alternative that sensitivity is at least 75% at the one-sided 0.05 significance level with power of 0.89 with 30 HSIL participants. The HPV test results from all three tests−APTIMA, HC2, and HPVE6E7−are all dichotomous, i.e., reported as either positive or negative (or unevaluable). With 270 women who are negative for HSIL on HRA, the null hypothesis that specificity is 50% can be tested against the alternative hypothesis that specificity is at least 65% at the one-sided 0.05 significance level with power of 0.99.

The novel methods of detection (HPV hybrid capture 2, HPV mRNA assays (APTIMA) and Arbor Vita Onco E6 HPV test) will be evaluated to determine if they improve sensitivity or specificity compared to routine anal cytology using McNemar's test. With 30 HSIL women, a 20% increase in sensitivity with 25% of participants with discordant results can be detected at the one-sided 0.05 significance level with 78% power. With 270 women negative for HSIL, a 20% increase in specificity with 25% of participants with discordant results can be detected at the one-sided 0.05 significance level with 99% power. Positive and negative predictive values will be assessed for each method of detection.

To determine incidence of HSIL, we will use the information from the women whose initial HRA examination is negative for HSIL. If these women are followed for an average of 1.8 months, we would expect 1.8 x 270 = 486 person-years of follow-up. The table below shows the 95% Poisson confidence intervals for two levels of the underlying incidence of HSIL with 486 person-years of observation:

Underlying incidence of HSIL per 100 person-years	95% Poisson confidence interval (per 100 person-years)
2.06	(1.11, 3.82)
3.09	(1.86, 5.12)

7.2 Primary Statistical Analyses

7.2.1 Primary analyses

To estimate the sensitivity and specificity of each of the methods of detection, the binomial proportion and its 95% confidence interval will be used. Among participants who are HRA positive for HSIL, McNemar's test will be used to compare routine anal cytology with each of the other methods of detection to determine if sensitivity in the diagnosis of HSIL is improved with the other methods. Similarly, among participants who are HRA negative for HSIL, McNemar's test will be used to compare routine anal cytology with each of the other methods of HPV detection to improve specificity. Positive and negative predictive values will be estimated for each method of detection.

The prevalence of HSIL will be estimated as the proportion of women who are HRA positive for HSIL at entry and its 95% confidence interval. Logistic regression analyses will be used to evaluate the association of potential risk factors (cervical HPV, abnormal cervical cytology, behavioral, and immunologic characteristics, such as plasma HIV-1 RNA, current and nadir CD4 count) with diagnosis of HSIL.

To estimate the incidence of HSIL among women who were HRA negative for HSIL at study entry, the Poisson rate and its 95% confidence interval will be estimated from the number of HSIL cases detected divided by the cumulative years of follow-up across these cases. Behavioral risk factors will be assessed by research staff administered surveys at each study visit. Included in these risk factors is the risk of ongoing sexual exposure to HPV in the study population. Logistic regression will be used to evaluate potential risk factors for incidence of HSIL.

To estimate the incidence of anal HPV among women who were negative for anal HPV at study entry, the Poisson rate and its 95% confidence interval will be estimated from the number of anal HPV cases detected divided by the cumulative years of follow-up across these cases. Logistic regression will be used to evaluate potential risk factors for incidence of anal HPV.

Analysis of the results of the Arbor Vita assay will be delayed after the primary analysis is performed using the results of the Hybrid Capture 2 and Aptima Assays, if the Arbor Vita assay is optimized to yield sufficient results from anal cytology specimens in the future.

7.2.2 Exploratory analyses

We will evaluate the acceptability of anal cancer screening based on survey responses regarding participant satisfaction at each study visit (Appendix XIII and XV) and phone call surveys (Appendix XIV) administered after study visits 1, 3,

and 5. Descriptive statistics will be used to characterize participants' acceptability of undergoing anal screening with cytology/HPV and HRA throughout the study to evaluate changes in perceptions. Generalized estimating equations (GEE) will be used to assess acceptability over time adjusting for intrapatient variability. Acceptability will be correlated with clinical and behavioral risk factors, e.g., history of sexual assault, depression, anxiety, medication compliance, sexual behaviors using GEE methods.

A fully de-identified dataset from the study, which will include data obtained on quality of life, anxiety, costs, and procedures, will be made available to Professor Scott Cantor, MD Anderson, for an economic evaluation of cost effectiveness modeling of anal cancer strategies in HIV-positive women.

8.0 DATA COLLECTION AND MONITORING

8.1 CRF Instructions

Access to the internet data entry system for this study, AdvantageEDC[SM], and instructions for recording of study data on CRFs will be provided by the AMC ODMC at www.amcoperations.com. Participating institutions are responsible for submitting data and/or data forms via AdvantageEDC[SM] 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.

8.2 Data Quality

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

8.3 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. 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.

8.4 Clinical Monitoring

The protocol chairs, AMC statistician, and AMC medical monitor will meet via conference call to review the protocol progress every 6 months until the final participant completes the last study evaluation. At all reviews, careful considerations should be given to the following items:

Prevalence and incidence of HSIL. The sample size calculation was done using a prevalence of 10%. Substantial differences in prevalence in this study may require recalculation of the sample size and length of follow-up.

Number of missing visits and number of early study discontinuations, and their effects on the length of intervals and loss to follow up.

Reported adverse events.

The protocol team members noted above will review these items and determine whether any modification to the study is required. If consensus about study modification or restarting the study is not reached among these members, then the issue will be referred to the AMC Executive Committee for a decision.

The protocol chairs will monitor the quality of HRA data on a per-site basis. Only the HRA results for the enrollment visit (V1) will be reviewed. Specifically, the protocol chairs will review the proportion of participants with HSIL at each site, stratified by cytology result (normal vs. abnormal). It is anticipated that the proportion of participants with HSIL to be at least 30% in those with abnormal cytology. The median number of biopsies performed

per participant at each site will also be reviewed.

Sites with performance evaluations that do not meet to the specified goals will contacted by the protocol chairs for discussion and then brought to the attention of the HPV working group's HRA certification committee for re-evaluation.

9.0 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 IRB Review and Informed Consent

The principles of IRB approval and informed consent described in the Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects (45 CFR Part 46) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB, which specifically approves the protocol and informed consent, before participant enrollment. The IRB must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IRB 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 IRB according to local procedures. The IRB 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 IRB, including a list of all reports and documents submitted.

Written informed consent will be obtained from the participant. The nature and 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.

9.2 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 IRB of the treating institution. A copy of the IRB's written approval must be sent to the ODMC.

9.3 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Clinical Trials 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 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	90	+	0	=	90
Not Hispanic or Latino	210	+	0	=	210
Ethnic Category: Total of all subjects	**300**	**+**	**0**	**=**	**300**
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	210	+	0	=	210
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	90	+	0	=	90
Racial Category: Total of all subjects	**300**	**+**	**0**	**=**	**300**
	(A1 = A2)		(B1 = B2)		(C1 = C2)

9.4 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB, the NIH, or designee.

9.5 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIH, or other government agencies as part of their duties to ensure that research participants are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

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

10.1 Study Participant Confidentiality

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only and de-identified from the participant. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA, OHRP, the AMC, or the NCI.

10.2 Study Discontinuation

This study may be discontinued at any time by the NCI, the AMC, the OHRP, or the FDA.

11.0 BIOHAZARD CONTAINMENT

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

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to the instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

12.0 REFERENCES

1. Crum-Cianflone NF, Hullsiek KH, Marconi VC, et al. Anal cancers among HIV-infected persons: HAART is not slowing rising incidence. *AIDS.* Feb 20 2010;24(4):535-543.
2. Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol.* Dec 2009;10(12):1152-1159.
3. D'Souza G, Wiley DJ, Li X, et al. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr.* Aug 1 2008;48(4):491-499.
4. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst.* Aug 19 2009;101(16):1120-1130.
5. Piketty C, Selinger-Leneman H, Grabar S, et al. Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy. *AIDS.* Jun 19 2008;22(10):1203-1211.
6. Silverberg M. 2010.
7. Chiao E, Krown SE. Non-AIDS Defining Cancers in HIV Infected Individuals. In: Volberding PA and Palefsky J, ed. *American Cancer Society, Atlas of Clinical Oncology* Hamilton, Ontario: BC Decker; 2006, pp. 359-379.
8. Abramowitz L, Jacquard AC, Jaroud F, et al. Human papillomavirus genotype distribution in anal cancer in France: The EDiTH V study. *Int J Cancer.* Sep 13 2010.
9. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: Updating the natural history of HPV and anogenital cancer. *Vaccine.* Aug 31 2006;24 Suppl 3:S3/42-51.
10. Chin-Hong PV, Palefsky JM. Human papillomavirus anogenital disease in HIV-infected individuals. *Dermatol Ther.* Jan-Feb 2005;18(1):67-76.
11. Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. *ANZ J Surg.* Aug 2006;76(8):715-717.
12. Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. *Br J Surg.* Sep 2005;92(9):1133-1136.
13. Kreuter A, Potthoff A, Brockmeyer NH, et al. Anal carcinoma in human immunodeficiency virus-positive men: results of a prospective study from Germany. *Br J Dermatol.* Feb 22 2010.
14. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med.* Oct 2012;136(10):1266-1297.
15. New York State AIDS Malignancy Consortium. *Criteria for the medical care of adults with HIV infection*. March 2004.
16. Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical

cytology screening. *Vaccine.* Aug 31 2006;24 Suppl 3:S3/63-70.

17. Siekas LL, Aboulafia DM. Establishing an anal dysplasia clinic for HIV-infected men: initial experience. *AIDS Read.* May 2009;19(5):178-186.
18. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* Apr 10 2009;58(RR-4):1-207; quiz CE201-204.
19. Shalev N, Olender SA, Chiasson MA. Targeted anal cancer screening in HIV-infected patients: prevalence of screening indicators. *AIDS.* Jul 31 2009;23(12):1613-1615.
20. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA.* May 19 1999;281(19):1822-1829.
21. Lam JM, Hoch JS, Tinmouth J, Sano M, Raboud J, Salit IE. Cost-effectiveness of screening for anal pre-cancers in HIV-positive men. *AIDS.* Dec 6 2010.
22. Nathan M, Singh N, Garrett N, Hickey N, Prevost T, Sheaff M. Performance of anal cytology in a clinical setting when measured against histology and high-resolution anoscopy findings. *AIDS.* Jan 28 2010;24(3):373-379.
23. Berry JM, Palefsky JM, Jay N, Cheng SC, Darragh TM, Chin-Hong PV. Performance characteristics of anal cytology and human papillomavirus testing in patients with high-resolution anoscopy-guided biopsy of high-grade anal intraepithelial neoplasia. *Dis Colon Rectum.* Feb 2009;52(2):239-247.
24. Chiao EY, Giordano TP, Palefsky JM, Tyring S, El Serag H. Screening HIV-infected individuals for anal cancer precursor lesions: a systematic review. *Clin Infect Dis.* Jul 15 2006;43(2):223-233.
25. Cuzick J, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet. 2003 Dec 6;362(9399):1871-6. PMID: 1466774.
26. Elmore JG, et al. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med. 1998 Apr 16;338(16):1089-96. PMID: 9545356.
27. Tandon R, Baranoski AS, Huang F, et al. Abnormal anal cytology in HIV-infected women. *Am J Obstet Gynecol.* Jul 2010;203(1):21 e21-26.
28. Hessol NA, Holly EA, Efird JT, et al. Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women. *AIDS.* Jan 2 2009;23(1):59-70.
29. Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *J Natl Cancer Inst.* Jun 6 2001;93(11):843-849.
30. Kojic EM, Cu-Uvin S, Conley L, et al. Human Papillomavirus Infection and Cytologic Abnormalities of the Anus and Cervix Among HIV-Infected Women in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (The SUN Study). *Sex Transm Dis.* Oct 14 2010.

31. Durante AJ, Williams AB, Da Costa M, Darragh TM, Khoshnood K, Palefsky JM. Incidence of anal cytological abnormalities in a cohort of human immunodeficiency virus-infected women. *Cancer Epidemiol Biomarkers Prev.* Jul 2003;12(7):638-642.

32. Salit IE, Lytwyn A, Raboud J, et al. The role of cytology (Pap tests) and human papillomavirus testing in anal cancer screening. *AIDS.* Jun 1 2010;24(9):1307-1313.

33. Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine.* Aug 31 2006;24 Suppl 3:S3/78-89.

34. Szarewski A, Ambroisine L, Cadman L, et al. Comparison of predictors for high-grade cervical intraepithelial neoplasia in women with abnormal smears. *Cancer Epidemiol Biomarkers Prev.* Nov 2008;17(11):3033-3042.

35. Device labeling for the Digene Hybrid Capture® 2 High-Risk HPV DNA Test®Hybrid Capture 2 (HC2). Qiagen, Inc. (2007). Available at: http://www.qiagen.com/resources/Download.aspx?id={0A98CB57-25B9-48A9-9C4F-4C66D1CDA47C}&lang=en&ver=1.

36. Device labeling for the Aptima HPV Assay. Gen-Probe Hologic, Inc. (2012). Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100042c.pdf.

37. Zhao FH, Jeronimo J, Qiao YL, Schweizer J, Chen W, Valdez M, Lu P, Zhang X, Kang LN, Bansil P, Paul P, Mahoney C, Berard-Bergery M, Bai P, Li J, Chen F, Stoler MH, Castle PE. An Evaluation of Novel, Lower-Cost Molecular Screening Tests for Human Papillomavirus in Rural China. Cancer Prev. Res. 2013 Sep;6(9):938-948.

38. Yang YS, Smith-McCune K, Darragh TM, Lai Y, Lin JH, Chang TC, Guo HY, Kesler T, Carter A, Castle PE, Cheng S. Direct human papillomavirus E6 whole-cell enzyme-linked immunosorbent assay for objective measurement of E6 oncoproteins in cytology samples. Clin Vaccine Immunol. 2012 Sep;19(9):1474-9.

39. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *Am J Med.* Jun 1 2000;108(8):634-641.

40. Czoski-Murray C, Karnon J, Jones R, Smith K, Kinghorn G. Cost-effectiveness of screening high-risk HIV-positive men who have sex with men (MSM) and HIV-positive women for anal cancer. *Health Technol Assess.* Nov 2010;14(53):iii-iv, ix-x, 1-101.

41. Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. *Med Care.* Mar 2007;45(3):259-263.

42. Kroenke K, Spitzer RL, Williams JB, Lowe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics.* Nov-Dec 2009;50(6):613-621.

43. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain.* Aug 2001;93(2):173-183.

44. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral

medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care.* Jun 2000;12(3):255-266.

45. Vajdic CM, Anderson JS, Hillman RJ, Medley G, Grulich AE. Blind sampling is superior to anoscope guided sampling for screening for anal intraepithelial neoplasia. *Sex Transm Infect.* Oct 2005;81(5):415-418.

46. Cantor SB, Levy LB, Cardenas-Turanzas M, et al. Collecting direct non-health care and time cost data: application to screening and diagnosis of cervical cancer. *Med Decis Making.* May-Jun 2006;26(3):265-272.

47. ArborVita, Inc. representative. Telephone communication. Feb-Mar 2014.

APPENDIX I: SCHEDULE OF EVENTS

Evaluation	Screening	Enrollment¥ (Visit 1) (Baseline)	Post-Procedure Call (2-5 weeks after V 1, 3, 5)	Visit 2* Month 6	Visit 3* Month 12	Visit 4* Month 18	Visit 5* Month 24
Informed consent	X						
Documentation of HIV	X						
Medical history, medication history, ANC, platelets	X[1]						
Medical record review, HIV viral load, CD4 count[2]		X					X
Pregnancy test (urine)	X	X[3]			X		X
Baseline questionnaire		X					
Post procedure questionnaire via phone call			X				
Follow-up questionnaire				X	X	X	X
Targeted physical and anogenital exam		X		X	X	X	X
Anal cytology[4]		X		X	X	X	X
Anal swab for HPV (1 in ThinPrep)		X		X	X	X	X
Anal swab in lysis tube for Arbor Vita		X		X	X	X	X
Cervical cytology[5]		X			X		X
Cervical swab for HPV (1 in ThinPrep)		X			X		X
HRA with biopsy of lesions[6]		X			X		X
Anal cytology slides[7]		X		X	X	X	X
Anal biopsy slides[7]		X			X		X
ACSR blood specimen (participant consent)		X					

* Visits 2-5 (and associated specimens) may occur within 14 days prior to the target visit date and up to 160 days after the target visit date.
¥ All Study Evaluations for Enrollment visit must be completed within 50 days before the enrollment visit.

1. Only collect ANC and platelets if results are not available from routine clinical care within 120 days before enrollment.
2. Only collect HIV viral load and CD4 counts/percentages if results are not available from routine clinical care within 120 days before Visit 1 and Visit 5.
3. Pregnancy test will not be required at Visit 1 if the pregnancy test for Screening/eligibility review was performed less than 72 hours prior to study entry.
4. Local anal cytology specimens may be collected in liquid medium as per standard of care of study site (either ThinPrep or Surepath).
5. For the enrollment visit local cervical cytology specimens may be collected up to 42 days before the enrollment visit date.
6. Perform HRA-directed biopsies up to 6 of the most abnormal appearing areas. Each study participant will have at least two biopsies at HRAs (visits 1, 3, 5). If fewer than two directed biopsies are taken from two different quadrants, then random biopsy/biopsies will be done such that there will be at least two biopsies from at least two different quadrants. These biopsies can be from the anal canal or perianus.
7. All baseline anal cytology slides for the first 6 months after a site is activated will be submitted for an evaluation of quality control. All anal histology slides taken during Visits 1-5 will be submitted to the AMC Biorepository for central pathology review. Slides will be submitted as per Appendix VI for details.

APPENDIX II: 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 III: ANAL SAMPLING PROCEDURES

All anal cytology specimens will be examined at the local institution.

The participant should undress from the waist down, and either bend over the exam table or lay on their side in the fetal position. The examiner should use one hand to spread the buttocks and expose the anal verge.

Procedure for obtaining an anal swab specimen

A Dacron swab moistened in tap water will then be inserted as far as is comfortable into the anus, a minimum of 1-2 inches. If there is difficulty inserting the swab, the participant should also retract their buttocks and the swab reoriented in the canal. With pressure on the distal end of the swab rotate it firmly in a circular fashion for approximately 20 seconds and slowly remove from the canal. Do not retract the buttocks when the swab is close to the verge to ensure that it is sampled as well. Immediately immerse the swab in a liquid-cytology vial agitating vigorously over 20 to 30 seconds to disperse the cells.

The order of anal specimen collection will be determined at the time of registration and will remain constant for a given participant for every study visit.

The three anal swab specimens will be collected from each study participant in the order as designated at the time of enrollment. **The sequence of collection for these three swabs will be randomly assigned by the data entry system, AdvantageEDC, at the time of enrollment**. The site should print the collection order for the specimens in the enrollment confirmation email message and save it to the study file for future reference.

Anal swab specimens for a given study participant will always be collected in the same sequence at every visit. For example, participant 1 may be assigned to have specimens collected in the order "local," "thinprep", and "lysis" at all visits, whereas participant 2 may be designated the order "thinprep," "lysis," and "local" at all visits, etc. The three swabs collected are:

- Dacron Swab "local" [Identified as "Dacron Swab (local cytology)" in the swab sequence assignment at enrollment]. This swab will be placed in the cytology medium required for local processing for anal cytology.
- Dacron Swab "thinprep" [Identified as "Dacron Swab (ThinPrep HPV)"]. This swab will be placed in a 20 mL ThinPrep (PreservCyt) media vial (for research anal HPV analyses) and stored in a refrigerator (2-8° C) as soon as possible after collection.
- Puritan Medical Products Dacron Swab "lysis" [Identified as "Swab for Arbor Vita ("lysis" tube)"]. This swab will be placed in a tube provided by Arbor Vita (a.k.a., "lysis" tube) immediately after collection. The swab stem will be broken to deposit the entire swab head so that the cap will fit on the tube. Instructions on isolating the swab head in the lysis tube can be found on the AMC AIDS Malignancy Consortium website at www.amcoperations.com. Anal swabs placed in the Arbor Vita-supplied tubes should be frozen immediately at -80° C. The sites may batch ship these specimens EVERY 3 months.

Note: While the anal specimen collected for Arbor Vita will be stored "dry," the swab may be pre-moistened with tap water before the sampling procedure for patient comfort.

Sites are strongly encouraged to implement local processes to ensure that the assigned anal

cytology swab specimen collection sequence is maintained during the study. Sites should label swab collection tubes with the assigned collection sequence using a marker before sampling. The actual collection sequence must be documented in the source for each anal sampling procedure. A sample source document for this purpose is provided on the AMC AIDS Malignancy Consortium website at www.amcoperations.com.**Sites will be required to report the actual sequence of swab collection in the data entry system.**

The Puritan swab will be provided by the AMC, and the "lysis" tube for the Arbor Vita swab will be provided by Arbor Vita. The ODMC will place all orders for the Puritan swabs and collection tubes for the dry swab specimen on the site's behalf. All requests for supplies may be placed with the AMC ODMC via email (amcpm@emmes.com) or fax (240-238-2842). This request may be made using the attached AMC-084 Cytology Supplies Request Form. The Cytology Supplies Request Form can be found on the AMC AIDS Malignancy Consortium website at www.amcoperations.com.

Arbor Vita: Use the Puritan™ Polyester-Tipped Applicator to obtain the anal specimen and then place the swab in a 1.5ml eppendorf tube (lysis tube) and store the lysis tubes at -80ºC. Site will then batch ship the lysis tubes on dry ice to the AMC Biorepository every 3 months. See the AMC-084 MOP for shipping instructions.

APPENDIX IV: HIGH RESOLUTION ANOSCOPY (HRA) AND ANAL BIOPSIES

Procedure for performing HRA

High resolution anoscopy should only be done **after** the specimens for anal cytology and HPV testing are collected. The patient will already be positioned for anal evaluation. A mixture of a topical anesthetic (e.g., 2% lidocaine jelly or EMLA ointment) and water-soluble lubricating jelly should be used as a lubricant. A digital anal/rectal exam should be performed noting any masses or areas of induration. The procedure for HRA is as follows:

1) Insert the plastic disposable anoscope, remove obturator, and place a cotton swab wrapped in gauze soaked in 3-5% acetic acid into anus.
2) Remove the anoscope over the swab and leave in place for 1 to 2 minutes.
3) Remove the swab and re-insert the anoscope. Carefully examine the anal canal with a colposcope.
4) Re-apply acetic acid as necessary to ensure adequate detection of lesions.
5) If acetowhitening is noted, note vascular characteristics, if present.
6) Lugol's solution (iodine) may be used to aid identification of possible AIN near the squamocolumnar junction.
7) Biopsy up to six of the most abnormal appearing areas (directed biopsies) clinically suspicious for AIN. Local anesthetic (e.g., 1% lidocaine with or without epinephrine or .5% bupivicaine) may be used at the provider's discretion prior to biopsy.
8) Each study participant will have *at least* two biopsies. If fewer than two directed biopsies are taken from two different quadrants, then random biopsy/biopsies will be done such that there will be *at least* two biopsies from *at least* two different quadrants.
9) Attain hemostasis prior to removal of the anoscope (with pressure, Monsel's solution, or silver nitrate).
10) An external genital exam should be performed to note the presence of condyloma and other abnormalities.
11) Apply acetic acid to perianal area and examine carefully with colposcope.
12) Biopsy any external (perianal) areas clinically suspicious for AIN, using a local anesthetic (e.g., 1% lidocaine with or without epinephrine or .5% bupivicaine) prior to biopsy.
13) Participants with signs or symptoms consistent proctitis or sexually transmitted infections other than HPV should be referred for appropriate diagnosis and treatment.

APPENDIX V: CERVICAL/VAGINAL SAMPLING PROCEDURES

Procedure for obtaining cervical/vaginal cytology samples

The participant should undress from the waist down, and lay on her back on the exam table. The examiner should follow standard pelvic exam procedures. Collection for two cervical* specimens will be collected. The cervical cytology specimen (using the "broom", cytobrush, and/or spatula) will be collected first, and will be placed in the standard liquid-based cytology media at each local institution (e.g., ThinPrep or SurePath). The second specimen will be collected by "broom," cytobrush, and/or spatula and dispersed in a 20 ml vial of ThinPrep (PreservCyte) to be used for all three HPV analyses.

See Appendix VI for local processing of the first sample for cytology.

See Appendix VII for processing and shipping of the second sample collected for HPV analyses.

***If the participant has had a hysterectomy, then the specimens should be collected from the vaginal apex instead of the cervix.**

APPENDIX VI: PROCEDURES FOR PROCESSING LOCAL CYTOLOGY/ HISTOLOGY SPECIMENS AND CENTRAL PATHOLOGY REVIEW

Local cytology/pathology specimen processing

1) *Local cytology reading*: Run the liquid cytology sample (ThinPrep or Surepath) as is, per protocol at the local institution. The reading from the cytopathology lab will be submitted in the appropriate eCRF in AdvantageEDC. The study investigators will have access to the cytopathology reading via the AMC Operations web site (secure access).
2) *Residual specimens:* If the participant consented to donate residual study specimens to the ACSR for future testing, the residual liquid cytology medium after performing the local anal and cervical cytology readings will be sent to AMC Biorepository within 4 weeks of specimen collection (see Appendix XI for labeling and shipping requirements).
3) *Histology:* Process as per protocol at the local institution. The reading from the pathology lab will be submitted in the appropriate eCRF in AdvantageEDC. The study investigators will have access to the cytopathology reading via the AMC Operations web site (secure access).

Suggested p16 immunohistochemical (IHC) staining for local pathologists

1) To differentiate between the H&E morphologic diagnosis of precancer (–IN 2 or –IN 3) and a mimic of precancer (e.g., processes known to be unrelated to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting). Strong and diffuse block-positive p16 results support a categorization of precancerous disease.
2) To clarify a diagnosis of –IN2 in an H&E morphologic interpretation of –IN 2 (under the old terminology), which is a biologically equivocal lesion falling between the morphologic changes of HPV infection (low-grade lesion) and precancer. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or non–block-positive staining strongly favors an interpretation of low-grade disease or a non–HPV-associated pathology

Central pathology review

- Please review the MOP for central pathology slide shipping instructions and central pathology review.

  For quality control, each site will submit all baseline histology study slides used for screening evaluation, including any stained slides, collected from the first six months after enrollment of the first study participant at a given study site. These slides should be batch shipped to the AMC Biorepository as soon as possible up to 9 months after enrollment of the first study participant at each study site. All anal histology slides taken during Visits 1-5 will also be submitted to the AMC Biorepository for central pathology review. The AMC Biorepository will distribute all slides except those originating from UCSF to Dr. Teresa Darragh at UCSF for review, and will ship all slides originating from UCSF to Baylor College of Medicine for review. Central review from the participating pathologists will be returned to study sites within 6-8 weeks of receipt.

APPENDIX VII: THINPREP HPV TESTING SPECIMEN PREPARATION AND SHIPMENT TO THE AMC BIOREPOSITORY

All anal and cervical specimens that are collected in ThinPrep for HPV testing on this protocol must be submitted to the AMC Biorepository within 4 weeks of collection. Prior to shipment, store all anal and cervical ThinPrep specimens for HPV testing at 2-8°C. Once received, the AMC Biorepository will aliquot and ship specimens for analysis at each of the three companies performing HPV testing for this protocol. Aliquot preparation requirements and the shipment schedule for distributing samples to each of the three companies are outlined in the AMC-084 Biorepository Manual of Procedures.

The "dry" Dacron swab in the lysis tube must be submitted to the AMC Biorepository within 3 months of collection. Prior to shipment, these anal swabs need to be stored at -80^{o} C. The AMC Biorepository will then ship the specimens to Arbor Vita.

Cervical Specimens for HPV Analysis

The protocol requires collection of cervical specimens for HPV analysis for each participant at 3 study visits: Baseline (0), 12, and 24 months. The ThinPrep media vial for cervical HPV analysis should be placed in refrigeration (2-8° C) as soon as possible after collection.

NOTE: Anal and Cervical ThinPrep Specimens MUST BE SHIPPED on ice packs. The anal swab in the lysis tube must be shipped on DRY ICE. Specimens should be shipped on **MONDAYS** (OR TUESDAY IF MONDAY IS A HOLIDAY) using PRIORITY OVERNIGHT service.

Ship the Specimens to:

Dr. Sylvia Silver
GW Biorepository
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

ThinPrep Sample Labeling

Samples must be labeled with the bar-coded labels provided. Each sample should be labeled with the following information:

Participant ID: "084-XXX-XXX"

Specimen Type: "Cytology Medium"

Specimen Purpose: "Cervical HPV" or "Anal HPV"

Date of Sample Collection: MM/DD/YYYY

Shipping Instructions

To ship anal and cervical ThinPrep specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally

approved diagnostic shipper, please follow instructions provided for that specific shipper. Use FedEx account #: 352207845.

Record of Specimens

This study will track specimens via GlobalTrace[SM], a component of the AMC AdvantageEDC[SM] system. The GlobalTrace shipment manifest must accompany all specimens.

APPENDIX VIII: AMC DATA AND SAFETY MONITORING PLAN

(Version 6.0 • March 17, 2017)

Monitoring the Progress of Trials and the Safety of Participants

All AMC protocols that collect safety data follow the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (http://ctep.cancer.gov/guidelines/index.html). All adverse events that meet the NCI's expedited reporting requirements are reported to the Investigational Drug Branch (IDB) of the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC site reports serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via CTEP-AERS; expedited reporting via AdvantageEDC/Advantage eClinical may be permitted for select commercial agent studies per protocol requirements. In some instances, the AMC sites may report serious adverse events directly to a commercial sponsor holding the IND, who will then report the event to the AMC ODMC. Most AMC protocols require sites to report all serious adverse events via CTEP-AERS and the AMC ODMC to forward a copy of the report to the sponsor. The AMC ODMC also distributes all IND safety reports to all investigators upon receipt, and makes these reports available on the password-protected section of the AMC Operations web site. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides listings of all reported adverse events and serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site where these reports are updated nightly. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment. The AMC Medical Monitor will review listings of all reported adverse events on a quarterly basis for safety concerns.

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 disease-oriented Working Group during scheduled conference calls. 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 Group Statistician determine whether these criteria have been met. 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

Group Statistician determine whether these criteria have been met.

For phase III trials and other select studies requiring additional oversight, the AMC has formed an independent Data and Safety Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a patient advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the protocol statistician, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The DSMB reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all phase III trials 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 concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the 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 is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group 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 NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group 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 formal amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, a summary of the serious adverse events reported to the DSMB is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to

the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site audits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDC/Advantage eClinical (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, AMC Medical Monitor, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. 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 adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

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 termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. 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) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) 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 AdvantageEDC/Advantage eClinical. 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. AMC ODMC staff routinely interacts with site staff to resolve any data 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 of taking action against 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 IX: MANAGEMENT OF ABNORMAL CYTOLOGY AND HISTOLOGY

Cervical Cytology

Women with an ASC-US cytology test of the cervix will undergo reflex HPV testing as is standard of care. Referral to colposcopy will be made if the HPV test is "positive."

Referral for colposcopic evaluation is recommended for cervical cytology of LSIL, HSIL, ASC-H and atypical glandular cells.

Anal Cytology

Anal cytology of ASC-H/HSIL+ should be further evaluated by HRA within three to six months of the cytology results. If a concurrent HRA (at visits 1, 3, and 5) does not identify anal HSIL, the HRA (and anal cytology) should be repeated within three to six months.

Management of anal HSIL

Management/treatment options for anal HSIL are up to the discretion of the Principal Investigator at each site.

APPENDIX X: ACSR SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

A. GENERAL

All specimens for ACSR donation will be shipped according to these instructions. To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED **Monday** through **Wednesday** as an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON FRIDAYS, SATURDAYS, OR SUNDAYS** in the GWU/ACSR Lab.

B. SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

BLOOD SPECIMENS

Draw two 8.5 cc (ml) yellow top (acid citrate dextrose [ACD] solution A) tubes of blood from study participant. With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol # 084
- AMC Participant ID#
- Date and time of collection
- Specimen type, i.e., WB=Whole Blood, P=Plasma, S=Serum, or Tissue
- Specimen purpose: Donation

Specimen Shipment

1) Seal the tops of the 8.5 cc yellow top tubes with parafilm.
2) Place the two sealed tubes into bubble wrap (provided in STP-210 kit).
3) Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
4) Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal."
5) Place poly-bag containing tubes into the white TYVEK bag and seal.
6) Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
7) Affix the FED-EX airbill on blank side of the shipper making sure that it is marked "FED-EX PRIORITY OVERNIGHT."
8) Mark "OTHER" in the airbill under "Packaging." Please use FedEx #: **352207845**.
9) Under airbill section "Special Handling," indicate "YES-SHIPPERS DECLARATION NOT REQUIRED."
10) Place "From/To" information onto areas provided on the shipper.

Blood specimens should be shipped by overnight express at room temperature to:

Dr. Sylvia Silver
GW Biorepository

George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

11) Make certain that shipper is already either pre-labeled with the "UN#3373" stamp, or make a paper label with "UN#3373" and affix it to the shipper.
12) Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in ml and affix to the shipper.
13) Affix airbill to shipper so that the 'UN' and 'VOLUME' labels are visible.
14) RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
15) Place the box in the FedEx pickup area at your site or call to request a package pickup.

Please Note: The shippers will be mailed back to each AMC site.

INSTRUCTIONS FOR BLOOD SPECIMENS COLLECTED ON THURSDAY OR FRIDAY:

Preparation of Plasma and Mononuclear Cells

Refer to the ACSR's SOP on Separation of Plasma and Mononuclear Cells on the AMC Operations web site for instructions on preparing plasma and PBMC aliquots. It is preferable that separation occurs as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours.

Freeze the cell suspension in 0.5 ml aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container, and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

*****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.**

C. RECORD OF SPECIMENS

This study will track specimens via GlobalTrace^{SM}, a component of the AMC AdvantageEDC^{SM} system. The GlobalTrace^{SM} shipment manifest must accompany all specimen shipments.

APPENDIX XI: RESIDUAL CYTOLOGY SPECIMEN HANDLING AND SHIPPING

GENERAL

If the participant consents to the donation of excess AMC-084 study specimens to the AMC Biorepository (described in the model Informed Consent form), residual cytology media from local anal and cervical cytology readings will be submitted to the AMC Biorepository. Prior to shipment, store all residual specimens from local anal and cervical liquid cytology readings at 2-8°C. **Specimens must be shipped to the AMC Biorepository within 4 weeks of collection.**

NOTE: Specimens MUST BE SHIPPED **Monday** through **Wednesday** on ice packs using PRIORITY OVERNIGHT service. Specimens are **NOT ACCEPTED ON FRIDAYS, SATURDAYS, OR SUNDAYS** at the AMC Biorepository at GWU.

Ship the Specimens to:

Dr. Sylvia Silver
GW Biorepository
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

Liquid Cytology Residual Sample Labeling

Samples must be labeled with the bar-coded labels provided. Each sample should be labeled with the following information:

Participant ID: "084-XXX-XXX"

Specimen Type: "Anal Cytology Medium" or "Cervical Cytology Medium"

Specimen Medium: "Surepath" "ThinPrep"

Specimen Purpose: "ACSR donation"

Date of Sample Collection: MM/DD/YYYY

Shipping Instructions

To ship anal and cervical residual specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper. Use FedEx account #: 352207845.

RECORD OF SPECIMENS

This study will track specimens via GlobalTrace^{SM}, a component of the AMC AdvantageEDC^{SM} system. The GlobalTrace^{SM} shipment manifest must accompany all specimen shipments.

APPENDIX XII: INFORMED CONSENT FOR OPTIONAL ACSR DONATION

Study Title for Study Participants:	Collecting Blood and Tissue Sample Donations for Research for HIV/AIDS-Related Cancers
Official Study Title:	Biospecimen Collection and Donation to the AIDS and Cancer Specimen Resource (ACSR)

What is the usual approach to donate blood and/or tissue to the ACSR?

You are being asked to donate blood and/or tissue for research. You are being asked to take part in this study because you have HIV infection and have been offered participation in an AMC clinical trial. The AMC works with the ACSR to collect donated samples from persons with HIV infection for research studies. People who do not take part in an AMC clinical trial can also donate samples to the ACSR.

What are my other choices if I do not take part in this study?

It is your choice to donate or not donate your blood and/or tissue samples. You may still take part in the AMC clinical study if you choose not to donate blood or biopsy samples. You may also choose to donate:

- Blood but not tissue, or
- Tissue but not blood.

What is the AIDS and Cancer Specimen Resource (ACSR)?

The National Cancer Institute (NCI) has set up the ACSR. The ACSR is a biorepository (bank) that collects human biological specimens (biospecimens) from persons who have HIV, HIV-related conditions, or AIDS-related cancers. The ACSR stores the samples and some of the donor's medical information for use in future research studies.

The ACSR has an independent research panel that approves researchers' study plans to use the ACSR's stored samples. The ACSR only gives samples and medical information to researchers after approving their projects. Researchers may use the biospecimens to study cancers and other diseases associated with HIV disease. This information may help us learn more about the causes of treat HIV-related diseases and cancers and to develop better ways to screen, diagnose, and treat them.

Why is this study being done?

The purpose of this study is to collect biospecimens for the ACSR. Researchers may study samples from the ACSR in combination with hundreds or thousands of other samples to explore how genetic factors may be related to HIV-related diseases and cancer. The information might help doctors in the future to identify who will or will not benefit from treatment. The samples may be used to learn more about how HIV-related diseases and cancers develop. The samples may also lead to new tests or discoveries. Finally, scientists may use the samples to study the genetic material from your cancer tissue and compare it to the material from your normal tissue (blood) to try to find the differences that exist. These studies could make it possible to identify many of the changes that are associated with diseases such as cancers. It may also help us tailor treatments to a patient's unique genetic make-up and/or to the genetic markers of the tumors.

What extra tests and procedures will I have if I take part in this study?

1) If you agree to donate blood, the medical team will draw about 2 tablespoons of blood to give to the ACSR. This takes about 10 minutes.
2) If you agree to donate tissue, your leftover tissue biopsy material will be donated to and stored by the ACSR. If it turns out that your study doctor needs more of your tissue for additional studies, the ACSR will return all of your tissue back to your study doctor.
3) Some of your clinical information will be released to the ACSR and entered into their database. The information given to the ACSR will not include your name or any information that could personally identify you.

No extra biopsies will be collected for the ACSR. We will only give tissue that is left over after making decisions about your treatment or diagnosis to the ACSR. The study doctor will not take any extra biopsies just for the ACSR.

We cannot tell you right now what future research these samples would be used for. Instead, we are asking that you give approval to give your samples for future testing without contacting you again. The results of whatever research is done on your samples will *not* be told to you or your doctor. The results of the tests will *not* be placed in your study records.

How long will ACSR keep my samples?

Your blood and/or tissue sample will be stored until it is used for research. The samples may be stored indefinitely.

What possible risks can I expect from taking part in this study?

- Blood Draw: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and, rarely, infection.
- Biopsy: The risks of biopsy include possible need for stitches depending on the size of the biopsy. There may be swelling, slight pain and a small amount of blood loss. There is also a chance of infection at the site of the biopsy.
- Confidentiality: While the ACSR and researchers who study ACSR samples will have no information that could identify you, there is a risk that someone could use information from genetic studies to trace your samples back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

Let your study doctor know of any questions you have about these possible risks. You can ask the study doctor questions about side effects at any time.

What possible benefits can I expect from taking part in this study?

This study is unlikely to help you. This study may help us learn things that may help people in the future.

The information may help to identify those who are at increased risk and those who may benefit from targeted treatment and screening. In turn, these studies could help find ways to prevent or improve treatments for HIV-related diseases and AIDS-related cancers.

Can I stop taking part in this study?

Yes, you may withdraw your samples from the ACSR at any time while you are taking part in the main study. We will not keep information that links you to your samples after the main study is over. After the study is over, the AMC and the ACSR will not be able to identify your specific samples. Contact the contact your AMC study coordinator if you choose to stop taking part. The coordinator can ask the ACSR to remove your sample and clinical information from the ACSR. However, if any research has already been done using some of your samples, the data will be kept and analyzed as part of those studies.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

There will be no cost to you for donating your samples to the ACSR. You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The AMC will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to seek payment for injury even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The AIDS Malignancy Consortium (AMC)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Office for Human Research Protections and the National Cancer Institute in the U.S.

To protect your privacy, the AMC does not keep identifying information that links study participants to specific samples. As a result, the AMC and ACSR will not be able to link the results from studies that use your samples back to you. Thus, information, including genetic information, that researchers may obtain in studies that use your biospecimens may not be directly linked to you and will not be placed in your medical record. However, some clinical and basic information obtained confidentially from the AMC will be attached with these data. It is possible that findings may one day help, for example, people of the same race or sex as you. It also is possible that genetic factors might come to be associated with people who have HIV and cancer through these kinds of studies.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at 1-800-4-CANCER (1-800-422-6237).

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Please circle your answer to show whether or not you would like to take part in each option:

1. **I agree to donate my blood to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.**

   YES NO

2. **I agree to donate my blood to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.**

   YES NO

3. **I agree to donate some of my tissue biopsy material that is not required for my treatment or diagnosis to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.**

   YES NO

4. **I agree to donate some of my tissue biopsy material to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related**

diseases and cancer.

YES NO

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the optional study.

_____	_____
Participant's Signature	Date of Signature
_____	_____
Signature of Person(s) conducting the Informed Consent Discussion	Date of Signature

APPENDIX XIII: BASELINE PARTICIPANT QUESTIONNAIRE

Screening HIV-Infected Women for Anal Cancer Precursors–Visit 1

Participant ID: 084 - __ __ __ - __ __ __

Date of administration: __ __ / __ __ / __ __ __ __

Administered by: _____

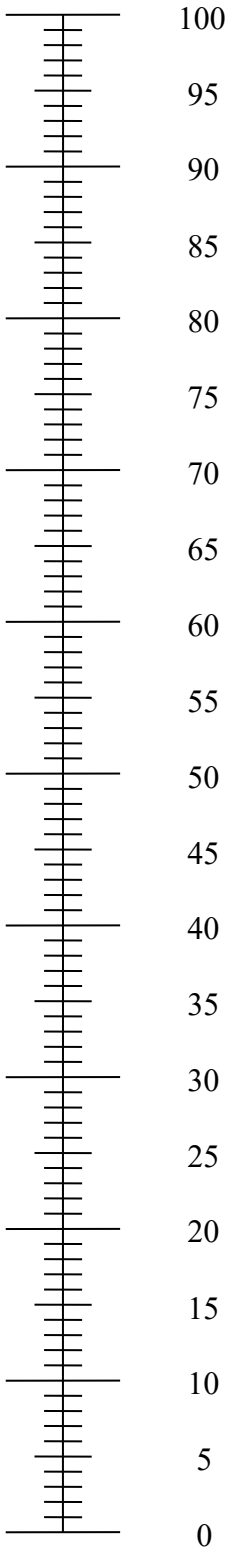
Location of administration (e.g., clinic or telephone): _____

Thank you for agreeing to speak with me today.

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

CURRENT HEALTH STATUS (EQ-5D-5L)

The best health you can imagine



The worst health you can imagine

To begin, I will ask some general health questions.

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now please write the number you marked on the scale in the box below

1. YOUR HEALTH TODAY = ☐

Please tell me which one of these statements best describes your health today (repeat for each section). Under each heading, please tick the ONE box that best describes your health TODAY.

2. MOBILITY:

I have **no problems** in walking about.	1 ☐
I have **slight problems** in walking about.	2 ☐
I have **moderate problems** in walking about.	3 ☐
I have **severe problems** in walking about.	4 ☐
I am **unable** to walk about.	5 ☐

3. SELF-CARE:

I have **no problems** washing or dressing myself.	1 ☐
I have **slight problems** washing or dressing myself.	2 ☐
I have **moderate problems** washing or dressing myself.	3 ☐
I have **severe problems** washing or dressing myself.	4 ☐
I am **unable** to wash or dress myself.	5 ☐

4. USUAL ACTIVITIES (e.g., work, study, housework, family, or leisure activities):

I have **no problems** doing my usual activities.	1 ☐
I have **slight problems** doing my usual activities.	2 ☐
I have **moderate problems** doing my usual activities.	3 ☐
I have **severe problems** doing my usual activities.	4 ☐
I am **unable** to do my usual activities.	5 ☐

5. PAIN/ DISCOMFORT:

I have **no** pain or discomfort.	1 ☐
I have **slight** pain or discomfort.	2 ☐
I have **moderate** pain or discomfort.	3 ☐
I have **severe** pain or discomfort.	4 ☐
I have **extreme** pain or discomfort.	5 ☐

6. ANXIETY/ DEPRESSION:

I am **not** anxious or depressed.	1 ☐
I am **slightly** anxious or depressed.	2 ☐
I am **moderately** anxious or depressed.	3 ☐
I am **severely** anxious or depressed.	4 ☐
I am **extremely** anxious or depressed.	5 ☐

ANXIETY AND DEPRESSION [PHQ-4]

The following answer choices are: “not at all”; “several days”; “more days than not”; “nearly every day”; and “don’t know”.

7. Over the past 2 weeks have you been bothered by these problems?

	Not at all	Several days	More days than not	Nearly every day	Don't know
Feeling nervous, anxious, or on edge	0	1	2	3	98
Not being able to stop or control worrying	0	1	2	3	98
Feeling down, depressed, or hopeless	0	1	2	3	98
Little interest or pleasure in doing things	0	1	2	3	98

PAST PAIN EXPERIENCE

These next questions are about pain.

Using the FACES Pain Rating Scale, please tell me how much pain you have experienced in the past for the following.

8. Toothache

No hurt	Hurts little bit	Hurts little more	Hurts even more	Hurts whole lot	Hurts worst	Not applicable
0	2	4	6	8	10	97

9. Menstrual Period Pain

No hurt	Hurts little bit	Hurts little more	Hurts even more	Hurts whole lot	Hurts worst	Not applicable
0	2	4	6	8	10	97

10. Cervical Pap Smear

No hurt	Hurts little bit	Hurts little more	Hurts even more	Hurts whole lot	Hurts worst	Not applicable
0	2	4	6	8	10	97

SEXUAL BEHAVIORS AND SEXUAL HISTORY

Contact during sex is an important way in which some women get abnormalities on the cervix and anus. We need your help in understanding how women's behavior can affect their health. For this reason, it is very important for you to answer some questions about your personal sexual behavior. Each question will specify the type of sex to which we refer. Please consider any sexual experiences, even sex that was upsetting or involuntary such as rape.

We assure you that your answers will be kept confidential. By providing this information, you will help us a great deal with this study.

Please listen to each question carefully and answer as honestly as possible, even if you only had that type of sexual experience one time. Although some of the behaviors or sexual practices we ask about may be new to you, they are far more common than you may think.

11. Have you ever experienced sexual assault?

Response	Code
Yes	1
No	2
I don't know	98
Decline to answer	99

Sex with Men

The next questions refer only to vaginal sex with men. This is when a man puts his penis, fingers or a sex toy/object in a woman's vagina.

12. Have you ever, any time in your life, had vaginal sex with a man?

No (skip to question 16)	**Yes**	**Decline to answer** (skip to question 16)
0	1	99

13. How many different **men** have you had vaginal sex with **in your entire life?**

None	1	2-5	6-10	More than 10	Unsure	Decline to answer
0	1	2	3	4	98	99

14. How many men have you had vaginal sex with **in the past 6 months**?

None	1	2-5	6-10	More than 10	Unsure	Decline to answer
0	1	2	3	4	98	99

15. How often were condoms used to cover the man's penis, sex toy or object when you had vaginal sex with a man **in the past 6 months**?

Never	Rarely	Sometimes but less than half	About half the time	More than half the time	Every time	Unsure	Decline to answer
0	1	2	3	4	5	98	99

Now I am going to ask you questions about anal sex with a man. This is when a man puts his penis, finger, sex toy or object in your anus.

16. Have you **ever**, any time in your life, had anal sex with a man?

No (skip to question 22)	**Yes**	**Decline to answer** (skip to question 22)
0	1	99

17. When was **the last time** a man put his penis in your anus?

Within the past week	**Within the past month**	**Within the past 6 months**	**Within the past year**	**Over one year ago**	**Unsure**	**Decline to answer**
1	2	3	4	5	98	99

18. How many different **men** have you had anal sex with **in your entire life**?

None	**1**	**2-5**	**6-10**	**More than 10**	**Unsure**	**Decline to answer**
0	1	2	3	4	98	99

19. How many men have you had anal sex with **in the past 6 months**?

None	**1**	**2-5**	**6-10**	**More than 10**	**Unsure**	**Decline to answer**
0	1	2	3	4	98	99

20. How often did you have anal sex with a man **in the past 6 months**?

Never	**Less than 1 time/month**	**1-3 times/ month**	**Once/ week**	**2-6 times/ week**	**Daily**	**Unsure**	**Decline to answer**
0	1	2	3	4	5	98	99

21. How often was a condom used to cover the man's penis, finger, sex toy or object when you had anal sex with a man **in the past 6 months**?

Never	**Rarely**	**Sometimes but less than half**	**About half the time**	**More than half the time**	**Every time**	**Unsure**	**Decline to answer**
0	1	2	3	4	5	98	99

SEXUALLY TRANSMITTED INFECTIONS

The following questions ask about infections and diseases that are sexually transmitted. Once again, I assure you that your answers will be kept confidential.

Please let us know if you have ever been diagnosed with or treated for any of the infections we ask about now.

22. Have you ever had anal warts? These are **warts** inside or around your anus.

No	Yes, in the past 6 months	Yes, but longer than 6 months ago	Unsure/ Don't know	Decline to answer
0	1	2	98	99

23. Have you ever had warts inside your vagina, on the vulva, or in both places?

No	Inside	Outside	Both	Unsure	Decline to answer
0	1	2	3	98	99

24. Have you ever had **herpes** around the vagina or anus? These are painful blistering sores around your private parts.

No	Yes, in the past 6 months	Yes, but more than 6 months ago	Unsure/ Don't know	Decline to answer
0	1	2	98	99

25. Have you ever had **Chlamydia**? This is an infection transmitted during sexual contact.

No	Yes, in the past 6 months	Yes, but more than 6 months ago	Unsure/ Don't know	Decline to answer
0	1	2	98	99

26. Have you ever had **Gonorrhea ("clap")?** This is an infection transmitted during sexual contact.

No	Yes, in the past 6 months	Yes, but more than 6 months ago	Unsure/ Don't know	Decline to answer
0	1	2	98	99

27. Have you ever had **pelvic inflammatory disease (PID) or infection of your fallopian tubes or ovaries**?

No	Yes, in the past 6 months	Yes, but more than 6 months ago	Unsure/ Don't know	Decline to answer
0	1	2	98	99

28. Have you ever had **syphilis**? This is an infection transmitted during sexual contact. (The treatment is weekly painful penicillin shots.)

No	Yes, in the past 6 months	Yes, but more than 6 months ago	Unsure/ Don't know	Decline to answer
0	1	2	98	99

CERVICAL CANCER SCREENING HISTORY

29. Have you ever had an abnormal Pap smear result when screened for cervical cancer?

No (skip to question 32)	Yes	Unsure/ Don't know
0	1	98

30. Did you have colposcopy after the abnormal Pap smear?

No (skip to question 32)	Yes	Unsure/ Don't know
0	1	98

31. If you had colposcopy, did you have any treatment after the colposcopy?

No (skip to question 32)	Yes	Unsure/ Don't know
0	1	98

PRE-PROCEDURE EXPLANATION AND QUESTIONS [Acceptability]

In addition to the previous questions, you have consented to have some procedures done today for this study. These procedures are an anal Pap smear, high resolution anoscopy, and a biopsy of any abnormal tissue or area that is seen.

Please tell me if you have any of the following concerns about having the following examinations or procedures. For each of these statements, please tell me whether you **agree** or **disagree**. Then you will be asked if you slightly or strongly agree/disagree with the statement.

32. ANAL PAP SMEAR

An anal Pap smear will be taken. This is like a cervical Pap smear. A Q-tip type swab will be inserted into the anus by the doctor or nurse practitioner to obtain cells that will be sent to the laboratory to check for abnormalities.

Statement	Strongly disagree	Slightly disagree	Neutral	Slightly agree	Strongly agree	Decline to answer
I am concerned about pain.	1	2	3	4	5	99
I feel the exam will be uncomfortable.	1	2	3	4	5	99
I feel at ease.	1	2	3	4	5	99
I am prepared to have the procedure.	1	2	3	4	5	99

33. HIGH RESOLUTION ANOSCOPY

High resolution anoscopy is done with use of a plastic tube instrument inserted in the anus to look at the tissue under a special light to see if there are warts or other abnormalities in the anal area. Vinegar is used to make any abnormal areas show up better under the light.

Any abnormalities seen will be biopsied, or removed, with a small cutting instrument to send to the laboratory for special analysis.

Statement	Strongly disagree	Slightly disagree	Neutral	Slightly agree	Strongly agree	Decline to answer
I am concerned about pain.	1	2	3	4	5	99
I feel the exam will be uncomfortable.	1	2	3	4	5	99
I feel at ease.	1	2	3	4	5	99
I am prepared to have the procedure.	1	2	3	4	5	99

34. Which of the following examinations or procedures concerns you the **very most** today? (Choose one)

Code	Procedure
0	No Concern
1	Anal Pap smear
2	High resolution anoscopy
3	Possible biopsy
99	Decline to answer

HEALTH BEHAVIOR QUESTIONS

Now I am going to ask you a few questions about yourself.

[from ACTG self report, questions E, H, QL0742(A5257)/ 12-31-08]

35. Are you on HIV medication(s)?

No (skip to question 37)	**Yes**	**Unsure/Don't know** (skip to question 37)
0	1	98

36. Rate your **ability** to take all of your HIV medications as specifically prescribed.

Very poor	**Poor**	**Fair**	**Good**	**Very good**	**Excellent**	**N/A**	**Unsure/ Don't know**	**Decline to answer**
1	2	3	4	5	6	97	98	99

SMOKING QUESTIONS

37. Altogether, have you smoked at least 100 or more cigarettes in your entire lifetime?

INTERVIEWER NOTE: IF NECESSARY: 5 packs = 100 cigarettes

No (skip to question 40)	**Yes**	**Unsure/Don't know** (skip to question 40)	**Decline to answer**
0	1	98	99

Ask <u>former and current smokers</u> the following questions:

38. When you were smoking <u>most heavily</u>, how many cigarettes did you smoke on an average day? (1 pack = 20 cigarettes)

_____ Cigarettes per day

39. For how long did you smoke this heavily? (If time unit is known, indicate the number of years.)

Code	**Years**
98	Unknown

COST/TRANSPORTATION QUESTIONS

40. What is the main source of your financial support, including food, rent, and other expenses? (Check participant's response. If more than one choice given, PROBE: Is one of these the most important source of your income? If participant answers "No," record all responses given)

Response	Code
Own job or salary.	1
Someone else's job or salary (Specify relationship):_____)	2
Public assistance, e.g., AFDC, SSI, food stamps	3
Other (Specify): _____)	8
Unknown	98

41. Which one best describes your hourly wage or annual income?

Hourly Wage	Annual Income
$0.00 - $4.99	$0.00 - $9,999
$5.00 - $7.25	$10,000 - $14,999
$7.26 - $9.99	$15,000 - $19,999
$10.00 - $14.99	$20,000 - $29,999
$15.00 - $19.99	$30,000 - $39,999
$20.00 - $24.99	$40,000 - $49,999
$25.00 - $29.99	$50,000 - $59,999
$30.00 - $34.99	$60,000 - $69,999
$35.00 - $39.99	$70,000 - $79,999
$40.00 - $49.99	$80,000 - $99,999
More than $50.00/hour	More than $100,000/year

42. Did you miss work today for this visit?

No	Yes	Not applicable/Don't Work
0	1	99

43. How did you get to the clinic today?

Response	Code
Drive yourself	1
Get a ride from someone else in a personal vehicle	2
Take public transportation such as the metro bus or metro rail	3
Take a taxi	4
Walk or ride bike, or	5
Get there some other way (SPECIFY) _____	6
Decline to answer	99

44. If you took private/public transportation, what was the fare? $_____

45. How much time (including travelling time) will you miss from your usual activities because of this appointment?

Response	Code
Less than 15 minutes	1
15 to 30 Minutes	2
31 Minutes to 60 Minutes (1 Hour)	3
61 Minutes to 90 Minutes	4
91 Minutes to 120 Minutes (2 Hours)	5
120 Minutes to 180 Minutes (2 to 3 Hours)	6
180 Minutes to 240 Minutes (3 to 4 Hours)	7
240 Minutes to 300 Minutes (4 to 5 Hours)	8
300 Minutes to 360 Minutes (5 to 6 Hours)	9
More than 360 Minutes (More than 6 Hours)	10

46. How far did you travel for this appointment? _____miles

47. If you drove, how much do you expect to pay for the parking? $_____

NA
99

48. If you are accompanied to your appointment by someone who missed work, what is the gender and age of this person?

Accompanied			Not accompanied
Male	**Female**	**Age**	0
1	2		

49. Did you have to get a caretaker today to attend to your children and/or an adult person living in your household in order to come to your appointment?

No (Skip to question number 53)	Yes
0	1

50. How much do you expect to pay the caretaker for today? (If no payment, skip to question 51)

$_____

51. Did the caretaker miss work in order to help you?

No (Skip to question number 52)	Yes
0	1

52. What is the gender and age of the caretaker?

Male	Female	Age
1	2	

DEMOGRAPHIC QUESTIONS

53. What is your marital status?

Response	Code
Married	1
Not married, living with someone	2
Divorced/separated	3
Widowed	4
Single/never married	5
Other: (specify)_____	6
Decline to answer	99

54. What is your country of origin (where were you born)?

Response	Code
United States of America	1
United States territory–Puerto Rico	2

Haiti	3
Cape Verde	4
Uganda	5
Nigeria	6
Cameroon	7
Kenya	8
Mexico	9
Other Latin America (specify)	10
Other Africa (specify)	11
Other: (specify)_____	99

55. If you were born outside the United States, what age were you when you first came to live in the United States?

Enter Age in Years	N/A	Unsure/Don't know	Decline to answer
	97	98	99

56. What is the last grade (highest level) of school that you completed?

Grade	Code
8th grade or less	1
Some high school	2
High school diploma	3
Some college or vocational school	4
Associate degree	5
College (4 year) degree	6
Graduate or professional degree	7
Don't know	98
Decline to answer	99

APPENDIX XIV: POST-PROCEDURE TELEPHONE FOLLOW-UP QUESTIONNAIRE AND SCRIPT

Screening HIV-Infected Women for Anal Cancer Precursors

POST PROCEDURE QUESTIONS

The following questions will be asked **2-5 weeks** after the procedures have been completed via a telephone follow up call, or a visit if preferred by the participant and/or investigator.

Participant ID: 084 - __ __ __ - __ __ __

Date of administration: __ __ / __ __ / __ __ __ __

Administered by: _____

Location of administration (e.g. clinic or telephone): _____

Date of last study procedure visit: __ __ / __ __ / __ __ __ __

Thank you for agreeing to speak with me today.

I will be asking some personal questions. Most of them are the same or similar to the original questions you answered previously. Again, if you feel uncomfortable answering any question or want to stop at any time, just let me know.

POST PROCEDURE QUESTIONS

1. Did you have bleeding following the last HRA procedure? (If No, skip to question 4.)

Response	Code
Yes	1
No	2

2. How many days did you have bleeding? _____ days
3. Did you feel the bleeding was:

Response	Code
Mild	1
Moderate	2
Severe	3

4. Did you have pain following the last HRA procedure? (If No, skip to question 9.)

Response	Code
Yes	1
No	2

5. How many days after the HRA procedure did you have pain? _____ days
6. Did you feel the pain was:

Response	Code
Mild	1
Moderate	2
Severe	3

7. Did you take any medication for the pain? (If no, skip to question 9.)

Response	Code
Yes	1
No	2

8. And if so, what medication(s)

Response	Code
Acetaminophen	1
NSAIDS	2
Narcotics	3

9. Did you miss work because of bleeding or pain? (If no, skip to question 12.)

Response	Code
Yes	1
No	2

10. If yes, was it because of the:

Response	Code
Bleeding	1
Pain	2
Both	3

11. How many days did you miss work due to either bleeding or pain? _____ days

12. Did you have any unscheduled visits to any healthcare provider because of bleeding or pain after the HRA?

Response	Code
Yes	1
No	2

13. How many times have you had high resolution anoscopy (HRA)? (If only one time, skip to question 15.)

Response	Code
1 time	1
2-4 times	2
5-10 times	3
More than 10	4

14. Comparing your experience with the first (or former) procedure to this most recent procedure, would you say that the most recent procedure was:

Response	Code
Better	1
Same	2
Worse	3
I don’t know	98

15. Before your recent HRA procedure, how informed were you about the purpose of HRA in screening for anal cancer?

Response	Code
Well informed	1
Somewhat informed	2
Poorly informed	3
I don't know	98

16. Before your recent HRA procedure, how informed were you about any discomfort that you could experience during the procedure?

Response	Code
Well informed	1
Somewhat informed	2
Poorly informed	3
I don't know	98

17. Before your recent HRA procedure, how informed were you about any discomfort/bleeding you might have after the procedure?

Response	Code
Well informed	1
Somewhat informed	2
Poorly informed	3
I don't know	98

18. Before your recent HRA procedure, how informed were you about self-care at home after the procedure?

Response	Code
Well informed	1
Somewhat informed	2
Poorly informed	3
I don't know	98

19. During your recent HRA procedure did you feel supported and well-cared for by the providers who performed the HRA?

Response	Code
Yes	1
No	2
I don't know	98

20. Some people who have experienced sexual abuse, rape, or other trauma in their lives find the HRA procedure particularly distressing. Have you have had an experience such as these in your lifetime? (IF NO, go to question 22).

Response	Code
Yes	1
No	2
I don't know	98

21. IF YES, did your most recent HRA procedure cause you to remember the trauma?

Response	Code
Yes	1
No	2
Not applicable	97
I don't know	98

22. During your recent HRA procedure did you feel your privacy was respected?

Response	Code
Yes	1
No	2
I don't know	98

23. How likely would you be to follow recommendations to repeat the HRA procedures?

Response	Code
Very unlikely	1
Somewhat unlikely	2
Neutral	3
Somewhat likely	4
Very likely	5
I don't know	98

Please tell me your experience with each of the examinations or procedures. For each of these statements, please tell me whether you **agree** or **disagree**. Then you will be asked if you slightly or strongly agree/disagree with the statement.

24. Anal Pap smear

Statement	Strongly disagree	Slightly disagree	Neutral	Slightly agree	Strongly agree	Decline to answer
I felt pain during the procedure.	1	2	3	4	5	99
I felt uncomfortable during the exam.	1	2	3	4	5	99
I felt at ease.	1	2	3	4	5	99
I was prepared to have the procedure.	1	2	3	4	5	99

25. High resolution anoscopy

Statement	Strongly disagree	Slightly disagree	Neutral	Slightly agree	Strongly agree	Decline to answer
I felt pain during the procedure.	1	2	3	4	5	99
I felt uncomfortable during the exam.	1	2	3	4	5	99
I felt at ease.	1	2	3	4	5	99
I was prepared to have the procedure.	1	2	3	4	5	99

26. Is there anything that will make getting the exam procedures the next time more comfortable for you?

Response	Code
Yes	1
No (Questionnaire complete)	2
I don't know	98

27. Would any of the following make the next HRA procedure more comfortable for you?

Response	Yes	No
More explanation about what to expect from a health care provider.	1	2
Medication to calm my nerves.	1	2
More effective pain medication.	1	2
Medication that will make me sleep during the procedure.	1	2

28. If above answers were all no, but you feel there is something that would make the procedures more comfortable for you, please tell me what that would be:

****AFTER COMPLETING QUESTIONNAIRE, PROVIDE THE PARTICIPANT THE RESULTS FROM HER PAP TESTS AND ANY BIOPSIES TAKEN, AND REVIEW ANY RECOMMENDATIONS FOR FOLLOW-UP.****

APPENDIX XV: FOLLOW-UP PARTICIPANT QUESTIONNAIRE

Screening HIV-Infected Women for Anal Cancer Precursors

FOLLOW-UP QUESTIONNAIRE FOR VISITS 2-5.

Participant ID: 084 - __ __ __ - __ __ __

Date of administration: __ __ / __ __ / __ __ __ __

Administered by: _____

Location of administration (e.g., clinic or telephone): _____

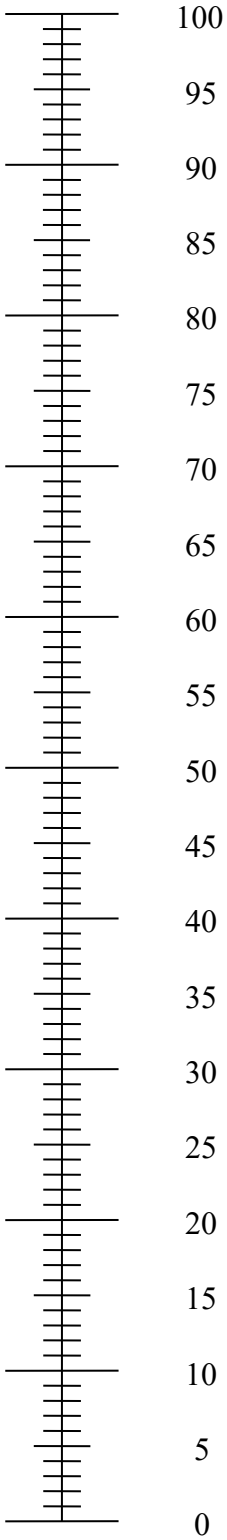
_____

Thank you for agreeing to speak with me today.

I will be asking some personal questions—most of them are the same or similar to the original questions you answered 6 months ago. Again, if you feel uncomfortable answering any question or want to stop at any time, just let me know.

CURRENT HEALTH STATUS (EQ-5D-5L)

The best health you can imagine



The worst health you can imagine

1. To begin, I will ask some general health questions.

   - We would like to know how good or bad your health is TODAY.
   - This scale is numbered from 0 to 100.
   - 100 means the best health you can imagine.
   - 0 means the worst health you can imagine.
   - Mark an X one the scale to indicate how your health is TODAY.
   - Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

Please tell me which one of these statements best describes your health today (repeat for each section). Under each heading, please tock the ONE box that best describes your health TODAY.

2. MOBILITY:

I have **no problems** in walking about.	1 ☐
I have **slight problems** in walking about.	2 ☐
I have **moderate problems** in walking about.	3 ☐
I have **severe problems** in walking about.	4 ☐
I am **unable** to walk about.	5 ☐

3. SELF-CARE:

I have **no problems** washing or dressing myself.	1 ☐
I have **slight problems** washing or dressing myself.	2 ☐
I have **moderate problems** washing or dressing myself.	3 ☐
I have **severe problems** washing or dressing myself.	4 ☐
I am **unable** to wash or dress myself.	5 ☐

4. USUAL ACTIVITIES (e.g., work, study, housework, family, or leisure activities):

I have **no problems** doing my usual activities.	1 ☐
I have **slight problems** doing my usual activities.	2 ☐
I have **moderate problems** doing my usual activities.	3 ☐
I have **severe problems** doing my usual activities.	4 ☐
I am **unable** to do my usual activities.	5 ☐

5. PAIN/ DISCOMFORT:

I have **no** pain or discomfort.	1 ☐
I have **slight** pain or discomfort.	2 ☐
I have **moderate** pain or discomfort.	3 ☐
I have **severe** pain or discomfort.	4 ☐
I have **extreme** pain or discomfort.	5 ☐

6. ANXIETY/ DEPRESSION:

I am **not** anxious or depressed.	1 ☐
I am **slightly** anxious or depressed.	2 ☐
I am **moderately** anxious or depressed.	3 ☐
I am **severely** anxious or depressed.	4 ☐
I am **extremely** anxious or depressed.	5 ☐

ANXIETY AND DEPRESSION [PHQ-4]

The following answer choices are: “not at all”; “several days”; “more days than not”; “nearly every day”; and “don’t know”.

7. Over the past 2 weeks have you been bothered by these problems?

	Not at all	Several days	More days than not	Nearly every day	Don't know
Feeling nervous, anxious, or on edge	0	1	2	3	98
Not being able to stop or control worrying	0	1	2	3	98
Feeling down, depressed, or hopeless	0	1	2	3	98
Little interest or pleasure in doing things	0	1	2	3	98

SEXUAL BEHAVIORS AND SEXUAL HISTORY

Contact during sex is an important way in which some women get abnormalities on the cervix and anus. We need your help in understanding how women's behavior can affect their health. For this reason, it is very important for you to answer some questions about your personal sexual behavior. Each question will specify the type of sex to which we refer. Please consider any sexual experiences, even sex that was upsetting or involuntary such as rape.

We assure you that your answers will be kept confidential. By providing this information, you will help us a great deal with this study.

Please listen to each question carefully and answer as honestly as possible, even if you only had that type of sexual experience one time.

8. Have you experienced sexual assault in the past 6 months?

Response	Code
Yes	1
No	2
I don't know	98
Decline to answer	99

Sex with Men

The next questions refer only to vaginal sex with men. This is when a man puts his penis, fingers or a sex toy/object in a woman's vagina.

9. Have you had vaginal sex with a man in the past 6 months?

No (skip to question 12)	**Yes**	**Decline to answer** (skip to question 12)
0	1	99

10. How many men have you had vaginal sex with **in the past 6 months**?

None	1	2-5	6-10	More than 10	Unsure	Decline to answer
0	1	2	3	4	98	99

11. How often were condoms used to cover the man's penis, sex toy or object when you had vaginal sex with a man in the past 6 months?

Never	Rarely	Sometimes but less than half	About half the time	More than half the time	Every time	Unsure	Decline to answer
0	1	2	3	4	5	98	99

Now I am going to ask you questions about anal sex with a man. This is when a man puts his penis, finger, sex toy or object in your anus.

12. Have you had anal sex with a man in the past 6 months?

No (skip to question 17)	Yes	Decline to answer (skip to question 17)
0	1	99

13. When was the last time a man put his penis in your anus?

Within the past week	Within the past month	Within the past 6 months	Unsure	Decline to answer
1	2	3	98	99

14. How many men have you had anal sex with **in the past 6 months**?

None	1	2-5	6-10	More than 10	Unsure	Decline to answer
0	1	2	3	4	98	99

15. How often did you have anal sex with a man **in the past 6 months**?

Never	Less than 1 time/month	1-3 times/ month	Once/ week	2-6 times/ week	Daily	Unsure	Decline to answer
0	1	2	3	4	5	98	99

16. How often was a condom used to cover the man's penis, finger, sex toy or object when you had anal sex with a man **in the past 6 months**?

Never	Rarely	Sometimes but less than half	About half the time	More than half the time	Every time	Unsure	Decline to answer
0	1	2	3	4	5	98	99

SEXUALLY TRANSMITTED INFECTIONS

The following questions ask about infections and diseases that are sexually transmitted. Once again, I assure you that your answers will be kept confidential.

Please let us know if, in the past 6 months, you have been diagnosed with or treated for any of the infections we ask about now.

17. Have you had anal warts in the past 6 months? These are **warts** inside or around your anus.

No	Yes, in the past 6 months	Unsure/ Don't know	Decline to answer
0	1	98	99

18. Have you had warts inside your vagina, on the vulva, or in both places in the past 6 months?

No	Inside	Outside	Both	Unsure	Decline to answer
0	1	2	3	98	99

19. Have you had **herpes** around the vagina or anus in the past 6 months? These are painful blistering sores around your private parts.

No	Yes, in the past 6 months	Unsure/ Don't know	Decline to answer
0	1	98	99

20. Have you had **Chlamydia in the past 6 months**? This is an infection transmitted during sexual contact.

No	Yes, in the past 6 months	Unsure/ Don't know	Decline to answer
0	1	98	99

21. Have you had **Gonorrhea ("clap") in the past 6 months?** This is an infection transmitted during sexual contact.

No	Yes, in the past 6 months	Unsure/ Don't know	Decline to answer
0	1	98	99

22. Have you had **pelvic inflammatory disease (PID) or infection of your fallopian tubes or ovaries in the past 6 months**?

No	Yes in the past 6 months	Unsure/ Don't know	Decline to answer
0	1	98	99

23. Have you had **syphilis in the past 6 months**? This is an infection transmitted during sexual contact. (The treatment is weekly painful penicillin shots.)

No	Yes in the past 6 months	Unsure/ Don't know	Decline to answer
0	1	98	99

PRE-PROCEDURE EXPLANATION AND QUESTIONS [Acceptability]

In addition to the previous questions, you have consented to have some procedures done today for this study. These procedures are an anal Pap smear, high resolution anoscopy and a biopsy of any abnormal tissue or area that is seen.

Please tell me if you have any of the following concerns about having the following examinations or procedures. For each of these statements, please tell me whether you **agree** or **disagree**. Then you will be asked if you slightly or strongly agree/disagree with the statement.

24. ANAL PAP SMEAR

[OPTIONAL EXPLANATION: An anal Pap smear will be taken. This is like a cervical Pap smear. A Q-tip type swab will be inserted into the anus by the doctor or nurse practitioner to obtain cells that will be sent to the laboratory to check for abnormalities.]

Statement	Strongly disagree	Slightly disagree	Neutral	Slightly agree	Strongly agree	Decline to answer
I am concerned about pain.	1	2	3	4	5	99
I feel the exam will be uncomfortable.	1	2	3	4	5	99
I feel at ease.	1	2	3	4	5	99
I am prepared to have the procedure.	1	2	3	4	5	99

25. ONLY FOR VISITS 3 AND 5

HIGH RESOLUTION ANOSCOPY

[OPTIONAL EXPLANATION: High resolution anoscopy is done with use of a plastic tube instrument inserted in the anus to look at the tissue under a special light to see if there are warts or other abnormalities in the anal area. Vinegar is used to make any abnormal areas show up better under the light.

Any abnormalities seen will be biopsied, or removed, with a small cutting instrument (after more numbing medication is injected) to send to the laboratory for special analysis.]

Statement	Strongly disagree	Slightly disagree	Neutral	Slightly agree	Strongly agree	Decline to answer
I am concerned about pain.	1	2	3	4	5	99
I feel the exam will be uncomfortable.	1	2	3	4	5	99
I feel at ease.	1	2	3	4	5	99
I am prepared to have the procedure.	1	2	3	4	5	99

26. Which of the following examinations or procedures concerns you the **very most** today? (Choose one)

FOR VISITS 3 AND 5

Code	Procedure
0	No concern
1	Anal Pap smear
2	High resolution anoscopy
3	Biopsy
99	Decline to answer

FOR VISITS 2 AND 4

Code	Procedure
0	No concern
1	Anal Pap smear
99	Decline to answer

HEALTH BEHAVIOR QUESTIONS

Now I am going to ask you a few questions about yourself.

[from ACTG self report, questions E, H, QL0742(A5257)/ 12-31-08]

27. Are you on HIV medication(s)?

No (skip to question 29)	**Yes**	**Unsure/ Don't know**
0	1	98

28. Rate your **ability** to take all of your HIV medications as specifically prescribed.

Very poor	**Poor**	**Fair**	**Good**	**Very good**	**Excellent**	**N/A**	**Unsure/ Don't know**	**Decline to answer**
1	2	3	4	5	6	97	98	99

SMOKING QUESTIONS

29. Have you smoked cigarettes in the past 6 months?

No (skip to question 31)	**Yes**
0	1

AMC Smoking

30. On average over the past 6 months, how many cigarettes have you smoked per day? (1 pack equals 20 cigarettes)

_____ (number of cigarettes)

COST/TRANSPORTATION QUESTIONS

31. Which one best describes your hourly wage or annual income?

Hourly Wage	Annual Income
$0.00 - $4.99	$0.00 - $9,999
$5.00 - $7.25	$10,000 - $14,999
$7.26 - $9.99	$15,000 - $19,999
$10.00 - $14.99	$20,000 - $29,999
$15.00 - $19.99	$30,000 - $39,999
$20.00 - $24.99	$40,000 - $49,999
$25.00 - $29.99	$50,000 - $59,999
$30.00 - $34.99	$60,000 - $69,999
$35.00 - $39.99	$70,000 - $79,999
$40.00 - $49.99	$80,000 - $99,999
More than $50.00/hour	More than $100,000/year

32. Did you miss work today for this visit?

No	Yes
0	1

33. How did you get to the clinic today?

Response	Code
Drive yourself	1
Get a ride from someone else in a personal vehicle	2
Take public transportation such as the metro bus or metro rail	3
Take a taxi	4
Walk or ride bike, or	5
Get there some other way (SPECIFY) _____	6
Decline to answer	99

34. If you took private/public transportation, what was the fare? $_____

35. How much time (including travelling time) will you miss from your usual activities because of this appointment?

Response	Code
Less than 15 minutes	1
15 to 30 Minutes	2
31 Minutes to 60 Minutes (1 Hour)	3
61 Minutes to 90 Minutes	4
91 Minutes to 120 Minutes (2 Hours)	5
120 Minutes to 180 Minutes (2 to 3 Hours)	6
180 Minutes to 240 Minutes (3 to 4 Hours)	7
240 Minutes to 300 Minutes (4 to 5 Hours)	8
300 Minutes to 360 Minutes (5 to 6 Hours)	9
More than 360 Minutes (More than 6 Hours)	10

36. How far did you travel for this appointment? _____miles

37. If you drove, how much do you expect to pay for the parking? $_____

NA
99

38. If you are accompanied to your appointment by someone who missed work, what is the gender and age of this person?

Accompanied			Not accompanied
Male	Female	Age	0
1	2		

39. Did you have to get a caretaker today to attend to your children and/or an adult person living in your household in order to come to your appointment?

No (Questionnaire complete)	Yes
0	1

40. How much do you expect to pay the caretaker for today? (If no payment, skip to next question)

$_____

41. Did the caretaker miss work in order to help you?

No	Yes
0	1

42. What is the gender and age of the caretaker?

Male	Female	Age
1	2	