



A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 10845

This file contains the current ACTG A5282 protocol, which includes the following documents:

- Letter of Amendment #3, dated 10 June 2015
- Clarification Memorandum #2, dated 2 January 2014
- Clarification Memorandum #1, dated 5 February 2013
- Letter of Amendment #2, dated 9 August 2012
- Letter of Amendment #1, dated 21 September 2011
- Protocol Version 1.0, dated 16 November 2010

Letter of Amendment #3 for:

A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 10845

Letter of Amendment Date: 10 June 2015

ACTG Network Coordinating Center

Social & Scientific Systems, Inc.
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LETTER OF AMENDMENT

DATE: June 10, 2015

TO: Non-US ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators Participating in the A5282 Study

FROM: A5282 Protocol Team

SUBJECT: Letter of Amendment #3 for Protocol A5282, Version 1.0, 11/16/2010, entitled "A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women"

The following information impacts the A5282 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this Letter of Amendment (LOA).

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit a LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. A LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

The following are changes to A5282, Version 1.0, 11/16/2010 (new language is in bold text and deleted language is in strikethrough):

1. All references to “careHPV” were replaced with “xpert hrHPV” since the former test is not available for the study (item a). Additional information about the xpert hrHPV test was provided (items b and c).
 - a. The schema (design and figure 1) and the following sections now read “xpert hrHPV” wherever “careHPV” used to appear: 1.3.5, 1.3.7, 3.0, 6.1, 6.3.10, 9.2.2.3, 9.2.2.8, 9.6.2.1, 9.6.2.2, and Appendix I/Attachment A.
 - b. The background was revised to delete the 5th section “careHPV, low-cost testing for hr-HPV.” The following section was added in its place and the associated reference is provided:

Background:

Xpert hrHPV Assay

The Cepheid Xpert HPV Assay (Xpert hrHPV) is a new, qualitative, real-time Polymerase Chain Reaction (PCR) assay for the detection of hrHPV DNA. The assay is formatted in a single-use GeneXpert Test cartridge and is run on the Cepheid GeneXpert® System, a multi-analyte, random access, molecular-diagnostic platform ranging in capacity from 1 to 80 test processing modules. Importantly, a single hrHPV DNA test can be completed in one hour, permitting same-day screening, diagnosis, and treatment which reduces the potential for lost to follow-up in lower-resource settings and permits decentralized, clinic-based (versus lab-based) testing. It uses ThinPrep (CytoLyt) media. Xpert gives five separate results: a) HPV16, b) HPV18/45, c) P3-HPV 31/33/35/52/58, d) P4-HPV51/59, and e) P5-HPV39/68/56/66. Xpert was compared to two validated hrHPV tests, cobas4800 (cobas, Roche Molecular Diagnostics) and hc2, and to histologic outcomes using specimens from colposcopic referral populations at 7 clinical sites in the US (n = 697) [26]. Xpert was equally sensitive for HSIL (n = 141) as cobas (90.8% vs. 90.8%) and more sensitive than hc2 (90.8% vs. 81.6%, p = 0.004). Xpert was more specific than cobas (42.6% vs. 39.6%, p = 0.02) and less specific than hc2 (42.6% vs. 47.7%, p < 0.001). hrHPV detection by the Xpert demonstrated excellent clinical performance for identifying women with HSIL that was comparable to currently available clinically-validated tests.

Reference:

26. Qiao YL, Sellers JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 2008;9(10):929-36. Einstein MH, Smith KM, Davis TE, et al. Clinical evaluation of the cartridge-based GeneXpert human papillomavirus assay in women referred for colposcopy. *J. Clin. Microbiol.* Jun 2014;52(6):2089-2095.

c. The 3rd section of the rationale, “PEPFAR objectives,” now reads:

Part of this study is being funded by a supplement from the U.S. NIH to conduct implementation science research of interest to the President’s Emergency Plan for AIDS Relief (PEPFAR). The PEPFAR objectives in section 1.3 will use screening and baseline evaluations from all women who give consent for this study. The availability of the **xpert hrHPV** ~~careHPV~~ test should broaden access to cervical cancer screening through the HPV test-and-treat strategy. It will be critical to understand how this test performs in HIV-infected women. ~~Although this assay has been conformité européenne (CE) marked, it will not be widely available until late 2011.~~ This study will compare **xpert hrHPV** ~~careHPV~~ results to two other HPV tests: HPV DNA PCR and aHPV. Cryotherapy is not recommended for women with extensive cervical lesions. Data from our Zambian investigators suggest that 15-20% of HIV-infected women will have such lesions and that half of these women will have CIN2/3 or invasive/microinvasive cancer on histology [40, 41]. Algorithms for cervical cancer screening must address treatment of these women to maximally impact mortality from cervical cancer.

2. Per the March 2015 interim DSMB review, biopsies are being added to study follow-up visits for all participants, regardless of preceding colposcopy results.

- Section 3.0, fourth paragraph, now reads: Participants in Arms A and B will be seen at regular intervals post entry for aHPV, HPV DNA PCR, cervical cytology, and cervical colposcopy and directed biopsies for a total follow-up length of 130 weeks. **At least two cervical biopsies should be performed at the week 78 and week 130 visits. Visible lesions should be biopsied preferentially. If no visible lesions are seen, then two random biopsies should be obtained.**
- Section 6.3.10, subsection on colposcopy and directed biopsies, now reads:

Post entry:

- Participants in Arms A and B will undergo colposcopy and directed biopsies at the weeks 26, 78, and 130 clinic visits. **At least two cervical biopsies should be performed at the week 78 and week 130 visits. Visible lesions should be biopsied preferentially. If no visible lesions are seen, then two random biopsies should be obtained.**
- Participants in Arm C who undergo LEEP post-entry will undergo colposcopy

and directed biopsies at the week 26 clinic visit.

Digital images and colposcopic impression will be submitted for review, along with location of cervical biopsies.

(The following paragraph supersedes Clarification Memo [CM] #2, dated 01/02/1014.) Directed biopsies will be obtained from areas suspicious for CIN. ~~Biopsies are taken only if lesions are seen upon colposcopy.~~ In the event lesions are not seen upon colposcopy but the cytology specimens show presence of HSIL, then the participant should return to the study clinic for repeat colposcopy and other diagnostics procedures such as endocervical curettage (ECC), random cervical biopsies (**if not already done**), or diagnostic LEEP. Results of these diagnostic tests must be recorded on the appropriate CRF. ~~Slides from biopsies of CIN2+ and biopsies without CIN2+ will be submitted for review.~~ If CIN2+ is detected by biopsy, the participant will undergo LEEP.

- c. Sample Informed Consent, What do I have to do if I am in this Study?, Groups A and B: At the study visit about 6, 18, and 30 months after the entry visit you will also have a colposcopy and biopsies if any abnormal areas are seen. **At months 18 and 30, you will have two biopsies performed whether or not abnormal areas are seen.**

3. Additional clarifications were made to Section 6.3.10.

- a. The subsection, "Diagnoses," now reads:

Diagnoses

(Per CM #1, dated 02/05/1013.) After entry, record any new diagnoses made since the last visit using the ACTG criteria for clinical events and other diseases.

(Per CM #1, dated 02/05/1013.) Except for invasive cancer, cervical cytology and histology results do not need to be recorded as events; these results will be entered on study-specific CRFs only.

(New language) Record all histology results from procedures for the diagnosis or treatment of cervical HSIL (such as cervical conization or hysterectomy) and from biopsies performed related to the presence or absence of squamous intraepithelial lesions on the appropriate CRFs.

- b. The subsection, "LEEP," now reads:

(The following paragraph supersedes item 4b in LoA #2, dated 08/09/1012.)

LEEP

Participants found to have CIN2+ by biopsy at any point during the study will be offered LEEP **or other excisional treatment** (except for participants in Arm A **prior to week 26** who have CIN2+ on pre-cryotherapy biopsy at entry). If the participant had a prior LEEP, treatment of recurrent **or incompletely treated**

CIN2+ is at the discretion of the site investigator. These participants will continue on study.

(No changes to the remainder of this subsection.)

4. Section 7.3, Other Diseases/Conditions, has been modified to request diagnostic slides for participants diagnosed with invasive cancer. A sentence has been added at the end of this section, reading: **“The diagnostic slides from any women diagnosed with invasive cancer should be submitted for central review as soon as possible.”**

The above information will be incorporated into the next protocol version as necessary if the protocol is amended.

Clarification Memorandum #2 for:

A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 10845

Clarification Memorandum Date: 2 January 2014

ACTG Network Coordinating Center

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CLARIFICATION MEMO

DATE: January 2, 2014

TO: Non-US ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators Participating in the A5282 Study

FROM: A5282 Protocol Team

SUBJECT: Clarification Memo # 2 to the A5282 Protocol, Version 1.0, 11/16/2010, entitled "A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women"

This clarification memo does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your IRB; however, as always, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this clarification memo with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately. These updates will be included in the next version of the A5282 protocol if it is amended at a future date.

The following is a clarification to protocol A5282, Version 1.0, 11/16/2010 –

Section 6.3.10 now reads: "Directed biopsies will be obtained from areas suspicious for CIN. Biopsies are taken only if lesions are seen upon colposcopy. In the event lesions are not seen upon colposcopy but the cytology specimens show presence of HSIL, then the participant should return to the study clinic for ~~endocervical curettage (ECC)~~ repeat colposcopy and other diagnostics procedure such as endocervical curettage (ECC), random cervical biopsies, or diagnostic LEEP. Results of these diagnostic tests must be recorded on the appropriate CRF. Slides from biopsies of CIN2+ and biopsies without CIN2+ will be submitted for review. If CIN2+ is detected by biopsy, the participant will undergo LEEP.

Clarification Memorandum #1 for:

A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 10845

Clarification Memorandum Date: 5 February 2013

ACTG Network Coordinating Center

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CLARIFICATION MEMO

DATE: February 5, 2013

TO: Non-US ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators Participating in the A5282 Study

FROM: A5282 Protocol Team

SUBJECT: Clarification Memo # 1 to the A5282 Protocol, Version 1.0, 11/16/2010, entitled "A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women"

This clarification memo does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your IRB; however, as always, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this clarification memo with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately. These updates will be included in the next version of the A5282 protocol if it is amended at a future date.

The following are clarifications to A5282, Version 1.0, 11/16/2010:

1. Section 6.3.2, "Medical History" now reads:

The medical history must **document any history of genital condyloma; any AIDS-defining illness or condition as defined by the Centers for Disease Control and Prevention; any history of cervical, vaginal, or vulvar LSIL or HSIL on cytology or histology; and menstrual history. The medical history must also include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses within 45 days prior to study entry.** For current criteria, refer to the appendix identified in the study CRF. Any allergies to any medications and their formulations **should be documented in the source documents only.**

2. Language in three subsections of Section 6.3.6, "Clinical Assessments," has been changed.

- a. Subsection "Signs/Symptoms" now reads:

At entry, all signs and symptoms Grade ≥ 3 that occurred within 45 days prior to entry must be recorded **on the CRF.**

Post entry, signs and symptoms Grade ≥ 3 must be recorded **on the CRF.**

In addition, post entry, all grades of signs and symptoms related to cervical cryotherapy or LEEP treatments that are contained within the DAIDS "Female Genital Grading Table for Use in Microbicide Studies" will be captured (<http://rsc.tech-res.com/safetyandpharmacovigilance/>). **Grade 1 or 2 signs and symptoms should be recorded on study-specific CRFs only. Grade ≥ 3 should be recorded on study-specific CRFs as well as on the generic event CRFs.**

- b. Subsection "Diagnoses" now reads:

After entry, record any new diagnoses made since the last visit using the ACTG criteria for clinical events and other diseases.

Except for invasive cancer, cervical cytology and histology results do not need to be recorded as events; these results will be entered on study-specific CRFs only.

- c. Subsection "Concomitant Medications" now reads:

Concomitant Medications

Record ART medications (including start and stop dates) **and** receipt of HPV vaccines, and receipt of medical or surgical treatment for ~~genital warts, vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VAIN)~~. Any antibiotics, hormonal treatment, or prescribed or over-the-counter treatments for gynecological conditions should be recorded.

These updates will be included in the next version of the A5282 protocol if it is amended.

Letter of Amendment #2 for:

A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 10845

Letter of Amendment Date: 9 August 2012

ACTG Network Coordinating Center

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LETTER OF AMENDMENT

DATE: August 9, 2012

TO: Non-US ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators Participating in the A5282 Study

FROM: A5282 Protocol Team

SUBJECT: Letter of Amendment #2 for Protocol A5282, Version 1.0, 11/16/2010, entitled "A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women"

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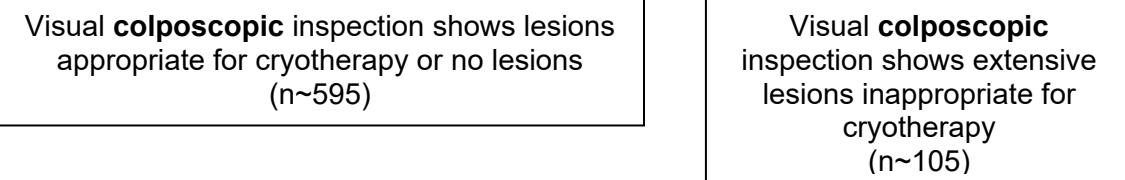
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Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit a LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS

PRO verifies that all the required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

The following are changes to A5282, Version 1.0, 11/16/2010:

1. Figure 1, Overview of Study Design



2. Clarification of contraception requirements if using Efavirenz (EFV)

a. Section 4.1.7, Contraception Requirements

NOTES: If participating in sexual activity that could lead to pregnancy, study participants taking **efavirenz should conform to local or WHO guidelines regarding prevention of pregnancy while on efavirenz.**

b. Sample Informed Consent, "What do I need to know about pregnancy and contraceptives?"

If you are taking certain anti-HIV drugs (Efavirenz), you and your partner **may need to follow additional guidelines to prevent pregnancy while using Efavirenz.** The study staff will discuss this with you.

3. Clarification of the definition of cervicitis

a. Eligibility Criterion 4.2.4, Visual evidence of bacterial STIs or suspicion of pelvic inflammatory disease.

NOTE: **Visually apparent cervicitis thought to be related to STIs** or suspected pelvic inflammatory disease must be treated with appropriate antibiotics at least 7 days prior to entry.

b. Section 7.2, Cryotherapy- and LEEP-related Complications

The risk of postoperative infection is very small and can probably be reduced even more by delaying surgical treatment until any woman with a likely diagnosis of pelvic inflammatory disease **or cervicitis thought to be related to clinically treatable STIs, vaginal trichomoniasis, or bacterial vaginosis** has been adequately treated and **has** recovered.

4. Clarification of LEEP for Participants in Arm A

a. Section 6.1, Schedule of Events

LEEP -- if CIN2+ is found on biopsy (**except the pre-cryotherapy biopsy results at entry for participants in Arm A**)

- b. Section 6.3.10, Other Laboratory Studies and Procedures

Colposcopy and Directed Biopsies

If CIN2+ is detected by biopsy **post-entry**, the participant will undergo LEEP.

LEEP

Participants found to have CIN2+ by biopsy at any point during the study will be offered LEEP (**except for participants in Arm A who have CIN2+ on pre-cryotherapy biopsy at entry**).

5. Screening Window and Lab Testing Timeframe Extended from 30 Days to 45 Days

- a. Section 6.2.1, Screening Evaluations

Screening evaluations to determine eligibility must be completed within **45** days prior to study entry, unless otherwise specified.

- b. Eligibility Criterion 4.1.2, The following laboratory values obtained within **45** days prior to study entry:
 - Absolute neutrophil count (ANC) $\geq 750/\text{mm}^3$
 - Platelet count $\geq 75,000/\text{mm}^3$
 - Hemoglobin (HgB) $> 8 \text{ gm/dL}$
- c. Eligibility Criterion 4.1.3, For candidates suitable for cervical cryotherapy (as defined in section 4.1.5 below), hr-HPV detected by aHPV within **45** days prior to study entry.

6. Section 6.3.10, Other Laboratory Studies and Procedures

Participants **should** refrain from any kind of sexual activity, douching, and inserting any intravaginal products for at least 48 hours prior to the collection of vaginal/cervical specimens.

The above information will be incorporated into the next protocol version as necessary if the protocol is amended.

Letter of Amendment #1 for:

A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 10845

Letter of Amendment Date: 21 September 2011

ACTG Operations Center

Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910

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LETTER OF AMENDMENT

DATE: September 21, 2011
TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators
FROM: A5282 Protocol Team
SUBJECT: Letter of Amendment #1 for Protocol A5282, Version 1.0, 11/16/2010 entitled "A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women"

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to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

The following are changes to A5282, Version 1.0, 11/16/2010 (changes in bold text or strikethrough):

1. Schema, Figure 1 Overview of Study Design

The Arm A box now reads: **Cervical biopsies + Immediate cryotherapy (N=140)**

2. Section 1.3, Secondary Objectives

- 1.3.6 To evaluate baseline/screening characteristics (detection of various HPV types, CD4, CD4 nadir, HIV RNA, **sexual history, and recent sexual activity**) associated with cytological abnormalities at baseline.
- 1.3.8 To report the proportion of HIV-infected women with extensive cervical lesions inappropriate for cryotherapy and examine possible factors associated with these lesions, including CD4 count, plasma HIV-1 RNA, ART use, HPV types detected, **sexual history, and recent sexual activity**.

3. Section 2.2, Rationale, PEPFAR Objectives

The PEPFAR objectives in section 1.3.5 will use screening and baseline evaluations from all women who give consent for this study.

4. Section 3.0, Study Design, 4th Paragraph

All participants in Arm A (HPV test-and-treat) will undergo one or two cervical biopsies followed by immediate cervical cryotherapy at entry. Up to two visible lesions should be biopsied. If no lesions are seen, then one normal-appearing area of the cervix should be biopsied at a location of the investigator's choosing to ensure that at least one biopsy is collected. Participants in Arm A will receive the results of the cytology, but participants will receive cryotherapy treatment regardless of the results.

5. Section 4.1.3

For candidates suitable for cervical cryotherapy (as defined in section 4.1.5 below), hr-HPV detected by aHPV within 30 days prior to study entry.

6. Section 5.1.1, Cervical Cryotherapy

One or two cervical biopsies will be performed. This will be followed by cervical cryotherapy: Two 3-minute freezes separated by 5 minutes of thawing. Refer to the A5282 MOPS for a detailed description of this procedure.

7. Section 6.1, Schedule of Events

The row "Cryotherapy (Arm A only)" now reads "**Cervical biopsies/cryotherapy (Arm A only).**"

8. Section 6.3.10, Other Laboratory Studies and Procedures

Colposcopy and Directed Biopsies

At entry:

- Participants in Arm A will ~~not have colposcopy and directed biopsies; these women will instead undergo have one or two cervical biopsies performed followed by immediate cervical cryotherapy.~~

LEEP

All specimens obtained by LEEP will be fixed in formalin and submitted for **local** review.

Cryotherapy (Arm A Only)

Participants in Arm A will undergo cervical cryotherapy within 7 days after entry. **Please see the A5282 MOPS for details. All women in Arm A should undergo one or two cervical biopsies immediately prior to cervical cryotherapy. Up to two visible lesions should be biopsied. If no lesions are seen, then one normal-appearing area of the cervix should be biopsied at a location of the investigator's choosing. At least one biopsy is collected.** Digital images obtained immediately prior to and following cryotherapy will be submitted for review.

9. Section 7.3, Other Diseases/Conditions, Invasive Cervical, Vaginal, or Vulvar Cancer, Last Paragraph

Participants who are diagnosed with cervical, vaginal, or vulvar cancer after enrolling into the study will continue to be followed on study. These participants will come into the clinic per the time points in Section 6.1 for study evaluations. These participants will receive additional treatments as indicated in the site-specific clinical management plan. **Any women in Arm A diagnosed with invasive cervical cancer on the biopsies obtained immediately prior to cryotherapy should be seen as soon as possible for evaluation by a local specialist and treated as per standard of care in that country.**

10. Section 9.2.2, Secondary Endpoints

9.2.2.11 Sexual history at baseline (age at first vaginal sex and lifetime number of vaginal sex partners) and recent sexual activity (number of vaginal sex partners and condom use within the previous 6 months).

11. Section 9.6, Analyses

9.6.1 Comparison of CIN2+ between Arms A and B

New text added as the second paragraph: **Participants in Arm A will undergo one or two cervical biopsies immediately prior to cryotherapy. If any of these biopsies show invasive cancer, then these participants will be considered as failures for the primary endpoint. Please note that CIN2 or CIN3 on the pre-cryotherapy biopsies will not be considered endpoints.**

Third paragraph now reads: Participants in Arm B may have biopsy done prior to week 26 based on the evaluation of baseline abnormal cervical cytology, **and**

~~whereas participants in Arm A will not have one or two cervical biopsies immediately prior to cryotherapy until week 26. Participants in Arm A or Arm B diagnosed prior to their week 26 visit with CIN2+ that is cleared according to the biopsy at their week 26 will not be considered failures for the primary endpoint analysis. They are counted as meeting the primary endpoint only if CIN2+ is found at week 26 or later. Unplanned biopsies in Arm A that occur prior to the week 26 visit will not be considered for the primary endpoint.~~

9.6.2.1 Arms A and B Only

Third paragraph now reads: These models will explore nadir CD4 count and baseline/screening characteristics (e.g., HIV RNA level, **current CD4 count, sexual history, and cytology outcome** and **recent sexual activity (time-updated variable)** as independent variables.

9.6.2.2 Arms A, B, and C

First paragraph now reads: Logistic regression models will be developed to explore the factors associated with cytological abnormalities at entry or screening, e.g., HPV types, CD4, nadir CD4, HIV RNA level, **sexual history, and recent sexual activity**.

Third paragraph now reads: We will assess the relationship of CD4 cell count (<200, 200-349, 350-499, ≥ 500), ART use (yes or no), plasma HIV RNA, **sexual history, and recent sexual activity** to the presence of these lesions. **We will also relate these variables to the presence or absence of CIN2+ at the month 6 visit among women in Arm C.**

12. Sample Informed Consent, "What do I have to do if I am in this study?"

Groups A and B

If you are in Group A, **the study doctor or nurse will tell you when to come back to the clinic again to receive the results of the Pap test from screening or will give the results of the Pap test to you at this visit (if available). Regardless of the test results, you will have one or two biopsies of your cervix immediately followed by cryotherapy of your cervix. The biopsies and cryotherapy will happen at the entry visit or within one week of the entry visit. The study doctor or nurse will tell you when to come back to the clinic again to receive the results of the biopsies.**

All Groups

To help ensure the quality of study procedures, medical experts other than the study doctor and nurse will review:

1. Pictures taken of the cervix right before and right after cryotherapy, colposcopy, and LEEP.
2. Some of the biopsy specimens.
3. ~~A portion of the specimen collected during LEEP.~~

The above information will be incorporated into the next protocol version as necessary if the protocol is amended.

A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

**The National Institute of Allergy
and Infectious Diseases**

Non-IND Protocol

**The ACTG Optimization of Co-Infection and
Co-Morbidity Management (OpMAN) Committee:**

Thomas B. Campbell, M.D., Chair

Protocol Chair:

Timothy Wilkin, M.D., M.P.H.

Protocol Co-Vice Chairs:

**Cynthia Firnhaber, M.D.
Vikrant Sahasrabuddhe, M.B.B.S.,
M.P.H., Dr.P.H**

DAIDS Clinical Representative:

Catherine Godfrey, M.D.

Clinical Trials Specialist:

Reena T. Allen, M.A.

**FINAL Version 1.0
November 16, 2010**



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APPENDIX I: SAMPLE INFORMED CONSENT

APPENDIX I, ATTACHMENT A: A5282 DEFINITIONS OF SCREENING PROCEDURES FOR CERVICAL CANCER

SITES PARTICIPATING IN THE STUDY

A5282 is limited to select sites outside of the United States that have prior experience with and capacity to perform cervical cancer screening and treatment procedures. The list of eligible sites can be found on the A5282 protocol-specific web page (PSWP).

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STUDY MANAGEMENT

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Protocol E-mail Group

Sites that are planning to register to this study must contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5282 e-mail group. Include the protocol number in the email subject line. Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management

For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the protocol chair and co-vice chairs. Send an e-mail message to actg.coreA5282@fstrf.org (ATTN: Drs. Wilkin, Firnhaber, and Sahasrabuddhe). Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory

For questions specifically related to laboratory tests, send an e-mail message to actg.coreA5282@fstrf.org.

Data Management

For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/participant registration, delinquencies, and other data management issues, contact the data manager.

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Ann Walawander directly.
- For other questions, send an e-mail message to actg.coreA5282@fstrf.org (ATTN: Ann Walawander).
- Include the protocol number, PID, and a detailed question.

Randomization (Arms A and B)/Participant Registration (Arm C)

For randomization/participant registration questions or problems and study identification number (SID) lists, send an e-mail message to rando.support@fstrf.org or call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at +1-716-898-7301.

Computer and Screen Problems

Contact the SDAC/DMC programmers. Send an e-mail message to actg.support@fstrf.org or call +1-716-834-0900 x7302.

Protocol Document Questions

For questions concerning the protocol document, contact the clinical trials specialist. Send an e-mail message to actg.coreA5282@fstrf.org (ATTN: Reena Allen).

STUDY MANAGEMENT (Cont'd)

Copies of the Protocol

To request hard copies of the protocol, send a message to ACTGOpsCenter@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG Web site (<https://www.actgnetwork.org>).

Protocol Registration

Send an e-mail message to Protocol@tech-res.com or call +1-301-897-1707.

Expedited Adverse Event (EAE) Reporting/Questions

Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or +1-301-897-1709; or fax 1-800-275-7619 or +1-301-897-1710.

Phone Calls

Any phone calls must be documented by e-mail to actg.coreA5282@fstrf.org. This will be the site's responsibility.

Protocol-Specific Web Page

Additional information concerning the general study management of ACTG studies can be found on the ACTG web site and specific information about A5282 can be found on the study's PSWP (<https://www.actgnetwork.org>).

GLOSSARY OF TERMS

ACTG	AIDS Clinical Trials Group
AE	adverse event
aHPV	Abbott RealTime hr-HPV (assay)
ANC	absolute neutrophil count
aOR	adjusted odds ratio
ART	antiretroviral therapy
AGUS	atypical glandular cells of undetermined significance
ASCUS	atypical squamous cells of undetermined significance
CDC	Center for Disease Control and Prevention
CE	conformité européenne (marked)
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CIN2+	cervical intraepithelial neoplasia grade 2, 3, or invasive cancer
CLIA	Clinical Laboratory Improvement Amendments (certification)
CSS	Community Scientific Subcommittee
CRF	case report form
CRS	clinical research site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DMC	Data Management Center
DSMB	Data and Safety Monitoring Board
E/CIA	enzyme or chemiluminescence immunoassay
EAE	expedited adverse event
EC	ethics committee
ECC	endocervical curettage
HC2	(Digene) Hybrid Capture-2™
HgB	hemoglobin
HERS	HIV Epidemiology Research Study
hr-HPV	high risk human papillomavirus
HR	hazards ratio
HSIL/LSIL	high-grade (H) or low-grade (L) squamous intraepithelial lesions
IATA	International Air Transport Association
IC	internal control
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	institutional review board
IRIS	immune reconstitution inflammatory syndrome
LEEP	loop electrosurgical excision procedure
MOPS	manual of procedures
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PATH	Program for Appropriate Technologies in Health
PEPFAR	(U.S.) President's Emergency Plan for AIDS Relief
PCR	polymerase chain reaction

GLOSSARY OF TERMS (Cont'd)

PID	patient identification number
PSWP	protocol-specific web page
RE	regulatory entity
RSC	(DAIDS) Regulatory Support Center
SCC	squamous cell carcinoma
SID	study identification number
SIL	squamous intraepithelial lesions
STI	sexually transmitted infection
SUSAR	suspected, unexpected serious adverse reaction
VAIN	vaginal intraepithelial neoplasia
VIA	visual inspection (of the cervix) aided by acetic acid
VIN	vulvar intraepithelial neoplasia
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

SCHEMA

A5282

A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

DESIGN

A5282 is a randomized clinical trial that will compare a human papillomavirus (HPV) test-and-treat-strategy with a cytology-based strategy. All participants will be screened with the Abbott RealTime high-risk HPV test (aHPV) to detect high-risk HPV (hr-HPV) infection.

If hr-HPV is detected, participants will be randomized to Arm A, immediate cryotherapy (HPV test-and-treat), or Arm B, cytology-based strategy. Participants will be eligible for Arm C under the following conditions: (i) if cervical lesions are seen that are inappropriate for cryotherapy or (ii) if hr-HPV is not detected but visual inspection shows lesions or cervical cytology results show high-grade squamous intraepithelial lesions (HSIL). Once on study, all participants will have cervical colposcopy and directed biopsies, cervical cytology, aHPV, HPV DNA polymerase chain reaction (PCR), and careHPV tests as part of their study follow-up.

DURATION

Participants in Arms A and B will be on study for 130 weeks (about 2.5 years). Participants in Arm C will be on study for up to 26 weeks (about 6 months).

SAMPLE SIZE

The study will randomize 280 hr-HPV-positive women to Arms A and B and enroll approximately 170 women in Arm C for a total study sample size of up to 450 participants.

POPULATION

HIV-infected women 18 years of age or older. Eligible participants should have no history of major cervical procedures or suspicion of cervical, vaginal, or vulvar cancer. See Section 4.0 for specific eligibility criteria.

STRATIFICATION

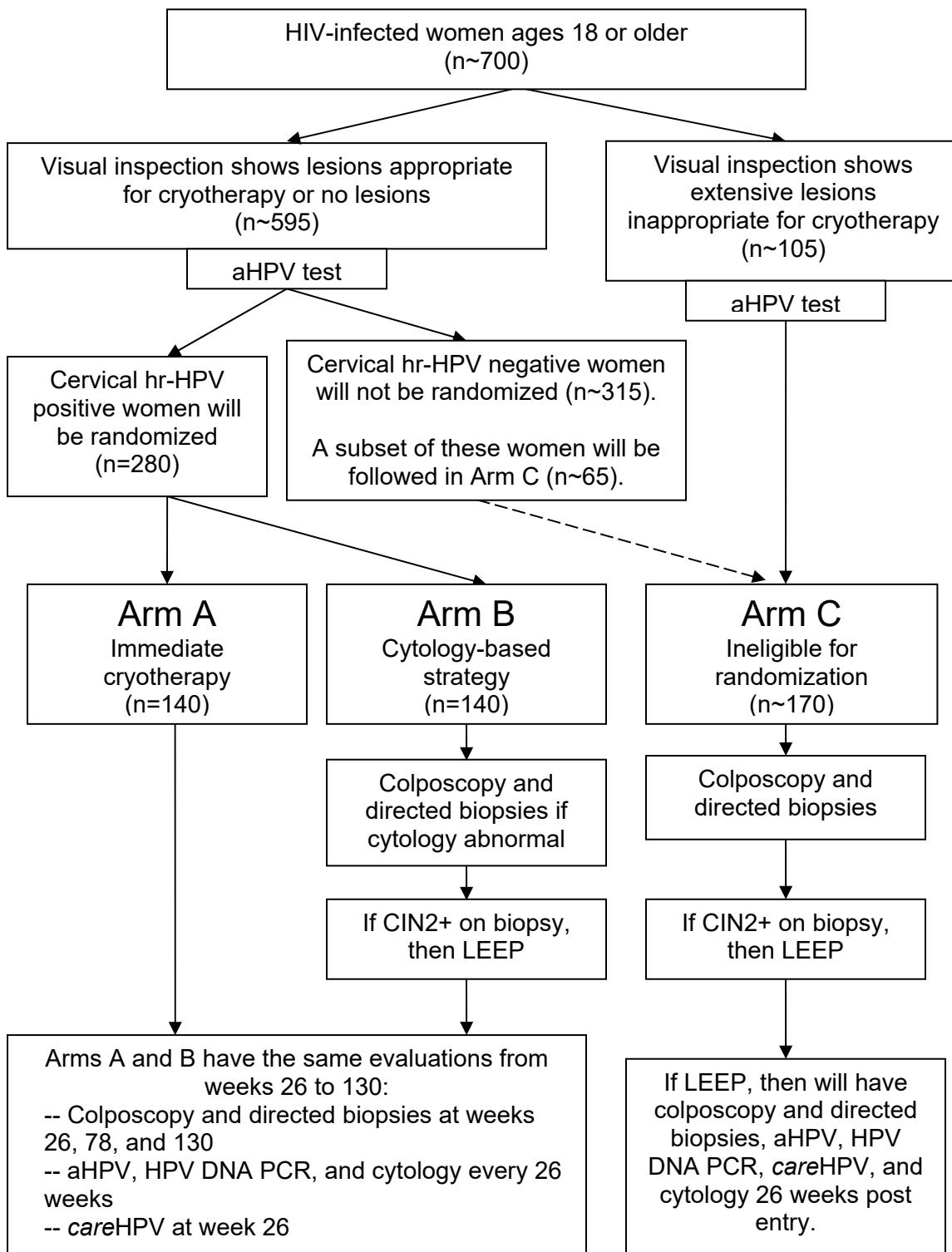
Randomization will be stratified by current use of antiretroviral therapy (ART) (i.e., any ART or no ART) with institutional balancing.

TREATMENTS

- Cervical cryotherapy.
- Loop electrosurgical excision procedure (LEEP) for biopsy-proven cervical intraepithelial neoplasia (CIN) 2+ (i.e., CIN2, CIN3, or invasive cancer).

SCHEMA (Cont'd)

Figure 1: Overview of Study Design



1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

In HIV-infected women with high-risk human papillomavirus (hr-HPV), immediate cryotherapy results in a lower probability of cervical intraepithelial neoplasia (CIN)2+ than a cytology-based strategy.

1.2 Primary Objective

To evaluate the effectiveness of immediate cryotherapy in HIV-infected women with hr-HPV compared to a cytology-based strategy by comparing cumulative CIN2+ rates.

1.3 Secondary Objectives

- 1.3.1 To evaluate the safety and tolerability of cervical cryotherapy (Arm A) in HIV-infected women.
- 1.3.2 To compare between arms the presence of cervical cytological abnormalities during the study.
- 1.3.3 To assess study discontinuation rates and reasons for discontinuation between arms.
- 1.3.4 To compare time to development of CIN2+ between those women with and without detection of hr-HPV by aHPV at 26 weeks, and those women with and without cervical cytological abnormalities after cervical cryotherapy in Arm A.
- 1.3.5 To assess detection frequencies of cervical HPV types (by DNA PCR) and the rates of hr-HPV by *careHPV* at study entry.
- 1.3.6 To evaluate baseline/screening characteristics (detection of various HPV types, CD4, CD4 nadir, and HIV RNA) associated with cytological abnormalities at baseline.

PEPFAR Objectives

- 1.3.7 To evaluate the sensitivity and specificity of *careHPV* for hr-HPV detection as measured by aHPV and HPV DNA PCR at study screening and the agreement beyond chance between these measures.
- 1.3.8 To report the proportion of HIV-infected women with extensive cervical lesions inappropriate for cryotherapy and examine possible factors associated with these lesions including CD4 count, plasma HIV-1 RNA, ART use and HPV types detected.

1.4 Tertiary Objectives (contingent on future funding)

- 1.4.1 To compare between arms the presence of hr-HPV by aHPV and HPV DNA PCR during the study.
- 1.4.2 To assess the HPV types detected (by DNA PCR) at the time of CIN2+ detection by cervical swab and in histopathology specimens.

2.0 INTRODUCTION

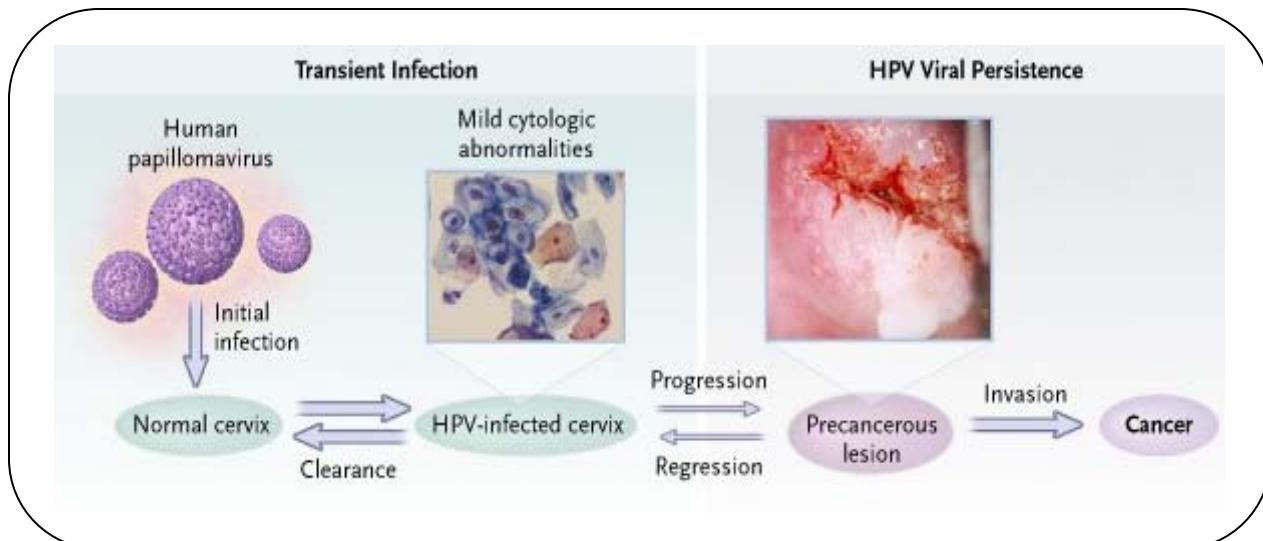
2.1 Background

Cervical Cancer and HIV

Cervical cancer is the second most common cancer among women worldwide [1, 2]. The most recent compilation of global data indicates that an estimated 490,000 new cases of and 275,000 deaths due to cervical cancer occur annually among women worldwide. Nearly 80% of these cases are in developing countries where screening programs are not well established and awareness about the disease is low. HIV-infected women appear to be at increased risk of cervical cancer both in resource rich and resource limited areas [3, 4]. See Figure 2 below for the current model for cervical cancer pathogenesis.

Compared with HIV-uninfected women, women with HIV are more often infected with multiple types of hr-HPV [5], are more likely to have persistent hr-HPV infections [6], and respond less well to treatments of cervical intraepithelial neoplasia (CIN) [7, 8]. With improved access to antiretroviral therapy (ART) and improved longevity, HIV-infected women are living longer allowing time for persistent hr-HPV infections and high-grade CIN2+ to progress to invasive cancer.

Figure 2: Model of Cervical Cancer Pathogenesis [9]



HPV types 16 and 18 account for 70% of cervical cancer cases worldwide [10, 11]. It is not clear whether that proportion is different in HIV-infected women [12]. A recent meta-analysis of epidemiologic studies of HPV infections in HIV-infected women suggested that HPV 16 was less likely to be found with cervical high-grade squamous intraepithelial lesions (HSIL) in HIV-infected women compared with HIV-uninfected women (32% vs. 45%), but HPV 18 was somewhat higher (13% vs. 7%) [13].

Cytology-based Cervical Cancer Screening

Cervical cancer screening programs are traditionally based on cervical cytology as the initial screening test. A cytology-based screening program is a three-visit process: 1) women have a speculum exam during which cervical cytology samples are obtained, 2) women with abnormal results undergo cervical colposcopy with directed biopsies of visible lesions, and 3) lesions with CIN2+ on histopathology are treated with excisional or ablative treatment [14, 15]. However, cervical cytology has an irreducible false negative rate of 30% [16]. Multiple cervical cytological assessments are necessary to achieve an acceptably high sensitivity for CIN2+. In resource rich settings, some have advocated for primary screening with hr-HPV testing instead of cytology [17].

HPV Test-and-Treat Strategies

It is challenging to establish and sustain cytology-based screening programs in resource limited settings [15, 18]. Such programs require trained cytotechnologists and qualified pathologists to interpret the results. An alternative strategy that has been proposed relies on testing for cancer-causing or “high-risk” types of HPV (hr-HPV) as the screening test for cervical cancer [9]. The underlying principle is that hr-HPV infection is a necessary cofactor for the vast majority of cervical cancers [19, 20]. If hr-HPV is present, women undergo ablative treatment of the transformation zone with same-visit cryotherapy to treat presumptive CIN2+ and/or areas of hr-HPV infection without actual CIN2+.

The HPV test-and-treat strategy was evaluated in a three-arm study comparing hr-HPV testing, VIA (visual inspection of the cervix after a wash of acetic acid) without the aid of a colposcope, and a control arm of delayed evaluation in a large clinical trial of South African women [21]. Women aged 35-65 received a test for hr-HPV (Digene Hybrid Capture-2 [HC2]TM, Qiagen, Gaithersburg, MD) and VIA at baseline. They returned to the clinic 2-6 days later for randomization to either cryotherapy if HPV-infected (n=2163), cryotherapy if VIA is abnormal (n=2227), or a 6-month delayed evaluation (n=2165). Women returned 6 months later for colposcopy with biopsy of suspicious lesions. Women who were either hr-HPV infected or had an abnormal VIA at entry and a subset of women who were hr-HPV uninfected or had a normal VIA at entry returned at 12 months for a second colposcopy.

The investigators found that the rate of CIN2+ was higher in the delayed evaluation group (3.55%, 95%CI [2.71%-4.39%]) compared to the VIA group (2.23%, 95% CI [1.57%-2.89%]) or HPV test-and-treat group (0.80%, 95% CI [0.40%-1.20%]). The HPV test-and-treat strategy was the most effective at preventing CIN2+. These differences persisted at the 12-month visit. Complications were minor with only one serious adverse event (AE), cervical bleeding, reported.

The HPV-based approach appeared to work particularly well among HIV-infected women [22]. Among approximately 300 HIV-infected women randomized to the HPV test-and-treat arm, 3.4% developed CIN2+ through 3 years of follow-up compared with 19.8% of approximately 300 HIV-infected women randomized to the control arm ($p < .001$). Nearly all CIN2+ (34/36 or 94%) developed among women infected with hr-HPV at baseline. When restricting the analysis to women with hr-HPV at baseline, the rate of CIN2+ was 40% among HPV-infected women randomized to the delayed evaluation arm compared with 7% among HPV-infected women in the HPV test-and-treat arm from follow-up visits month 6 through month 36. These results suggest that an HPV test-and-treat strategy is efficacious in HIV-infected women and should be considered as a cervical cancer prevention strategy.

Investigators recently published results from a large, cluster-randomized trial conducted in India of three cervical cancer screening tests compared to a control group with no screening [23]. HIV status was not reported. The three screening tests were testing for hr-HPV (Digene HC2), VIA, and cervical cytology. If the screening test was abnormal, then women were referred for cervical colposcopy and directed biopsy of lesions. All women with CIN2+ were offered treatment with LEEP. Only one screening test was performed for each woman. Fifty-two clusters with a total of 131,746 women were randomly assigned to the four groups. The death rate from cervical cancer was .52 that of the control group during 8 years of follow-up (95% CI [.33-.83]). There was no significant difference between the VIA or the cytology groups compared to the control group. This suggests that hr-HPV testing was the most effective screening test when performed at a single time point.

Abbott RealTime High Risk-HPV Test

The Abbott RealTime hr-HPV (aHPV) test detects 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in cervical specimens. Abbott has completed European certification for this assay. It is an automated test that utilizes real-time polymerase chain reaction (PCR) technology. By using a multi-color detection system, this test differentiates signals from HPV 16, HPV 18, and the non-HPV 16/18 high-risk types in the same reaction, giving 3 results for each test. The test also features an internal control (IC) for specimen adequacy by detecting an endogenous human β -globin sequence. In addition, external positive and negative controls are included in each run to assess run validity. Test results are automatically reported by assay software that evaluates key characteristics of real-time PCR data against quality assurance parameters to assess result validity [24].

The aHPV assay was compared with Digene HC2 in a clinical trial enrolling 702 women who underwent testing using both assays, HPV DNA PCR, cytology, and colposcopy with directed biopsies [25]. The aHPV was positive in 100/100 (100%) of women with CIN3+ compared to 97% for Digene HC2. The aHPV was positive in 224/229 (97.8%) of women with CIN2+ compared with 219/229 (95.6% for Digene HC2). The specificity, positive and negative predictive values were similar for the two assays. The concordance was 92%, and the agreement beyond chance was excellent, Cohen's $\kappa = 0.77$ (95% CI 0.72-0.83). When using HPV DNA PCR as the gold standard, the accuracy of aHPV in detecting high-risk HPV was significantly higher than that of Digene HC2 (98.7% versus 92.9%, $P < 0.0001$).

careHPV: Low-cost Testing for hr-HPV

With support from the Gates Foundation, the Program for Appropriate Technologies in Health (PATH) has partnered with Qiagen Inc., Gaithersburg, MD (formerly Digene Inc.) to adapt the Digene HC2 assay for use in resource limited settings [careHPV website]. The resulting *careHPV*™ test has been field-tested yielding comparable results to the Digene HC2 performed in developed countries [26]. The *careHPV* detects the presence of 14 hr-HPV types without distinguishing between the types. Qiagen will commercially distribute *careHPV* in 2010 priced at approximately \$5US per sample [careHPV website]. Results of the *careHPV* are available within 2 hours, multiple samples can be run at one time, and samples can be analyzed in basic laboratory facilities. The current prototype is portable and can be powered by a battery in areas where electricity is unreliable. The reagents used in this test are in dry form and heat-stabilized so that they do not require storage at specific temperature or humidity. Samples are not read by a luminometer but by exposure of a strip of film.

careHPV was evaluated in a cross-sectional study of 2388 HIV-negative women age 30-54 in China [26]. Samples for *careHPV*, Digene HC2, and cervical cytology were collected and VIA performed and compared against colposcopy with directed biopsies. Seventy women were diagnosed with CIN2+. The *careHPV* had a sensitivity and specificity of 90% and 84.2%, respectively, for CIN2+. Digene HC2 had a sensitivity and specificity of 97.1% and 85.6%, respectively. Of note, VIA was only 41% sensitive for CIN2+. Qiagen has completed European certification for the *careHPV* assay.

Outcomes to Treatment of Cervical Cancer Precursors

HIV-infected women are at greater risk for recurrent CIN2+ after treatments [7, 8, 27]. Continued detection of HPV post treatment is a strong predictor of recurrent disease in HIV-uninfected women and likely for HIV-infected women as well [14, 15]. Few studies have investigated the effect of ablative (e.g., cryotherapy) or excisional (e.g., LEEP) treatments on HPV clearance in HIV-infected women. Massad and colleagues [27] reported on 170 HIV-infected women from the Women's Interagency HIV Study (WIHS) and HIV Epidemiology Research Study (HERS) cohorts who underwent cervical treatment for CIN. They found that HPV was commonly detected among women who had abnormal cervical cytology after treatment. Half of the women had recurrent CIN through 3 years of follow-up post procedure. However, much of the recurrent disease was low-grade CIN. Recurrence was more common among HIV-infected women with hr-HPV detected after treatment (HR=2.5, 95% CI [1.3-6.5]) and among those treated for CIN2+ (HR=2.4, 95% CI [1.4-4.8]).

More data are available for HIV-uninfected women. Elfgren and colleagues [28] reported on 109 women treated for CIN with either cervical conization or cryotherapy. Eighty-four (81%) were positive for HPV. Thirty-one women were treated with cervical cryotherapy; 15 (48%) were positive for at least one of the same types 3 months later and approximately 20% 12 months after cervical cryotherapy. Of note, HPV clearance was greater for women who underwent cervical conization. Aerssens and colleagues reported on 122 women who underwent either cervical cryotherapy (n=55) or LEEP (n=67) [29]. Forty-four percent of women who underwent cryotherapy had the same type of HPV detected 6 weeks after treatment compared with 25% in the LEEP group. The efficacy of cryotherapy for clearing HPV infection in the absence of CIN is not known.

Prevalence of hr- HPV and CIN at Select ACTG Sites

Johannesburg, South Africa. Firnhaber and colleagues of the University of Witwatersrand recently published data on the prevalence of HPV infections and cervical squamous intraepithelial lesions (SIL) on cytology in HIV-infected women in Johannesburg, South Africa recruited from the government outpatient HIV clinic [30]. One thousand and ten HIV-infected women with a median age of 34 and CD4 count of 231 cells/ μ L were screened with cervical cytology and a subset screened with HPV DNA PCR. Five hundred and three (50%) of these women had an abnormal cervical cytology: 84 (8%) had atypical squamous cells, 237 (23%) low-grade lesions and 182 (18%) had high grade lesions. Among the 191 women with HPV DNA PCR results, 138 (72%) had one or more types of hr-HPV detected by PCR and 51% had more than one hr-HPV type detected. Among 90 women with normal cytology, 54 (60%) had one or more types of hr-HPV detected. HPV 16 was detected in 42% of women with HSIL and HPV 18 in 3%. High risk-HPV by DNA PCR was related to current CD4 count: 72 (82%) of women with a CD4 <200 cells/mm³ had hr-HPV by PCR compared with 7 (41%) of women with a CD4 >500 cells/mm³.

Pune, India. Investigators have shown that in a cross-sectional assessment of 303 HIV-infected women, 83 (27.7%) had colposcopic-histopathological evidence of CIN1+ lesions and 50 (16.5%) had evidence of advanced CIN2+ neoplastic disease [31]. High risk-HPV by Digene HC2 was detected in 41.7% (124/297) of participants. On multivariable ordinal logistic regression, the independent predictors of increasing severity of CIN included (i) receiving ART [adjusted odds ratio (aOR): 2.16 (1.15, 4.04), p=0.02] and (ii) being hr-HPV positive [aOR: 1.91 (1.12, 3.26), p=0.02].

Port-au-Prince, Haiti. Cervical cancer is the leading cause of cancer death in Haitian women, with an estimated 1300 deaths annually [32]. After the introduction of ART for HIV-infected patients in Haiti in 2003, malignancies became the third leading cause of AIDS mortality, behind wasting syndrome and tuberculosis. Colleagues from GHESKIO have examined treatment outcomes in a cohort of 910 adults with AIDS who started ART in 2003 at the GHESKIO center. In HIV-infected women receiving ART in Haiti, cervical cancer was the most common cause of cancer death occurring at a rate of 3 deaths per 1000 patient-years [33]. Investigators have screened 500 women enrolled in a randomized clinical trial of early versus delayed ART (sponsored by the U.S. National Institutes of Health [NIH], U01 AI058257). The median age is 36 years. The median CD4 cell count at enrollment was 312 cells/ μ L. The median follow-up is over 2 years with 96% retention. This trial was interrupted by the Data and Safety Monitoring Board (DSMB) after an interim review showed the mortality was 76% lower in the early treatment group [34]. Four hundred and seventy women were studied. Per the baseline Pap test, 53 women (11%) had ASC-US, 100 (22%) had low-grade squamous intraepithelial lesions (LSIL), and 35 (7%) had HSIL. By HPV testing with the Digene assay, 268 (57%) had a hr-HPV type detected. By colposcopy, 45 (10%) of the 470 women were diagnosed with a high grade CIN2+ lesions.

Lusaka, Zambia. In a cross-sectional study in Lusaka, Zambia, HSIL and cytology suggestive of squamous cell carcinoma (SCC) were detected in 52% of HIV-infected women accessing ART [35]. The prevalence of cervical hr-HPV by PCR was 85.3% (128/150 women). High risk-HPV by PCR was significantly greater among women with CD4 cell counts less than 200 cells/ μ L: 44/53 (83%) versus 87/91 (96%), $p=.001$, and the only hr-HPV types significantly associated with HSIL or SCC by cytology were HPV 31 and HPV 58. HPV 16 was detected in 22% of women with HSIL, and HPV 18 was detected in 13%. Multiplicity of HPV types (median was 4 high-risk types) and heterogeneity (36 of 37 detectable types by PCR were found) were prominent [36].

Table 1: Data on hr-HPV and CIN in HIV-infected Women from Select Clinical Research Sites (CRSs) Participating in A5282

Country (City)	CRS	Sample Size	Median CD4 (cells/ μ L)	Hr-HPV Prevalence	Any SIL on Cytology	HSIL+ Cytology	CIN+ by Histology	Reference
Haiti (Port-au-Prince)	GHESKIO	470	312	57% by Digene HC2	40%	7%	10%	Unpublished
India (Pune)	NARI	303	343	41% by Digene HC2	34%	6%	16.5%	38
South Africa (Johannesburg)	WITS	1010	231	72% by PCR *	50%	18%	Not assessed	30, 39
Zambia (Lusaka)	University Teaching Hospital	150	165	90% by PCR	76%	52%	Not assessed	36

* PCR performed on a subset of women (n=191) in South Africa.

Potential Risks of Study Treatments

- Cervical biopsies
 - Common, not serious
 - Pain during biopsy
 - Mild bleeding
 - Rare
 - Heavy bleeding requiring treatment to stop the bleeding
 - Infection of the cervix requiring antibiotics
 - Possible increased risk of miscarriage after multiple cervical biopsies
- Cervical cryotherapy
 - Common, not serious
 - Pain and cramping during the procedure (1%)
 - Profuse watery vaginal discharge (>10%)
 - Heavy, odorous discharge (1%)
 - Mild cervical bleeding (2%)
 - Cervical infection (1-2%)
 - Retraction of squamocolumnar junction into cervical canal, which makes subsequent exams more difficult

- Rare
 - Severe cramps and abdominal pain requiring parenteral medications (<1%)
 - Pelvic inflammatory disease (<1%)
 - Heavy cervical bleeding (very rare, potentially serious)
 - Cervical stenosis (very rare, potentially serious)
 - Vaginal injury from unintentional freezing (very rare, not serious)
 - Vasovagal reactions during procedure (<1%)
 - Potential increased risk of transmitting HIV to sexual partners post-procedure
- LEEP
 - Common, not serious
 - Transitory pain from local anesthetic into the cervix
 - Blood tinged, dark brown mucus for 1-2 weeks post LEEP
 - Dull ache/cramping during procedure
 - Postoperative cramping/pain (common, relieved by analgesics)
 - Uncommon, serious:

Intraoperative/perioperative

 - Anesthetic reaction/vasovagal syncope <1%
 - Severe intra/perioperative bleeding <2%
 - Electrical injury of vaginal wall (rare)
 - Perforation of uterus <1%

Postoperative

 - Moderate to severe postoperative bleeding <2%
 - Cervical or endometrial infection/pelvic inflammatory disease (rare, mostly if not treated perioperatively by antibiotics)
 - Cervical stenosis, due to scarring: <1-2%: more in menopausal women
 - Cervical incompetence: resulting in miscarriage or pre-term labor <2%
 - Infertility (rare)
 - Potential increased risk of transmitting HIV to sexual partners post procedure [37]

2.2 Rationale

Age Range

HPV testing is used in the screening algorithm of HIV-uninfected women age 30 or older. HPV testing has not been traditionally used for younger women because of the high-incidence of transient, insignificant HPV infections. However, HIV-infected young people have been noted to have a high prevalence of CIN2/3 as well as cases of invasive cancer. Therefore, the protocol team has opted to include younger women in this study.

Arm C

Women falling into either of the following two categories will be followed in Arm C: (i) women who have extensive cervical lesions that are inappropriate for cervical cryotherapy and (ii) high-risk HPV negative women with cervical lesions or a HSIL cytology. In a large screen-and-treat evaluation from Zambia, approximately 15% of women undergoing evaluation were thought to have lesions inappropriate for cryotherapy and were referred for LEEP [40]. In a recent presentation from Zambia, 20% of HIV-infected women had lesions inappropriate for cryotherapy. Of these women, 15%

had invasive cancer and another 33% had CIN2 or 3. Inclusion of this category of women in the present study will yield a larger number of participants for assessment of the HPV genotypes found in CIN2+ biopsy specimens (possible future study) and for the effect of LEEP on prevalent hr-HPV infections. In addition, these study populations will provide important data for implementation of the HPV test-and-treat strategy, as outlined in section 1.3.8, including the role of HPV testing in the management of women presenting with such conditions.

PEPFAR Objectives

Part of this study is being funded by a supplement from the U.S. NIH to conduct implementation science research of interest to the President's Emergency Plan for AIDS Relief (PEPFAR). The PEPFAR objectives in section 1.3.5 will use screening and baseline evaluations from all women who give consent for this study. The availability of the *careHPV* test should broaden access to cervical cancer screening through the HPV test-and-treat strategy. It will be critical to understand how this test performs in HIV-infected women. Although this assay has been conformité européenne (CE)-marked, it will not be widely available until late 2011. This study will compare *careHPV* results to two other HPV tests: HPV DNA PCR and aHPV. Cryotherapy is not recommended for women with extensive cervical lesions. Data from our Zambian investigators suggest that 15-20% of HIV-infected women will have such lesions and that half of these women will have CIN2/3 or invasive/microinvasive cancer on histology [40, 41]. Algorithms for cervical cancer screening must address treatment of these women to maximally impact mortality from cervical cancer.

Summary

An HPV test-and-treat strategy may become the standard of care for cervical cancer screening in resource limited settings because it is safe, effective, and inexpensive. A phase II study that randomizes women with hr-HPV was chosen because these women are at highest risk for CIN2+ and maximizes the efficiency of the study. Although limited data suggest an HPV test-and-treat strategy is effective in HIV-infected women, further study is needed before it can be broadly applied in this population. The protocol team proposes a proof-of-concept study in HIV-infected women to compare the effectiveness of immediate cryotherapy in women identified with high-risk HPV in screening to cytology-based strategy. It is imperative to understand how to apply an HPV test-and-treat strategy in HIV-infected women to reduce the morbidity and mortality due to cervical cancer.

3.0 STUDY DESIGN

A5282 is a randomized clinical trial of an HPV test-and-treat-strategy compared to cytology-based strategy. The study population is composed of HIV-1-infected women ages 18 years or older. No restrictions are in place for ART regimens, which will be initiated or continued according to the local standard of care. Sites should strongly consider initiating ART in women with a CD4 <350 cells/ μ L, if feasible. ART is not provided by the study. To be eligible, participants must have no history of cervical, vaginal, or vulvar cancer; no prior cervical cryotherapy, cervical conization, or hysterectomy; and no prior receipt of HPV vaccines.

The screening laboratory evaluations include CD4 cell count, plasma HIV-1 RNA viral load, and complete blood count. All participants will undergo a speculum examination at screening to obtain cervical specimens for cytology, aHPV, and HPV DNA PCR. Participants will be screened for hr-HPV with aHPV. This test semi-quantitatively detects the presence of type 16, type 18, or the presence of any of the other 12 types of hr-HPV (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). A separate specimen will be collected and stored for *careHPV* testing, which detects the 14 types listed above.

At screening, the examiner will also perform a visual inspection and colposcopy without biopsies to determine whether the candidate's cervix is suitable for cryotherapy. Participants with cervical lesions inappropriate for cryotherapy (as defined in Section 4.1.8) are not eligible for randomization but will be eligible to register to Arm C. Participants without hr-HPV (by aHPV) will also be eligible to register to Arm C if lesions were seen on the screening colposcopy or if the screening cytology shows HSIL.

The study will randomize 280 participants with hr-HPV (by aHPV) to Arm A or Arm B. Randomization will be stratified by current use of ART (i.e., any ART or no ART) with institutional balancing. Participants in Arm A (HPV test-and-treat) will undergo cervical cryotherapy at entry. Participants in Arm A will receive the results of the cytology, but participants will receive cryotherapy treatment regardless of the results. Participants in Arm B will follow a cytology-based management plan involving three steps – cytology, colposcopy with directed biopsies, and LEEP (as needed). Participants in Arms A and B will be seen at regular intervals post entry for aHPV, HPV DNA PCR, cervical cytology, and cervical colposcopy and directed biopsies for a total follow-up length of 130 weeks. A separate specimen will be collected 26 weeks post entry and stored for *careHPV* testing.

Participants in Arm C will undergo colposcopy and directed biopsies. If CIN2+ is found by biopsy, then LEEP will be performed and a follow-up visit 26 weeks after these procedures will be scheduled for aHPV, HPV DNA PCR, *careHPV*, cervical cytology, and cervical colposcopy and directed biopsies. After the week 26 visit, Arm C participants will go off study.

All participants undergoing cryotherapy or LEEP will be seen 4 weeks post-procedure to assess for AEs from the procedure. Quality assurance procedures are in place for reviews of digital impressions rendered during colposcopies (no lesions seen, lesions seen/appropriate for cryotherapy or lesions seen/not appropriate for cryotherapy). Slides from biopsies with and without CIN2+ will be reviewed regionally or centrally (see the A5282 Manual of Procedures [MOPS] for details). HPV DNA PCR and *careHPV* will be performed on stored specimens and results will not be used for clinical management.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry

and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: For sites located in countries other than the United States, the term "licensed" refers to a kit that has been certified or licensed by an oversight body within that country and validated internally.

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

4.1.2 The following laboratory values obtained within 30 days prior to study entry:

- Absolute neutrophil count (ANC) $\geq 750/\text{mm}^3$
- Platelet count $\geq 75,000/\text{mm}^3$
- Hemoglobin (HgB) $> 8 \text{ gm/dL}$

4.1.3 For candidates suitable for cervical cryotherapy (as defined in section 4.1.8 below), hr-HPV detected by aHPV within 30 days prior to study entry.

NOTE: Participants with a visual inspection showing extensive lesions inappropriate for cryotherapy do not require an aHPV test result prior to enrollment.

4.1.4 For women without hr-HPV detected by aHPV, presence of lesions on visual inspection or HSIL cervical cytology.

4.1.5 Suitable candidate for cervical cryotherapy, defined as:

- No visible cervical lesions.
-- OR --
- Any visible lesions are located entirely on the ectocervix and are no more than 2 to 3 mm into the endocervical canal, AND
- visible lesions cover less than 75% of the cervix, AND
- all visible lesions are deemed appropriate for cryotherapy by the treating health care provider.

NOTE: Participants with cervical lesions inappropriate for cryotherapy are not eligible for randomization and should be followed in Arm C.

4.1.6 For participants of reproductive potential, negative serum or urine pregnancy test with a sensitivity of $<25 \text{ mIU/mL}$ within 48 hours prior to study entry.

NOTE: Reproductive potential is defined as women who have not been postmenopausal for at least 24 consecutive months (i.e., who have had

menses within the preceding 24 months) or women who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy).

4.1.7 Contraception requirements

All study participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or in vitro fertilization) from the time of study entry until 12 weeks after study entry.

If participating in sexual activity that could lead to pregnancy, the study participant must agree to use at least one reliable form of contraceptive from the time of study entry until 12 weeks after study entry. At least one of the following contraceptives MUST be used appropriately:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- IUD
- Hormone-based contraceptive

NOTE: If participating in sexual activity that could lead to pregnancy, study participants taking efavirenz must use two forms of contraceptives.

Study participants who are not of reproductive potential (defined as women who have been postmenopausal for at least 24 consecutive months or have undergone surgical sterilization [e.g., hysterectomy, bilateral oophorectomy, or salpingectomy]) are eligible without requiring the use of contraceptives. Participant-reported history is acceptable documentation of sterilization, menopause, and a female's reproductive potential.

4.1.8 If recently gave birth, must be at least 12 weeks postpartum.

4.1.9 Females \geq 18 years of age at study entry.

4.1.10 Ability and willingness of participant or legal guardian/representative to provide written informed consent.

4.2 Exclusion Criteria

4.2.1 Current or prior history of cervical, vaginal, or vulvar cancer.

4.2.2 Prior cervical cryotherapy, LEEP, cervical conization, or total or partial hysterectomy.

4.2.3 Cervical, vaginal, or vulvar lesions that are suspicious on clinical exam for cancer.

4.2.4 Visual evidence of bacterial STIs or suspicion of pelvic inflammatory disease.

NOTE: Cervicitis or suspected pelvic inflammatory disease must be treated with appropriate antibiotics at least 7 days prior to entry.

- 4.2.5 Prior vaccination with an HPV vaccine.
- 4.2.6 Hemophilia.
- 4.2.7 Currently on anticoagulation therapy other than acetylsalicylic acid.
- 4.2.8 Serious illness requiring systemic treatment and/or hospitalization within 21 days prior to study entry.
- 4.2.9 Active drug or alcohol use or dependence or any other condition that, in the opinion of the site investigator, would interfere with the participant's ability to adhere to study requirements.

4.3 Study Enrollment Procedures

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

For studies at non-US sites, protocol activation is required prior to enrolling participants into the study.

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

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

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant or legal guardian/representative will be asked to read and sign the approved ICF.

For participants from whom a signed ICF has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Subject Enrollment System.

4.3.2 Randomization (Arms A and B)/Participant Registration (Arm C)

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.4 Coenrollment Guidelines

Sites are strongly encouraged to coenroll participants in A5243, "Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses." Coenrollment in A5243 does not require permission from the A5282 protocol chairs.

Participants cannot be coenrolled in A5240, "A Phase II Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Human Papillomavirus Vaccine in HIV-1-Infected Females."

Sites should consult the A5282 PSWP for other studies in which participants can be coenrolled, or contact the protocol chair and co-vice chairs via e-mail as described in the Study Management section for permission to enroll participants who are being followed in other clinical trials.

5.0 STUDY TREATMENT

5.1 Intervention, Administration, and Duration

5.1.1 Cervical Cryotherapy

Two 3-minute freezes separated by 5 minutes of thawing. Refer to the A5282 MOPS for a detailed description of this procedure.

5.1.2 LEEP

Refer to the A5282 MOPS for a detailed description of this procedure.

5.2 Study Product Formulation and Preparation

Not applicable.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

Not applicable.

5.4 Concomitant Medications

5.4.1 Required Medications

If participating in sexual activity that could lead to pregnancy, participants must agree to use at least one reliable form of contraceptive (as defined in section 4.1.10) from the time of study entry until 12 weeks after study entry.

5.4.2 Prohibited Medications

None.

5.4.3 Precautionary Medications

Participants who require anticoagulation medication other than acetylsalicylic acid should not undergo cervical biopsies, LEEP, or cryotherapy.

Site investigators are encouraged, but not required, to delay HPV vaccinations for participants in Arms A and B until 24 weeks post entry.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

Evaluation	Screening	Entry (day 0)	Post Entry Evaluations					4 weeks post cervical treatment
			Week 26 (Final Visit for Arm C)	Week 52	Week 78	Week 104	Week 130 (Final Visit for Arms A and B) / Disc Evals	
Documentation of HIV-1	X							
Medical history / Medication history	X							
Nadir CD4 cell count	X							
Complete physical examination (PE)	X							
Clinical assessments	X	X	X	X	X	X	X	
Hematology	X							
Pregnancy test	within 48 hours prior to entry		whenever suspected, prior to cryotherapy and prior to LEEP					
CD4 cell count	X							
Plasma HIV-1 RNA	X							
Speculum examination and colposcopy	X							
Real-time aHPV and Stored HPV DNA PCR	X							
Stored aHPV and Stored HPV DNA PCR			X	X	X	X	X	
Stored careHPV	X		X					
Cervical cytology	X		X	X	X	X	X	
Colposcopy and directed biopsies		See Section 6.3.10	X		X		X	
LEEP			only if CIN2+ is found on biopsy					
Cryotherapy (Arm A only)		X						
Assessment of targeted AEs		X						X
Sociodemographic and sexual behavior questionnaire		X	X	X	X	X	X	

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant's starting any study treatment. Screening evaluations to determine eligibility must be completed within 30 days prior to study entry, unless otherwise specified.

The cytology and HPV evaluations cannot be performed while the participant is menstruating. If a participant has visual evidence of bacterial STIs or an examination consistent with pelvic inflammatory disease, then samples for cytology and HPV testing should not be obtained. The participant should be treated according to the local standard of care, in which case screening evaluations can be performed a minimum of 7 days after initiating treatment.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database. Cytology, colposcopic visual impression, and HPV testing on screening failures will also be captured on a case report form (CRF) and entered into the ACTG database.

6.2.2 Entry Evaluations

Participants should receive study treatment within 7 days after randomization/registration, unless contraindicated (see Section 6.3.10).

6.2.3 Post Entry Evaluations

Post Entry Evaluations

Study visits will be conducted in the clinic at week 26 +/- 6 weeks for participants in all arms and at weeks 52, 78, and 104 +/- 6 weeks for participants in Arms A and B only. Additional visits will be necessary between these time points to discuss cytology and/or histology test results and subsequent management plans with participants.

Post Cervical Treatment Evaluations

Participants will be seen in the clinic 4 weeks +/- 10 days after cryotherapy or LEEP for assessment of procedure-related AEs.

Study Completion Evaluations

The final study visit will occur at week 26 +/- 6 weeks for participants in Arm C and at week 130 +/- 12 weeks for participants in Arms A and B. The off-study CRF must be completed and keyed into the database for each participant after completing the evaluations required at the final study visit unless CIN2+ is found, in which case the off-study CRF should be completed and keyed into the database after the participant undergoes LEEP and completes the 4-week post treatment assessment of procedure-related AEs.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized/Registered Participants Who Do Not Undergo Study Treatment

Participants who are randomized to Arm A or B or registered to Arm C but do not undergo study treatment will not be discontinued from study. Instead, these participants will be followed on study and should complete the study evaluations as per Section 6.1 up to week 130 (Arms A and B) or week 26 (Arm C).

Premature Study Discontinuation Evaluations

Participants who discontinue study participation prior to the final study visit will be asked to come into the clinic to complete the study evaluations as noted in the "Week 130 (Final Visit) / Disc Evals" column of Section 6.1. The participant will discontinue from the study after completing these evaluations. Refer to Section 8.0 for criteria for discontinuation.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS web site for information about what must be included in the source document:

<http://www.niaid.nih.gov/labsandresources/resources/daidsclinsrch/documents/sourcedocappndx.pdf>.

All stated evaluations are to be recorded on the CRF and entered into the ACTG database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event:

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/in capacity
- Congenital anomaly/birth defect
- Other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above).

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009) and Addendum 1-Female Genital Grading Table for Use in Microbicide Studies, which can be found on the DAIDS RSC web site: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

6.3.1 Documentation of HIV-1

Refer to Section 4.1.1 regarding assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Medical History

The medical history must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses, and menstrual history. For current criteria, refer to the appendix identified in the study CRF. Any allergies to any medications and their formulations must be documented.

6.3.3 Medication History

A medication history of ART use must be present, including start dates of all ART agents currently being received, and date of first ART.

6.3.4 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. 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 cells/mm³) will suffice.

6.3.5 Complete Physical Examination

A complete physical examination should be done prior to entry and is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema; Karnofsky performance test; and assessment of WHO clinical staging of HIV/AIDS.

The complete physical exam will also include signs and symptoms, diagnoses, and vital signs (temperature, pulse, and blood pressure).

6.3.6 Clinical Assessments

Targeted Physical Examination

Post entry, a targeted physical examination is to include vital signs (temperature, pulse, and blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the previous visit.

Signs and Symptoms

At entry, all signs and symptoms Grade ≥ 3 that occurred within 45 days prior to entry must be recorded; post entry, signs and symptoms Grade ≥ 3 must be recorded. Post entry, all grades of signs and symptoms related to cervical cryotherapy or LEEP treatments that are contained within the DAIDS "Female Genital Grading Table for Use in Microbicide Studies" will be captured (<http://rsc.tech-res.com/safetyandpharmacovigilance/>).

Diagnoses

Record all diagnoses identified by the ACTG criteria for clinical events and other diseases.

Concomitant Medications

Record ART medications (including start and stop dates), receipt of HPV vaccines, and receipt of medical or surgical treatment for genital warts, vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VAIN). Any antibiotics, hormonal treatment, or prescribed or over-the-counter treatments for gynecological conditions should be recorded.

Adherence Assessment

The site should discuss and encourage ongoing adherence to ART at each study visit if the participant is receiving ART. Any concerns about adherence should be communicated to the participant's primary care provider. This should be documented in the source documents only.

6.3.7 Laboratory Evaluations

At screening, entry, and post entry record all Grade ≥ 3 laboratory values.

Hematology

ANC, platelet count, and HgB.

Pregnancy Test

For women with reproductive potential, a negative serum or urine β -HCG (urine test must have a sensitivity of <25 mIU/mL) pregnancy test must be performed within 48 hours prior to study entry, prior to cryotherapy and LEEP (if done), and post entry whenever pregnancy is suspected. (See section 7.4 for the management of study participants who become pregnant after entry.)

6.3.8 Immunologic Studies**CD4 Cell Count**

Obtain absolute CD4 cell count and percentage from a DAIDS-approved laboratory. These results should be communicated to the participant's primary care provider to assist in the management of her HIV infection, including the initiation of ART as indicated, and the site must document this communication in the source documents.

6.3.9 Virologic Studies**Plasma HIV-1 RNA**

Obtain HIV-1 RNA viral load levels from a DAIDS-approved laboratory. These results should be communicated to the participant's primary care provider to assist in the management of her HIV infection, and the site must document this communication in the source documents.

6.3.10 Other Laboratory Studies and Procedures

Refer to the A5282 MOPS for detailed instructions on how to perform colposcopy and biopsies, collect specimens for aHPV, HPV DNA PCR, and *careHPV*, perform cervical cytology, cryotherapy, and LEEP, and detailed plans for the quality assurance of clinical procedures.

Participants must refrain from any kind of sexual activity, douching, and inserting any intravaginal products for at least 48 hours prior to the collection of vaginal/cervical specimens.

Speculum Examination and Colposcopy

Participants will undergo a speculum examination at screening to obtain cervical specimens for HPV testing and cytology. If participants have visual evidence of bacterial STIs or an examination consistent with pelvic inflammatory disease, then samples for HPV testing and cytology should not be obtained. Instead, these women should be treated according to the local standard of care, in which case screening evaluations can be performed a minimum of 7 days after initiating treatment.

A trained examiner will also perform colposcopy at screening to determine whether the participant's cervix is suitable for cryotherapy and for visual impression only. Digital images will be taken using a video colposcope provided to sites by the study, and submitted for review along with the colposcopic impression provided by the examiner as to the degree of CIN (no lesions seen, lesions seen appropriate for cryotherapy, lesions seen not appropriate for cryotherapy). Refer to the A5282 MOPS for detailed procedures.

No biopsies are to be obtained at screening unless the examiner is suspicious of invasive cervical, vaginal, or vulvar cancer, in which case the participant will not be enrolled into the study and will be managed as per section 7.3.

aHPV

A cervical specimen will be obtained at screening for real-time aHPV testing. Post-entry, specimens will be obtained for aHPV and stored locally (refer to the A5282 MOPS).

HPV DNA PCR

Specimens will be stored for HPV DNA PCR. Testing will be performed on the same specimen as the aHPV. Specimens may be shipped to the U.S. for HPV typing at a central laboratory, if permitted by in-country regulations, or batch tested at a local or regional laboratory. Specimens obtained by LEEP will also be stored locally for possible future testing by HPV DNA PCR.

careHPV

A cervical cytobrush specimen will be obtained for *careHPV* and stored locally in the appropriate media (refer to the A5282 MOPS).

Cytology

Cervical cytology specimens will be obtained and processed locally in real-time (refer to the A5282 MOPS). Pap smears will be interpreted locally. Results should be communicated to the participant's primary care provider, and the site must document this communication in the source documents.

Colposcopy and Directed Biopsies

At entry:

- Participants in Arm A will not have colposcopy and directed biopsies; these women will instead undergo cryotherapy.
- Participants in Arm B will undergo colposcopy with directed biopsies if the screening cytology is abnormal, i.e., the result reveals atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGUS), low grade squamous intraepithelial lesion (LSIL), or HSIL.
- Participants in Arm C will undergo colposcopy and directed biopsies if the screening cytology shows HSIL or if cervical lesions were seen upon visual inspection.

Post entry:

- Participants in Arms A and B will undergo colposcopy and directed biopsies at the weeks 26, 78, and 130 clinic visits.
- Participants in Arm C who undergo LEEP post-entry will undergo colposcopy and directed biopsies at the week 26 clinic visit.

Digital images and colposcopic impression will be submitted for review, along with location of cervical biopsies.

Directed biopsies will be obtained from areas suspicious for CIN. Biopsies are taken only if lesions are seen upon colposcopy. In the event lesions are not seen upon colposcopy but the cytology specimens show presence of HSIL, then the participant should return to the study clinic for endocervical curettage (ECC). Slides from biopsies of CIN2+ and biopsies without CIN2+ will be submitted for review. If CIN2+ is detected by biopsy, the participant will undergo LEEP.

LEEP

Participants found to have CIN2+ by biopsy at any point during the study will be offered LEEP. If the participant had a prior LEEP, treatment of recurrent CIN2+ is at the discretion of the site investigator. These participants will continue on study. All specimens obtained by LEEP will be fixed in formalin and submitted for review. Digital images obtained immediately prior to and following LEEP will also be submitted for review.

Participants will be advised to abstain from vaginal intercourse and douching for 6 weeks after a LEEP, or the use of condoms during this period will be advised. Participants will return to the site for an assessment of AEs 4 weeks after LEEP, or sooner if significant AEs occur.

LEEP should not be performed while the participant is menstruating. Additionally, if a participant has visual evidence of bacterial STIs or an examination consistent with pelvic inflammatory disease, then LEEP should be deferred. The participant should be treated according to the local standard of care, in which case LEEP can be performed a minimum of 7 days after initiating treatment.

Cryotherapy (Arm A Only)

Participants in Arm A will undergo cervical cryotherapy within 7 days after entry. Digital images obtained immediately prior to and following cryotherapy will be submitted for review.

Participants will be advised to abstain from vaginal intercourse and douching for 6 weeks after cryotherapy, or the use of condoms during this period will be advised. Participants will return to the site for an assessment of targeted AEs 4 weeks after cryotherapy, or sooner if significant AEs occur.

Cryotherapy should not be performed while the participant is menstruating. Additionally, if a participant has visual evidence of bacterial STIs or an examination consistent with pelvic inflammatory disease, then cryotherapy should be deferred. The participant should be treated according to the local standard of care, in which case cryotherapy can be performed a minimum of 7 days after initiating treatment.

6.3.11 Questionnaires

Assessment of Targeted AEs

AEs related to cryotherapy or LEEP will be recorded and graded according to the DAIDS "Female Genital Grading Table for Use in Microbicide Studies," which can be found on the DAIDS RSC web site: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

Sociodemographic and Sexual Behavior Questionnaire

A standardized questionnaire will be used to collect data on sociodemographic indicators as well as sexual behavior indicators (e.g., age at first sexual intercourse, lifetime number of sexual partners, frequency of vaginal intercourse in the preceding 6 months, and number of partners in the preceding 6 months). After entry, only recent sexual activity will be assessed.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Grade 3 or Higher Events

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

7.2 Cryotherapy- and LEEP-related Complications

Vaginal Bleeding

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

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

Vaginal Infection

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

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

7.3 Other Diseases/Conditions

Invasive Cervical, Vaginal, or Vulvar Cancer

Each clinical research site conducting A5282 will develop its own plan for the clinical management of invasive cervical, vaginal, or vulvar cancer. Plans will be submitted to the A5282 protocol team for review prior to the enrollment of women at the site.

Participants with visual evidence for cervical, vaginal, or vulvar cancer at the screening visit will not be enrolled into the study. After it is determined that these women are ineligible, biopsies of lesions suspicious for cancer are recommended to confirm the diagnosis. Although these women will not be enrolled into the study, all of the screening results with the exception of HPV DNA PCR results will be provided to the participants and their health care providers. These women will then be followed as per the site-specific clinical management plan.

Participants who are diagnosed with cervical, vaginal, or vulvar cancer after enrolling into the study will continue to be followed on study. These participants will come into the clinic per the time points in Section 6.1 for study evaluations. These participants will receive additional treatments as indicated in the site-specific clinical management plan.

Other Gynecological Conditions

Cervical polyps, VIN, VAIN and vulvovaginal warts will be managed according to local standard of care.

7.4 Pregnancy

Participants who become pregnant after study entry will continue to be followed on study. These participants will come into the clinic to complete study evaluations as per the schedule in Section 6.1 but will not undergo LEEP, cryotherapy, or cervical biopsy until 6 weeks after the pregnancy is completed. If there is suspicion of invasive cancer, clinical management is left to the discretion of the site investigator.

Pregnancy outcome for the participant and the infant will be recorded on a CRF at the end of the pregnancy.

If pregnancy occurs for a participant on study who is on ARVs, sites are strongly encouraged to register the pregnancy with The Antiretroviral Pregnancy Registry as soon as the site becomes aware of it. More information is available at www.apregistry.com.

8.0 CRITERIA FOR STUDY DISCONTINUATION

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Clinical reasons believed life threatening by the physician, even if not addressed in Section 7.0 of the protocol.
- At the discretion of the ACTG, IRB/EC, the U.S. Office for Human Research Protections (OHRP), the U.S. National Institute of Allergy and Infectious Diseases (NIAID), or investigator.

9.0 STATISTICAL CONSIDERATIONS**9.1 General Design Issues**

The study has two components: (1) a randomized open label comparison between immediate cryotherapy (Arm A) and cytology-based strategy (Arm B) in participants detected with hr-HPV and (2) a brief cohort follow-up for participants for whom cryotherapy is inappropriate (Arm C).

The study sample size is driven by the randomized component of the study, which is primary for the study. It is a proof-of-concept study to evaluate if a “test-and-treat” strategy for HPV is promising in HIV-infected women in resource limited settings. As such, the primary analysis will be conducted with a one-sided test to assess if immediate cryotherapy (Arm A) reduces the week 26 through week 130 cumulative rate of CIN2+ (CIN 2, CIN 3, or invasive cancer) compared to the cytology-based strategy (Arm B).

Should immediate cryotherapy be worse than the cytology-based strategy, the proposed “test-and-treat” strategy will not be pursued. Therefore, it is not important to have formal statistical evidence for the negative result. The study is powered well at 90% so that the chances of missing a positive result, thereby missing an opportunity to pursue a promising cervical screening strategy, are small.

Approximately 105 participants for whom cryotherapy is inappropriate will be followed in the study for 26 weeks (Arm C). Type-specific HPV detections and cervical cytology and biopsy outcomes will be assessed.

9.2 Endpoints

9.2.1 Primary Endpoint

CIN2+ (CIN2, CIN3 or invasive cancer) by biopsy 26 weeks post randomization through 130 weeks post randomization, as determined by local review at a DAIDS-assessed laboratory.

9.2.2 Secondary Endpoints

- 9.2.2.1 Targeted AEs reported post cryotherapy (Arm A).
- 9.2.2.2 Targeted AEs reported post LEEP.
- 9.2.2.3 Detection of hr-HPV by *careHPV* at study visits.
- 9.2.2.4 Cervical cytology results at study visits.
- 9.2.2.5 Time to CIN2+ diagnosis by biopsy, as determined by local review at a DAIDS-assessed laboratory.
- 9.2.2.6 Early study discontinuation rates and reasons.
- 9.2.2.7 Nadir CD4 and CD4 count and HIV RNA levels at screening.
- 9.2.2.8 *careHPV* results, HPV DNA PCR results, and aHPV results.
- 9.2.2.9 Colposcopic impression from screening (no lesions seen, lesions seen that are appropriate for cryotherapy, lesions seen that are NOT appropriate for cryotherapy).
- 9.2.2.10 CIN3+ (CIN3 or invasive cancer) by biopsy 26 weeks post randomization through 130 weeks post randomization, as determined by local review at a DAIDS-assessed laboratory.

9.2.3 Tertiary Endpoints (contingent on future funding)

- 9.2.3.1 Detection of type-specific HPV by DNA PCR at study visits.

9.2.3.2 Confirmed detection of type-specific HPV by DNA PCR at two consecutive study visits.

9.3 Randomization and Stratification

The participants with hr-HPV by aHPV, and for whom cryotherapy is appropriate, will be randomized with equal probability to Arm A or B to receive immediate cryotherapy at study entry (Arm A) or to follow the cytology-based strategy (Arm B). Randomization to Arms A and B will be stratified by the current use of ART (any ART or no ART). There will also be institutional balancing to help ensure roughly equal sizes of Arms A and B at a given site. Enrollment will continue until the study has accrued at least 140 participants in each of Arms A and B. Approximately 170 participants will be enrolled in Arm C. There is no required minimum number of participants to be enrolled in Arm C. Randomization will be by permuted blocks with institutional balancing.

9.4 Sample Size and Accrual

For the primary analysis, cumulative occurrence of CIN2+ on biopsy from week 26 to week 130 will be compared between Arms A and B.

The study reported by Kuhn et al [22] implies about a 43% cumulative rate of CIN2+ among women infected with HIV at entry in the delayed evaluation arm compared to about 7% in the HPV test-and-treat arm (comparable to Arm A) for HIV-infected and hr-HPV positive women with 3-year follow-up. However, unlike the delayed evaluation arm in Kuhn's study, some of the women in Arm B in the current study may be diagnosed with CIN2+ based on the abnormal baseline cervical cytology that leads to colposcopy and possibly successful treatment within 26 weeks. Hence, the CIN2+ rate in Arm B is likely to be less than 43% approximated from the delayed evaluation arm in Kuhn's study. It is approximated that 24% of the hr-HPV-positive, HIV-infected women will be diagnosed with CIN2+ at the first colposcopy, based on the baseline HPV prevalence and the month 6 colposcopy results reported by Kuhn et al [22]. Assuming that the sensitivity of cervical cytology is approximately 80% and the efficacy of the treatment is 90%, it is approximated that 17% of the HPV-infected women in Arm B will be diagnosed with CIN2+ and treated successfully prior to week 26. Taking into account that these CIN2+ events will not count as events in the A5282 study, using an assumed exponential distribution for time to event to adjust for the shorter follow up time in A5282 compared to the Kuhn study, and using the three year cumulative event rates of 7% and 43% in the Kuhn study's HPV-and-treat arm and delayed evaluation arm, respectively, we estimate the cumulative CIN2+ event rate from week 26 to week 130 in Arm A and Arm B to be about 6% and 20%, respectively.

As a proof-of-concept study, the protocol team plans to conduct a one-sided test using time-to-event methods that adjust for interval censored data at a type 1 error rate of 5% to show improvement with immediate cryotherapy (Arm A) with at least 90% power. Assuming a 20% rate in Arm B and 6% rate in Arm A leads to a study sample size of 111 in each arm. Table 2 below presents a conservative estimate [42] of the power to detect various rate differences between the study arms with the sample size of 111 in

each arm using a Fischer's exact test. Based on simulations, the actual analysis method will have at least as much power as presented in Table 2.

Table 2: Assumed Rates and Sample Sizes

Arm B Rate	Arm A Rate	Arm Difference	Power
0.22	0.07	0.15	91%
	0.06	0.16	95%
	0.05	0.17	97%
0.20	0.07	0.13	84%
	0.06	0.14	90%
	0.05	0.15	94%
0.18	0.07	0.11	74%
	0.06	0.12	82%
	0.05	0.13	88%

Accounting for up to 20% overall for loss to follow-up (assumed to be not associated with the endpoint), the study will enroll 140 participants in each study arm. The protocol team expects about 40% of the participants screened for this study to be detected with hr-HPV and eligible for randomization to Arms A and B. It is approximated that screening about 700 participants will lead to 280 participants for Arms A and B. The remaining participants, approximated to be about 170, will be followed in Arm C. Not more than 170 participants will be enrolled in Arm C for follow-up in this study.

We anticipate accrual to be completed 15 months from the time the protocol is released to the sites.

9.5 Monitoring

The study will be reviewed at least annually by the NIAID Co-Infections and Complications DSMB, starting 6-12 months after the accrual of the first participant. As a proof-of-concept study in comparison between Arms A and B, formal interim analyses to conclude early superiority of immediate cryotherapy in reducing the cumulative rate of CIN2+ over 2 years will not occur. To consider futility, the DSMB will review the rates and predicted confidence bounds using the accumulated data and the simulated data for the unobserved remainder under the observed trend and under the design assumptions. The DSMB will review the AEs related to cryotherapy and overall reported AEs in the study arms. The DSMB will also review early discontinuation rates in the study arms and the reasons for discontinuation. The DSMB will also review baseline data critical to our sample size calculations including proportion diagnosed with CIN2+ in the control arm at entry which we assume to be 17%.

Reports on toxicity events will be provided to the DAIDS Medical Officer following the standard schedule for DSMB-monitored studies. Frequent reports on accrual and the conduct of the study will be provided to the protocol team. The schedules and formats of these reports will be outlined in the study monitoring plan.

9.6 Analyses

9.6.1 Comparison of CIN2+ between Arms A and B

For the primary analysis, time-to-event methods will be used to estimate the cumulative rate of the primary endpoint (from week 26 to week 130 after study entry) to account for lost to follow-up. The protocol team plans to use the Turnbull estimation for the proportions of participants without CIN2+ diagnosis by the end of the study, stratified by the study stratification factors [43]. The generalized Greenwood's formula for the standard error will be used for the variance and inverse variance method to account for strata [44]. The proportions in Arms A and B will be compared using asymptotic normal distributions. A one-sided 95% upper confidence bound on the difference (Arm B proportion minus Arm A proportion) between these proportions will also be provided. A stratified log-rank test will be conducted as a secondary analysis to compare the time to development of CIN2+ between Arms A and B. The primary analysis will be conducted as intent-to-treat on all participants randomized to the study Arms A and B. In other words, participants will be included in the analyses even if cryotherapy is not performed in Arm A and participants do not adhere to the strategy in Arm B. Per-protocol analysis will also be performed on only the participants who adhere to the specified procedures in Arms A and B, as secondary analysis. Participants without complete biopsy data will be censored at their last visit with a biopsy result (i.e., weeks 26, 78, 130).

Participants in Arm B may have biopsy done prior to week 26 based on the evaluation of baseline abnormal cervical cytology, whereas participants in Arm A will not have biopsies until week 26. Participants in Arm B diagnosed prior to their week 26 visit with CIN2+ that is cleared according to the biopsy at their week 26 will not be considered failures for the primary endpoint analysis. They are counted as meeting the primary endpoint only if CIN2+ is found at week 26 or later. Unplanned biopsies in Arm A that occur prior to the week 26 visit will not be considered for the primary endpoint.

The pathologic classification for the primary endpoint will be the determination by the local review at a DAIDS-assessed laboratory. Central review will be done for quality assurance.

9.6.2 Analyses of Secondary Endpoints

Secondary objectives will be evaluated with 2-sided tests or 2-sided confidence intervals with a significance level of 5%. The study is not powered to test the secondary study objectives formally, and no adjustment will be made to the type I error rates to account for multiple testing.

9.6.2.1 Arms A and B Only

The primary endpoint analysis method will be applied using an endpoint of CIN3+ (CIN3 or invasive cancer), as determined by local review at a DAIDS-assessed laboratory.

The targeted AEs reported after cryotherapy (Arm A) will be described separately. The study discontinuation rates will be compared between Arms A and B, using Fisher's exact tests, and time to discontinuation will be compared using a log-rank test. The reasons for study discontinuations will also be summarized.

The proportions of participants with hr-HPV detection by aHPV will be compared between Arms A and B at each study visit after study entry using Fisher's exact tests. Logistic mixed effects models will be developed for the longitudinal data on detection of hr-HPV at post entry visits to make a comparison between Arms A and B. These models will explore nadir CD4 count and baseline/screening characteristics (e.g., HIV RNA level and cytology outcome) as independent variables. Similar analyses will be conducted to assess cytological abnormalities.

Within Arm A, cryotherapy outcomes will be assessed using McNemar's test for correlated proportions. Proportions of participants with and without cytological abnormalities at baseline and at 26 weeks after cryotherapy will be estimated. The HPV types detected at the time of abnormalities will also be summarized.

Time to CIN2+ diagnosis will be compared between those with and without detection of hr-HPV by aHPV and by *care*HPV at 26 weeks after cryotherapy, using a log-rank test in Arm A. It will also be compared between those with and without cervical cytological abnormality at 26 weeks after cryotherapy.

9.6.2.2 Arms A, B and C

The frequencies of HPV types by DNA PCR and the rate of hr-HPV by aHPV and *care*HPV detected at screening will be summarized. Detection rates of multiple HPV types will also be described. Logistic regression models will be developed to explore the factors associated with cytological abnormalities at entry or screening, e.g., HPV types, CD4, nadir CD4, and HIV RNA level.

The sensitivity and specificity of *care*HPV for hr-HPV detection will be assessed based on aHPV results and HPV DNA PCR results on the types included in *care*HPV, using the screening data. The agreement between the *care*HPV and aHPV, and *care*HPV and HPV DNA PCR methods for categorizing the HPV type, beyond what would be expected by chance, will be estimated with Cohen's *Kappa* statistic [45].

The targeted AEs reported after LEEP in all study arms will be described.

We will report the proportion of women with cervical lesions inappropriate for cryotherapy. We will report the prevalence of CIN2+, hr-HPV test results, and cytological abnormalities in these women. Specifically, we will assess the sensitivity, specificity, positive and negative predictive value of hr-HPV detection by careHPV and aHPV for CIN2+ in this subgroup. We will explore the inter-rater reliability of such assessments by blinded review of digital colposcopic images. We will assess the relationship of CD4 cell count (<200, 200-349, 350-499, ≥500), ART use (yes or no), and plasma HIV RNA to the presence of these lesions.

10.0 PHARMACOLOGY PLAN

Not applicable.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

CRFs will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization/participant registration.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the U.S. NIAID will visit participating CRSs to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, the U.S. NIAID, or the U.S. OHRP for confirmation of the study data.

11.4 Expedited Adverse Event (EAE) Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS Expedited Adverse Event (EAE) Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The suspected, unexpected serious adverse reaction (SUSAR) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- There are no study agents for this protocol. All Grade 3 and 4 SAEs that are related to study procedures should be reported.
- In addition to the SUSAR Reporting Category identified above, other AEs that must be reported in an expedited manner are cervical, vaginal, and vulvar cancers and miscarriages.

11.4.3 Grading Severity of Events

The DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification August 2009) and Addendum 1-Female Genital Grading Table for Use in Microbicide Studies are used and available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, SUSARs, as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 HUMAN PARTICIPANTS

12.1 IRB/EC Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB/EC responsible for oversight of the study. A signed consent form will be obtained from the participant or legal guardian/representative. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant or legal guardian/representative and this fact will be documented in the participant's record.

12.2 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 ACTG, IRB/EC, the U.S. NIAID, the U.S. OHRP, or any host country regulatory entities.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, the U.S. NIAID, the U.S. OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies.

14.0 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 U.S. NIH.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

15.0 REFERENCES

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APPENDIX I

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT

For protocol:

A5282, FINAL Version 1.0, Dated 11/16/10, A Randomized Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-infected Women

SHORT TITLE FOR THE STUDY: A5282, FINAL Version 1.0, Dated 11/16/10, Comparison of Two Strategies for the Prevention of Cervical Cancer in HIV-infected Women

INTRODUCTION

You are being asked to take part in the research study named above because you are a woman infected with HIV (the virus that causes AIDS). This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

Women sometimes develop cancer in an area called the cervix, which is the opening to the uterus, or womb. Women who have HIV are more likely to get this kind of cancer than women who do not have HIV. Nearly all of these cancers are caused by another virus, called human papilloma virus (or HPV). Other times, the cause of this cancer is not known.

We are looking for a better way to prevent cervical cancer. This study is comparing two different methods to prevent cancer of the cervix in women who have HIV. This study will also see if these methods are safe and tolerable in women who have HIV.

First, a test for HPV will be done. HPV is the virus that usually causes cervical cancer. Some types of HPV are more likely to cause cervical cancer than others. These types are called high risk. Women with high risk types of HPV virus in their cervix will be assigned to one of two different approaches. In the standard approach, two procedures are done to check for cancer cells in the cervix. The first procedure is called a Pap test. For this test, a sample of cells is collected from the cervix and looked at under a microscope. If there are signs of abnormal cells, another sample is taken with a biopsy, which is when a small piece of cervical tissue is removed

APPENDIX I (Cont'd)

to be looked at more closely. If the biopsy shows abnormal cells, one more procedure, called LEEP, will be done to remove the abnormal cells. The purpose of removing the cells is to prevent cervical cancer from developing.

The second approach is experimental and involves a freezing procedure called cryotherapy. During this procedure, cells in the cervix that have the HPV high risk virus will be frozen and killed. This approach to preventing cervical cancer is called "test and treat."

In this study, women will be assigned at random to one of two methods to prevent cancer. The first method is the standard method, using the Pap test, biopsy, and if needed LEEP (which is used only when abnormal cells are found). The second method is experimental, using the cryotherapy (freezing) procedure for all women who have high risk types of HPV virus.

Cryotherapy is not the preferred option for all women. Women who are not eligible for cryotherapy will be followed in the study and receive other standard treatments appropriate for them.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Definitions

This consent form includes specific terms used to describe screening procedures for cervical cancer that will be done in this study. These terms are defined in Attachment A of this consent form and include:

1. Speculum exam
2. Pap test and HPV testing
3. Cervical colposcopy
4. Cervical biopsy
5. Cervical cryotherapy
6. LEEP

Before the study starts

If you agree to join this study, you will be asked to sign this consent form. After you have signed this form, you will be asked to come to the clinic for a screening visit. Tests will be done at the screening visit to make sure you meet the requirements for joining the study. The study doctor or nurse will tell you how long the screening visit may take.

The screening visit will include:

- Proof of your HIV infection. If there is no record available, another HIV test will be done. You may have to sign a separate consent form before this is done.
- A complete physical exam. You will also be asked to answer questions about your medical history, medications you are taking now and have taken in the past, and how you have been feeling. You will be asked a question about your lowest ever CD4 cell count (the number of white blood cells that fight infection) unless a record of this is already available.
- A speculum exam, colposcopy without biopsy, and collection of cervical samples using a small brush. A picture will be taken of the cervix during the colposcopy. The study doctor or

APPENDIX I (Cont'd)

nurse will insert three (3) small brushes in and around the cervix for a Pap test and three (3) different tests for HPV.

- A complete blood count. You will have about 1 teaspoon of blood drawn from a vein in your arm for these tests.
- A blood or urine pregnancy test, if you are able to become pregnant. About 1 teaspoon of blood will be drawn from a vein in the arm or you will give a urine sample at the clinic for the pregnancy test. You will not be able to enroll in this study if you are pregnant.
- A CD4 cell count and an HIV viral load test (a measure of how much HIV is in your blood). About 4 teaspoons of blood will be drawn from a vein in your arm.

The study staff will discuss test results with you throughout your participation in this study. The results of the complete blood count, CD4 count, and HIV viral load will be provided to your medical providers to assist in the treatment of your HIV infection.

Depending on the results of the screening tests, the study doctor or nurse will tell you when to come back to the clinic for the entry visit or will tell you if this study is not a good fit for you. You cannot take part in this study if the screening tests show signs of cervical cancer. Instead, you will have biopsies done for confirmation. The study doctor or nurse will talk to you about your choices and connect you to the appropriate medical care.

If you do NOT enroll into the study

If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use the information we collect from you. As part of this screening visit, some demographic (e.g., age, gender, race), clinical (e.g., disease condition, diagnosis, HPV test results, pictures from colposcopy), and laboratory (e.g., CD4 cell count, HIV viral load) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study. This information may also help to understand what puts women with HIV at higher risk for abnormal Pap tests and to understand how well the HPV tests work in women with HIV.

Entry visit

If cryotherapy is a good option for you, at entry you will be assigned into Group A or Group B. You will be assigned by chance (as if by the toss of a coin [*or the site may insert a culturally-appropriate description of randomization*]). Your chance of being assigned to either of these groups is equal. You, your doctor, and the study staff will be told which group you are in.

If cryotherapy is not a good option for you, you will be eligible for Group C. If the test for high-risk HPV is negative but there are areas that might be damaged by HPV or the screening Pap test is very abnormal, you will also be eligible for Group C.

All of the groups are as follows:

- Group A: HPV test-and-treat
- Group B: Pap-screening
- Group C: Women not eligible for cryotherapy

Groups A and B

At entry:

APPENDIX I (Cont'd)

- You will be asked about any medicine changes you have had since the screening visit.
- You will be asked to complete a questionnaire about your sexual behavior, family, and living arrangements.
- You will be asked how you have been feeling. You may have a physical exam depending on how you feel.

If you are in Group A, you will have cryotherapy of your cervix at or within one week of the entry visit.

If you are in Group B, the study doctor or nurse will tell you when to come back to the clinic to receive your Pap test result or will give the result of the Pap test to you at this visit. If the Pap test is abnormal, you will have cervical colposcopy and biopsies of areas that look abnormal. The study doctor or nurse will then tell you when to come back to the clinic again to receive the results of the biopsies. If the biopsies show HPV-damaged areas, you will undergo LEEP, a procedure to remove these areas.

For both groups, you will return to the clinic about 6, 12, 18, 24, and 30 months after the entry visit. At these visits:

- You will have a Pap test and cervical samples collected using a small brush for high-risk HPV tests.
- You will be asked about any medicine changes you have had since your last study visit.
- You will be asked to complete a questionnaire about sex you have had recently.
- You will be asked how you have been feeling. You may have a physical exam depending on how you feel.

At the study visit about 6, 18, and 30 months after the entry visit you will also have a colposcopy and biopsies if any abnormal areas are seen.

You will have a pregnancy test done (blood or urine):

- At anytime throughout the study if you think you may be pregnant.
- Before you have cryotherapy, if scheduled. (If you are pregnant, cryotherapy will not be done.)
- Before you have a LEEP, if done.

The study doctor or nurse will tell you how long each visit may take. The study visit at 130 weeks (about 2 ½ years) is the last study visit for Groups A and B.

Group C

At entry, you will have the same tests done as mentioned above for Groups A and B. Also, you will have colposcopy and biopsies at entry if any abnormal areas are seen. If these tests show HPV-damaged areas, then you will have a LEEP.

If you have a LEEP, you will be asked to return to the clinic about 6 months after entry. At this visit:

- You will be asked about any medicine changes you have had since your last study visit.
- You will be asked to complete a questionnaire about sex you have had recently.

APPENDIX I (Cont'd)

- You will be asked how you have been feeling. You may have a physical exam depending on how you feel.
- You will have a colposcopy and biopsies if any abnormal areas are seen.
- You will have a Pap test and cervical samples collected using a small brush for high-risk HPV tests.

The study doctor or nurse will tell you how long each visit may take. The study visit at about 6 months is the last study visit for Group C.

All groups

You should not have vaginal sex, douche, or place anything inside the vagina for 48 hours (2 days) before the following procedures: speculum exam, Pap test, HPV testing, cervical colposcopy, cervical biopsy, cryotherapy, and LEEP.

Whenever you have a Pap test or cervical biopsy during the study, you will return to the clinic to discuss the results with the study doctor or nurse. The study doctor or nurse will tell you how long this may take. The study doctor or nurse may ask you to complete additional procedures depending on the results. These additional procedures may include colposcopy with biopsies or LEEP. You will be given instructions on how to prepare for these procedures and what to expect after the procedures are completed (such as normal side effects).

Throughout the study, whenever you have cryotherapy or LEEP:

- You will return to the clinic about one month later to complete a questionnaire about how you have been feeling since the procedure.
- We ask that you not have vaginal sex or douche for 6 weeks after the procedure. There are two reasons for not having sex. First, there is a small chance this procedure may cause an infection of the cervix. Second, there is a possibility of the presence of more blood and HIV in the vagina after the procedure. These things could place your partner at higher risk for getting HIV. To be safer, it is recommended that if you have vaginal sex, your sexual partner uses a condom.

To help ensure the quality of study procedures, medical experts other than the study doctor and nurse will review:

- Pictures taken of the cervix right before and right after cryotherapy, colposcopy, and LEEP.
- Some of the biopsy specimens.
- A portion of the specimen collected during LEEP.

The study doctor or nurse will share the results of these reviews with you when they become available.

At anytime throughout the study, if tests reveal the presence of cervical cancer, the study doctor or nurse will talk to you about your choices and connect you to the appropriate medical care. You will be asked to stay in the study. If you decide to stay in the study, you will continue to come to the clinic for study visits and receive all tests for your group.

APPENDIX I (Cont'd)

If you do not have cryotherapy or LEEP at the start of the study

If you do not have cryotherapy (Group A only) or LEEP at the start of the study, you will still be asked to continue in the study. If you decide to stay in the study, you will come to the clinic for the study visits and receive all tests for your group.

If you do not complete study visits up to week 130 (Groups A and B) or week 26 (Group C)

If you end your participation in the study before the last study visit for your group, you will be asked to come to the clinic for one last visit before going off study. At this visit:

- You will be asked about any medicine changes you have had since your last study visit.
- You will be asked to complete a questionnaire about sex you have had recently.
- You will be asked how you have been feeling. You may have a physical exam depending on how you feel.
- You will have colposcopy and biopsies if any abnormal areas are seen.
- You will have a Pap test and cervical samples collected using a small brush for high-risk HPV tests.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 450 people will join Groups A, B, and C.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 2 ½ years if you are in Group A or B and about 6 months if you are in Group C.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- continuing the study may be harmful to you.
- the study is stopped or cancelled.

WHAT ARE THE RISKS OF THE STUDY?

Use of certain medications

If you are taking a drug used to stop blood from clotting (including aspirin and ibuprofen), tell your study doctor or nurse. Some of these medications may prevent you from having cervical biopsies, cryotherapy, or LEEP done.

Completing questionnaires

Answering questions about sexual behaviors may cause embarrassment.

APPENDIX I (Cont'd)

Blood draw

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness; and in rare cases, fainting or infection.

Cervical colposcopy, speculum exam, Pap test, and HPV testing

These tests can be uncomfortable. Occasionally there can be some bleeding, a tingling feeling, or slight stinging. These tests may cause embarrassment. Some people may feel anxiety while waiting for the test results.

Cervical biopsy

- Pain during biopsy
- Mild bleeding similar to a menstrual period
- Rarely, the following problems can occur
 - Heavy bleeding can occur requiring treatment to stop the bleeding
 - Infection of the cervix requiring antibiotics (drugs used to stop or slow down the growth of bacteria and germs)
 - Damage to the cervix making it more difficult to carry a pregnancy

Cervical cryotherapy

- Pain and cramping during the procedure
- Heavy, watery discharge from the vagina for 1 to 2 weeks
- Heavy, foul-smelling discharge from the vagina
- Mild bleeding similar to a menstrual period
- Infection of the cervix requiring antibiotics
- Rarely, the following problems can occur
 - Severe cramps and stomach pain requiring pain medications
 - Infection of your uterus and surrounding areas
 - Heavy bleeding requiring treatment to stop the bleeding
 - Narrowing of the cervix making it difficult for menstrual bleeding to occur
 - Accidental freezing of the vagina during the procedure
 - Dizziness or fainting during the procedure
 - Damage to the cervix making it more difficult to carry a pregnancy
 - Damage to the cervix making it difficult to become pregnant

LEEP

- Pain from injections of numbing medication into the cervix
- Blood tinged or dark brown mucus from the vagina for 1 or 2 weeks
- Dull ache or cramping during the procedure
- Pain or cramping after the procedure
- Infection of the cervix requiring antibiotics
- Rarely, the following reactions can occur
 - Dizziness, fainting or allergic reaction to the numbing medications
 - Severe bleeding of the cervix requiring sewing of the cervix
 - Accidental damage of the vagina
 - Accidental damage of the uterus
 - Infection of the uterus and surrounding areas
 - Narrowing of the cervix making it difficult for menstrual bleeding to occur

APPENDIX I (Cont'd)

- Damage to the cervix making it more difficult to carry a pregnancy
- Damage to the cervix making it difficult to become pregnant

Spreading HIV

For some time after you have cryotherapy or LEEP, it is possible the condition of the cervix may make it more likely to spread HIV to a sexual partner. For this reason, we ask that you not have vaginal sex for 6 weeks after the procedure. If you choose to have vaginal sex, we ask that your sexual partner use a condom.

WHAT DO I NEED TO KNOW ABOUT PREGNANCY AND CONTRACEPTIVES?

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell the study doctor or nurse right away. The study staff will talk to you about your choices.

You and your partner must use at least one reliable method of birth control that you discuss with the study staff for at least a portion of the time that you are in the study. You must use at least one method of birth control from the day of the entry visit until 12 weeks (3 months) after the entry visit. You must choose at least one of the birth control methods listed below:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive

If you are taking certain anti-HIV drugs (Efavirenz), you and your partner must use at least two of these methods of birth control. The study staff will discuss this with you.

If you become pregnant during the study, you will be asked to stay in the study. If you decide to stay in the study, you will continue to have most of the study tests. There are three (3) study tests that you will not have until 6 weeks after the pregnancy is completed: cervical biopsy, cervical cryotherapy, and LEEP. If you agree, study staff will contact you to ask you about the outcome of the pregnancy, even if it is after you stop taking part in the study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. A possible benefit is receiving cervical treatments that reduce the risk of developing cervical cancer. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and/or HPV.

APPENDIX I (Cont'd)

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Having screening tests for cervical cancer from your doctor
- Not having screening tests for cervical cancer
- Participating in another study, if you qualify

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to help keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by (insert name of site) IRB/EC, the U.S. National Institutes of Health, U.S. Office for Human Research Protections (OHRP), (insert any host country regulatory entities to review study documents), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

If you are diagnosed with cancer of the cervix, then you will be referred for appropriate treatment. This is not a part of the study and is not paid for by the study.

WILL I RECEIVE ANY PAYMENT?

[Sites may insert language about remuneration or delete this section if not applicable.]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the U.S. National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

APPENDIX I (Cont'd)

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by U.S. National Institutes of Health, and will not result in any penalty or loss of benefits to which you are otherwise entitled.

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

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

For questions about your rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

APPENDIX I (Cont'd)

SIGNATURE PAGE

PART A. CONSENT TO JOIN THE STUDY

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

Participant's Name (print)

Participant's Signature and Date

Participant's Legally Authorized Representative (as appropriate) (print)

Legally Authorized Representative's Signature and Date

Study Staff Conducting Consent Discussion (print)

Study Staff's Signature and Date

Witness's Name (print)
(As appropriate)

Witness's Signature and Date

PART B. LEFTOVER SAMPLES

Some of your cervical specimens that are left over after all required study testing and quality assurance reviews are done may be stored locally (with usual protectors of identity) and used for ACTG-approved HIV-related research locally or in the United States. These leftover samples may be stored for an indefinite length of time. We cannot ensure that you will be told the results of the research done on these samples.

Storage of leftover samples is not necessary to participate in the study. Even if you agree now, you may withdraw your approval for the storage of your leftover samples at anytime in the future. Please indicate with your initials below whether or not you approve the use of your leftover samples.

YES

NO

APPENDIX I
ATTACHMENT A
A5282 Definitions of Screening Procedures for Cervical Cancer

1. Speculum exam

A speculum is an instrument that a doctor or nurse inserts into the vagina to gently stretch the opening. This allows the doctor or nurse to examine the cervix, collect specimens from the cervix, and do the procedures mentioned below.

2. Pap test and HPV testing

This is a procedure in which a doctor or nurse uses a small brush and a small wooden spatula to gently scrape cells from the cervix. It will take about 5 minutes to collect these specimens. For a Pap test, the cells are looked at under a microscope to check for any problems. For HPV testing, the cells are tested to see if HPV is present and which of the 30 types of HPV are present. The three (3) types of HPV tests used in this study are:

- Abbott RealTime test for high-risk types of HPV -- This test is approved for use in Europe. You will receive the results of this test.
- careHPV -- This is an investigational test for high risk HPV. This will be done at a later point. You will not receive the results of this test.
- HPV DNA PCR -- This test identifies the specific types of HPV that are present. This will be done at a later point. You will not receive the results of this test.

3. Cervical colposcopy

This is a speculum exam in which acetic acid (such as common table vinegar) is placed on the cervix. This causes cervical cells that are not normal to appear white in color. A doctor or nurse then uses a colposcope to look at the cervix. A colposcope is a large microscope that is positioned approximately 30 centimeters from the vagina. A bright light on the end of the colposcope lets the doctor or nurse clearly see the cervix. It will take about 15 minutes to do this procedure.

4. Cervical biopsy

This is done during a cervical colposcopy. A doctor or nurse gently removes a small amount of skin from areas of the cervix that appear to be damaged by HPV. It will take about 5 minutes to do this procedure.

If it appears to the doctor or nurse that the HPV-damaged area is going inside the cervix, then a probe will be placed inside the cervix to gently scrape cells to test for abnormal cells (this process of gently scraping cells is called endocervical curettage, or ECC). It will take about 5 minutes to do this procedure.

The tissue sample (or biopsy) is sent to the laboratory to look for abnormal cells.

5. Cervical cryotherapy

This is a treatment that freezes a section of the cervix. A doctor or nurse will insert a speculum into the vagina. For this treatment, the doctor or nurse will not inject the cervix with medication to numb the cervix. A special instrument called a probe will be inserted to reach the parts of the cervix that are abnormal. A freezing material in the probe will allow the doctor or nurse to freeze and destroy the affected skin on the cervix. For this study, freezing will occur for 3 minutes, the cervix will be allowed to thaw for 5 minutes, and freezing will be repeated for another 3 minutes.

6. LEEP

LEEP is short for loop electrosurgical excision procedure. This procedure uses a thin wire loop to remove abnormal areas from the cervix. A doctor or nurse will insert a speculum into the vagina and will inject the cervix with medication to numb the cervix. The wire loop is attached to a machine that gives off small electric current. The wire is passed under the areas damaged by HPV to remove them. It will take about 20 minutes to do this procedure.