

SUMMARY OF CHANGES

Feasibility Study of Safety, Toxicity, and Compliance of Concomitant Chemoradiotherapy for HIV-Associated Locally-Advanced Cervical Cancer (Version 3.0)

NCI Protocol #: AMC-081
Local Protocol #: AMC-081

NCI Version Date: 20 February 2015
Update Date: 20 February 2015

I. Changes made in Amendment v3.0

#	Section	Comments
1.	<u>Cover page</u>	<p><u>Changed from:</u> Version 2.0 28 May 2013 NCI Version Date: 28 May 2013 Update Date: 14 April 2014</p> <p><u>Changed to:</u> Version 3.0 NCI Version Date: 20 February 2015 Update Date: 20 February 2015</p>
2.	<u>Footer</u>	<p><u>Changed from:</u> AMC # 081 (Version 2.0) 14 April 2014 NCI Version Date 28 May 2013</p> <p><u>Changed to:</u> AMC # 081 (Version 3.0) 20 February 2015 NCI Version Date 20 February 2015</p>
3.	<u>Signature page</u>	<p><u>Changed from:</u> Version 2.0 28 May 2014</p> <p><u>Changed to:</u> Version 3.0 20 February 2015</p>
4.	<u>Abbreviation List</u>	<p><u>Changed from:</u> Text added.</p> <p><u>Changed to:</u> IROC Houston QA Center - Imaging and Radiation Oncology Core Houston QA Center</p>
5.	<u>Abbreviation List</u>	<p><u>Changed from:</u> RPC – Radiology Physics Center</p> <p><u>Changed to:</u> Text removed.</p>

#	Section	Comments
6.	<u>Protocol Roster</u>	<p><u>Changed from:</u> Email: amcpm@emmes.com</p> <p><u>Changed to:</u> Email: amipm@emmes.com</p>
7.	<u>Protocol Roster</u>	<p><u>Changed from:</u> Radiological Physics Center</p> <p><u>Changed to:</u> Imaging and Radiation Oncology Core Houston QA Center</p>
8.	<u>Study Synopsis</u>	<p><u>Changed from:</u> All participants with CD4 counts $> 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $40 \text{ mg}/\text{m}^2$ (maximum of 70 mg) concomitant with radiotherapy (external beam and brachytherapy). The first 3 participants with CD4 counts $\leq 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $25 \text{ mg}/\text{m}^2$ (maximum of 43.75 mg) with radiotherapy (external beam and brachytherapy). Based on review of the safety data from the first 3 participants, all other participants with CD4 counts $\leq 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $40 \text{ mg}/\text{m}^2$ (maximum of 70 mg) or no cisplatin with radiotherapy (external beam and brachytherapy). All participants will concomitantly receive combination antiretroviral therapy (ART) with an acceptable regimen that adheres to national guidelines for treatment of HIV infection.</p> <p><u>Changed to:</u> All participants with CD4 counts $> 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $40 \text{ mg}/\text{m}^2$ concomitant with radiotherapy (external beam and brachytherapy). The first 3 participants with CD4 counts $< 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $25 \text{ mg}/\text{m}^2$ with radiotherapy (external beam and brachytherapy). Based on review of the safety data from the first 3 participants, all other participants with CD4 counts $\leq 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $40 \text{ mg}/\text{m}^2$ or no cisplatin with radiotherapy (external beam and brachytherapy). All participants will concomitantly receive combination antiretroviral therapy (ART) with an acceptable regimen that adheres to national guidelines for treatment of HIV infection.</p>
9.	<u>1.0</u>	<p><u>Changed from:</u> Radiation Physics Center</p> <p><u>Changed to:</u> Imaging and Radiation Oncology Core Houston Quality Assurance Center</p>
10.	<u>3.1.9</u>	<p><u>Changed from:</u> At the investigator's discretion, participants who are suitable for treatment with radical intent using concurrent chemotherapy and pelvic radiation. Subjects who undergo emergency radiation therapy (Refer to Section 4.2) prior to enrollment may participate.</p> <p><u>Changed to:</u> In the opinion of the investigator the protocol treatment is appropriate for the participant.</p>
11.	<u>3.2.9</u>	<p><u>Changed from:</u> Text added.</p> <p><u>Changed to:</u> Participants with enlarged para-aortic lymph node involvement on imaging that is</p>

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		suspicious for metastasis
12.	<u>3.4</u>	<p><i>Changed from:</i> This includes weekly cisplatin at 40 mg/m² (maximum of 70 mg) concomitant with radiotherapy (external beam and brachytherapy).</p> <p><i>Changed to:</i> This includes weekly cisplatin at 40 mg/m² concomitant with radiotherapy (external beam and brachytherapy)</p>
13.	<u>3.5.1</u>	<p><i>Changed from:</i> After an informed consent form has been signed by the participant, the participant must be registered for screening (AMC-081, Segment A) on-line via the AMC AdvantageEDCSM Internet Data Entry System.</p> <p><i>Changed to:</i> After an informed consent form has been signed by the participant, the participant must be registered for screening (AMC-081, Screening Segment) on-line via the AMC AdvantageEDCSM Internet Data Entry System.</p>
14.	<u>3.5.2</u>	<p><i>Changed from:</i> After a the screening evaluations are completed and the participant is determined to be eligible the participating site will complete the protocol-specific eligibility checklist and enroll the participant into AMC-081 Segment B on-line via the AMC AdvantageEDCSM Internet Data Entry System. The participating site will ensure the participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist. Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 1 week prior to the initiation of treatment (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair upon successful registration.</p> <p>If the on-line system is inaccessible for Registration (Segment B), the site should notify the AMC ODMC via email at 081protocolteam@emmes.com or via phone at 001-301-251-1161 for further instructions. If the AMC ODMC cannot be reached, please follow the manual randomization procedures detailed in the AMC-081 Manual of Procedures.</p> <p><i>Changed to:</i> After the screening evaluations are completed and the participant is determined to be eligible the participating site will complete the protocol-specific eligibility checklist and enroll the participant into AMC-081 Treatment Segment (Segment B) on-line via the AMC AdvantageEDCSM Internet Data Entry System. The participating site will ensure the participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist. Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 1 week prior to the initiation of treatment (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair upon successful registration.</p> <p>If the on-line system is inaccessible for Registration (Treatment Segment), the site should notify the AMC ODMC via email at 081protocolteam@emmes.com or via phone at 001-301-251-1161 for further instructions. If the AMC ODMC cannot be reached, please follow the manual randomization procedures detailed in the AMC-081 Manual of Procedures.</p>

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15.	<u>4.0</u>	<p><i>Changed from:</i> To be eligible, participants with invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix must have undergone clinical staging by physicians according to FIGO staging criteria (See Appendix VI).</p> <p><i>Changed to:</i> To be eligible, participants with invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix must have undergone clinical staging by physicians according to FIGO staging criteria see (Appendix VI).</p>
16.	<u>4.2.2</u>	<p><i>Changed from:</i> Cisplatin 40 mg/m² (max 70 mg) IV over 30-60 minutes given weekly on days 1, 8, 15, 22, 29 and 36 for a total of 6 weekly cycles.</p> <p><i>Changed to:</i> Cisplatin 40 mg/m² IV over 30-60 minutes given weekly on days 1, 8, 15, 22, 29 and 36 for a total of 6 weekly cycles.</p>
17.	<u>4.4</u>	<p><i>Changed from:</i> Drug will be shipped through a third party vendor. Instructions for drug ordering are available on the AMC website (www.amcoperations.com).</p> <p><i>Changed to:</i> Drug will be paid for by the AMC. Instructions for drug ordering/drug purchase will be provided to each clinical site by the AMC Operations and Data Management Center. All investigators prescribing study agent for an AMC study must have an active NCI-investigator registration.</p>
18.	<u>4.6</u>	<p><i>Changed from:</i> Radiation therapy (RT) must be started within 7 days of enrollment into Segment B; CT scan of the pelvis is required for external RT field and block definition.</p> <p><i>Changed to:</i> Radiation therapy (RT) must be started within 7 days of enrollment into the Treatment Segment (Segment B); CT scan of the pelvis is required for external RT field and block definition.</p>
19.	<u>4.6.1.2.1</u>	<p><i>Changed from:</i> Following the completion of the whole pelvic RT, the participant will receive 35-43.6 Gy to Point A (see Appendix VIII Description of points A, B and ICRU Bladder/Rectum) by intracavitary implant with a standard medical radiation source listed on the American Association of Physicists in Medicine (AAPM) source registry (http://rpc.mdanderson.org). The dose table (see Section 4.6) should be utilized to ensure adequate dose delivery.</p> <p><i>Changed to:</i> Following the completion of the whole pelvic RT, the participant will receive 35-43.6 Gy to Point A (Refer to Appendix VIII Description of points A, B and ICRU Bladder/Rectum) by intracavitary implant with a standard medical radiation source listed on the American Association of Physicists in Medicine (AAPM) source registry (http://irochouston.mdanderson.org). The dose table (Refer to Section 4.6) should be utilized to ensure adequate dose delivery.</p>

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20.	4.6.1.2.2	<p><i>Changed from:</i> See Appendix VII (HDR Brachytherapy) for guidelines of vaginal surface dose, normal tissue tolerances, packing and imaging.</p> <p><i>Changed to:</i> Refer to Appendix VII (HDR Brachytherapy) for guidelines of vaginal surface dose, normal tissue tolerances, packing and imaging.</p>
21.	4.6.1.2.5	<p><i>Changed from:</i> Each HDR brachytherapy fraction will give 6-9 Gy/fraction to Point A. (see Appendix VIII Description of points A, B and ICRU Bladder/Rectum). Each participant may be treated with up to four HDR implants with the HDR total dose ranging from 18-28 Gy (Total HDR dose) that is equivalent to an LDR delivered of 35-43.6 Gy depending on the total external beam dose given (see Appendix VII HDR Brachytherapy).</p> <p><i>Changed to:</i> Each HDR brachytherapy fraction will give 6-9 Gy/fraction to Point A. (Refer to Appendix VIII Description of points A, B and ICRU Bladder/Rectum). Each participant may be treated with up to four HDR implants with the HDR total dose ranging from 18-28 Gy (Total HDR dose) that is equivalent to an LDR delivered of 35-43.6 Gy depending on the total external beam dose given (Refer to Appendix VII HDR Brachytherapy).</p>
22.	4.6.1.2.7	<p><i>Changed from:</i> (See Appendix VII: HDR Brachytherapy).</p> <p><i>Changed to:</i> (Refer to Appendix VII: HDR Brachytherapy).</p>
23.	4.6.3.2	<p><i>Changed from:</i> Intracavitary RT may be delivered by cesium-137 or equivalent radiation source for LDR brachytherapy or cobalt-60 or iridium-192 for HDR brachytherapy in standard or commonly used tandem and ovoid applicators. Only the medical radiation brachytherapy sources listed on the AAPM source registry (http://rpc.mdanderson.org) may be used.</p> <p><i>Changed to:</i> Intracavitary RT may be delivered by cesium-137 or equivalent radiation source for LDR brachytherapy or cobalt-60 or iridium-192 for HDR brachytherapy in standard or commonly used tandem and ovoid applicators. Only the medical radiation brachytherapy sources listed on the AAPM source registry (http://irochouston.mdanderson.org) may be used.</p>
24.	4.6.4	<p><i>Changed from:</i> External Radiation Fields (see Appendix IX Blank Diagram Anterior and Appendix X Blank Diagram Lateral)</p> <p><i>Changed to:</i> External Radiation Fields (Refer to Appendix IX Blank Diagram Anterior and Appendix X Blank Diagram Lateral)</p>
25.	4.6.4.4	<p><i>Changed from:</i> The upper border of the true pelvis field is defined as 1 cm above the inferior aspect of the sacroiliac joint (see Appendix VIII Description of ICRU Bladder/Rectal Dose Reporting Points). Parametrial block should be a minimum of 4-5 cm wide if bilateral parametrial boost is used and may be shaped to the point A isodose. Unilateral parametrial boost would be used if only unilateral involvement was noted (see Section 4.6.1.3).</p>

#	Section	Comments
		<p><i>Changed to:</i></p> <p>The upper border of the true pelvis field is defined as 1 cm above the inferior aspect of the sacroiliac joint (Refer to Appendix VIII Description of ICRU Bladder/Rectal Dose Reporting Points). Parametrial block should be a minimum of 4-5 cm wide if bilateral parametrial boost is used and may be shaped to the point A isodose. Unilateral parametrial boost would be used if only unilateral involvement was noted (Refer to Section 4.6.1.3).</p>
26.	4.6.6	<p><i>Changed from:</i></p> <p>The Radiological Physics Center (RPC), a National Cancer Institute funded organization with guidance from the AAPM, will supervise the dosimetry control for this clinical trial. To participate in the trial, the institution must demonstrate the ability to achieve an accuracy of $\pm 5\%$ in measuring calibrated reference beam output of their external beam therapy units on an annual basis. Each participant record will be reviewed by the RPC to verify that each participant received their radiation therapy dose to within $\pm 5\%$ for delivering the external beam prescribed dose and $\pm 15\%$ for the brachytherapy boost.</p> <p><i>Changed to:</i></p> <p>The Imaging and Radiation Oncology Core Houston QA Center (IROC Houston QA Center), a National Cancer Institute funded organization with guidance from the AAPM, will supervise the dosimetry control for this clinical trial. To participate in the trial, the institution must demonstrate the ability to achieve an accuracy of $\pm 5\%$ in measuring calibrated reference beam output of their external beam therapy units on an annual basis. Each participant record will be reviewed by the IROC Houston QA Center to verify that each participant received their radiation therapy dose to within $\pm 5\%$ for delivering the external beam prescribed dose and $\pm 15\%$ for the brachytherapy boost.</p>
27.	5.1.1	<p><i>Changed from:</i></p> <p>Physical examination including: weight and height for BSA calculation, performance status (see Appendix II), general physical exam, and pelvic exam if judged as necessary by the investigator.</p> <p><i>Changed to:</i></p> <p>Physical examination including: weight and height for BSA calculation, performance status (Refer to Appendix II), general physical exam, and pelvic exam if judged as necessary by the investigator.</p>
28.	5.1.2	<p><i>Changed from:</i></p> <p>SGOT, alkaline phosphatase, bilirubin</p> <p><i>Changed to:</i></p> <p>SGOT, SGPT, alkaline phosphatase, bilirubin</p>
29.	5.2.1	<p><i>Changed from:</i></p> <p>ART adherence assessment will be collected on Day 8, Day 15, Day 22, Day 29, Day 36, and on the final day of radiation therapy. Physical Examination on Day 22 prior to treatment and at treatment discontinuation. Anal and cervical swabs to evaluate the exploratory objectives within 4 weeks of the completion of chemo radiation therapy (refer to Appendix XI) Serum to evaluate the exploratory study objectives within 4 weeks of the completion of chemo radiation therapy (refer to Appendix XI)</p> <p><i>Changed to:</i></p> <p>ART adherence assessment will be collected on Day 8, Day 15, Day 22, Day 29, and Day</p>

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		36. Physical examination on Day 22 prior to treatment.
30.	<u>5.2.2</u>	<p><u>Changed from:</u> Text added.</p> <p><u>Changed to:</u> Assessments at the Time of Chemo-Radiation Therapy Completion</p> <p>The following assessments must be completed within 7 days of chemo-radiation therapy completion unless otherwise specified. These assessments are required for all participants regardless of the reason for treatment discontinuation (e.g. treatment completion or early discontinuation)</p> <ul style="list-style-type: none"> • Review of interim medical history including concomitant medications and adverse events. • ART adherence assessment • Physical examination <p>The following assessments must be completed either on the final day of chemo-radiation therapy or within 4 weeks after the final dose of chemo-radiation therapy:</p> <ul style="list-style-type: none"> • Anal and cervical swabs to evaluate the exploratory study objectives (refer to Appendix XI) • Serum to evaluate the exploratory study objectives (refer to Appendix XI)
31.	<u>5.3</u>	<p><u>Changed from:</u> Text added.</p> <p><u>Changed to:</u> Participants are to be followed at 3 intervals for 1 year after completing protocol treatment. CT imaging will be repeated at the 6-month time point after discontinuing treatment only for participants that have not clinically progressed; other imaging modalities can be employed off-study, as appropriate and at the discretion of the treating physician, at other time points. Participants that progress or relapse during the 12 month study follow-up period will be followed for survival only.</p>
32.	<u>5.4</u>	<p><u>Changed from:</u> Text added.</p> <p><u>Changed to:</u> Participants will only be followed for survival following the diagnosis of disease progression or recurrence. Treatment for progressive/recurrent disease will be at the discretion of the site investigator and will not be coordinated or paid for as part of the study.</p>
33.	<u>5.5</u>	<p><u>Changed from:</u> 5.5 Premature Treatment Discontinuation Evaluations</p> <p>For participants who withdraw from treatment (discontinuation prior to completing the prescribed therapy), the following evaluations should be performed whenever possible:</p> <ul style="list-style-type: none"> • Physical examination • Review of interim medical history including concomitant medications and adverse events • Anal and cervical swabs to evaluate the exploratory study objectives within 4 weeks of the completion of chemo-radiation therapy (refer to Appendix XI) • Serum to evaluate the exploratory study objectives within 4 weeks of the

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		<p>completion of chemo-radiation therapy (refer to Appendix XI)</p> <p><u>Changed to:</u> <i>Text removed</i></p>												
34.	5.5	<p><u>Changed from:</u> SGOT, alkaline phosphatase, bilirubin</p> <p><u>Changed to:</u> SGOT, SGPT, alkaline phosphatase, bilirubin</p>												
35.	6.1.1.2	<p><u>Changed from:</u> This interruption should be limited to \leq 1 week if possible (see Section 6.1.2).</p> <p><u>Changed to:</u> This interruption should be limited to \leq 1 week if possible (Refer to Section 6.1.2).</p>												
36.	6.1.1.3	<p><u>Changed from:</u> Topical steroids and treatment interruption may be necessary also (see Section 6.1.2).</p> <p><u>Changed to:</u> Topical steroids and treatment interruption may be necessary also (Refer to Section 6.1.2).</p>												
37.	6.1.1.4	<p><u>Changed from:</u> The Study Chair should be notified of any Grade 4 toxicity (see Section 6.1.2).</p> <p><u>Changed to:</u> The Study Chair should be notified of any Grade 4 toxicity (Refer to Section 6.1.2).</p>												
38.	6.2.1	<p><u>Changed from:</u> The first three subjects who are enrolled who have a CD4 count \leq 200 mm³ (0.2 x 10⁹/L) (inclusive) will be prescribed a dose of 25mg/m² (Dose Level -2, see 6.2.2).</p> <p><u>Changed to:</u> The first three subjects who are enrolled who have a CD4 count \leq 200 mm³ (0.2 x 10⁹/L) (inclusive) will be prescribed a dose of 25mg/m² (Dose Level -2, refer to Section 6.2.2).</p>												
39.	6.2.3	<p><u>Changed from:</u> The following levels should be used for cisplatin dose reductions:</p> <table border="1"> <thead> <tr> <th>Dose Level 0</th> <th>Dose Level -1</th> <th>Dose Level -2</th> </tr> </thead> <tbody> <tr> <td>40 mg/m² (max 70 mg)</td> <td>30 mg/m² (max 70 mg)</td> <td>25 mg/m² (max 70 mg)</td> </tr> </tbody> </table> <p>There will be no dose reduction below dose level -2 (i.e. cisplatin will be discontinued if further toxicity occurs). Maximum doses refer to subjects with BSA >1.75 m².</p> <p><u>Changed to:</u> The following levels should be used for cisplatin dose reductions:</p> <table border="1"> <thead> <tr> <th>Dose Level 0</th> <th>Dose Level -1</th> <th>Dose Level -2</th> </tr> </thead> <tbody> <tr> <td>40 mg/m²</td> <td>30 mg/m²</td> <td>25 mg/m²</td> </tr> </tbody> </table> <p>There will be no dose reduction below dose level -2 (i.e. cisplatin will be discontinued if further toxicity occurs).</p>	Dose Level 0	Dose Level -1	Dose Level -2	40 mg/m ² (max 70 mg)	30 mg/m ² (max 70 mg)	25 mg/m ² (max 70 mg)	Dose Level 0	Dose Level -1	Dose Level -2	40 mg/m ²	30 mg/m ²	25 mg/m ²
Dose Level 0	Dose Level -1	Dose Level -2												
40 mg/m ² (max 70 mg)	30 mg/m ² (max 70 mg)	25 mg/m ² (max 70 mg)												
Dose Level 0	Dose Level -1	Dose Level -2												
40 mg/m ²	30 mg/m ²	25 mg/m ²												

#	Section	Comments
40.	<u>Appendix I</u>	<p>The row under Tests and Observations reading “SGOT, alkaline phosphatase, bilirubin” was edited to read “SGOT, SGPT, alkaline phosphatase, bilirubin.”</p> <p>The column Following Completion of Protocol Therapy was renamed as Chemo-Radiation Therapy Completion or Premature Treatment Discontinuation.</p> <p>The column After Diagnosis of Recurrence was renamed as 3, 6, 9, and 12 Month Follow-up.</p> <p>The column Premature Treatment Discontinuation was changed to After Diagnosis of Recurrence.</p> <p>In the column Chemo-Radiation Therapy Completion or Premature Treatment Discontinuation, the following indications were removed CT Scan with contrast of pelvis and abdomen; CD4+ T-cell count; and HIV Viral load.</p> <p>In the column 3, 6, 9, and 12 Month Follow-up, the following indications were removed: chest X-ray and serum for HPV-serology.</p> <p>In the column 3, 6, 9 and 12 Month Follow-up, the following indications were added: Physical exam and ART adherence.</p> <p>In the column After Diagnosis of Recurrence, the following indications were removed: Physical exam; ART adherence; and Anal and cervical swabs for HPV-associated disease research.</p> <p>In the column After Diagnosis of Recurrence, the following indications were added: Chest X-ray; CD4+ T-cell Count; and HIV viral load</p> <p>In the column Premature Study Discontinuation, the following indications were added: anal and cervical swabs for HPV-associated disease research; and serum for HPV-serology</p> <p>Footnote 6 “CT with contrast of abdomen and pelvis. Scans are only required if more than 3 months have elapsed since the last CT scan” was removed.</p> <p>Footnote 9 “Anal and cervical swabs and serum for HPV-associated disease research will be collected within 4 weeks following the discontinuation of treatment” has been changed to “Anal and cervical swabs and serum for HPV-associated disease research will be collected on the final day of chemo-radiation therapy or within 4 weeks following the final chemo-radiation therapy.”</p> <p>Footnote 10 “Assessment must be completed within 7 days of the completion of chemo-radiation therapy. This visit is required for all participants and refers both to scheduled completion of treatment and premature treatment discontinuation” was added.</p>
41.	<u>Appendix VII</u>	<p><i>Changed from:</i> These ICRU #38 and institutional bladder and rectal dose points must be calculated but dose modifications should not be made solely based upon these calculations (See Appendix IX).</p> <p><i>Changed to:</i> These ICRU #38 and institutional bladder and rectal dose points must be calculated but dose modifications should not be made solely based upon these calculations (Refer to Appendix IX).</p>

#	Section	Comments
42.	<u>Appendix XII</u>	<p><i>Changed from:</i> Participation in the annual mailed OSLD/TLD program conducted by the RPC for an independent basic check of the machine output.</p> <p><i>Changed to:</i> Participation in the annual mailed OSLD/TLD program conducted by the IROC Houston QA Center for an independent basic check of the machine output.</p>
43.	<u>Appendix XII</u>	<p><i>Changed from:</i> Submission of a complete treatment plan (to include treatment plan summary, beam-on times, isodose lines, dose volume histograms, beams eye views (BEV), daily treatment record), and completed on-line external beam dosimetry form found on the RPC website (http://rpc.mdanderson.org) under forms shall be submitted for review by the RPC and protocol PI. This review verifies that the dose reported is that required by the protocol, no data entry errors have occurred in the calculation, and that there are no transcription and/or reporting errors. The RPC's participant review may require the participating site to submit additional dosimetry data, as specified by the RPC, for the therapy machine used to treat the participant if a dose delivery discrepancy is determined.</p> <p><i>Changed to:</i> Submission of a complete treatment plan (to include treatment plan summary, beam-on times, isodose lines, dose volume histograms, beams eye views (BEV), daily treatment record), and completed on-line external beam dosimetry form found on the IROC Houston QA Center website (http://irochouston.mdanderson.org) under forms shall be submitted for review by the IROC Houston QA Center and protocol PI. This review verifies that the dose reported is that required by the protocol, no data entry errors have occurred in the calculation, and that there are no transcription and/or reporting errors. The IROC Houston QA Center's participant review may require the participating site to submit additional dosimetry data, as specified by the IROC Houston QA Center, for the therapy machine used to treat the participant if a dose delivery discrepancy is determined.</p>
44.	<u>Appendix XII</u>	<p><i>Changed from:</i> Submission of a complete treatment plan to include source strength, for LDR: source loading and total time, for HDR: dwell positions and dwell times, orthogonal AP and lateral films with magnification factors, and completed on-line Gynecological Brachytherapy Protocol Compliance form found on the RPC website (http://rpc.mdanderson.org) under forms shall be submitted for review by the RPC and protocol PI. This review verifies that the dose reported is that required by the protocol, no data entry errors have occurred in the calculation, and that there are no transcription and/or reporting errors. If a dose delivery discrepancy is determined, the RPC's participant review may require the participating site to submit additional brachytherapy dosimetry data that was used to treat the participant, as specified by the RPC.</p> <p><i>Changed to:</i> Submission of a complete treatment plan to include source strength, for LDR: source loading and total time, for HDR: dwell positions and dwell times, orthogonal AP and lateral films with magnification factors, and completed on-line Gynecological Brachytherapy Protocol Compliance form found on the IROC Houston QA Center website (http://irochouston.mdanderson.org) under forms shall be submitted for review by the IROC Houston QA Center and protocol PI. This review verifies that the dose reported is that required by the protocol, no data entry errors have occurred in the calculation, and that there are no transcription and/or reporting errors. If a dose delivery discrepancy is determined, the IROC Houston QA Center's participant review may require the</p>

#	Section	Comments
		participating site to submit additional brachytherapy dosimetry data that was used to treat the participant, as specified by the IROC Houston QA Center .

II. Changes made in Editorial and Administrative Amendment Version 2.1

#	Section	Comments
1.	<u>Global</u>	<p><i>Changed from:</i> Adverse Event Expedited Reporting System (AdEERS)</p> <p><i>Changed to:</i> CTEP Adverse Event Reporting System (CTEP-AERS)</p>
2.	<u>7.1</u>	<p><i>Changed from:</i> An electronic system for expedited submission of AE reports is available at https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\$.startup.</p> <p><i>Changed to:</i> An electronic system for expedited submission of AE reports is available at https://eapps-ctep.nci.nih.gov/ctepaers/.</p>
3.	<u>Appendix V</u>	<p><i>Changed from:</i> Version 4.0 September 13, 2010</p> <p><i>Changed to:</i> Version 5.0 January 28, 2014</p>
4.	<u>Appendix XI</u>	<p><i>Changed from:</i> COLLECTION AND SHIPPING INSTRUCTIONS FOR FORMALIN FIXED TISSUE SLIDES OF CANCER BIOSPY TISSUES, SERUM CERVICAL AND ANAL SWABS FOR EXPLORATORY OBJECTIVE SPECIMENS</p> <p><i>Changed to:</i> COLLECTION AND SHIPPING INSTRUCTIONS FOR SERUM, AND CERVICAL AND ANAL SWABS FOR EXPLORATORY OBJECTIVE SPECIMENS</p>
5.	<u>Appendix XI</u>	<p><i>Changed from:</i> DNA from the cancer portion of the SIL portion of the biopsy will be studied for DNA methylation. This will allow us to determine in a descriptive way if the methylation patterns are different and might provide some clues regarding the role of HPV methylation in progression to cancer.</p> <p><i>Changed to:</i> DNA from the swab material will be used to allow us to determine in a descriptive way if the methylation patterns are different and might provide some clues regarding the role of HPV methylation in progression to cancer.</p>



AMC PROTOCOL #081

Feasibility Study of Safety, Toxicity, and Compliance of Concomitant Chemoradiotherapy for HIV-Associated Locally-Advanced Cervical Cancer

A Multi-Center Trial of the AIDS Malignancy Clinical Trials Consortium

Sponsored by:

National Cancer Institute
Division of Cancer Treatment and Diagnosis

Study Drug and Therapy:

Cisplatin (NSC #119875),
Concomitant Radiation Therapy

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Version 3.0

NCI Version Date: 20 February 2015
Update Date: 20 February 2015

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site ____, agree to conduct and follow this protocol: **AMC Protocol #081 - Feasibility Study of Safety, Toxicity, and Compliance of Concomitant Chemoradiotherapy for HIV-Associated Locally-Advanced Cervical Cancer (Version 3.0 20 February 2015)**, as written according to AMC, NCI and FDA guidelines. I understand that no deviations from the above protocol eligibility criteria or waivers for protocol deviations will be permitted.

Signature

Date (ddmmmyyyy)

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ABBREVIATIONS LIST

AAPM	American Association of Physicists in Medicine
ADCL	Accredited Dosimetry Calibration Laboratory
AIDS	Acquired immunodeficiency syndrome
AIN	Anal intraepithelial neoplasia
AMC	AIDS Malignancy Consortium
ANC	Absolute Neutrophil Count
AP/PA	Anterior Posterior/Posterior Anterior
BED	Biological Equivalent Dose
BEV	Beams Eye View
CBC	Complete Blood Count
CDDP	Cisplatin, cisplatinum, or cis-diamminedichloroplatinum(II)
CIN	Cervical intraepithelial neoplasia
CT	Computed tomography
CT A/P	Computed tomography of abdomen/pelvis
EBRT	External beam radiation therapy
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
FNA	Fine needle aspiration biopsy
GOG	Gynecologic Oncology Group
H&E	Hematoxylin and eosin staining
HAART	Highly Active Antiretroviral Therapy
HDR	High dose rate
HIV	Human Immunodeficiency virus
HPV	Human papilloma virus
HSIL	High-grade squamous intraepithelial lesion
IAEA	International Atomic Energy Agency
ICRU	International Commission on Radiation Units
IMRT	Intensity-Modulated Radiation Therapy
IROC Houston QA Center	Imaging and Radiation Oncology Core Houston QA Center
ITT	Intent to treat
IV	Intravenous
IVP	Intravenous pyelogram
LACC	Locally advanced cervical cancer
LDR	Low dose rate
Min	Minute
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NSC	National Safety Council
NYHA	New York Heart Association
ODMC	Operations and Data Management Center
OHRP	Office for Human Research Protections

OSLD	Optically Stimulated Luminescent Dosimeter
PFS	Progression free survival
PI	Principal Investigator
QA	Quality Assurance
RCT	Radiation concomitant therapy
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SSD	Source-skin distance
SSDL	Secondary Standards Dosimetry Laboratories
SWOG	Southwest Oncology Group
TLD	Thermoluminescent dosimeter
WPRT	Whole pelvic radiation therapy

SITES PARTICIPATING IN THE STUDY

This protocol will be open for subject enrollment at the AMC core sites in Africa named in the protocol roster, as approved by the AMC Executive Committee and the AMC HPV Working Group for participation. The approval will be based on the capacity to perform concomitant chemoradiotherapy as required by this protocol.

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STUDY SYNOPSIS

TITLE:	Feasibility Study of Safety, Toxicity, and Compliance of Concomitant Chemoradiotherapy for HIV-Associated Locally-Advanced Cervical Cancer
DESIGN:	Open-label, single arm feasibility study
DURATION:	36 months (24 months of recruitment and 12 months of follow-up)
SAMPLE SIZE:	45 women will be enrolled with the goal of 38 evaluable women for primary analysis
POPULATION:	HIV-infected women with incident locally-advanced cancer of the cervix (LACC), Stages IB2, IIA*, IIB, IIIB, IVA (squamous, adenocarcinoma, adenosquamous) (*Stage IIA tumor must be > 4 cm)
REGIMEN:	All participants with CD4 counts $> 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $40 \text{ mg}/\text{m}^2$ concomitant with radiotherapy (external beam and brachytherapy). The first 3 participants with CD4 counts $\leq 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $25 \text{ mg}/\text{m}^2$ with radiotherapy (external beam and brachytherapy). Based on review of the safety data from the first 3 participants, all other participants with CD4 counts $\leq 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$) will receive weekly cisplatin at a dose of $40 \text{ mg}/\text{m}^2$ or no cisplatin with radiotherapy (external beam and brachytherapy). All participants will concomitantly receive combination antiretroviral therapy (ART) with an acceptable regimen that adheres to national guidelines for treatment of HIV infection.
PRIMARY OBJECTIVES:	<ol style="list-style-type: none">1) To determine if it is feasible to administer a regimen of cisplatin/RT in HIV-infected women with LACC on ART. This regimen is considered standard therapy for women with LACC who are not HIV infected. Feasibility will be assessed based on:<ul style="list-style-type: none">• Treatment completion proportion: the proportion of participants who complete the cisplatin/RT regimen• Screening ratio: the number of potential participants screened per enrolled participant• Availability proportion: follow-up completion proportion at 6 and 12 months2) To evaluate the safety and tolerability of concomitant chemoradiotherapy with cisplatin in HIV-infected women

EXPLORATORY AND FUTURE RESEARCH OBJECTIVES:

with LACC who are also receiving concomitant ART.

- 1) Determine the 1-year progression-free survival (PFS) of HIV-infected women with locally-advanced invasive cervical cancer (LACC) Stage IB, II, III, and IVA who receive weekly cisplatin concomitant with radiotherapy and ART.
 - Determine PFS in all registered participants, regardless of completion (intent to treat-ITT)
 - Determine the PFS in the subset of participants who complete the prescribed chemotherapy/radiotherapy
 - Compare PFS in these subjects with PFS of HIV-uninfected subjects as reported in the literature, stage for stage
- 2) To describe the effects of treatment on participants' CD4 counts, HIV viral load and concurrent AIDS-defining conditions
- 3) To describe cervical cancer recurrence patterns in HIV-infected participants with LACC defined as loco-regional and/or distant recurrences.
- 4) Determine 1-year overall survival and causes of death, (i.e., cancer-related, HIV-related, or other).
- 5) To evaluate the effects of weekly cisplatin concomitant with radiotherapy on adherence to ART
- 6) Collect serum and cervical and anal swab material for the following exploratory analyses:
 - a. To describe the distribution of HPV DNA types and HPV strain variants in cervical and anal swabs collected at baseline, prior to initiation of study treatment;
 - b. To assess the concordance between HPV DNA types and HPV strain variants detected in cervical and anal swabs collected at baseline, prior to initiation of study treatment;
 - c. To investigate the effect of study treatment on HPV persistence in cervical and anal swabs and its relationship to cervical cancer persistence or recurrence;
 - d. To describe the gene methylation profiles in cervical and anal swabs collected at baseline, prior to initiation of study treatment;
 - e. To assess the concordance between gene methylation

- profiles detected in cervical and anal swabs collected at baseline, prior to initiation of study treatment;
- f. To investigate the relationship between baseline gene methylation profiles and cervical cancer persistence or recurrence;
 - g. To measure serum antibody titers to HPV 16 and HPV 18 at baseline and on study, and to determine whether baseline titers or changes during therapy correlate with cervical cancer persistence or recurrence.

1.0 INTRODUCTION

The standard of care for the treatment of locally-advanced cervical cancer (LACC) is concurrent chemoradiotherapy using cisplatin as the chemotherapeutic radiosensitizing agent. This regimen is the current standard of care based on multiple randomized, controlled trials (RCT) that showed improved efficacy when cisplatin was added to radiation therapy, even in high-risk patients who have histologic evidence of metastatic disease to pelvic and/or para-aortic lymph nodes (1-3). Evidence from 5 randomized clinical trials (RCTs) (GOG 85, RTOG 9001, GOG 120, SWOG 8797, GOG 123) prompted an NCI alert in February 1999 that recommended consideration of concomitant chemoradiotherapy for all patients with cervical cancer (4). A Cochrane database review of 19 RCTs in LACC confirmed improvement in overall survival and progression free survival (PFS) (5). The addition of chemotherapy also appears to afford higher objective response rates; however, it was noted that the survival increase did come at the cost of significant hematologic and gastrointestinal toxicity in subsets of LACC patients.

Like many AIDS-related malignancies, HIV-associated invasive cervical cancer appears to have decreased in incidence in the U.S. due to an understanding of the need for aggressive treatment of precancerous cervical lesions in the setting of HIV. Nevertheless, LACC in HIV is still a major problem worldwide. None of the pivotal RCTs proving the benefits of adding cisplatin to radiation therapy included HIV-infected women with LACC, so efficacy data in the setting of HIV are limited to retrospective analyses. Acute and long term toxicity data in LACC in the setting of modern antiretroviral therapy (ART) do not exist for two main reasons: 1) HIV-associated cervical cancer is rare in developed countries, and 2) in countries which have a large number of HIV-associated cervical cancer patients, modern ART was not regularly used until recently due to lack of access or financial means to pay for the medications.

Optimal cisplatin-based treatments have evolved since the early studies in the mid-1980s. Many of the early regimens consisting of cisplatin alone or in combination with other chemotherapeutic agents, such as 5-FU or hydroxyurea, were inpatient regimens that required intravenous (IV) hydration and mannitol continuously for 5 days (2, 3, 6, 7). Because of the ease of weekly dosing and the lower cost of outpatient administration, a trend to use outpatient weekly cisplatin (40 mg/m^2) emerged despite no RCT showing efficacy or toxicity equivalency to inpatient 5-day regimens (8,9). Other dosing regimens commonly used worldwide include cisplatin 75 mg/m^2 every 3 weeks for 2 cycles during radiotherapy (unpublished data, but used in South Africa and many Southeast Asian sites per personal communications at the State of the Science of Cervical Cancer Meeting, Manchester, England, 2009).

Unfortunately, little is known about the effects of ART on standard treatments for cervical cancer with regards to drug-drug interactions because HIV-infected women with LACC have been typically excluded from clinical trials (10). Many antiretroviral agents are notorious for causing drug-drug interactions. Co-administration of standard cytotoxic and targeted therapies with ART could impair the efficacy or increase the toxicity of these combined therapies. Additionally, HIV-infected patients with cervical cancer often have a poor nutritional status while they are undergoing high-dose pelvic radiation therapy. While there are no prospective studies in cervical cancer, the combination of factors that causes poor marrow reserve in other AIDS malignancies can lead to increased toxicity and reduced efficacy in HIV-infected women with cervical cancer compared with their non-HIV-infected counterparts (11). Also, while

standard dosing for weekly cisplatin is 40 mg/m² when given concurrently with RT, there are some data that suggest that this weekly dose might be too high for some patient populations, especially in Africa (21).

As stage increases with LACC, the incidence of local pelvic or para-aortic lymph node metastasis increases. Patients who have histologic evidence of metastatic disease to pelvic and/or para-aortic lymph nodes have a worse prognosis. Patients with positive para-aortic lymph nodes represent about 20% of all women diagnosed with invasive cervical cancer in the United States; the percentage of women with para-aortic lymph node involvement is often higher in HIV-infected women with cervical cancer (12-18). While there is no prospective evaluation of outcomes for HIV-infected individuals with LACC with nodal disease, historically, they do worse than their non-HIV-infected counterparts do. In HIV-negative women, 6% of early stage cervical cancers (i.e., cancer confined to the cervix) and as high as 25% of advanced stage cervical cancer patients (i.e., locally advanced or metastatic) will have histologically positive para-aortic lymph nodes. Survival for this subset of patients is poor and quoted from 20%-33%. The GOG reported a 33% disease-free survival and 39% overall survival at 3 years in patients with positive para-aortic lymph nodes treated with 5-FU and cisplatin with radiation therapy (19). We will assess whether the nodal status of patients enrolled in this trial is a prognostic characteristic of decreased survival, tolerability, and/or response.

The International Atomic Energy Agency (IAEA) has recently sponsored a prospective clinical trial in HIV-infected women with LACC (H. Lukka et al, unpublished data). This is an international trial to compare relapse-free survival after 3 years between HIV-infected women with LACC treated with radiation alone and those treated with concomitant chemoradiotherapy with cisplatin. Sites include South Africa (n=73), Tanzania (n=126), Zimbabwe (n=16), Uganda (n=47), and India (n=46). Radiation was prescribed as per standard of local care which included external beam radiation therapy (EBRT) with both high-dose rate (HDR) and low-dose rate (LDR) brachytherapy, depending on capacity and local standards with total doses being similar (however, these are still unaudited data). Only 16% of the participants recruited on this trial received or had access to HAART. Monitoring for efficacy is still ongoing as of September 2011. It has been noted that there is a considerable amount of subjects that have not followed up for care on this trial. This is one of the reasons to perform this feasibility study. In summary:

- 1) Concomitant chemoradiotherapy with cisplatin-containing regimens show superior efficacy for LACC when compared with radiotherapy alone in HIV-uninfected women.
- 2) This has not been proven in the setting of HIV, where cervical cancer is common particularly in regions of the world that do not have robust screening programs. In fact, there are limited data regarding HIV-associated LACC in the literature primarily due to the exclusion of these women from the majority of clinical trials. Also, cisplatin-containing regimens have not been studied in cohorts of women on HAART throughout their treatment.
- 3) The optimal dosing for cisplatin when combined with radiation has not been prospectively tested in the setting of differing degrees of viremic suppression with HIV infection in patients receiving ART. There is evidence to suggest there are differences in efficacy and toxicity with lower doses in HIV-uninfected women with LACC (21).
- 4) AMC-081 represents the initial clinical trial of cervical cancer in HIV-infected individuals on ART to be conducted in a resource-limited environment.

- 5) AMC-081 represents the first AMC cervical cancer trial and one of its first international trials. Hence, this is a feasibility study to assess the treatment completion rate, screening rate and safety of a regimen that is standard for women with cervical cancer who are not HIV infected.
- 6) This trial will also integrate the Imaging and Radiation Oncology Core Houston Quality Assurance Center and will provide important information for QA/QC for future AMC trials requiring RT in Africa.
- 7) This trial will provide estimates of treatment completion rates, screening rates, follow-up rates and preliminary estimates of response rates that will inform development of planning a phase II trial that will evaluate efficacy endpoints.
- 8) AMC-081 will provide the first prospectively-collected data on HPV DNA types and strain variants, gene methylation patterns, and HPV serology in HIV-infected women with invasive cervical cancer in Africa and, in a preliminary way, will provide important information on their potential utility as markers for persistence or recurrence in HIV-associated cervical cancer.

1.1 Study Rationale

To advance the science in HIV-associated cervical cancer in the HAART era, this prospective feasibility trial in HIV-infected women with LACC will be performed at African AMC sites to determine and establish baseline data important for future evaluation of treatment regimens in this patient population using the standard, simple to administer, outpatient regimen of cisplatin concomitant with RT. Secondary analyses will include overall and progression-free survival. This trial represents the next step in the science of HIV-associated cervical cancer treatment for numerous reasons:

- 1) For this protocol, all participants will be receiving ART. All participants must be on combination antiretroviral therapy with an acceptable regimen that adheres to national guidelines for treatment of HIV infection. This trial would provide additional toxicity data in subjects with LACC on ART.
- 2) Most current trials in LACC in HIV-uninfected women include additional cytotoxic chemotherapy for higher risk patients (e.g. ANZOG/GOG/RTOG/NCIC/GEICO/NSGO ‘Outback’ trial), targeted therapies (e.g. bevacizumab), or additional maintenance therapy. This trial would represent the baseline of comparison for future trials in HIV-associated LACC using cisplatin in combination with other therapies.
- 3) While this study will not stratify by stage or nodal involvement, all participating sites will be required to perform baseline imaging (CT A/P with contrast) to assess tumor size and enlarged nodes. GOG trials in HIV-uninfected women with positive nodes who are treated with concomitant chemoradiotherapy with cisplatin alone have poorer survival and increased toxicity compared with those with unenlarged nodes (22-26). In this trial, we will assess whether the presence of positive nodes by imaging is a poor prognostic characteristic among HIV-infected women with LACC.

1.2 Rationale for Exploratory/Translational Testing

1.2.1 HPV DNA Testing

High-risk HPV types have been implicated in the etiology of cervical cancer (28-30), and its precursor, high-grade cervical intraepithelial neoplasia (CIN) (29,31); and anal cancer (32-33) and its putative precursor, high-grade anal intraepithelial neoplasia (AIN) (34-37). More than 100 HPV types have been identified, which by definition differ from one another by at least 10% of their DNA sequences (38). Of the HPV types conferring the highest risk for high-grade disease and invasive cancer, HPV types 16 and 18 are the most common (32,38), with HPV 16 infection being the single most common HPV type in anogenital cancer (39).

However, it is not known if the distribution of HPV types in cervical cancer developing in HIV-infected is different from that developing in HIV-uninfected women, where it has clearly been shown that HPV 16 and 18 are present in approximately 50% and 20% of cancers, respectively. We will also collect cervical and anal swabs at baseline prior to initiation of therapy, and at completion or premature discontinuation of therapy. The post-treatment samples will allow us to examine in an exploratory analysis, the effect of treatment on HPV persistence, and determine whether HPV persistence is related to disease recurrence. We also propose to study anal samples for HPV DNA at these time points. Studies have shown a relationship between cervical and anal cancer, and little is known about anal HPV in women with cervical cancer. We can also examine the effect of cervical cancer treatment on anal HPV persistence.

Therapy for cervix cancer has changed over the last decade. Chemotherapy has been shown to be beneficial and has been added to our armamentarium of surgery and radiation. Nevertheless, in an era of personalized medicine, the potential biological differences of cervix cancer associated with different HPV types and host variation have not been adequately evaluated as determinants of cervix cancer outcome and/or response to therapy. Prior studies were conducted in the era of radiation alone, not concomitant chemoradiotherapy, and none address HIV-associated cervical cancer (40-42). Moreover, cervix cancer in an advanced state and in the setting of HIV has a poor prognosis. Since HPV types associated with cancer have divergent risks and associations with tumor types, we expect that knowledge of the HPV type will help to identify patients most at risk for treatment failure, recurrence, and response to surgery, radiation and/or chemotherapy.

Although detection of an oncogenic HPV type is associated with increased risk of anogenital cancer, recent studies of cervical lesions suggest that differences in the genome sequence within variants of a given HPV type, such as HPV 16, may substantially affect the level of risk. Thus, “European” or “prototype” variants of HPV 16 were associated with lower risk of CIN 2 or 3 and cervical cancer than were “non-European” or “non-prototype” variants (43). This was shown to be the case for AIN as well compared to “prototype” HPV 16 variants. MSM with anal “non-prototype” HPV 16 variants were more than three times as likely to develop AIN 3 (43-44). In a study by Palefsky et al., an elevated risk for AIN 2 or 3 was

associated with infection with G131 European variants of the HPV 16 E6 protein when compared with the prototype HPV 16 strain (44).

Amino acid differences in the E6 and E7 proteins are likely to be at least partly responsible for the differential pathogenicity of the various HPV types. However, the amino acid sequences of these proteins vary not only across HPV types, but within type as well. More than 25 sequence variants of HPV 16 have been reported, and a phylogeny-based classification incorporating the L1, L2, and E6 genes has been proposed by Yamada et al (45). Differential pathogenicity of HPV 16 variants has been reported for cervical HSIL (43,46-47), invasive cervical cancer (48), and anal HSIL (49). In a study of variants in the L1 region, Hildesheim et al (50) reported that detection of non-European variants, as is typically found in Africa, was associated with increased risk of cervical cancer. Nothing is currently known of the HPV variants in HIV-associated cervical cancer, nor is there an understanding of concomitant anal HPV infection in the setting of cervical cancer and HIV in Africa or the US.

1.2.2 DNA Methylation in HIV-associated cervical cancer

DNA methylation is a mechanism used by cells to regulate gene expression (51-53). It involves the addition of a methyl group to cytosine nucleotides by enzymes called DNA methyltransferases (54). Typically, the methylated cytosines are clustered in chromosomal regions rich in cytosine and guanine dinucleotides (CpG islands) found in the promoter region, which is involved in regulating gene expression. In general, methylation of this region results in altered expression of the adjacent gene. The mechanism for this is not entirely clear but involves the disruption of the association of transcription factors with the DNA. DNA methylation is also associated with histone deacetylation, which compacts the chromatin and further represses gene expression.

DNA methylation has an important role in tumorigenesis (55). Methylation-induced alteration of genes that limit cell growth, termed tumor suppressor genes, is an important step in tumorigenesis, in addition to point mutations or deletions. Many tumor suppressor genes are specifically methylated in tumors but not in normal tissues. Methylation of tumor suppressor genes has been detected in virtually every type of malignancy, including cervical cancer. The profile of methylated genes appears relatively specific for each tumor type. For example, p16INK4a gene methylation is noted in many different tumors, such as colorectal, lung, breast, and cervical carcinoma. But other genes such as p15INK4b are methylated in leukemia and lymphoma, but not in lung, colon, or breast cancers (56). In other words, many tumors have gene methylation profiles that are specific for the tumor type.

In prior studies of CIMP profiles in women with different grades of CIN and cancer, there are differences in the quantity and profile of methylated genes across grades of CIN and cervical cancer (57-61). Differential methylation of MGMT, for instance, exists across all grades of CIN and cancer appears to be a late event.

There is also differential methylation with other genes, such as CDKN2A gene, which expresses the p16ink4A protein. In addition to the gene that encodes for p16ink4A and MGMT, others include HIC1, APC, RAR β , GSTP1, Fas, MMP-1, and TNF- α . Little is known about methylation in cervical cancer tumors of HIV-infected women.

The predictive nature and timing of gene methylation in identifying cervical cancer recurrences have not yet been elucidated. We plan to examine the methylation profile in cervical and anal swab samples from participants in this trial and will, in a preliminary fashion, examine their relationship to disease recurrence in our cohort.

1.2.3 HPV Serology

Antibodies to conformational epitopes on synthetically produced virus-like particles (VLPs), structurally similar to the HPV virion, have been shown to develop in response to HPV infection (62-65). Serologic responses directed at type-specific epitopes on VLPs are often detectable when there is clinical evidence of disease. Serologic titers can be quantified and related to clinical disease status (63, 65-66). In fact, it appears that higher titers might correlate with worsening grade CIN and cancer (67). Neither seropositivity nor antibody titers have been explored as a marker for persistence or recurrence in HIV-associated cervical cancer.

2.0 STUDY OBJECTIVES

2.1 Hypotheses

- 2.1.1 Treatment compliance will be comparable to what has been previously reported in retrospective studies (27).
- 2.1.2 The toxicity of weekly cisplatin in HIV-infected women on HAART is worse than that reported in HIV-uninfected women but manageable with limited dose reductions and dose delays.
 - 2.1.2.1 Recurrence patterns for HIV-associated LACC will be similar to that in HIV-uninfected women with LACC.
 - 2.1.2.2 Patients with poorly-controlled HIV (defined as CD4 count of $\leq 200/\mu\text{L}$ and/or HIV viral load ≥ 400 copies/mL) will have higher likelihood of distant recurrences.
- 2.1.3 The PFS at 1 year in HIV-infected women on ART who complete the prescribed cisplatin and RT doses of concomitant chemoradiotherapy with weekly cisplatin is similar, stage for stage, to the PFS in HIV-uninfected women stage for stage in LACC.
- 2.1.4 The subset of participants with poorly-controlled HIV as defined by baseline CD4 T-cell count and viral load will have worse PFS when compared with participants with well-controlled HIV infection.
- 2.1.5 Baseline measures of HPV types and strain variants, gene methylation patterns, and HPV serology and/or changes induced by therapy will be associated with the risk of subsequent recurrence of HIV-associated LACC.

2.2 Primary Objectives

- 2.2.1 To determine if it is feasible to administer a regimen of cisplatin/RT in HIV-infected women with LACC on ART. This regimen is considered standard therapy for women with LACC who are not HIV infected. Feasibility will be assessed based on:
 - 2.2.1.1 Treatment completion proportion – the proportion of participants who complete the cisplatin/RT regimen
 - 2.2.1.2 Screening ratio: the number of potential participants screened per enrolled participant
 - 2.2.1.3 Availability proportion: follow-up completion proportion at 6 and 12 months

2.2.2 To evaluate the safety and tolerability of concomitant chemoradiotherapy with cisplatin in HIV-infected women with LACC who are also receiving concomitant ART.

2.3 Exploratory Objectives

2.3.1 To determine the 1-year progression-free survival (PFS) of HIV-infected women with locally-advanced invasive cervical cancer (LACC) Stage IB, II, III, and IVA who receive weekly cisplatin concomitant with radiotherapy and ART.

2.3.1.1 Determine PFS in all registered participants, regardless of completion (intent to treat-ITT)

2.3.1.2 Determine the PFS in the subset of participants who complete the prescribed chemotherapy/ radiotherapy

2.3.1.3 Compare PFS in these subjects with PFS of HIV-uninfected subjects as reported in the literature, stage for stage.

2.3.2 To describe the effects of treatment on participants' CD4 counts, HIV viral load and concurrent AIDS-defining conditions.

2.3.3 To describe cervical cancer recurrence patterns in HIV-infected participants with LACC defined as loco-regional and/or distant recurrences.

2.3.4 Determine 1-year overall survival and causes of death (i.e., cancer-related, HIV-related, or other).

2.3.5 To evaluate the effects of weekly cisplatin concomitant with radiotherapy on adherence to ART.

2.3.6 Collect serum and cervical and anal swab material for the following exploratory analyses:

2.3.6.1 To describe the distribution of HPV DNA types and HPV strain variants in cervical and anal swabs collected at baseline, prior to initiation of study treatment;

2.3.6.2 To assess the concordance between HPV DNA types and HPV strain variants detected in cervical and anal swabs collected at baseline, prior to initiation of study treatment;

2.3.6.3 To investigate the effect of study treatment on HPV persistence in cervical and anal swabs and its relationship to cervical cancer persistence or recurrence;

2.3.6.4 To describe the gene methylation profiles in cervical and anal swabs collected at baseline, prior to initiation of study treatment;

- 2.3.6.5 To investigate the relationship between baseline gene methylation profiles and cervical cancer persistence or recurrence;
- 2.3.6.6 To measure serum antibody titers to HPV 16 and HPV 18 at baseline and on study, and to determine whether baseline titers or changes during therapy correlate with cervical cancer persistence or recurrence.

3.0 PARTICIPANT SELECTION

All protocol participants must meet all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to subject enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

3.1 Inclusion Criteria

- 3.1.1 Participants (who have been adequately clinically staged by standard clinical guidelines) with primary, untreated, histologically-confirmed, documented invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, FIGO stages IB2, IIA, IIB, IIIA, IIIB, and IVA. (Stage IIA tumors must be greater than 4 cm.)
- 3.1.2 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: The term “licensed” refers to a U.S FDA-approved kit or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally.

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

- 3.1.3 The following laboratory tests within 14 days of study enrollment:
 - Hemoglobin \geq 10 g/dL (6.2 mmol/L)
 - Platelet count \geq 100,000/mm³ ($100 \times 10^9/L$)
 - ANC \geq 1500/mm³ ($1.5 \times 10^9/L$) (Participants receiving transfusion, erythropoietin, or myeloid growth factor support will be eligible for this study)
 - Creatinine clearance \geq 60 mL/min (1.00 mL/s) calculated by the Cockcroft-Gault equation for women
 - AST and ALT \leq 3 X ULN
 - Total bilirubin \leq 2 X ULN unless related to antiretroviral use (e.g., atazanavir and indinavir), then the direct bilirubin must be \leq 2 X ULN

- 3.1.4 Adults, 18 years of age or older. DOB and age should be determined based on best possible information or documentation available.
- 3.1.5 All patients must be prescribed combination antiretroviral therapy with the goal of virological suppression using an acceptable regimen that adheres to national guidelines for treatment of HIV infection. Further details can be found in [Section 4.2.3](#). Non-suppressed, treatment experienced patients, defined as patients with a viral load > 400 copies/mL who have been on antiretroviral therapy for more than 4 months can be enrolled if an alternative ART regimen is available that includes at least two ART drugs that, in the opinion of the site investigator, are expected to have activity based on genotypic testing (if available) and treatment history.
- 3.1.6 Ability to understand and the willingness to provide informed consent to participate.
- 3.1.7 ECOG performance status of ≤ 2 .
- 3.1.8 Participants of childbearing potential, defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months), must have a negative urine or serum pregnancy test within 3 weeks prior to enrollment and agree to use an effective form of contraception (e.g., barrier contraception, highly effective hormonal contraception).
- 3.1.9 In the opinion of the investigator the protocol treatment is appropriate for the participant.
- 3.1.10 Life expectancy of greater than 12 months.

3.2 Exclusion Criteria

- 3.2.1 Participants who have undergone hysterectomy.
- 3.2.2 Acute active (such as tuberculosis or malaria), serious, uncontrolled infection. Participants with a CD4 count $\leq 50/\text{mm}^3$ ($0.05 \times 10^9/\text{L}$) will be excluded if they have had an opportunistic infection within the past 3 months, or if there is evidence of resistance to antiretroviral therapy (i.e., HIV viral load ≥ 400 copies/mL despite combination antiretroviral therapy for at least 4 months).
- 3.2.3 Prior invasive malignancy other than LACC diagnosed within the past 24 months, excluding anal intraepithelial neoplasia, non-melanoma skin carcinoma, or Kaposi's sarcoma that has not required systemic chemotherapy within the past 24 months.
- 3.2.4 Pregnancy or breast-feeding. Radiation therapy to the pelvis is contraindicated during any stage of pregnancy.

- 3.2.5 A medical or psychiatric illness that precludes ability to give informed consent or is likely to interfere with the ability to comply with the protocol stipulations.
- 3.2.6 Participants with circumstances that will not permit completion of the study or required follow-up. For instance, if travel to and from treatment site is an issue.
- 3.2.7 Participants with carcinoma of the cervical stump.
- 3.2.8 Participants with history of cardiovascular disease manifested as:
- History of myocardial infarction
 - Unstable angina
 - Currently taking medication for treatment of angina
 - History of coronary artery bypass surgery
 - New York Heart Association class 3 or 4 heart failure ([Appendix III](#))
- 3.2.9 Participants with enlarged para-aortic lymph node involvement on imaging that is suspicious for metastasis.

3.3 Number of Participants to be Enrolled

This study will enroll 45 participants, of whom we anticipate 38 will be evaluable. Once all sites are open for accrual, we anticipate the accrual rate to be 4-6 per month. Accrual is expected to take an estimated 24 months. All participants will have a minimum of 12 months of follow-up. We anticipate that at least 50% of recruited participants will be Stage 3 and 4A.

Accrual Targets					
Ethnic Category	Sex/Gender				
	Female		Male		Total
Hispanic or Latino	0	+	0	=	0
Not Hispanic or Latino	45	+	0	=	45
Ethnic Category: Total of all subjects	45 (A1)	+	0 (B1)	=	45 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	45	+	0	=	45
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	0	+	0	=	0
Racial Category: Total of all subjects	45 (A2)	+	0 (B2)	=	45 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

3.4 Recruitment Procedures

This study will be open at AMC African sites that have the capacity to deliver concomitant chemoradiotherapy as prescribed in this protocol. This includes weekly cisplatin at 40 mg/m² concomitant with radiotherapy (external beam and brachytherapy). Participating sites will need to have ART available for all enrolled participants that adheres to national guidelines for treatment of HIV infection. Sites that have this capacity will be approved by the leadership of this protocol. Participants will be either from primary clinics or from referrals that have HIV infection and incident LACC. Participants may originate from different health care settings.

3.5 Enrollment Procedures

This study will be available for enrollment at AMC core sites in Africa. Sites must have this protocol approved by their Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and any relevant national and local authorities. Sites must also receive approval by the protocol leadership and register with the AMC Operations and Data Management Center (ODMC) before they may enroll participants. Protocol registration instructions and forms will be made available on the AMC Operations web site (www.amcoperations.com). Participating sites may not order study drug until protocol registration with the AMC ODMC is complete.

3.5.1 Registration for Screening

After an informed consent form has been signed by the participant, the participant must be registered for screening (AMC-081, Screening Segment) on-line via the AMC AdvantageEDCSM Internet Data Entry System. After successful registration into the screening segment, the participant will receive a nine-digit participant ID and will then enter the screening process. Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 3 weeks prior to the initiation of treatment. Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair upon successful registration.

Please reference the AMC-081 MOP for additional details regarding the required tests prior to enrollment in the screening segment.

If the on-line system is inaccessible for Screening Registration (Segment A), the site should notify the AMC ODMC via email at 081protocolteam@emmes.com or via phone at 001-301-251-1161 for further instructions. Please reference the AMC-081 MOP for additional instructions.

3.5.2 Enrollment

After the screening evaluations are completed and the participant is determined to be eligible the participating site will complete the protocol-specific eligibility checklist and enroll the participant into AMC-081 Treatment Segment (Segment B) on-line via the AMC AdvantageEDCSM Internet Data Entry System. The

participating site will ensure the participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist. Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 1 week prior to the initiation of treatment (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair upon successful registration.

If the on-line system is inaccessible for Registration (Treatment Segment), the site should notify the AMC ODMC via email at 081protocolteam@emmes.com or via phone at 001-301-251-1161 for further instructions. If the AMC ODMC cannot be reached, please follow the manual randomization procedures detailed in the AMC-081 Manual of Procedures.

3.6 Required Pathology Material and Data

Local pathology must be performed according to local standard procedures to confirm the diagnosis of invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix. The local pathology review must be done prior to enrollment to confirm participant eligibility. Appropriate pathology reports from the participating institution are required to be maintained for source documentation.

A central pathology review will be performed according to [Appendix IV](#). The purpose of the central pathology review is to provide a consistent review and confirmation of the diagnosis and histology of cervical carcinoma for all study participants. This requirement applies to all cases, regardless of the country in which the subject is enrolled.

4.0 STUDY MODALITIES

To be eligible, participants with invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix must have undergone clinical staging by physicians according to FIGO staging criteria see [\(Appendix VI\)](#).

4.1 Staging

4.1.1 Clinical Staging

Participants must have a chest x-ray and a CT of the abdomen and pelvis with contrast. Stage should be assigned and documented as permitted under FIGO staging criteria. The para-aortic lymph node region must be negative for metastasis by CT with contrast.

Additional procedures, such as IVP, ultrasound, cystoscopy, proctoscopy, or barium enema may be performed at the discretion of the investigator.

4.1.2 All participants with cancer confined to the pelvis (Stages IB2, IIA, IIB, IIIB, IVA) will receive pelvic irradiation and concurrent cisplatin as outlined below.

4.2 Cancer Treatment Therapies

4.2.1 Radiation Therapy

See dose table below [\(Section 4.6\)](#) for details and appropriate fractionation schemes.

- 41.4-45.0 Gy/1.8 Gy per fraction/23-25 fractions/five weeks pelvic RT.
- 35-43.6 Gy intracavitary brachytherapy in one to two implants LDR or 18-28 Gy intracavitary brachytherapy in 2-4 fractions HDR.
- 5.40 - 9.00 Gy/1.8 Gy/3-5 fractions/3-5 days parametrial boost to involved parametria.
- Overall treatment time not to exceed eight weeks.

4.2.2 Chemotherapy

Cisplatin 40 mg/m² IV over 30-60 minutes given weekly on days 1, 8, 15, 22, 29 and 36 for a total of 6 weekly cycles.

4.2.3 Antiretroviral Therapy Regimen

4.2.3.1 All patients must be prescribed combination antiretroviral therapy with the goal of virological suppression using an acceptable regimen that adheres to national guidelines for treatment of HIV infection. Patients can already be on a regimen and remain on that regimen during treatment on this protocol. Subjects can begin ART on the day of enrolling in this study to meet eligibility criteria.

4.2.3.2 Although specific drugs will not be prohibited, when considering ART, please note the following:

- Cisplatin-associated neuropathy may be worsened by co-administration of didanosine (ddI) or stavudine (d4T)
- Anemia and neutropenia associated with cisplatin may be worsened by co-administration of Zidovudine (ZDV)
- Cisplatin-associated renal insufficiency may be worsened by co-administration of tenofovir

Whenever possible, co-administration of these antiretroviral agents should be avoided while study subjects are receiving cisplatin as part of this study. If co-administration is unavoidable and graded toxicities occur that require modification of the cisplatin dose, it is strongly recommended that, where available, the use of alternative antiretroviral drugs without overlapping toxicities, be considered before modifying the cisplatin dose.

4.3 Chemotherapy

4.3.1 Cisplatin (Platinol®-AQ –NSC #119875)

4.3.1.1 Formulation: Cisplatin is supplied as a sterile aqueous solution, each ml containing 1 mg cisplatin and 9 mg sodium chloride. Cisplatin is supplied in multidose vials containing either 50mg or 100mg of cisplatin.

NOTE: Aluminum reacts with cisplatin causing precipitation formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

4.3.1.2 Storage: Store at 15 to 25°C. Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

4.3.1.3 Adverse effects: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside ototoxicity, ocular toxicity, and allergic reactions.

Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia, and acute myeloid leukemia.

NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible. Gentamicin ototoxicity is also potentiated by cisplatin and should be avoided whenever possible.

Severe renal toxicity can be largely avoided by induction of diuresis before, during and after treatment. Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if BUN \geq 30 mg/dL (10.7 mmol/L) or creatinine clearance $<$ 40 mL/min (0.67 mL/s) or creatinine $>$ 2.0 mg/dL (177 μ mol/L) develop. If serum creatinine is \geq 1.5 mg/dL (133 μ mol/L) on the planned treatment date, please see cisplatin dose modifications in [Section 6.2](#).

- 4.3.1.4 Supplier: Cisplatin will be purchased commercially and provided by the AMC.

*Refer to Package Insert for additional information.

4.4 Drug Orders, Transfers, Returns, and Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Drug Accountability Record Form (DARF) (available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the Pharmaceutical Management Branch at 001-301-496-5725). The DARFs document the drug delivery date to the site, inventory at the site, use by each study participant, and disposal of the drug (if applicable). A site-specific accountability record, either manual or electronic, may be used if it includes all the information required on the NCI Investigational Drug Accountability Record and if the paper printout is identical to the NCI accountability record. A separate DARF is required for each protocol using the same agent. The investigator will ensure that the drugs are used only in accordance with this protocol.

Drug will be paid for by the AMC. Instructions for drug ordering/drug purchase will be provided to each clinical site by the AMC Operations and Data Management Center. All investigators prescribing study agent for an AMC study must have an active NCI-investigator registration.

4.5 Emergency Radiation Therapy to Stop Bleeding Prior to Treatment

In some cases of locally-advanced cervical cancer, particularly exophytic tumors, radiation therapy is required to stop bleeding emergently. Emergency RT is generally delivered in 3-5 fractions of 2-3 Gy per fraction. Patients who receive emergency radiation therapy to stop tumor bleeding either prior to enrollment or during screening will be allowed to proceed or be registered on this protocol as long as the other eligibility and ineligibility criteria are met. If a subject who is in either screening or pre-screening has received emergency radiation therapy, then definitive radiation therapy should be started as soon as possible so the total treatment time does not exceed 56 days.

4.6 Radiation Therapy Procedures

Radiation therapy (RT) must be started within 7 days of enrollment into the Treatment Segment (Segment B); CT scan of the pelvis is required for external RT field and block definition. If the participating site cannot perform CT simulation and yet has 3D planning software, a diagnostic CT scan with contrast should be available for treatment planning purposes.

Table of Doses

This protocol allows for external beam doses ranging from 41.4-45 Gy but still requires the treating physician to treat primary disease to 80-85 Gy target dose using the appropriate brachytherapy boost as outlined in the following two tables.

Table of Acceptable Combined External Beam and LDR Brachytherapy regimens

Ext. Beam Dose (1.8-2 Gy/fraction)*	LDR (1-2 implants)
41.4 Gy/23 fractions	38.6-43.6 Gy total
43.2 Gy/24 fractions	36.8-41.8 Gy total
45 Gy/25 fractions	35-40 Gy total

Table of Acceptable HDR Brachytherapy regimens

Number of Insertions	HDR Doses
2	9 Gy/fraction
3	7-8 Gy/fraction
4	6-7 Gy/fraction

*Any combination of EBRT and LDR/HDR dose regimen is acceptable. Higher dose per fraction should be considered only for larger, more advanced tumors. If a higher dose is being considered, the local Radiation Oncologist needs to consult with one of the Radiation Oncology PIs.

4.6.1 Standardized Radiotherapy

4.6.1.1 External Irradiation (IMRT will not be allowed on this study.)

All participants will receive 41.4-45 Gy external beam RT delivered to the pelvis in 23-25 fractions of 1.8 Gy. Treatments are to be delivered daily, five fractions per week and should be completed within 5 weeks \pm 3 days. Participants should be treated with bladder distention (although this is not mandatory), and bowel exclusion devices (e.g. belly boards) are allowed. If overall treatment time for external pelvic RT exceeds 38 days, the reason for the delay must be documented. If intracavitary RT cannot be performed, shrinking field technique should be performed to bring the gross tumor volume with adequate margins (minimum 1 cm) to a minimum total dose of 65 Gy. An attempt should be made to exclude all small bowel from treatment field after 50.4 Gy.

4.6.1.1.1 Dose Specification

The dose to the pelvis shall be calculated at the intersection of the axes of the 4-field box. The dose to point B shall also be calculated using an off-axis calculation (or identified on the isodose distribution). In patients not undergoing brachytherapy, point B dose will be calculated at the point on pelvic side wall (at the level of superior wall of acetabulum). Heterogeneity corrected dose calculations are not allowed.

The dose to CENTRAL STRUCTURES shall be the sum of the dose at the intersection of the axes of the 4-field box and the dose to point A from the intracavitary treatment. The dose to SIDE WALL STRUCTURES shall be calculated bilaterally (reported separately) and shall be the sum of the dose at the intersection of the axes from the 4-field box plus the intracavitary dose to point B plus the contribution from the parametrial fields. For 2 dimensional planning, the dose at the central axis and pelvic side walls shall not differ by more than 10%. For 3 dimensional planning, the dose range shall be within 95% to 107% of the prescription dose.

Fractionation: Conventional fractionation will consist of one fraction per day, total five fractions per week.

Therapy interruptions: If interruption of radiation should occur for greater than two weeks, the protocol Radiation Oncology Study Chair must be notified.

Dose deviations: A discrepancy in dose (as specified in the protocol) of 6-10% and >10% will be considered as minor and major deviations from the protocol, respectively

4.6.1.2 Intracavitary Brachytherapy

For each participant, institutions will select the dose rate to be used for brachytherapy—either HDR or LDR.

4.6.1.2.1 Low-Dose Rate (LDR) Brachytherapy

Following the completion of whole pelvic RT, the participant will receive 35-43.6 Gy to Point A (Refer to [Appendix VIII](#) Description of points A, B and ICRU Bladder/Rectum) by intracavitary implant with a standard medical radiation source listed on the American Association of Physicists in Medicine (AAPM) source registry (<http://irochouston.mdanderson.org>). The dose table (Refer to [Section 4.6](#)) should be utilized in order to ensure adequate total dose delivery. The participant may receive the LDR

dose in one or two implants at the discretion of the radiation oncologist.

Ideally, external should finish within 35 days and brachytherapy within 3 weeks of completion of whole pelvic RT (WPRT). The first implant should be performed promptly upon completion of WPRT. If external is delayed up to 38 days, and two brachytherapy sessions are planned, the second session shall be completed within 18 days of the completion of WPRT to keep the total RT duration to within 56 days.

4.6.1.2.2 High-Dose Rate (HDR) Brachytherapy

Refer to [Appendix VII](#) (HDR Brachytherapy) for guidelines of vaginal surface dose, normal tissue tolerances, packing and imaging.

4.6.1.2.3 HDR Schema

- Dose to Point A with each HDR brachytherapy fraction: 6 - 9 Gy.
- Number of weekly HDR brachytherapy procedures: no more than four.
- Total HDR brachytherapy dose to Point A: 18-28 Gy.

4.6.1.2.4 Timing

HDR brachytherapy should start by week 4. When HDR brachytherapy begins, at least one implant will be performed per week with no external beam therapy given on the day of the insertion. If the majority of the external beam radiation has been given (>20 fractions), then two implants per week could be done separated by at least 72 hours in order to complete all treatment within eight weeks.

4.6.1.2.5 Doses

Each HDR brachytherapy fraction will give 6-9 Gy/fraction to Point A. (Refer to [Appendix VIII](#) Description of points A, B and ICRU Bladder/Rectum). Each participant may be treated with up to four HDR implants with the HDR total dose ranging from 18-28 Gy (Total HDR dose) that is equivalent to an LDR delivered of 35-43.6 Gy depending on the total external beam dose given (Refer to [Appendix VII](#) HDR Brachytherapy).

4.6.1.2.6 HDR Instruments

It is strongly recommended that tandem and ovoids be used for HDR brachytherapy. However, tandem and rings are considered acceptable. A tandem and cylinder is allowed only for participants where tandem and ovoid application is not possible due to extent of disease.

4.6.1.2.7 Determination of Normal Tissue Tolerance

In order to stay below an LDR equivalent of 70 Gy to the rectum (Biological Equivalent Dose (BED):120 Gy₃) for four HDR implants, including the 45 Gy contribution from the external beam radiation, the rectum should receive less than 4.1-6.1 Gy for each HDR fraction of 6-9 Gy (68% of the prescribed dose to Point A). The dose to the bladder should be less than 4.6-6.9 Gy per each HDR fraction of 6-9 Gy (77% of the prescribed dose to Point A). As in LDR brachytherapy, every attempt should be made to deliver tumoricidal doses, even if the late responding tissues receive a slightly higher dose. (Refer to [Appendix VII](#): HDR Brachytherapy).

4.6.1.3 Parametrial Boost to Involved Parametrium

Participants may receive a parametrial boost at the discretion of the treating radiation oncologist. The radiation oncologist will choose the dose to be used to the involved parametrium based on bulk of parametrial disease at presentation.

The parametrial boost shall be 5.4-9.0 Gy in 3-5 fractions of 1.8 Gy per fraction given AP/PA daily to midplane if unilateral or bilateral parametrial boost is used. The prescription point should be at the center of the unblocked portion of the field. The parametrial boost should be delivered if possible between implant 1 and 2 or immediately after implant 1 if only one implant is used. The total elapsed time for completion of external whole pelvis, intracavitary RT, and parametrial RT shall not exceed 56 days. If a subject who is either in screening or before study entry has received emergency radiation therapy as described in [Section 4.5](#), then definitive radiation therapy should be started as soon as possible so the total treatment time does not exceed 56 days.

4.6.2 Dose Distribution for All Regimens

A four-field box technique with parallel opposed AP/PA and two opposing lateral fields should be used. AP/PA only fields are allowed in thin women but are strongly discouraged and should only be used with 10 MV or higher energy

beams. Dose distribution across clinical target volume shall not vary more than 10% from the recommended dose. All fields must be treated daily.

4.6.3 Radiation Equipment

- 4.6.3.1 Radiation sources must be of megavoltage energy with an SSD of 80 cm or greater. The minimum beam energy allowed on a linear accelerator is 4MV photons. If Cobalt-60 or 4MV is being used, a 4 field box shall be used for patients with a separation of >18 cm. The peak infield dose should not exceed the dose at the isocenter by more than 10%. All participants will undergo simulation for localization and verification of external RT treatment portals. CT scan with contrast is required in pre-treatment planning. If the participating site cannot perform CT simulation and yet has 3D treatment planning software, a diagnostic CT scan with contrast shall be available for treatment planning purposes. Orthogonal films shall be performed for each implant. Intracavitary treatment will be delivered with standard applicators. Interstitial brachytherapy is not permitted on this trial. If it is felt to be clinically imperative to deliver interstitial brachytherapy, it will be considered a major treatment deviation.
- 4.6.3.2 Intracavitary RT may be delivered by cesium-137 or equivalent radiation source for LDR brachytherapy or cobalt-60 or iridium-192 for HDR brachytherapy in standard or commonly used tandem and ovoid applicators. Only the medical radiation brachytherapy sources listed on the AAPM source registry (<http://irochouston.mdanderson.org>) may be used.

4.6.4 External Radiation Fields (Refer to [Appendix IX](#) Blank Diagram Anterior and [Appendix X](#) Blank Diagram Lateral)

4.6.4.1 Whole Pelvis Field

The external RT target volume shall encompass, with adequate margins, the primary cervical tumor and its gross extension and any grossly involved pelvic lymph nodes as well as possible microscopic extension to pelvic lymph nodes and the uterus.

The use of IMRT will not be allowed on this study.

4.6.4.2 AP/PA pelvic fields

The superior border will be through the L4-5 interspace unless the target volume (e.g. involved iliac lymph nodes or local disease) would not be encompassed adequately in a cephalad direction. In the latter case, a 2 cm margin should be added to the highest level of pathologic abnormality, but should not be cephalad to the L-3/L-4 interspace. The

lateral border will be 2 cm beyond the lateral margins of the bony pelvis. The inferior border will be inferior to the obturator foramen or the lowest extension of disease with at least a 3 cm margin. The inferior extent of cervical cancer or vaginal extension should be marked so that the inferior border of disease can be documented. Uninvolved normal tissues may be blocked although the position of the uterus should be drawn on at least one anterior and lateral field to ensure adequate coverage by transfer of the volume from imaging of the pelvis onto the simulation films. Any bulky adenopathy in the pelvis from imaging scans should be documented on the simulation films as well.

4.6.4.3 Lateral Pelvis Fields

The anterior border should be a horizontal line drawn just anterior to the symphysis pubis, and the posterior border a horizontal line at the posterior border of the sacrum. Superior and inferior borders will be the same as for the anterior and posterior fields. If clips are present from the lymph node dissection to document the position of the lymph nodes, then these should be used as a guide when anterior blocks are designed to shield small bowel. At least 3 cm should not be blocked anterior to the L-5 vertebral body. Also the anterior two-thirds of the L-5 vertebral body should not be blocked.

Posterior blocking should be designed such that gross disease is encompassed with at least a 2 cm margin. The outer table of the sacrum should be blocked to protect the sacral plexus on lateral fields.

4.6.4.4 Parametrial Boost Fields

The superior border should be reduced to include only the true pelvis. The upper border of the true pelvis field is defined as 1 cm above the inferior aspect of the sacroiliac joint (Refer to [Appendix VIII](#) Description of ICRU Bladder/Rectal Dose Reporting Points). Parametrial block should be a minimum of 4-5 cm wide if bilateral parametrial boost is used and may be shaped to the point A isodose. Unilateral parametrial boost would be used if only unilateral involvement was noted (Refer to [Section 4.6.1.3](#)).

4.6.5 Simulation and portal films should be available to the AMC for auditing purposes along with the participant records for the whole pelvic RT fields and parametrial boost. Orthogonal AP and lateral simulation films will be taken following each intracavitary insertion. The orthogonal films and calculations of the intracavitary insertion shall also be made available for auditing purposes for the AMC along with the participant records. Copies of the CT, MRI or other relevant scans, if performed, documenting the relevant tumor volume shall be made available as well.

4.6.6 Radiation Therapy Quality Control and Documentation

The Imaging and Radiation Oncology Core Houston QA Center (IROC Houston QA Center), a National Cancer Institute funded organization with guidance from the AAPM, will supervise the dosimetry control for this clinical trial. To participate in the trial, the institution must demonstrate the ability to achieve an accuracy of $\pm 5\%$ in measuring calibrated reference beam output of their external beam therapy units on an annual basis. Each participant record will be reviewed by the IROC Houston QA Center to verify that each participant received their radiation therapy dose to within $\pm 5\%$ for delivering the external beam prescribed dose and $\pm 15\%$ for the brachytherapy boost.

The radiation therapy quality assurance process is described in [Appendix XII](#).

4.6.7 Expected Toxicity

Gastrointestinal: Nausea and vomiting may occur, especially after the first few treatments. It is recommended that participants be pretreated with anti-emetics before each daily treatment. The use of antiemetics, like any prescribed concomitant medications, will require documentation. Intractable nausea and vomiting beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is rarely seen as a result of radiation alone. Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic radiation. It is recommended that instructions be given to participants for a low fiber, low fat, and bland diet. Most participants will require antidiarrheal medications during therapy.

Should GI toxicity become severe enough to require hospitalization for IV fluid replacement, treatment should be discontinued temporarily until the participant's condition improves. Study Chairs must be notified and documentation of appropriate use of antiemetics may be requested.

Radiation therapy to the pelvis with the concomitant use of chemotherapy on this protocol may enhance the expected toxicity from radiation therapy alone. The expected adverse effects and the guidelines for treatment modifications are described in [Section 6.0](#).

4.6.8 General Radiation Schedule

Radiation therapy (RT) Schedule (with low-dose or high-dose rate):

Day Number	
Day 1	Start whole pelvic radiation therapy (WPRT)
Approximately Day 35	Complete WPRT
After Day 35	Start brachytherapy and deliver parametrial boosts, if prescribed*
Day 50, but no later than Day 56	Complete all radiation therapy*

***If a subject who is either in screening or in the pre-screening period has received emergency radiation therapy, then definitive radiation therapy should be started as soon as possible so the total treatment time does not exceed 56 days.**

*Parametrial boost not required in Stage IB2 and IIA participants. Number of fractions left to the discretion of physician.

4.7 Duration of Study

Each participant should complete the study treatment unless disease progression occurs or toxicity prohibits further therapy. Regardless of whether the treatment is completed, the participant should be followed at least at month 6 and month 12 after the completion of treatment.

Participants should be contacted by clinic staff by appropriate communication mechanisms in order to encourage and maintain the participant's follow-up with their study visits. Follow-up mechanisms may be done by phone, text, email or reminder cards. If a participant is unable or unwilling to come to the clinic for a follow-up visit, clinic staff may obtain information regarding the patient's general health, adverse events, medication changes, or other appropriate changes verbally or via an email or text message from the participant. This information must also be documented within the participant's medical record by a note or copy of the email, phone call, or text message.

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Screening Evaluations

The following will be obtained within the time frames specified in [Appendix I](#):

5.1.1 Within 28 days prior to initiating protocol therapy

- Medical history for eligibility
- Physical examination including: weight and height for BSA calculation, performance status (Refer to [Appendix II](#)), general physical exam, and pelvic exam if judged as necessary by the investigator.
- Tumor measurements and clinical staging
- CT scan with contrast of pelvis and abdomen
- Chest X-ray
- CD4+ T-cell count
- HIV viral load

5.1.2 Within 14 days prior to initiating protocol therapy

- CBC and differential
- Calculated creatinine clearance
- SGOT, SGPT, alkaline phosphatase, bilirubin
- Electrolytes (sodium, potassium, chloride, magnesium)
- Pregnancy test (serum or urine)
- Review of interim medical history including concomitant medications
- Slides for central pathology review--formalin-fixed tissue H&E and unstained slides from original cancer biopsy tissues (refer to [Appendix IV](#))
- Optional: Cytoscopy per local standard of care for clinical staging
- Optional: Intravenous pyelogram (IVP) per local standard of care for clinical staging
- Anal and cervical swabs to evaluate the exploratory study objectives (refer to [Appendix XI](#))
- Serum to evaluate the exploratory study objectives (refer to [Appendix XI](#))

5.2 Evaluations during Chemo-Radiation Treatment

5.2.1 Weekly During Chemo-Radiation (Day 1, 8, 15, 22, 29, 36, (- 2 days))

The following laboratory results will be obtained on the same day or up to 2 days prior to cisplatin administration unless otherwise noted:

- CBC and differential
- Calculated creatinine clearance
- Electrolytes (sodium, potassium, chloride, magnesium)
- Review of interim medical history including concomitant medications and adverse events
- ART adherence assessment will be collected on Day 8, Day 15, Day 22, Day 29, and Day 36.

- Physical Examination on Day 22 prior to treatment.

5.2.2 Assessments at the Time of Chemo-Radiation Therapy Completion

The following assessments must be completed within 7 days of chemo-radiation therapy completion unless otherwise specified. These assessments are required for all participants regardless of the reason for treatment discontinuation (e.g. treatment completion or early discontinuation).

- Review of interim medical history including concomitant medications and adverse events.
- ART adherence assessment.
- Physical examination.

The following assessments must be completed either on the final day of chemo-radiation therapy or within 4 weeks after the final dose of chemo-radiation therapy:

- Anal and cervical swabs to evaluate the exploratory study objectives (refer to [Appendix XI](#)).
- Serum to evaluate the exploratory study objectives (refer to [Appendix XI](#)).

5.3 Evaluations after Completion of Therapy

Participants are to be followed at 3 intervals for 1 year after completing protocol treatment. CT imaging will be repeated at the 6-month time point after discontinuing treatment only for participants that have not clinically progressed; other imaging modalities can be employed off-study, as appropriate and at the discretion of the treating physician, at other time points. Participants that progress or relapse during the 12 month study follow-up period will be followed for survival only.

5.3.1 Month 3 (+/- 4 weeks)

- Physical examination
- Review of interim medical history including concomitant medications and adverse events

5.3.2 Month 6 (+/- 4 weeks)

- Physical examination
- CT scan with contrast of pelvis and abdomen
- CD4+ T-cell count
- HIV viral load
- Review of interim medical history including concomitant medications and adverse events

5.3.3 Month 9 (+/- 4 weeks)

- Physical examination
- Review of interim medical history including concomitant medications and adverse events

5.3.4 Month 12 (+/- 4 weeks)

- Physical examination
- CT scan with contrast of pelvis and abdomen
- CD4+ T-cell count
- HIV viral load
- Review of interim medical history including concomitant medications and adverse events

5.4 Evaluations after Diagnosis of Recurrence

For participants who experience a recurrence of disease, the following evaluations should be performed, preferably at the time of or up to 2 weeks after diagnosis:

- CT scan with contrast of pelvis and abdomen
- Chest X-ray
- CD4+ T-cell count
- HIV viral load
- Review of interim medical history including concomitant medications and adverse events
- Serum to evaluate the exploratory study objectives (refer to [Appendix XI](#))

Participants will only be followed for survival following the diagnosis of disease progression or recurrence. Treatment for progressive/recurrent disease will be at the discretion of the site investigator and will not be coordinated or paid for as part of the study.

5.5 Premature Study Discontinuation Evaluations

For participants who withdraw from the study prematurely (discontinuation prior to 12 month follow-up for any reason), the following evaluations should be performed whenever possible, preferably at the time of or up to 1 month after withdrawal from the study:

- Physical examination
- If more than 3 months after last CT scan, CT scan with contrast of pelvis and abdomen
- Review of interim medical history including concomitant medications and adverse events
- If not done within 3 months of withdraw date, the following diagnostic and laboratory tests should be done:
 - Chest X-ray
 - CD4+ T-cell count
 - HIV viral load
 - CBC and differential
 - Calculated creatinine clearance
 - SGOT, SGPT, alkaline phosphatase, bilirubin
 - Electrolytes (sodium, potassium, chloride, magnesium)

6.0 TREATMENT MODIFICATIONS

6.1 Radiation Therapy

It is in the participant's best interest to receive the radiation therapy on time. Every effort should be made to encourage the participant to comply with the radiation treatment prescribed where possible since time to completion of therapy is correlated with survival. The goal is to complete radiation therapy in 56 days.

6.1.1 Expected Toxicity

All toxicities will be graded according to the Common Toxicity Criteria (CTCAE v4.0).

6.1.1.1 Blood/Bone Marrow (Hematologic)

Hematologic toxicity is seen infrequently unless pelvic radiation is accompanied by chemotherapy. A CBC should be obtained weekly, and if the ANC falls below $1500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$) or the platelet count drops below $100,000/\text{mm}^3$ ($100.0 \times 10^9/\text{L}$), counts should be obtained twice weekly. Treatment may proceed if $\text{ANC} > 1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$), and platelet count $> 50,000/\text{mm}^3$ ($50.0 \times 10^9/\text{L}$).

Every effort should be made to maintain hemoglobin $\geq 10\text{g/dL}$ (6.2 mmol/L). It is up to the individual investigator's discretion as to how best to achieve this.

6.1.1.2 Gastrointestinal

Nausea and vomiting is rather unusual after pelvic radiation. If nausea occurs, the subsequent use of prophylactic antiemetics is strongly encouraged. Antiemetic regimens are at the discretion of the investigator. Anti-emetics may be given when symptoms occur if not given prophylactically prior to treatment. Intractable nausea or vomiting is rarely seen with pelvic radiation alone and is usually the result of another process, i.e., bowel obstruction. Increased bowel activity with diarrhea usually can be controlled with low fiber, low fat, bland diets and antidiarrheal medications. Should GI toxicity become severe, hospitalization may be required at which time the treatment may be interrupted temporarily until the participant's condition improves. This interruption should be limited to ≤ 1 week if possible (Refer to [Section 6.1.2](#)).

6.1.1.3 Renal/Genitourinary

Acute toxicity of the urinary tract is manifested by cystitis. Maintaining high fluid intake is important. Bladder antispasmodics, analgesics and antibiotics are recommended. Hematuria is not usually seen with acute cystitis and suggests bladder invasion by tumor. Acute vulvovaginitis is

seen when the pelvic fields extend inferiorly to include the vulvoperineal area. Treatment of acute vulvoperineal reaction may require warm saline soaks, wearing loose clothing and keeping the area dry. Topical steroids and treatment interruption may be necessary also (Refer to [Section 6.1.2](#)).

6.1.1.4 Dermatologic/Skin (Cutaneous)

With the use of megavoltage external beam radiation therapy, skin reactions in the treatment field are infrequent. However, cutaneous reactions are more likely to develop if sites such as the inguinal area, vulva, and the perineum are in the radiation fields. During radiation therapy, mild irritation and redness of the skin may occur within the radiation fields. Some participants may experience more intense skin reaction such as dry or moist desquamation depending upon the energy of the megavoltage beam, number of fields used per day, need to cover distal vagina and therefore flashing perineum and use of chemotherapy. Hair loss in the pubic area may occur which can be permanent. Late subcutaneous fibrosis, telangiectasia, and skin atrophy are uncommon sequelae.

Almost all participants with vulvar/perineal skin in the treatment fields can expect to develop acute moist desquamation during the course of external beam radiation therapy.

Acute skin reactions may be treated according to the institutional preferences. Aquaphor or steroid creams may be used for CTCAE v4.0 Grade 1-2 reactions and it is not necessary to interrupt the radiation therapy. For CTCAE v4.0 Grade 3-4 skin reactions when generalized macular, papular or vesicular eruptions have developed, or there is generalized exfoliative or ulcerative dermatitis in the treatment fields, radiation therapy should be interrupted until skin reaction improves to Grade 2 or better. Treatment may require symptomatic management of pain, use of warm saline soaks, coating ointments, wearing loose clothing, and keeping the area dry. Radiation therapy should be resumed as soon as the skin reactions have improved to no worse than Grade 2.

The Study Chair should be notified of any Grade 4 toxicity (Refer to [Section 6.1.2](#)).

6.1.2 Radiation Dose Modifications

6.1.2.1 Blood Bone Marrow (Hematologic) Adverse Effects

External RT will be delayed for $ANC \leq 1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$) or platelet count $\leq 50,000/\text{mm}^3$ ($50.0 \times 10^9/\text{L}$). External RT may continue if $ANC < 1000/\text{mm}^3$ and platelets are $> 50,000/\text{mm}^3$. If external RT is delayed, counts will be obtained twice weekly while participant is on

break and treatment resumed when counts are ANC > 1000/mm³ and platelets > 50,000/mm³. If longer than a two-week break is required, the Study Chair should be contacted during this break.

Febrile neutropenia requiring intravenous antibiotics or thrombocytopenia with bleeding requiring platelet transfusion will require holding radiation therapy until symptoms resolve (fever or bleeding) and the hematologic parameters described above are met.

6.1.2.2 Gastrointestinal Adverse Effects

Participants will be treated with a low residue diet and anti-peristaltic drugs. External RT will be interrupted for CTCAE v4.0 Grade 3 or 4 GI toxicity. If longer than a two-week break is required, the Study Chair should be contacted during this break. Use of prophylactic antiemetics is strongly recommended.

6.1.2.3 Renal/Genitourinary Adverse Effects

External RT will be delayed for CTCAE v4.0 Grade 3 or 4 bladder toxicity. If longer than a two-week break is required, the Study Chair should be contacted during this break.

6.1.2.4 Dermatologic/Skin (Cutaneous) Adverse Effects

RT will not be delayed for moist desquamation, and if a break is felt to be clinically indicated, the Study Chair should be contacted prior to this break.

6.1.3 Participants with longer than a 3-week break during combined chemotherapy and pelvic radiotherapy, or during brachytherapy will be removed from the protocol-directed therapy. However, they should re-start radiotherapy off study as soon as the toxicities have improved to an acceptable level.

6.2 Drug Therapy

6.2.1 Safety run-in dosing for enrolled subjects who have CD4 count $\leq 200/\text{mm}^3$ (0.2 x 10⁹/L)

The first three subjects who are enrolled who have a CD4 count $\leq 200 \text{ mm}^3$ (0.2 x 10⁹/L) (inclusive) will be prescribed a dose of 25mg/m² (Dose Level -2, refer to [Section 6.2.2](#)). This was the recommended MTD achieved in a prior African trial in HIV-infected women with LACC (21). Once the first three subjects with low CD4 count are enrolled, enrollment will be held for subjects with CD4 counts $\leq 200/\text{mm}^3$ until toxicity assessment is completed by the protocol team after the completion of treatment (or discontinuation from treatment) for all three subjects.

6.2.2 Definition of Dose-Limiting Toxicity for Cisplatin

Dose-limiting non-hematologic toxicities for cisplatin are defined as any grade 3 or worse peripheral neuropathy or ototoxicity OR any grade 4 GI toxicity that are at least possibly related to cisplatin. Dose-limiting hematologic toxicities for cisplatin are defined as any grade 4 anemia, thrombocytopenia, or neutropenia that are at least possibly related to cisplatin.

- 1) If no patient out of the initial three on this dose level exhibits a DLT, then escalate to dose level 0.
- 2) If one patient out of the initial three patients on a dose level exhibits a DLT, then up to three additional patients will be added. If a second patient develops a DLT, even if it is before there are six total patients on that level, then the MTD has been exceeded and no additional patients should be added to this or any higher doses. Thus, the MTD is defined as the highest dose level at which $\leq 1/6$ patients have a DLT. If ≥ 2 patients on a dose level experience a DLT, then the MTD will have been exceeded and no additional patients will be added at that dose level or any higher level.

If dose-limiting toxicity occurs at dose level -2, cisplatin will be discontinued for the remainder of the treatment with radiation therapy alone. The protocol team will review the toxicity and frequency of dose reductions of subjects enrolled in this safety run-in. If the protocol team determines that there is unacceptable toxicity and frequent dose reductions at the 40 mg/m^2 dose in enrolled subjects with a CD4 count $\leq 200/\text{mm}^3$ ($0.2 \times 10^9/\text{L}$), the protocol team will consider reducing the dose for all enrolled subjects with low CD4 counts to dose level -1 or dose level -2 for the remainder of the trial.

6.2.3 Dose Modifications for Cisplatin

If different dose levels for cisplatin are required because of two different types of toxicities, use the dose level requiring the greatest reduction. There will be no dose re-escalation once the cisplatin is dose reduced.

The following levels should be used for cisplatin dose reductions:

Dose Level 0	Dose Level -1	Dose Level -2
40 mg/m^2	30 mg/m^2	25 mg/m^2

There will be no dose reduction below dose level -2 (i.e. cisplatin will be discontinued if further toxicity occurs).

Chemotherapy should not be administered during a radiation therapy delay.

All chemotherapy-related toxicities will also be graded according to the Common Toxicity Criteria (CTCAE v4.0).

Radiotherapy will not be omitted or delayed for chemotherapy-related toxicities unless the investigator considers that the participant is too sick to be treated.

6.2.4 Cisplatin Modifications

6.2.4.1 Blood/Bone Marrow (Hematologic) Adverse Effects

Granulocyte, ANC or Platelet Counts

Based on counts within 2 days prior to each scheduled cisplatin dose, give the following:

ANC or granulocytes/μL		Platelets/μL	Cisplatin
$\geq 1,500$	and	$\geq 100,000$	No Dose Reduction
1,499-1,000	or	99,999-75,000	Reduce by one dose level*
< 1,000	or	< 75,000	Hold*

Treatment should resume as soon as recovery from toxicity allows. If treatment is delayed for >2 weeks, notify the Study Chair. External RT should continue while drug is withheld.

*If the maximum number of prior dose reductions of cisplatin have been made, treatment may be held for up to two weeks for blood count recovery. Treatment will resume at the same dose level as there are no more dose reductions allowed.

Nadir blood counts or febrile neutropenia

For nadir neutropenia in the absence of fever or with fever which is successfully treated by oral antibiotics, there will be no dose adjustment.

Hold cisplatin during febrile neutropenia. For febrile neutropenia (ANC $\leq 500/\text{mm}^3$ ($0.5 \times 10^9/\text{L}$) and temperature $\geq 100.5^\circ\text{F}$ or 38°C) requiring intravenous antibiotics, the dose of cisplatin should be reduced by 1 dose level for the next and subsequent doses of chemotherapy.

For Grade 4 nadir thrombocytopenia (platelets $\leq 10,000$ ($10.0 \times 10^9/\text{L}$)), the dose of cisplatin should be reduced by 1 dose level for the next dose and for all subsequent doses of chemotherapy.

6.2.4.2 Gastrointestinal Toxicity

Diarrhea is more likely attributable to radiation treatment in this setting. The cisplatin dose will **not** be reduced for diarrhea.

All patients should receive antiemetics to prevent nausea and vomiting. Specific antiemetic therapy is left to the discretion of the investigator. If vomiting is severe, study subjects may require hospital admission and

treatment with any effective antiemetic regimen. Cisplatin doses will NOT be modified for nausea or vomiting.

6.2.4.3 Weight Loss

If a subject has weight loss of more than 10% from their baseline weight at enrollment while receiving cisplatin/RT, the BSA for the cisplatin dose will be recalculated based on the new weight for the remainder of the cisplatin doses.

6.2.5 Nephrotoxicity

If serum creatinine is ≥ 1.5 mg/dL (133 μ mol/L) on the planned treatment date, estimate the creatinine clearance (CrCl) by the Cockcroft and Gault Equation for women:

$$\text{CrCl (mL/min)} = (140 - \text{age in years}) \times (\text{Weight in kg} \times 0.85) / (72 \times \text{serum creatinine})$$

Denominator for SI units (mL/s) = $(48816 \times \text{serum creatinine in } \mu\text{mol/L})$

Calculated Creatinine Clearance (CrCl)	Management
< 60 but ≥ 50 mL/min (<1.00 but ≥ 0.84 mL/s)	Hydrate as clinically indicated. Treatment with cisplatin may continue at a one level reduction in the cisplatin dose.
< 50 but ≥ 40 mL/min (< 0.84 but ≥ 0.67 mL/s)	Hold cisplatin for one week and hydrate as clinically indicated. If repeat CrCl ≥ 50 mL/min (0.84 mL/s) after one week, may resume with a one level reduction in the cisplatin dose. If CrCl does not recover to ≥ 50 mL/min (0.84 mL/s) within one week, permanently discontinue cisplatin.
< 40 mL/min (< 0.67 mL/s)	Permanently discontinue cisplatin.

6.2.5.1 Hypomagnesemia

Hypomagnesemia is not an indication for stopping therapy. Oral or parenteral magnesium supplementation is indicated for serum magnesium levels ≤ 1.5 mEq/L (0.75 mmol/L).

6.2.5.2 Neurological Toxicity

For Grade 1 neurotoxicity, there will be no modification in the cisplatin dose. For patients with \geq Grade 2 neurotoxicity, hold the cisplatin dose

and delay for up to 2 weeks waiting for neurotoxicity to improve to < Grade 1. If neurotoxicity recovers to < Grade 1, resume therapy with a dose reduction of cisplatin by one dose level. If neurotoxicity does not improve to < Grade 1 within 2 weeks, cisplatin will be permanently discontinued. If \geq Grade 2 neurotoxicity recurs after 1 dose level reduction, cisplatin will be given at Dose Level -2 upon resolution of neurotoxicity to Grade 0-1. If \geq Grade 2 neurotoxicity recurs at Dose Level -2, or if neurotoxicity does not improve to < Grade 1 within 2 weeks, cisplatin will be permanently discontinued.

6.2.5.3 Ototoxicity

Discontinue cisplatin for \geq grade 3 ototoxicity.

6.2.5.4 Allergic Reactions

Discontinue cisplatin if \geq grade 3 anaphylaxis occurs.

6.2.5.4.1 Other Grade 3/4 Non-Hematologic Toxicity

If a patient develops Grade 3 or 4 non-hematologic toxicity not detailed above (excluding nausea, vomiting, anorexia, fatigue, fever without Grade 3/4 neutropenia or alopecia), hold cisplatin therapy. Treatment can be restarted if the toxicity has resolved to \leq Grade 1 by the time of the next treatment. Subsequent doses of cisplatin should then be reduced by 1 dose level.

6.2.6 Completion of Chemotherapy

If all 6 cycles of chemotherapy cannot be administered during external radiotherapy (whole pelvis and parametrial boost), the 6th cycle should be given during brachytherapy but not on the same day as brachytherapy.

Chemotherapy may not be given after completion of radiotherapy.

7.0 ADVERSE EVENTS MONITORING AND REPORTING

This study will utilize the Common Terminology Criteria for Adverse Event (CTCAE) version 4.0 for adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. The document “NCI Guidelines: Adverse Event Reporting Requirements for NCI Investigational Agents” clearly outlines reporting criteria.

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

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

The Common Terminology Criteria for Adverse Events (CTCAE) is designed as an instrument to be used to document AEs identified through a combination of clinical and laboratory evaluation. CTCAE is NOT a tool to assist with data extraction from source documents without the direct participation and supervision of clinical investigators. AE grading and assignment of attribution require documentation by medical personnel who are directly involved in the clinical care of protocol subjects.

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to severity for the purposes of regulatory reporting to NCI as follows:

Grade	Description
0	No AE (or within normal limits)
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cauter) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined below (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated,

unlikely, possible, probable, or definite). (International Conference of Harmonization [ICH] E2A, E6).

Life-Threatening Adverse Event

Any AE that places the patient or subject, in view of the Investigator, at immediate risk of death from the reaction. It does NOT include an AE that, had it occurred in a more severe form, might have caused death (FDA 21 CFR 312.32, ICH E2A).

Serious Adverse Event (SAE)

Any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

- 1) Death.
- 2) A life-threatening adverse drug experience.
- 3) Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events that result in an inpatient hospital stay equal to or greater than 24 hours must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. Hospitalization is used as an indicator of the seriousness of the AE and should ONLY be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example, a hospital visit where a patient is admitted for observation or minor treatment such as hydration and released in less than 24 hours should not be reported, but do report an admission for a myocardial infarction.

Toxicity

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

Expectedness (Unexpected Adverse Event)

An unexpected AE is any AE, the specificity or severity of which is not consistent with the Instructions for Use or other documentation; or, if an IB or equivalent is not required or available, the specificity or severity of which is not consistent with the risk

information described in the general investigational plan. Additionally the ICH E2A defines an unexpected adverse drug reaction as an AE, the nature and severity of which is not consistent with the applicable product information (for example, Investigator's Brochure for investigational agent). The investigator shall report all SAEs immediately to the sponsor except for those that the protocol identifies as not requiring immediate reporting (EC Directive of 2001; Article 16, #1).

CTEP Adverse Event Reporting System (CTEP-AERS)

An electronic system for expedited submission of AE reports is available at <https://eapps-ctep.nci.nih.gov/ctepaers/>. A username and password are not required for this system.

Attribution

An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily "caused by a therapeutic intervention." After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention ¹	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related to investigational agent/intervention ¹	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

¹NOTE: AEs listed as "possibly, probably, or definitely" related to the investigational agent/intervention in CTEP-AERS are considered to have a suspected "reasonable causal relationship" to the investigational agent/intervention (ICH E2A). For routine, CDUS adverse event reporting purposes, "Attribution" defines the relationship between the adverse event and the investigational agent(s)/intervention as defined in Clinical Data Update System (CDUS) Instructions and Guidelines that can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/cdus_ig_3r4.pdf.

7.2 Expedited AE Reporting Procedures

Expedited AE reporting for this study must use CTEP-AERS, accessed via the CTEP home page (<http://ctep.cancer.gov>). The reporting procedures to be followed are presented in the CTEP, NCI Guidelines: Adverse Event Reporting Requirements which can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). These requirements are briefly outlined in the table below.

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

Expedited Reporting Requirements for AEs that occur within 30 Days of Last Protocol Treatment

Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent 1, 2

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for \geq 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization \geq 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization \geq 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

All Grade 4 and Grade 5 AEs

Expedited 10 calendar day reports for:

Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

Grade 3 adverse events

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

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

Expedited AE reporting timelines defined:

“24 hours; 5 calendar days” - The Investigator must initially report the AE via CTEP-AERS, according to the procedures outlined in section 6.2, within 24 hours of learning of the event, and followed by a complete AE report submitted via CTEP-AERS within 5 calendar days of the initial 24-hour report. Use the NCI protocol number and

protocol-specific subject ID assigned during trial registration on all reports. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic CTEP-AERS report MUST be submitted immediately upon re-establishment of internet connection.

“10 calendar days”— A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the Investigator learning of the event. Use the NCI protocol number and protocol-specific subject ID assigned during trial registration on all reports.

Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited AE reporting exclusions.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS according to the guidelines as described above.

7.2.1 National and Local Adverse Event Reporting

All Grade 4 related and unexpected events and all Grade 5 events are communicated to the study chair and regulatory agencies as mandated in this protocol. These reports are reviewed by the study chair (or designated co-chair) within two working days for considerations of amendments.

7.3 Routine AE Reporting

All AEs reported through CTEP-AERS must also be reported in routine study data submissions using the Adverse Event electronic case report form (eCRF). All AEs, except for expected Grade 1 events listed below, should be reported. All deaths that occur on study should be reported in the Adverse Event form and the Death Form, regardless of attribution to the protocol agents.

The following grade 1 AEs will not require reporting in the Adverse Event eCRF.

Grade 1 Expected Adverse Events for Radiation Therapy (listed by CTCAE Category and term):

GASTROINTESTINAL DISORDERS: diarrhea, proctitis, rectal pain

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: dermatitis radiation

RENAL AND URINARY DISORDERS: urinary tract pain, cystitis noninfectious

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: dyspareunia, pelvic pain, vaginal pain

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: skin hyperpigmentation, skin hypopigmentation, alopecia

Grade 1 Expected Adverse Events for Cisplatin:

BLOOD AND LYMPHATIC SYSTEM DISORDERS: anemia

EAR AND LABYRINTH DISORDERS: tinnitus

GASTROINTESTINAL DISORDERS: nausea, constipation, diarrhea, abdominal pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: fatigue

INVESTIGATIONS: creatinine increased, weight loss

METABOLISM AND NUTRITION DISORDERS: anorexia

NERVOUS SYSTEM DISORDERS: dysgeusia, paresthesia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: alopecia

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Treatment Discontinuation

- 8.1.1 Treatment breaks longer than 3 weeks during combined chemotherapy and pelvic radiotherapy, or during brachytherapy.
- 8.1.2 Requirement for prohibited concomitant medications.
- 8.1.3 Completion of treatment as defined in the protocol.
- 8.1.4 Request by participant to terminate treatment.
- 8.1.5 Clinical reasons believed life threatening or no longer in the best interest of the participant by the site investigator, such as pregnancy or breastfeeding, even if not addressed in the toxicity section of the protocol.
- 8.1.6 Request by the investigator if s/he thinks the participant to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self

8.2 Premature Study Discontinuation

- 8.2.1 Request by the participant to withdraw.
- 8.2.2 Lost to follow-up. Lost to follow-up will be defined for this purposes of this study as 6 months of inability to contact or determine the participant's vital status, in spite of at least 3 documented attempts to contact the participant.
- 8.2.3 Request by the protocol chairs, AMC, IRB, NCI, OHRP, local government agencies, or pharmaceutical sponsors.

9.0 EVALUATION CRITERIA

9.1 Outcome Measures

The major parameters of the outcome measures are feasibility. Also, we will determine the safety and tolerability of concomitant chemoradiotherapy with cisplatin in HIV-infected women with LACC who are also receiving concomitant ART.

- 9.1.1 Treatment completion proportion is the proportion of subjects who enroll and complete the cisplatin/RT regimen.
- 9.1.2 Screening ratio is the number of potential participants screened per enrolled participant
- 9.1.3 Availability proportion is the follow-up completion proportion at 6 and at 12 months.
- 9.1.4 Safety and tolerability will be evaluated through tracking the number of dose delays, dose reductions, missing doses, and compliance

9.2 Exploratory Outcome Measures

- 9.2.1 Progression Free Survival is defined as the date from protocol registration to date of first documented reappearance (recurrence) or progression of disease or death. Since all subjects will be followed for 12 months after treatment, we will determine the 1-year PFS rate.
- 9.2.2 Recurrence is defined as increasing clinical, radiological or histological evidence of disease since study entry.
 - 9.2.2.1 Site of First Recurrence (e.g., para-aortic or supraclavicular lymph nodes, lung, liver, bone, etc.) will also be documented.
- 9.2.3 Overall Survival will be defined as observed length of life from entry to protocol to death; or for living participants, the date of last contact.
- 9.2.4 Local Control is coded as successful if no recurrence or disease progression is within the pelvic field. Persistence of tumor three months after completion of therapy will be coded as a failure. It is coded as a failure if there is any clinically documented evidence of recurrence or disease progression within the pelvic field.
- 9.2.5 Effects of treatment on the participant's HIV disease status will be determined by tracking the CD4 count, viral load, and concurrent AIDS-defining conditions.
- 9.2.6 Effects of treatment on the participant's HPV status, and the association of these factors with treatment outcomes, will be determined by measuring HPV DNA types and strain variants and gene methylation in cervical and anal swabs, and by measuring antibodies to HPV in serum.

10.0 DATA MANAGEMENT

CRFs will be provided for each subject via the AMC AdvantageEDCSM Internet Data Entry System upon enrollment. Data will be recorded on the CRFs using the unique subject identification number assigned at registration. Subjects must not be identified by name, initials, birth date, or any other personally identifying numbers or codes. Any study documents that are transmitted outside of the site must be labeled with the 9-digit subject ID number, protocol number, or other study-generated codes. Sample CRFs will be available on the AMC Operations and Data Management Center website.

10.1 Data Quality

It is the responsibility of the AMC Operations and Data Management Center to assure the quality of data for the study. This role extends from protocol development to generation of the final study database.

10.2 CRF Instructions

Instructions concerning the recording of study data on CRFs will be provided by the AMC.

10.3 Records to Be Kept

CRFs will be provided for each subject via the AMC AdvantageEDCSM Internet Data Entry System upon enrollment. Subjects must not be identified by name on any study documents. Data will be recorded on the CRFs using the unique subject identification number assigned at registration. Sample CRFs will be available on the AMC ODMC website (www.amcoperations.com).

10.4 Role of Data Management

Instructions concerning the recording of study data on CRFs will be provided by the AMC ODMC. The AMC Internet Data Entry System User's Guide can be found on the AMC ODMC web site (www.amcoperations.com). Each site is responsible for entering data and submitting forms according to the target submission dates set forth by the AdvantageEDCSM system.

It is the responsibility of the AMC ODMC to assure the quality of electronic data reported for each AMC study. This role extends from protocol development to generation of the final study databases.

11.0 STATISTICAL CONSIDERATIONS

11.1 Statistical Analysis Plan

Treatment completion rate will be estimated as proportion of all women who complete cisplatin of those who initiate cisplatin treatment. The binomial proportion and its 95% confidence interval will be used to estimate the treatment completion rate.

The screening ratio will be estimated as the number of patients screened divided by the number of patients enrolled on the study. The Poisson rate and its 95% confidence interval will be used to estimate the screening ratio.

The Kaplan-Meier method will be used to describe the progression-free survival (PFS) and overall survival (OS). We will generate KM curves for Stage I/II participants as well as Stage III/IV participants. The stratified log-rank test will be used to evaluate the association of HAART use, node positivity including enlarged pelvic nodes, stratified for stage. Those factors that are significantly associated with PFS and OS will be incorporated into a proportional hazards model. The one-year PFS and OS will be estimated using the cumulative proportion progression free (for PFS) or surviving (for OS) and its 95% confidence interval.

Frequency tables will be used to summarize the occurrences of adverse events by severity grade. Frequencies of specific adverse events will be tabulated.

Toxicity assessment: All toxicities will be reported on standard case report forms at visits and graded by NCI CTC v4.0. There will be standard dose reduction schedules. All dose delays, dose reductions, and missing doses will be tracked via CRFs during therapy. These will be tabulated and reported as rates.

Adherence assessments are planned weekly during cisplatin therapy and at the end of protocol therapy. Participants will be considered inadherent to ARV if they report missing doses on more than one adherence assessment. The proportion of participants who were inadherent to ARV during protocol therapy will be estimated using the binomial proportion and its exact 95% confidence interval.

To determine the HPV DNA types and HPV strain variants present in cervical cancer and in the anus of cervical cancer patients, frequency tables of HPV DNA types and HPV strain variants will be constructed for cervical and anal samples at baseline, end of treatment and at recurrence (if applicable). The binomial proportion and its 95% confidence interval will be used to estimate the proportion of each HPV DNA type and each HPV strain variant that occurs in at least 5% of patients in cervical or anal specimens. Concordance between anal and cervical specimens with respect to detection of specific HPV DNA types and HPV strain variants will be assessed using McNemar's chi-square test.

Changes in HPV DNA types and strain variants between baseline and post-treatment measurements will be assessed using McNemar's chi-square test for each DNA type and

strain variant. Proportional hazards models and logistic regression models will be used to evaluate the association of change in DNA types with progression free survival and local control, respectively.

The binomial proportion and its 95% confidence interval will be used to estimate the proportion of patients who have abnormally methylated genes for each gene tested.

Gene methylation profiles will be summarized at baseline.

Concordance between gene methylation profiles between cervical and anal swabs will be assessed at baseline using the kappa statistic.

The chi-square test will be used to assess the association between baseline gene methylation profiles and cervical persistence or recurrence.

The logistic regression model will be used to assess the effects of HPV-16 and HPV-18 serologic titer levels with disease persistence or recurrence using the logarithmic transformation for the titer levels. Similarly, the effects of changes in HPV-16 and HPV-18 titer levels from baseline to treatment on outcome measures (progression free survival, local control) will be assessed using proportional hazards models and logistic regression models.

11.2 Sample Size Considerations

The primary outcome measure for this trial is treatment completion rate. A treatment completion rate of 70% or above would be sufficient to consider this regimen for further study. To test the null hypothesis that the treatment completion rate is 0.50 against the alternative that it is 0.70 at the one-sided 0.0510 level with 0.90 power will require 38 evaluable patients. To allow for potential 15% dropout, 45 patients will be enrolled in the study.

We will recruit 45 participants from the AMC core sites in Africa over an estimated 2 year period of time and have a minimum of 1 year of follow-up. We anticipate that at least 50% of recruited participants will be Stage 3 and 4. This will be helpful in stratified analyses by stage and node positivity.

11.3 Site(s) of Recurrence

The site(s) of first disease recurrence will be classified as: pelvic-only, extrapelvic-only or pelvic-and-extra-pelvic or no recurrence and tabulated by treatment group. The test of the hypotheses that first site of recurrence is independent of randomized treatment will be assessed with a logistic model adjusted for FIGO stage, tumor size, lymph node involvement and type of brachytherapy. In addition, empirical plots of cumulative incidence of recurrence will summarize incidence of recurrence by treatment arm.

11.4 Toxicity Analysis

The toxicity data will be tabulated by treatment. The scale will be the Common Toxicity Criteria grading system (i.e., 1-5), but combining Grades 1 and 2. Five toxicity categories (CTCAE v4.0) will be tested: gastrointestinal (nausea, vomiting diarrhea), genito-urinary (acute toxicity manifested by cystitis, and acute vaginitis), and dermatologic (inguinal area, vulva, perineum, acute rash/desquamation, generalized macular, vesicular eruptions, and ulcerative dermatitis), blood/bone marrow and neurologic toxicities. Fisher's exact test will be employed to assess observed frequency differences for (incidence of maximum grade) specific adverse events by treatment arm.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 IRB/IEC Review and Informed Consent

The principles of IRB/IEC review and informed consent described in the Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects (45 CFR part 46) must be followed. IRB/IEC approval of the protocol and the informed consent form must be given in writing before research may commence at the institution.

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

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

Written informed consent will be obtained from the subject. The nature, significance and risks associated with the study must be explained to the subject. The informed consent 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 subject to keep.

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

12.2 Changes to the Protocol and Informed Consent Form

Any change or addition to this protocol or the model informed consent requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC and national regulatory body approval depending upon the local regulations. All versions of the local informed consent form and any other written patient materials must also be approved by the IRB/IEC before presenting any such documents to participants. A copy of the written approval of the IRB/IEC and the national regulatory body (if applicable) must be sent to the ODMC for every protocol amendment and consent modification.

12.3 Women and Minorities

This study is being conducted by the AMC, a NCI-sponsored clinical trials consortium. As part of the AMC's contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority subjects reflects the percentage representation of these populations in their geographic region. As such, it is expected that the representation of subjects on this trial will reflect the constitution of the respective populations.

12.4 Subject Confidentiality

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

12.5 Study Discontinuation

This study may be discontinued at any time by the NCI, the AMC, or the Office for Human Research Protections (ORHP).

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APPENDIX I: SCHEDULE OF EVENTS

The following observations and tests are to be performed and recorded on the appropriate form(s):

Tests and Observations	Prior to Entry	Weekly During Chemo-Radiation	Chemo-Radiation Therapy Completion or Premature Treatment Discontinuation ¹⁰	3, 6, 9, and 12 Month Follow-up	After Diagnosis of Recurrence	Premature Study Discontinuation ⁶
Medical History	X ¹					
Physical exam	X ¹	X ²	X ²	X ²		X
Tumor measurements and clinical staging	X ¹					
CT scan with contrast of pelvis and abdomen	X ¹			X ³	X	X
Chest X-ray †	X ¹				X	X ⁷
CD4+ T-cell count	X ¹			X ⁴	X	X ⁷
HIV viral load	X ¹			X ⁴	X	X ⁷
CBC + differential	X ⁵	X				X ⁷
Calculated creatinine clearance	X ⁵	X				X ⁷
SGOT, SGPT, alkaline phosphatase, bilirubin	X ⁵					X ⁷
Electrolytes (Na, K, Cl, Mg)	X ⁵	X				
Serum or urine pregnancy test *	X ⁵					X ⁸
Review of interim medical history		X	X	X ⁸	X	X
Slides for central pathology review	X ⁵					
ART Adherence		X	X	X		
Cytoscopy, IVP	X ^{5,+}					
Anal and cervical swabs for HPV-associated disease research	X ⁵		X ⁹			X
Serum for HPV-serology	X ⁵		X ⁹		X	X

X¹ Must be obtained within 28 days prior to initiating protocol therapy

X² At day 22 prior to treatment, at treatment discontinuation, and every 3 months for 1 year.

X³ CT with contrast of abdomen and pelvis to be done prior to study entry, 6 months +/- 4 weeks and 12 months +/- 4 weeks after concomitant chemoradiotherapy. Can perform CT without contrast only if recent creatinine ≥ 1.5 mg/dL (within 4 weeks of scan).

X⁴ Every 6 months while on protocol

X⁵ Must be obtained within 14 days prior to initiating protocol therapy. If ANC $\leq 1,500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$) or platelets $\leq 50,000/\text{mm}^3$ ($50 \times 10^9/\text{L}$), repeat twice per week until over these values or subject off trial.

X⁶ Evaluations should be performed whenever possible, preferably at the time of or up to 1 month after withdrawal from study.

- X⁷ Tests are required if not done within the last 3 months.
- X⁸ Every 3 months for 1 year.
- X⁹ Anal and cervical swabs and serum for HPV-associated disease research will be collected on the final day of chemo-radiation therapy or within 4 weeks following the final chemo-radiation therapy.
- X¹⁰ Assessments must be completed within 7 days of the completion of chemo-radiation therapy. This visit is required for all participants and refers to both to scheduled completion of treatment and premature treatment discontinuation
- * Excludes participants who have had a bilateral tubal ligation prior to study entry or who are postmenopausal.
- † Chest CT scan with contrast may be substituted for chest x-ray
- ⁺ Cystoscopy and IVP are not required for eligibility per protocol, but if the enrolling physician feels they are clinically indicated for accurate staging, they should be done according to local standard of care. The costs of these procedures will not be borne by the study budget.

APPENDIX II: PERFORMANCE STATUS SCALE

ECOG Performance Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry out all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work or office work).
2	In bed < 50% of the time. Ambulatory and capable of all self care, but unable to carry out work activities. Up and about for more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self care. Confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead

APPENDIX III: THE NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION SCALE

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX IV: CENTRAL PATHOLOGY REVIEW AND HANDLING OF TISSUES

Handling of Tissues

The designated pathologist at each site will collect the tissues from each patient enrolled in the protocol. One hematoxylin and eosin stained slide plus 3 unstained tissue slides must be made available for centralized pathology review. The unstained slides will be used in the event that additional stains (e.g., hematoxylin and eosin or immunohistochemical stains) are required to confirm the diagnosis (e.g., to differentiate a poorly differentiated adenocarcinoma of the uterus from a primary cervical cancer). A de-identified copy of the local pathology report must be submitted with the slides for central pathology review.

Slides for centralized pathology review should be batched at each site, and shipped via World Courier, every six months to the AMC study laboratory. Specimen storage, shipping and labeling requirements are detailed in the AMC-081 Manual of Procedures.

If any of the blank slides are not needed for central pathology review, then the slides will be destroyed.

Record of Specimens

This study will track specimens via GlobalTraceSM, a component of the AMC AdvantageEDCSM system. The GlobalTraceSM shipment manifest must accompany all specimen shipments.

Pathology Review

Specimens received from AMC will undergo histopathologic diagnosis and classification as follows:

1. H&E
2. Pathologist interpretation.
3. Additional stains for pathologic confirmation and subclassification, if needed for atypical and unusual cases, from unstained slides.

APPENDIX V: AMC DATA AND SAFETY MONITORING PLAN

Version 5.0 • January 28, 2014

Monitoring the Progress of Trials and the Safety of Participants

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

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

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the Protocol Chair and also by the appropriate disease-oriented Working Group during scheduled conference calls. For Phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met. For Phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage Phase II

trial, is based on meeting criteria stated in the protocol, and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met.

For Phase III trials, the AMC has formed an independent Data Safety and Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a patient advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the Statistician listed on the protocol, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The AMC Data Safety and Monitoring Board reviews AMC Phase III studies in accordance with the National Cancer Institute's Policy for Data Safety and Monitoring. Confidential reports of all Phase III trials are prepared by the AMC Group Statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the AMC DSMB Charter. This report addresses specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the Group Chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The Group Chair is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group Chair before the recommendations of the DSMB are carried out. In the unlikely event that the Protocol Chair does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group Chair, Group Chair, DSMB Chair, and NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a formal amendment will be required prior to any implementation of a change to the study.

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

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

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

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event

reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site monitoring visits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDCSM (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. If the site does not follow with a CTEP-AERS report, the AMC ODMC contacts sites to request an expedited report. Additionally, the protocol chair, AMC ODMC, and the AMC Medical Monitor review reported adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting via CTEP-AERS. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

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

In the event that termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. For Phase I and II trials, the Protocol Chair also has the option of asking the AMC DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

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

In accordance with NCI guidelines, the AMC ODMC conducts monitoring visits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a plan to correct

deficiencies within 30 days. If needed, a repeat site visit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option of taking action against the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX VI: CLINICAL STAGING - CARCINOMA OF THE CERVIX UTERI FIGO CLASSIFICATION 1995

PRE-INVASIVE CARCINOMA STAGE 0: Carcinoma in situ, intraepithelial carcinoma.
(Cases of Stage 0 should not be included in any therapeutic statistics)

INVASIVE CARCINOMA STAGE I: Carcinoma strictly confined to the cervix.

STAGE IA: Invasive cancer identified only microscopically. (All gross lesions, even with superficial staging, are Stage IB cancers) Invasion is limited to measured stromal invasion with maximum depth of 5.0 mm and no wider than 7.0 mm.

STAGE IA1: Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm.

STAGE IA2: Measured invasion of stroma greater than 3 mm and no greater than 5 mm and no wider than 7 mm.

STAGE IB: Clinical lesions confined to the cervix or pre-clinical lesions greater than Stage IA.

STAGE IB1: Clinical lesions no greater than 4.0 cm in size.

STAGE IB2: Clinical lesions greater than 4 cm in size.

STAGE II: The carcinoma extends beyond the cervix but has not extended on to the pelvic wall. The carcinoma involves the vagina, but not the lower third.

STAGE IIA: No obvious parametrial involvement.

STAGE IIB: Obvious parametrial involvement.

STAGE III: The carcinoma has extended on to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydro-nephrosis or non-functioning kidney.

STAGE IIIA: No extension on to the pelvic wall.

STAGE IIIB: Extension on to the pelvic wall and/or hydro-nephrosis or non-functioning kidney.

STAGE IV: The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allotted to Stage IV.

STAGE IVA: Spread of the growth to adjacent organs.

STAGE IVB: Spread to distant organs.

Notes on Staging:

Stage IA carcinoma should include minimal microscopically evident stromal invasion as well as small cancerous tumors of measurable size. Stage IA should be subdivided into those lesions with minute foci or invasion visible only microscopically as Stage IA1 and the macroscopically measurable microcarcinomas as Stage IA2 in order to gain further knowledge of the clinical behavior of these lesions. The term IB occult should be omitted.

The diagnosis of both Stage IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion. As noted above, the lower limit of Stage IA2 should be that it can be measured macroscopically (even if dots need to be placed on the slide before measurement) and the upper limit of Stage IA2 is given by measurement of the two largest dimensions in any given section. The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7 mm. Vascular space involvement, either venous or lymphatic, should not alter the staging but should be specifically recorded as it may affect treatment decisions in the future.

Lesions of greater size should be staged as IB.

As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

A patient with a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to Stage IIB. It is impossible at clinical examination to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory. Therefore, the case should be placed in Stage III even if according to the other findings the case should be allotted to Stage I or Stage II.

The presence of the bullous edema as such should not permit a case to be allotted to Stage IV. Ridges and furrows into the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the growth at palpation (i.e., examination from the vagina or the rectum during cystoscopy). A cytological finding of malignant cells in washings from the urinary bladder requires further examination and a biopsy from the wall of the bladder.

The depth of invasion should be no more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.

APPENDIX VII: HDR BRACHYTHERAPY

I. Vaginal Surface Dose – HDR (03/23/2009)

The vaginal mucosa will receive 138-140% of the prescribed dose to Point A—8.28-12.6 Gy. The vaginal mucosa dose is defined on the lateral surface of the ovoids taken through a coronal section. Computerized dosimetry is required for each HDR insertion.

In patients with either significant vaginal narrowing due to tumor infiltration or normal anatomy, tandem and cylinders may be necessary to encompass the volume of disease. Since little or no packing will be possible in these patients, the vaginal mucosa dose should not exceed 110-120% of the prescribed dose to Point A, unless the bladder and rectum are receiving doses within normal tissue tolerance.

II. Normal Tissue Tolerance

In LDR brachytherapy, most institutions attempt to keep the total bladder dose below 75 Gy and the total rectal dose below 70 Gy, unless the tumor is poorly regressing and/or observing these normal tissue tolerances would compromise tumoricidal radiation doses. The total bladder and rectal dose will be less in HDR brachytherapy because of the dose rate effect. There are a number of methods available to calculate these normal tissue doses. The linear quadratic model (LQM), total rectal and bladder dose, in addition to the ratio of bladder or rectal dose divided by the Point A dose, have been employed to calculate normal tissue tolerance. Certainly, if the total bladder and/or rectal dose equals or exceeds the above LDR guidelines, or if the ratio of the normal tissue dose to the Point A dose is 80% or greater, then the packing will need to be re-evaluated. The LQM is probably the most accurate model at present to evaluate normal tissue tolerance to account for the dose rate effect. Using the LQM, a dose to the late responding tissues of 70 Gy corresponds to a Gy3 of 120 (Gy3-not real dose, but biologically effective one to the late responding tissues). A total dose of 75 Gy corresponds to a Gy3 of 130. These Gy3 terms are helpful in calculating the total doses to the normal tissues when adjusting for the dose rate effect.

In order to stay below an LDR equivalent of 70 Gy to the rectum (120 Gy3) for five HDR insertions, including the 45 Gy contributions from the external beam radiation, the rectum should receive less than 4.1-6.1 Gy for each HDR fraction of 6-9 Gy (68% of the prescribed dose to Point A). The dose to the bladder should be less than 4.6-6.9 Gy per HDR fraction of 6-9 Gy (77% of the prescribed dose to Point A). As in LDR brachytherapy, every attempt should be made to deliver tumoricidal doses, even if the late responding tissues receive a slightly higher dose. (03/23/2009)

III. Packing

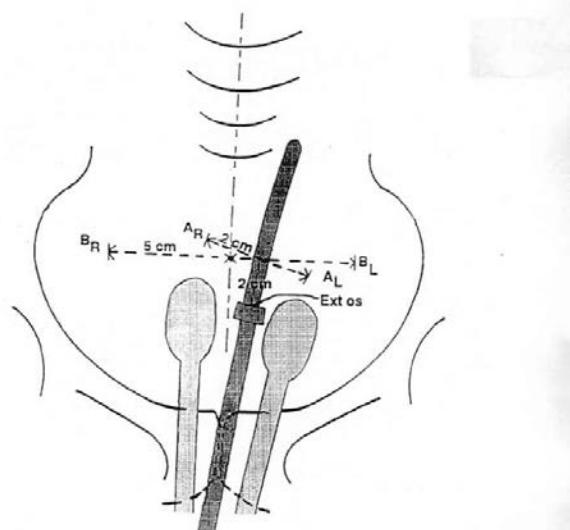
For both LDR and HDR brachytherapy, careful attention should be paid to the bladder and rectal packing. Radio-opaque gauze is recommended to determine the location of the packing for calculation of ICRU #38 bladder and rectal doses. Using the posterior blade of a speculum may facilitate rectal packing. Bladder and rectal points will be taken for normal

tissue tolerance for both HDR and LDR brachytherapy according to ICRU recommendations (ICRU #38) as well as standard institutional bladder and rectal points. These ICRU #38 and institutional bladder and rectal dose points must be calculated but dose modifications should not be made solely based upon these calculations (Refer to [Appendix IX](#)).

IV. Imaging - HDR

A dedicated brachytherapy suite in which an orthogonal x-ray pair can be taken is the ideal setting for the HDR insertions. This will allow for patient immobilization and a reduction in the overall time spent with applicators in the gynecologic tract. If patients must be moved to another room for an orthogonal x-ray pair, every attempt should be made to maintain rigid immobilization. Since the HDR tandem diameter is only 2.5 mm, as opposed to a LDR tandem diameter of 5.0 mm, sounding the uterus is often easier with a potential increased risk for uterine perforations. If a uterine perforation is suspected, it is highly recommended that a transabdominal ultrasound be performed to rule out this event. Ultrasound may also facilitate uterine sounding with difficult insertions.

APPENDIX VIII: DESCRIPTION OF POINTS A AND B AND ICRU BLADDER/RECTAL DOSE REPORTING POINTS

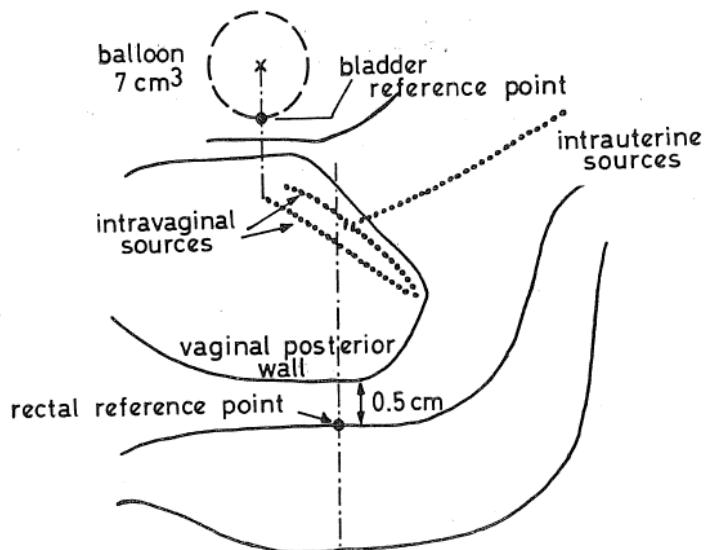


RPC 02/92

Point A is defined as 2 cm along the intrauterine tandem in the superior direction from the flange, and 2 cm perpendicular to the tandem in the lateral direction.

Point B is defined as 2 cm along the intrauterine tandem in the superior direction from the flange, and 5 cm lateral from the midline of the patient.

Description of ICRU 38 Bladder/Rectal Dose Reporting Points

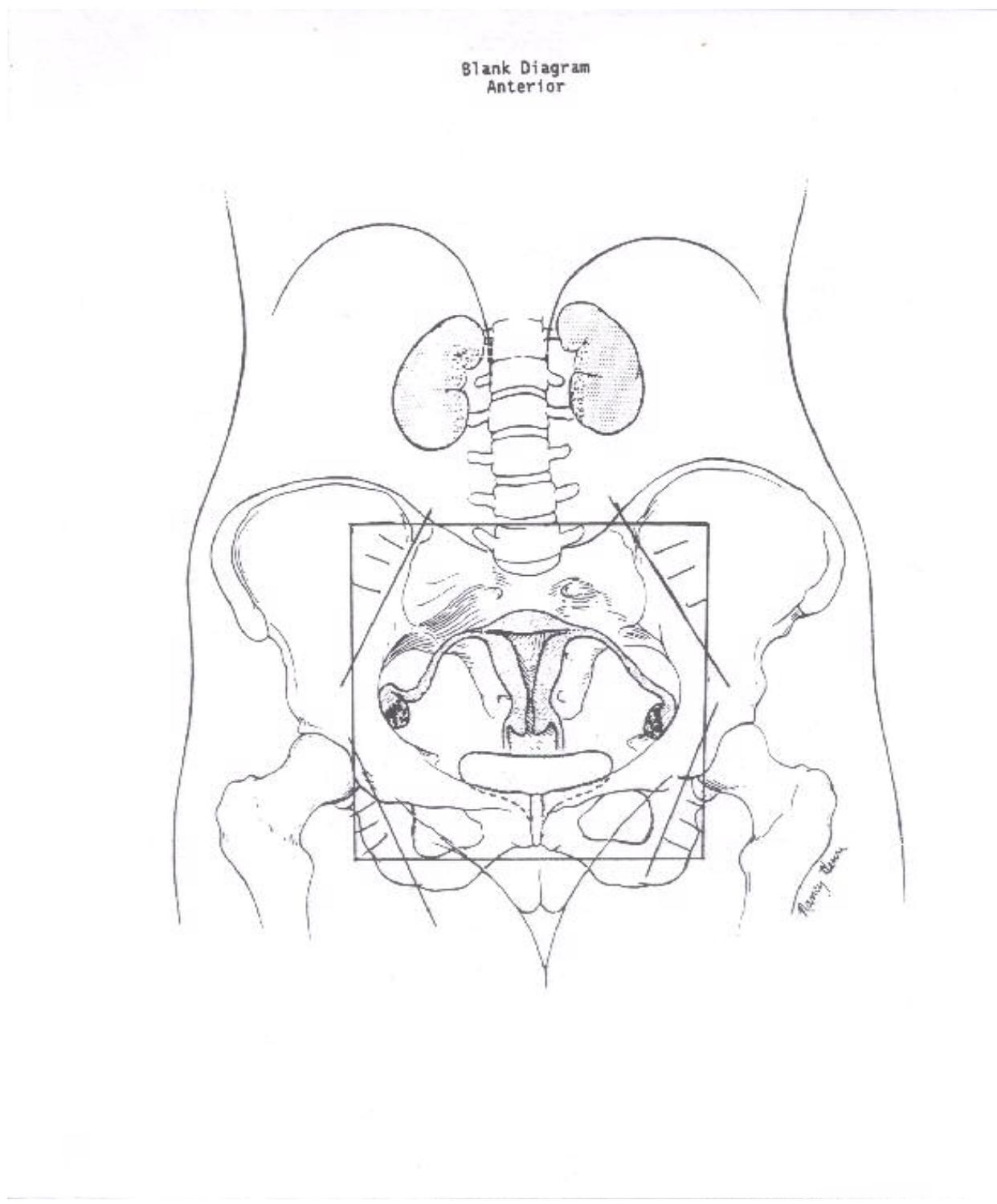


The bladder reference point is obtained as follows. A Foley catheter is used. The balloon must be filled with 7 cm^3 of radio-opaque fluid. The catheter is pulled downwards to bring the balloon against the urethra. On the lateral radiograph, the reference point is obtained on an anterio-

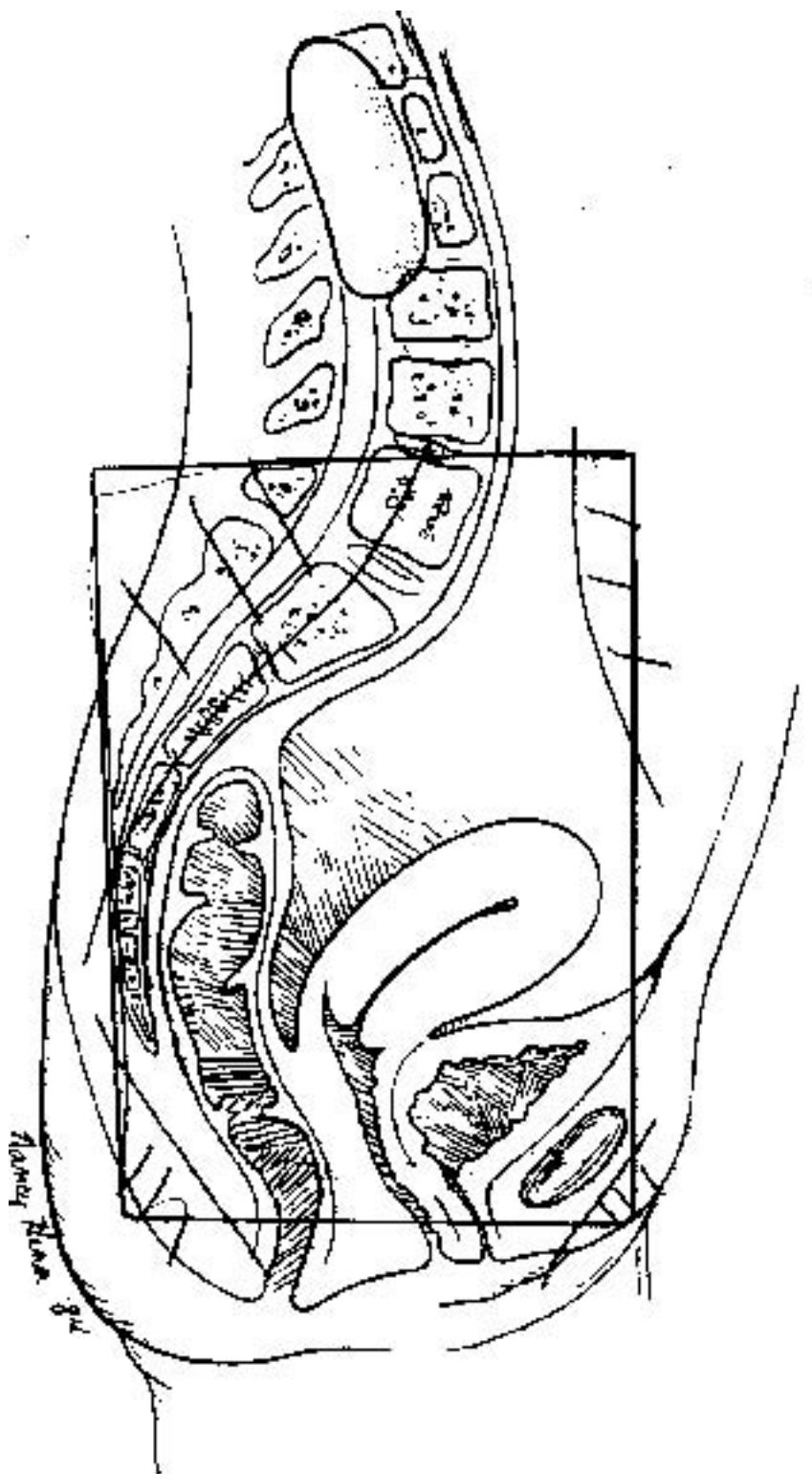
posterior line drawn through the center of the balloon. The reference point is taken on this line at the posterior surface of the balloon. The frontal radiograph, the reference point is taken at the center of the balloon.

The point of reference for the rectal dose is obtained as follows. On the lateral radiograph, an anteroposterior line is drawn from the lower end of the intrauterine source (or from the middle of the intravaginal sources). The point is located on this line 5 mm behind the posterior vaginal wall. The posterior vaginal wall is visualized, depending upon the technique, by means of an intravaginal mould or by opacification of the vaginal cavity with a radio-opaque gauze used for the packing. On the AP radiograph, this reference point is at the lower end of the intrauterine source or at the middle of the intravaginal source(s).

APPENDIX IX: BLANK DIAGRAM ANTERIOR



APPENDIX X: BLANK DIAGRAM LATERAL



APPENDIX XI: COLLECTION AND SHIPPING INSTRUCTIONS FOR SERUM AND CERVICAL AND ANAL SWABS FOR EXPLORATORY OBJECTIVE SPECIMENS

SPECIMEN COLLECTION

The specimen collection requirements for exploratory objective specimens are detailed in the AMC-081 Manual of Procedures.

SAMPLE SHIPPING AND LABELING

Specimens should be batched at each site, and shipped via World Courier, every six months to the study laboratory. The shipping and labeling requirements are detailed in the AMC-081 Manual of Procedures.

RECORD OF SPECIMENS

This study will track specimens via GlobalTraceSM, a component of the AMC AdvantageEDCSM system. The GlobalTraceSM shipment manifest must accompany all specimen shipments.

HPV DNA TESTING

To perform HPV DNA testing on cervical and anal swab specimens, the swabs will be obtained following the procedures listed in the AMC-081 MOP and inserted into Specimen Transport medium (STM). The swab should then be cut with sterile or single-use scissors to allow the swab to fit in the vial. The cap should then be replaced securely and sealed with tape or parafilm. The specimens must then be stored at -20°C or -80°C prior to shipping every 6 months. The specimens should be shipped Monday through Wednesday on dry ice to:

Maria Da Costa
University of California, San Francisco
513 Parnassus Ave Room S-420
San Francisco, CA 94143-0654
TEL: 001-415-476-8885

Laboratory methods: A crude DNA preparation is made from the STM/swab specimen. First the specimen is incubated at 56°C for 1 hour, then proteinase K (Invitrogen Life Technologies) is added to a concentration of 250 µg/ml and incubated at 50°C overnight. In the morning the proteinase K is heat inactivated, and 200 µl of the specimen is ethanol precipitated and suspended in 25 µl Tris-EDTA buffer. Five µl of sample are used for PCR amplification. PCR products from positive samples were also typed by dot-blot hybridization using 38 individual type-specific probes as well as 2 separate mixtures of types.

The presence or absence of HPV and beta-globin DNA is determined using DNA hybridization. Negative controls for each blot consist of amplification of DNA of BJAB cells and tubes

containing all reaction components except target DNA. Positive controls consist of amplification of DNA from 100 SiHa cells as well as amplified DNA from the individual HPV types being sought. Five percent of the samples are amplified in duplicate. Six μ L of the PCR amplification mixtures are applied to dot blots and the DNA is fixed on the membrane. To detect HPV DNA, the membranes are pretreated in 0.1 x sodium chloride-sodium phosphate-EDTA (SSPE), 0.5% sodium dodecyl sulfate for 30 min at 65°C. Probes consisting of amplified biotinylated DNA from HPV 16, HPV 18, HPV 11 and HPV 51 are denatured and added in the presence of 2 mg/mL sheared salmon sperm DNA to the hybridization buffer and hybridized at 55°C for at least 1.5 h. After washing, streptavidin-horse radish peroxidase (SA-HRP) (Vector Laboratories, Burlingame, CA) is added to the blots at a concentration of 30 ng/mL in 250 mL of wash solution and binding allowed to occur with gentle agitation for 15 min at room temperature. After vigorous washing, detection of HPV types is performed using Enhanced ChemiLuminescent detection (ECL) (Amersham, Arlington Heights, IL) according to the manufacturer's instructions. Type-specific probing is performed using biotinylated oligonucleotide probes at a final concentration of 0.5 pmol/mL for the following HPV types individually: 6/11, 16, 18, 26/69, 30, 31, 32/42, 33, 34, 35, 39, 45, 51, 52, 53, 54, 56, 57/2/27, 58, 59, 61, 62, 66, 67, 68, 70, 71, 72, 73, 81, 82, 83, 84, 85, 86/87, 90/106, 97, 102/89, as well as 2 separate mixtures. Mix1 contains 7, 13, 40, 43, 44, 55, 74, and 91, and Mix2 contains 3, 10, 28, 29, 77, 78, and 94. A sample is considered HPV positive when it was positive with the consensus probes. Specimens positive with the consensus probes but negative with the individual type probes are considered to have one or more "other" types. Specimens negative for beta-globin gene amplification are excluded from analysis.

DNA Methylation Analysis

DNA from swab material will be used to allow us to determine in a descriptive way if the methylation patterns are different and might provide some clues regarding the role of HPV methylation in progression to cancer. DNA will be treated with sodium bisulfite using the EZ DNA Methylation Kit (Zymo Research, Orange, CA) in preparation for MSP. The methylation-specific PCR reactions will utilize 10 ng of the sodium bisulfite-treated DNA in 12.5 μ L of 2x Brilliant SYBR Green QPCR Master Mix (dNTPs, Taq DNA polymerase, 2.5 mM MgCl₂) (Stratagene), 30 nM ROX reference dye, and 500 nM of forward and reverse primers, in a final volume of 25 μ L. Real-time methylation-specific PCR will be performed on a Mx3000 Thermocycler (Stratagene, La Jolla, CA). The methylation-specific primer sequences are listed in [Table X](#). The real time methylation-specific PCR reaction utilizes the following conditions: Segment one - one cycle - 95°C for 10 minutes; Segment two - 65 cycles - 95°C for 30s, then 60°C-64°C (depending on primers) for 30s, then 72°C for 30s; Segment three - one cycle - 72°C for 30s, then 95°C for 1 minute, then 55°C for 30s. Normal male white blood cell genomic DNA (Novagen, Madison, WI) will be used as a negative DNA control and CpGenome Universal Methylated DNA, Human Male (Chemicon International, Temecula, CA) will be used as a positive control. Unmethylated MyoD primer sets will be used to confirm the presence of PCR-amplifiable DNA in each sample. Each gene will be scored as positive or negative for methylation; the assay will not be quantitative. The individual target gene will be considered positive for methylation if there is a PCR product detected at the appropriate temperature of the dissociation curve, and the gene will be considered negative if there is no peak at the appropriate

temperature of the dissociation curve. Samples will be considered non-informative if there is no PCR product generated from the gene of interest and the unmethylated MyoD control.

Table X. Real-Time Methylation Specific PCR Primers and Probes

Locus	5' to 3' Forward Primer	5' to 3' Reverse Primer
<i>MYOD1</i>	CCAACTCCAAATCCCCTCTCTAT	TGATTAATTAGATTGGGTTAGAGAAGGA
<i>APC</i>	TTATATGTCGGTTACGTGCGTTATAT	GAACCAAAACGCTCCCCAT
<i>hMLH1</i>	CTATGCCGCCTCATCGT	CGTTATATATCGTCGTAGTATTCTGT
<i>MGMT</i>	GCGTTTCGACGTTCGTAGGT	CACTCTCCGAAAACGAAACG
<i>GSTP1</i>	AGTTGCGCGGCGATTTC	GCCCCAATACTAAATCACGACG
<i>p16^{INK4a}</i>	TTATTAGAGGGTGGGGCGGATCGC	GACCCCGAACCGCGACCGTAA
<i>CDH1</i>	AATTTAGGTTAGAGGGTTATCGCGT	TCCCCAAAACGAAACTAACGAC
<i>RARβ</i>	AAGTAGTAGGAAGTGAGTTGTTAGA	CCAAATTCTCCTTCAAATAA
<i>HIC1</i>	GTTAGGCGGTTAGGGCGTC	CCGAACGCCCTCATCGTAT
<i>TSLC1</i>	GTGAGTGACGAAATTGTAATGTTGGTT	AATCTAACTTCTTACACCTTATTAAAA
<i>RASSF1A</i>	GCGTTGAAGTCGGGGTTC	CCCGTACTCGCTAACCTTAAACG
<i>DAPK</i>	GGATAGTCGGATCGAGTTAACGTC	CCCTCCCAAACGCCGA
<i>FHIT</i>	TTGGGGCGCGGGTTGGGTTTACGC	CGTAAACGACGCCGACCCACTA
<i>PTEN</i>	GGTTTTCGAGGCCTCG	CGCCTCACAAACGACTCAACT
<i>p14^{ARF}</i>	GTGTTAAAGGGCGGCGTAGC	AAAACCCCTCACTCGCGACGA
<i>VHL</i>	TGGAGGATTGCGTACGC	GAACCGAACGCCGCGAA
<i>p73</i>	GGACGTAGCGAAATCGGGTTTC	ACCCCGAACATCGACGTCCG
<i>FANCF</i>	TTTTGCGTTGGAGAACGTTTC	ATACACCGCAAACCGCCGACGAACAAACG
<i>BRCA1</i>	TCGTGGTAACGGAAAAGCGC	AAATCTCAACGAACTCACGCCG
<i>TNFRSF10C</i>	TTACCGTACGAATTAGTTAAC	ATCAACGACCGACCGAAACG
<i>TNFRSF10D</i>	GGGATAAAGCGTTCGATC	CGACAAACAAAACCGCG

SERUM SPECIMENS

HPV Serology

Serology to measure neutralizing antibodies against HPV 16 and HPV 18 will be performed using a pseudovirion (PsV)-based neutralizing assay (PBNA). HPV-16 and HPV-18 PsVs were

prepared as described. PsVs will be synthesized using the 293TT cell line transfected with the p16sheLL, p18sheLL and pYSEAP plasmids. PsVs will be purified by loading on a 2% agarose gel column. The crude stock and column-purified stock will be titrated using 293TT cells. Neutralization assays will be performed using established methods. PsVs carrying the SEAP-encoding plasmid will be incubated with participants' sera for 1 hour on ice. The mix will be added to the 293TT cells and SEAP activity will be measured in the medium after 72 hours. SEAP in 25 μ l of culture supernatant will be detected using the Great Escape SEAP 2.0 detection kit (Clontech, Mountain View, CA) per the manufacturer's instructions. Chemiluminescence will be read on a microplate reader (Dynatech Laboratories, Chantilly, VA). Negative controls consist of sera known to lack neutralizing HPV antibodies. Positive controls consist of assays performed with addition of heparin (1mg/ml) and sera known to contain neutralizing antibodies from HPV-16- and HPV-18-vaccinated individuals. The neutralization titer will be defined as the reciprocal of the highest dilution of test serum that reduce the SEAP activity by at least 50% in comparison with the reactivity in the wells that receive PsV but no antibody. All assays will be done in duplicate at four different dilutions-1:100, 1:200, 1:400 and 1:800. Data for each serum sample at each dilution represent an average of the duplicate wells. Samples that do not reduce SEAP activity by 50% or more at a 1:100 dilution will be considered to be seronegative for analysis. In some cases where the titers are higher than 800 the assays will be repeated with higher dilutions to obtain accurate titers.

APPENDIX XII: RADIATION THERAPY QUALITY ASSURANCE PROCESS

External Beam Therapy

A. Machine QA: all of the following are required:

- 1) Participation in the annual mailed OSLD/TLD program conducted by the IROC Houston QA Center for an independent basic check of the machine output.
- 2) Submission of machine output calibration as per AAPM TG-51 protocol or IAEA TRS 277 or 398 protocols.
- 3) Provide standards lab (SSDL or ADCL) calibration certificates for the ion chamber and electrometer used in the calibration of the reference beam output for the external beam RT.

B. External Beam Treatment Plan

Submission of a complete treatment plan (to include treatment plan summary, beam-on times, isodose lines, dose volume histograms, beams eye views (BEV), daily treatment record), and completed on-line external beam dosimetry form found on the IROC Houston QA Center website (<http://irochouston.mdanderson.org>) under forms shall be submitted for review by the IROC Houston QA Center and protocol PI. This review verifies that the dose reported is that required by the protocol, no data entry errors have occurred in the calculation, and that there are no transcription and/or reporting errors. The IROC Houston QA Center's participant review may require the participating site to submit additional dosimetry data, as specified by the IROC Houston QA Center, for the therapy machine used to treat the participant if a dose delivery discrepancy is determined.

Brachytherapy

A. Machine QA: all of the following are required:

- b. Submit sample brachytherapy source assay document plus a copy of manufacturer source certificate.
- c. Submit copies of standards lab (SSDL or ADCL) calibration certificates for brachytherapy chamber and electrometer used in source assay.

B. Brachytherapy Treatment Plan

Submission of a complete treatment plan to include source strength, for LDR: source loading and total time, for HDR: dwell positions and dwell times, orthogonal AP and lateral films with magnification factors, and completed on-line Gynecological Brachytherapy Protocol Compliance form found on the IROC Houston QA Center website (<http://irochouston.mdanderson.org>) under forms shall be submitted for review by the IROC Houston QA Center and protocol PI. This review verifies that the dose reported is that required by the protocol, no data entry errors have occurred in the calculation, and that there are no transcription and/or reporting errors. If a dose delivery discrepancy is determined, the IROC Houston QA Center's participant review may require the participating site to submit

additional brachytherapy dosimetry data that was used to treat the participant, as specified by the IROC Houston QA Center.