This is ACTG A5282 SAP Version 1.0 with names of authors, names of publication writing team members and analysis timeline redacted.

ACTG 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

ClinicalTrials.gov Identifier: NCT01315353

Statistical Analysis Plan

Version 1.0

13 July 2017

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1 Introduction

This document describes the proposed content for the primary statistical analysis report for ACTG study A5282. The plan includes the key analyses that will form the core of presentation or publication used to disseminate the primary conclusions of the study. It is recognized that this statistical analysis plan (SAP) may be modified by the Study Team as new information becomes available or to reflect recommendations made by the Data Safety Monitoring Board (DSMB).

2 Study Overview

2.1 Study Design

A5282 is a randomized clinical trial designed to compare a human papillomavirus (HPV) test-and-treat strategy with a cytology-based strategy for the prevention of CIN2+ (cervical intraepithelial neoplasia [CIN] grade 2 [CIN2], 3 [CIN3], or invasive cancer). The study has two components:

(1) a randomized open-label comparison between immediate cryotherapy (test-and-treat strategy; Arm A) and cytology-based strategy (Arm B) in participants detected with high-risk HPV (hr-HPV), and
(2) a brief cohort follow-up for participants for whom cryotherapy is inappropriate (Arm C).

The study is a proof-of-concept study to evaluate if a “test-and-treat” strategy is promising in HIV-infected women in resource limited settings.

All participants are screened with the Abbott RealTime hr-HPV test (aHPV) to detect hr-HPV infection. [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).]

At screening, the examiner also performs a visual inspection and colposcopy without biopsies to determine whether the candidate’s cervix is suitable for cryotherapy. Candidates suitable for cervical cryotherapy have:

(i) no visible cervical lesions, or
(ii) 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.

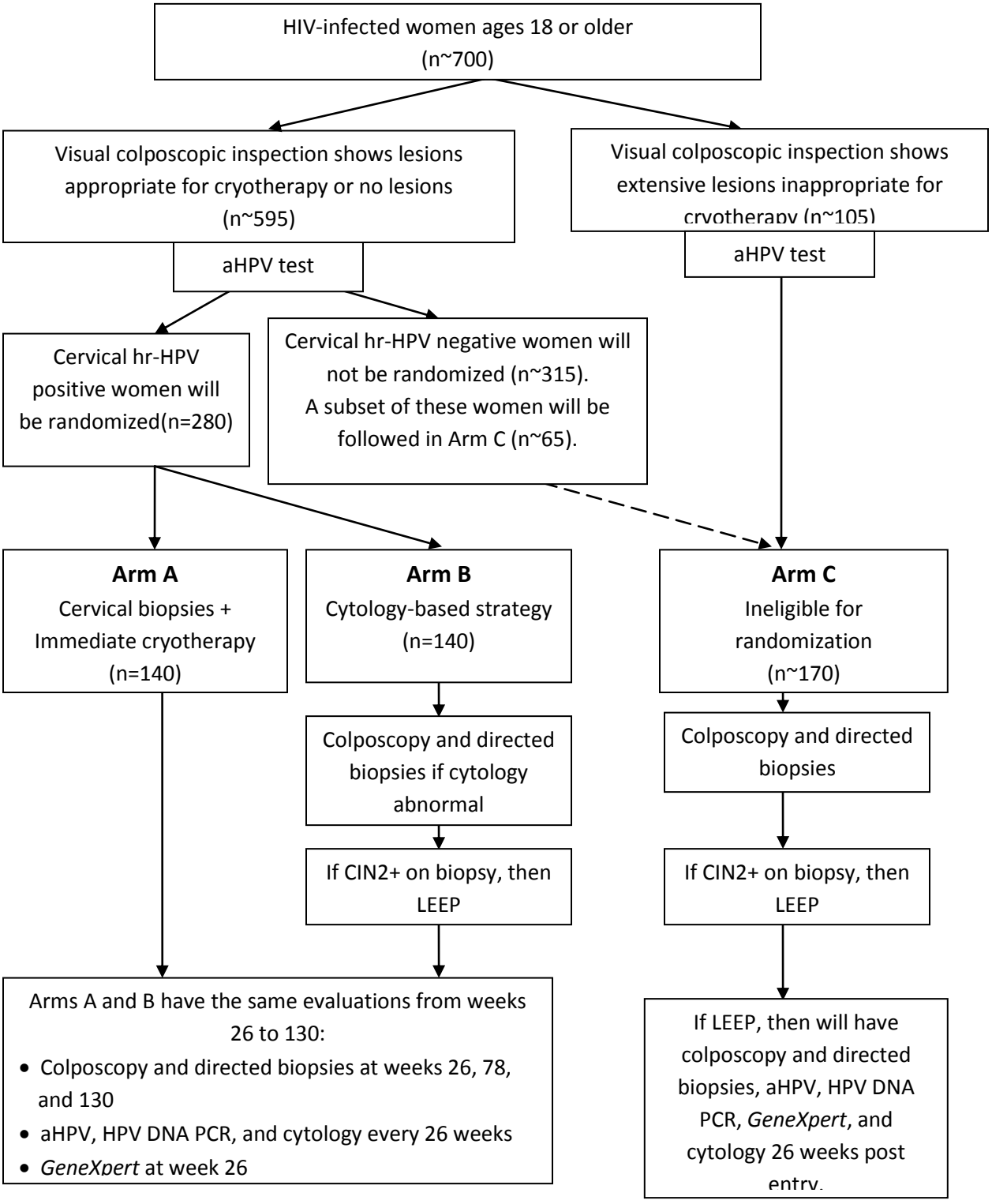
Participants with cervical lesions inappropriate for cryotherapy are not eligible for randomization (Arms A or B) but are eligible to register to Arm C. Participants without hr-HPV (by aHPV) are also eligible to register to Arm C if lesions were seen on the screening colposcopy or if the screening cytology shows high-grade squamous intraepithelial lesions (HSIL).

Participants in Arm A undergo cervical cryotherapy at entry. Participants in Arm A receive the results of the cytology, but participants receive cryotherapy treatment regardless of the results. Participants in Arm B follow a cytology-based management plan involving three steps – cytology, colposcopy with directed biopsies, and loop electrosurgical excision procedure (LEEP), as needed. Participants in Arms A and B are seen at regular intervals post entry for evaluation using aHPV, HPV DNA PCR, cervical cytology, and cervical colposcopy and directed biopsies for a total follow-up length of 130 weeks.

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

All participants undergoing cryotherapy or LEEP are seen 4 weeks post-procedure to evaluate potential 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+ are reviewed regionally and possibly centrally. HPV DNA PCR and GeneXpert are performed on stored specimens and results are not used for clinical management.

Figure 1: Overview of Study Design



2.2 Primary Hypothesis

The primary hypothesis of the study is, in HIV-infected women with hr-HPV, immediate cryotherapy results in a lower probability of CIN2+ than a cytology-based strategy.

2.3 Study Objectives

The primary objective of the study is to evaluate the effectiveness of immediate cryotherapy (Arm A) in HIV-infected women with hr-HPV compared to a cytology-based strategy (Arm B) by comparing cumulative CIN2+ rates from week 26 to week 130.

The secondary objectives are:

- **To evaluate the safety and tolerability of cervical cryotherapy (Arm A) in HIV-infected women.**
- **To compare between arms the presence of cervical cytological abnormalities during the study.**
- **To assess study discontinuation rates and reasons for discontinuation between arms.**
- **To compare the 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.**
- To assess detection frequencies of cervical HPV types (by DNA PCR) and the rates of hr-HPV by GeneXpert at study entry.
- 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.
- To evaluate the sensitivity and specificity of GeneXpert for hr-HPV detection as measured by aHPV and HPV DNA PCR at study screening and the agreement beyond chance between these measures. [PEPFAR Objective]
- 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. [PEPFAR Objective]

The tertiary objectives are:

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

NOTE: Only the highlighted objectives will be addressed by the current analysis plan. The other objectives were addressed in previous analyses.

3 Statistical Considerations

Unless otherwise indicated, analysis will use data from all subjects who enrolled successfully to A5282 arms A and B.

For categorical measures, number of subjects and percent will be provided. For continuous measures, median, lower and upper quartiles, minimum and maximum will be provided. In data listings, participants will be identified by an anonymous patient identifier generated at the statistical center. Dates will not be shown, but will be converted to time (e.g. weeks) since randomization.

Time to CIN2+ will be computed as the number of weeks between randomization and the week 26 to week 130 biopsy week when CIN2+ was first detected. For those who did not develop CIN2+, event time will be censored at the latest among the following: time of last biopsy or last colposcopy or last pap smear. The cumulative rate of CIN2+ will be estimated using Kaplan-Meier methods. A one-sided 95% upper confidence bound on Arm B minus Arm A cumulative rates accounting for baseline ART use (i.e. [using inverse variance as weights,] weighted estimate of treatment difference across baseline ART use) will be provided.

The per-protocol secondary analysis of the primary endpoint will only include:

a. Arm A participants who had week 0 cryotherapy, and
b. Arm B participants with: 1) baseline NILM cytology, 2) baseline abnormal cytology (ASCUS or greater) with one or more cervical biopsies that show NILM or CIN1 as the most severe result, 3) baseline abnormal cytology (ASCUS or greater) who underwent cervical colposcopy with no lesions seen, or 4) women who had LEEP performed prior to week 16 after the week 0 CIN2+ on biopsy regardless of cytology result.

All programs that generate derived data will be validated. The calculations of time to CIN2+ and confidence interval for the primary endpoint (one-sided 95% upper confidence interval for arm B proportion minus arm A proportion) will be double-programmed.

4 Outline of Planned Analyses

4.1 Background

4.1.1 Study History

Summary of changes and clarifications of the protocol.

4.1.2 Accrual

Tables of accrual by month and site (CRS) by arm.

4.1.3 Study Status

Table with:

- number of participants enrolled
- number of participants who completed study
- number of participants who discontinued the study prematurely
- follow-up time on study
- listing of participants who discontinued the study prematurely and reasons for discontinuation.
- listing of deaths and description.

4.1.4 Treatment Status

Table with:

- listing of Arm A participants who did not have cryotherapy and reasons
- listing of Arm B participants who did not have LEEP after CIN2+ diagnosis
- listing of Arm B participants with abnormal cytology who do not have biopsies obtained at baseline

4.1.5 Baseline Summaries

- Baseline demographics, sociodemographic and health variables: age, race/ethnicity, IV drug use history, ART use, CD4 count, nadir CD4 count, highest level of education complete, average annual household income, number of children
- Baseline sexual history: age of first vaginal sex, total number of vaginal sex partners
- Baseline cytology and Abbott hr-HPV results

4.2 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

Note: LEEP outcome prior to week 16 will be considered baseline evaluation and will not be used as an endpoint.

Tables (ITT and per-protocol): cumulative rates of arm A and arm B subjects who developed CIN2+ from week 26 to week 130; one-sided 95% upper CI for arm B proportion minus arm A proportion.

SDAC validation: The calculation of time to CIN2+ and the one-sided 95% upper CI will be double-programmed.

In addition, (to evaluate design assumptions and precursory design assumptions,) the following will be reported:

- Arm A and Arm B: CIN2+ rate from week 26 to week 130
- Arm A and Arm B: week 0 invasive cancer
- Arm B: number (%) diagnosed with CIN2+ at baseline
- Arm B: number (%) with CIN2+ at baseline who were successfully treated before week 26. Note that we only have a limited number of participants with cervical (non-LEEP) biopsy results before week 26.
- number (%) of subjects with abnormal pap smear and CIN2+ at baseline
- number (%) of subjects with CIN2+ at baseline who were successfully treated before week 26.

4.2.1 Secondary endpoint: Time to CIN2+ diagnosis by biopsy, as determined by local review at a DAIDS-assessed laboratory

Figures (ITT and per-protocol): survival curves with p-value from stratified log-rank test comparing arms A and B.

Figure: For Arm A, survival curves with p-value from log-rank test comparing participants with and without hr-HPV at week 26 based on: (a) aHPV, and (b) Xpert

Figure: For Arm A, survival curves with p-value from log-rank test comparing participants with and without cervical cytologic abnormalities at week 26.

Figures (ITT): survival curves with p-value from stratified log-rank test comparing arms A and B.

Figures (ITT): survival curves with p-value from stratified log-rank test comparing arms A and B for those with: (a) CIN2+ on histology at baseline, (b) CIN1 on histology at baseline, (c) NILM cytology result at baseline, (d) ASCUS/LSIL cytology result at baseline and (e) HSIL/ASC-H cytology result at baseline.

4.2.2 Secondary endpoint: 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.

NOTE: Time to CIN3+ will be computed as the number of weeks between randomization and the biopsy week when CIN3+ was detected. For those who did not develop CIN3+, event time will be censored at the latest among the following: time of last biopsy or last colposcopy or last pap smear.

Tables (ITT and per-protocol): cumulative rates of arm A and arm B subjects who developed CIN3+ from week 26 to week 130; two-sided 95% CI for arm B proportion minus arm A proportion.

Figures: survival curves with p-value from stratified log-rank test comparing arms A and B

4.2.3 Secondary endpoint: Targeted AEs reported post cryotherapy (Arm A)

Table: Listing of targeted AEs with number (%) of arm A subjects with the AE

4.2.4 Secondary endpoint: Targeted AEs reported post LEEP

Table: Listing of targeted AEs with number (%) of subjects with the AE

4.2.5 Secondary endpoint: Cervical cytology results at study visits

Table (based on arms A and B): Cytology results (normal, abnormal:LSIL, abnormal:HSIL) at study visits with p-value from Fisher's test.

Table (based on arm A only): (Crosstabulation of) Cytology results at baseline and week 26 with p-value from McNemar's test.

Tables (based on arms A and B cytology results after study entry): Results of longitudinal logistic mixed effects models with independent variables nadir CD4 count, baseline/screening characteristics (e.g., HIV RNA level, current CD4 count, sexual history and cytology outcome) and recent sexual activity (time-updated variables on number of vaginal sex partners and frequency of condom use within the previous 6 months) ***[EXPLORATORY]***

4.2.6 Secondary endpoint: Early study discontinuation rates and reasons (arms A and B)

Table: Number (%) subjects who discontinued; p-value from Fisher's exact test.

Table/Listing: For subjects who discontinued study prematurely, the following will be listed: off study week, reason for early study discontinuation.

Figure: KM plot of time to discontinuation with p-value from log-rank test. The time to study discontinuation will be the number of weeks between off-study date and randomization date.

4.2.7 Secondary endpoint: aHPV results (detected, not detected) after study entry

Table (based on arms A and B): hr-HPV aHPV results at study visits after entry with p-value from Fisher's test.

Tables (based on arms A and B): Results of longitudinal logistic mixed effects models with independent variables nadir CD4 count, baseline/screening characteristics (e.g., HIV RNA level, current CD4 count, sexual history and cytology outcome) and recent sexual activity (time-updated variables on number of vaginal sex partners and frequency of condom use within the previous 6 months) ***[EXPLORATORY]***

NOTE: In case of limited aHPV results, Fisher's/logistic will only be done at select weeks.