The impact of HIV infection on cervical cancer presentation and survival in Uganda

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Abstract

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Objectives: To determine how HIV infection impacts cervical cancer stage and overall survival (OS) among Ugandan women.

Methods/Materials: Women diagnosed with cervical cancer were followed between 2013 and 2015 at the Uganda Cancer Institute (UCI). A Poisson regression model was fit to calculate prevalence ratios (PR) for the association between HIV infection and late stage at cancer diagnosis. The association between HIV infection and OS after cervical cancer diagnosis was evaluated using a Cox proportional hazards model.

Results: 53 HIV-positive and 96 HIV-negative participants were enrolled. Median age at diagnosis was 44 years (IQR 39-48) for HIV-positive and 54 years (IQR 47-62) for HIV-negative participants. 77% of HIV-positive participants were receiving antiretroviral therapy. Median baseline CD4 count was 373 cells/mm3 (IQR 300-502) for HIV-positive participants versus 926 cells/mm3 (IQR 639-1045) for HIV-negative participants. Thirty-two percent of HIV-positive participants were diagnosed with late stage cervical cancer (III-IV) versus 39% of HIV-negative participants (p=0.4).

After adjusting for age, number of live births, and cost of transportation, no association was found between late stage at cancer diagnosis and HIV status (PR 1.03, 95%CI 0.60-1.78, p=0.9). Most women presenting for care received treatment (85% of HIV-positive versus 75% of HIV-negative), though almost half who received radiotherapy did not receive adequate treatment. There were 35 deaths among HIV-positive and 45 among HIV-negative participants. The median OS was significantly shorter for HIV-positive participants (14.7 months vs 24.3 months for HIV-negative participants, p=0.05). After adjusting for age and stage, HIV infection was weakly, but not statistically significantly, associated with OS (HR 1.35, 95%CI 0.83-2.17).

Conclusions: Cervical cancer remains morbid and often incompletely treated in Uganda. HIV infection was not associated with the stage of cervical cancer at diagnosis, but may be weakly associated with shorter survival, although our limited sample size prohibits definitive statistical evidence.

Introduction

Cervical cancer is the fourth most common type of cancer in women worldwide, and the most common cancer in women in East Africa.[1] It was recognized as an "AIDS-defining cancer" early in the HIV epidemic, in large part because of the higher incidence of cervical cancer among HIV-positive individuals.[2] Even in the era of antiretroviral therapy (ART), the incidence of cervical cancer is at least four times higher among HIV-positive than HIV-negative women.[3–6] Taken together, today the burden of cervical cancer is most extreme in Sub-Saharan Africa, where the high prevalence of HIV has contributed to an elevated incidence of and mortality from cervical cancer.[1]

Almost all cases of cervical cancer are caused by oncogenic strains of the human papillomavirus (HPV).[7] The majority of sexually active adults will acquire an HPV infection at some point in their lives,[8] but only a minority will develop cervical cancer.[9] While women with healthy immune systems are likely to clear HPV infections over time, women with HIV are more likely to experience persistent HPV infection.[10,11] They are therefore more likely to experience cervical dysplasia and exhibit more rapid progression to cancer.[12,13] Some studies also suggest that women with HIV present with cancer at a later stage compared to women without HIV infection.[12,14] Although there are few studies investigating the relationship between HIV infection and cervical cancer treatment or survival, they suggest that once diagnosed with cancer, HIV-positive patients may be less likely to complete treatment, more likely to experience toxicity from treatment, and less likely to survive.[15–18] Programmatic interventions, such as integrating cervical cancer screening into HIV care, could reduce some of the observed differences between HIV-positive and HIV-negative women. Yet these strategies may not compensate for the immune dysfunction and T-cell depletion that characterizes HIV infection,[19] or subtle functional immune deficits that may potentially exist and persist in women whose HIV infection is optimally treated.[20,21]

There currently exist sparse data regarding outcomes, and therefore optimal management of cervical cancer in lower resourced settings—which is where cervical cancer is most prevalent today and where maximal resources to treat cervical cancer are not available. While an estimated 85% of new cervical cancer cases occur in less developed regions of the world,[1] clinical trials in cervical cancer treatment have occurred in high-resource settings with low HIV prevalence and often exclude HIV-positive women.[22–24] The widespread availability of ART has improved the life expectancy and changed the mortality profile of people living with HIV.[25] Consequently, it is increasingly important to better understand whether, and in what way, diagnostic and treatment approaches should be modified in HIV-positive individuals—particularly in lower resource settings where there is delayed access to ART, less widespread cervical cancer screening, and difficulty obtaining definitive cancer treatment.[26]

Uganda is a low-income economy[27] with an estimated adult HIV prevalence of 7.1%.[28] Unlike many other low-income economies, it has a well-respected national cancer center that has had the ability to provide surgical, radiotherapy, and chemotherapy services. However, similar to many other low-income economies, the healthcare system and its patients often lack the resources to initiate or complete treatment after a cancer diagnosis. Understanding the presentation and outcomes of cervical cancer in patients who do seek care in these environments can help inform better care delivery. The secondary aim of this study is to compare cervical cancer stage at diagnosis between HIV-positive and HIV-negative individuals and to describe features of HIV infection and sociodemographic characteristics that may be associated with late stage at diagnosis. The primary aim of this study is to characterize the relationship between HIV disease and the prognosis of invasive cervical cancer in Uganda.

Materials and methods

Study design and participants

We conducted a prospective cohort study of cervical cancer patients diagnosed between August 2013 and August 2015 at the Uganda Cancer Institute (UCI) in Kampala, Uganda, which is the country's only national cancer referral hospital. Adult women undergoing diagnostic workup for suspected cervical cancer were referred to the study for assessment. Patients were eligible for inclusion if they 1) had pathologically confirmed cervical cancer, 2) underwent at least their initial evaluation at the UCI, 3) were able to provide written informed consent, and 4) were able to commit to attending all study visits during the three-year observation period.

Data collection

On enrollment, a standard set of assessments was made for each participant, including medical and demographic history, physical exam, blood draw, and tumor biopsy. Participants returned for follow-up visits to review treatment history and health status 6, 12, 24, and 36 months after enrollment. Patients were contacted by phone if they missed their follow-up visit, and were considered lost to follow-up if no contact had been made with them in person or by phone after 15 months. Treatment information was abstracted from UCI medical records using structured data abstraction forms. All biopsy specimens were reviewed at the same pathology laboratory in Kampala. Cancer stage was assessed using the International Federation of Gynecology and Obstetrics staging system with a clinical exam at enrollment by the study gynecologist.[29] As part of their care at the UCI, patients also underwent a chest x-ray and abdominal ultrasound prior to initiating treatment. Hemoglobin measurements obtained as part of each patient's routine care at the UCI were recorded, and considered a baseline hemoglobin if within two months prior to and one month after enrollment. Grade 3-4 anemia during treatment was defined as hemoglobin less than 8.0 g/dL, according to the Common Terminology Criteria for Adverse Events version 4.0.[30] Patients who received treatment were considered to have received adequate radiation therapy if their combined external-beam and brachytherapy equivalent dose (EQD2) was at least 73.75 Gy. This is the EQD2 dose for 45 Gy of external beam radiation delivered over 15 fractions followed by 25 Gy of low-dose rate brachytherapy delivered in one fraction, which is the minimal dosing used in definitive treatment regimens at the UCI. The cost of patient transport was the amount patients were reimbursed for transport to and from each study visit. All patients received at least 20,000 Ugandan Shillings (USh), with additional amounts provided by the study based on the patient's reported cost of transportation from her home.

Statistical analysis

Demographic, clinical, and treatment characteristics were summarized using descriptive statistics. The primary exposure of interest was HIV serostatus, which was assessed on enrollment blood draw. The secondary outcome of interest is FIGO stage at diagnosis. Stages I and II were considered early, and stages III and IV were considered late. The primary outcome of interest was overall survival (OS), which was the time period from enrollment to the date of death or last known contact with this study or the UCI. Patients were censored at the time of their last known contact.

For the secondary outcome of interest, a Poisson regression using robust standard errors was used to calculate prevalence ratios (PR) as measures of the association between HIV serostatus and late stage of cancer at diagnosis, adjusted for age, number of live births, and cost of transportation to the UCI. These covariates were chosen due to their hypothesized relationship with stage at diagnosis and the potential for targeted interventions in the future. The

cost of transportation to the UCI—rather than distance to the UCI—was used because cost was found to be closely correlated to distance but felt to be the more concrete reflection of the logistics involved in seeking cancer care. Univariable associations between these covariates and stage at diagnosis were also assessed. Descriptive statistics were used to describe HIV-specific treatment characteristics by stage of cancer diagnosis among the HIV-positive patients.

For the primary outcome, the Kaplan-Meier method was used to compare OS in HIV-positive and HIV-negative cervical cancer patients using the log-rank test. A Cox proportional hazards model was used to determine the adjusted association between HIV serostatus and OS. A directed acyclic graph (DAG) illustrating causal assumptions between key clinicopathologic characteristics was developed to determine the role of each in this analysis and reason for which each characteristic should be included in a multivariable Cox model (Figure 1). As seen in the DAG, only age at diagnosis met criteria as a potential confounder. While stage at diagnosis does not meet the criteria as a potential confounder, it was also included in our model to confirm or refute its role as a mediator. Because the majority of cervical cancer tumors in Uganda are squamous histology and poorly or undifferentiated grade, these factors were not included in the final model.

To characterize the precision of PRs and hazard ratios (HRs), 95% confidence intervals were calculated using robust standard errors. STATA version 13 (StataCorp) statistical software was used for all analyses. This study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center, Makerere University School of Medicine Research Ethics Committee, the Mulago Research Ethics Committee and the Uganda National Council for Science and Technology.

Results

From August 2013 to August 2015, 149 women enrolled in this study. There were 53 (35.6%) HIV-positive and 96 (64.4%) HIV-negative participants. The demographic, clinical, and treatment characteristics of the study population are shown in Table 1. The HIV-positive group was younger than the HIV-negative group (median age 44 and 54 respectively) and had fewer live births. The HIV-positive group had a higher level of education and more of the HIV-positive group had the minimum transport cost to the UCI. The cervical cancer stage distribution was similar, and the majority of tumors were of squamous histology and poorly or undifferentiated tumor grade. HIV-positive individuals had lower median CD4 count at enrollment (373 versus 926 cells/mm^3) and lower baseline hemoglobin (10.5 versus 12.0 g/dL) compared to HIV-negative individuals. Notably, the majority of HIV-positive individuals with data available were enrolled in care for their HIV, were using ART, and had undetectable viral loads.

HIV associations with stage at diagnosis

Seventeen (32.1%) HIV-positive and 37 (38.5%) HIV-negative patients presented with late stage cervical cancer. Table 2 shows the unadjusted and adjusted prevalence ratios (PRs) for late stage at cancer diagnosis for HIV serostatus, age, number of live births, and cost of transportation to the UCI. The unadjusted PR for late stage at cancer diagnosis comparing HIV-positive with HIV-negative participants was 0.83 (95%CI 0.52-1.33); the adjusted PR was 1.03 (95%CI 0.60-1.78). These, in addition to the prevalence ratios for age, number of live births, and transport cost to the UCI, were not statistically significant, although the PRs increased with increasing transport cost (unadjusted trend p=0.02, adjusted trend p=0.34).

Table 3 shows HIV-specific treatment characteristics by cervical cancer stage at diagnosis among the HIV-positive patients. Persons presenting with late-stage disease tended to have lower CD4 cell counts, but the quantity of HIV in plasma was similar. Among those who presented at an early stage, a somewhat higher percentage were enrolled in HIV care services compared to those who presented at a late stage (91% vs. 82%).

Treatment characteristics

Among patients for whom treatment status was known, a greater proportion of HIV-positive individuals received cancer treatment compared to HIV-negative individuals (85% and 75% respectively), although among those who received radiation as part of their upfront therapy, a similar proportion received adequate radiation therapy (57% and 58% respectively). The majority of patients who received treatment received definitive radiation and/or chemotherapy.

Among those who received treatment, the median interval from study enrollment until treatment initiation was 41 days (IQR 27-77) among HIV-positive individuals and 41 days (IQR 29-57) among HIV-negative individuals. The median duration of treatment was 45 days among HIV-positive individuals (IQR 20-72) and 52 days among HIV-negative individuals (IQR 24-71). Hemoglobin measurements were not obtained during treatment for 30 (73%) of HIV-positive and 41 (66%) of HIV-negative individuals who received treatment. Among patients for whom hemoglobin was drawn, 1 HIV-positive and 3 HIV-negative patients experienced grade 3-4 anemia during treatment.

HIV associations with overall survival

The median follow-up was 14.8 months. One HIV-positive and one HIV-negative participant was lost to follow-up. There were 35 deaths among HIV-positive and 45 deaths among HIV-negative individuals. Three HIV-negative and 1 HIV-positive individuals died within 41 days of enrollment, which is the median time from enrollment to treatment initiation. Five HIV-positive and none of the HIV-negative patients died within 30 days of their last treatment. One-year survival was 65% among HIV-positive and 69% among HIV-negative participants. Two-year survival was 30% among HIV-positive and 51% among HIV-negative patients. The median survival among HIV-positive individuals was 14.7 months and among HIV-negative individuals was 24.3 months. As seen in Figure 2, HIV-positive patients had shorter unadjusted OS compared to HIV-negative patients (p=0.05, log-rank), with a divergence in survival curves starting at 12 months.

The median hemoglobin at enrollment was 10.6 g/dL for the bottom quartile of survival, 10.6 g/dL for the second quartile, 11.5 g/dL for the third quartile, and 12.0 g/dL for the fourth (longest) quartile. The median CD4 count at enrollment was 607 cells/mm^3 for the bottom quartile of survival, 630 cells/mm^3 for the second quartile, 855 cells/mm^3 for the third quartile, and 613 cells/mm^3 for the fourth quartile.

Table 4 shows the univariable and multivariable Cox regression analyses of characteristics in relation to overall survival. On univariable analysis, HIV infection was associated with an increased hazard of death (HR 1.55, 95%CI 1.01-2.39). Late FIGO stage (HR 2.27, 95%CI 1.45-3.57) but not older age (HR 0.98, 95%CI 0.97-1.00) were significantly associated with OS.

After adjusting for age and FIGO stage, there was a weaker association between HIV infection and OS (HR 1.35, 95%CI 0.83-2.17). Both late FIGO stage (HR 2.77, 95%CI 1.73-4.44) and older age (HR 0.98, 95%CI 0.96-1.00) were significantly associated with OS.

Discussion

In this prospective study, we found that among newly diagnosed and treated Ugandan cervical cancer patients, mortality was high and rates of optimal treatment were low, irrespective of HIV status. While the stage at diagnosis distribution was similar between HIV-positive and HIV-negative women, there was an approximately 60% poorer survival in HIV-positive patients, with a divergence in survival curves starting at 12 months. A multivariable model that included age and FIGO stage showed a somewhat weaker association between HIV serostatus and hazard of death, most likely reflecting a confounding effect of age rather than a mediating effect of stage (given that the latter was not associated with HIV serostatus).

While this study may have been underpowered to fully explore correlates of poor survival in persons with HIV, younger age and late cancer stage remained significantly associated with decreased survival in our multivariate analysis, although the association with age was weak. Consistent with our findings, other studies in higher resourced settings and among the HIV-negative population reliably show higher stage to be associated with decreased survival.[31,32] Survival rates in these settings are much better than in our study where two-year survival was 30% among HIV-positive and 51% among HIV-negative patients. In contrast, five-year survival from 2005 to 2011 in the United States was 68% overall, and 57% among women with more advanced disease.[32] There are likely many contributors to this difference in survival—potentially including HIV prevalence—but differences in stage and treatment rates are likely the major contributors. In the United States, 46% of cervical cancer is diagnosed when the cancer is localized, for which the 5-year survival is 92%.[32] In our study, 15% of patients had stage I disease at diagnosis. Additionally, almost all women diagnosed with cervical cancer in the United States receive some form of treatment.[33,34] While 85% of HIV-positive and 75% of HIV-negative individuals received treatment in our study, treatment status was unknown for a large number of women in our study. Therefore these proportions are likely overestimates. Furthermore, the majority of people who received radiation therapy in our study did not receive adequate radiotherapy nor concurrent chemotherapy, which has been shown to result in improved progression-free and overall survival.[35]

Patients in Uganda generally face multiple challenges in seeking out healthcare, including fear or lack of familiarity with healthcare facilities, low health literacy, inconsistent availability of treatment modalities, long wait times, difficulties financing care, and competing family and work obligations. The healthcare system at times faces challenges with healthcare provider turnover, obtaining and maintaining equipment, accessing diagnostic information, managing patient volume, and obtaining patient medical records. These are likely similar to challenges faced in Botswana. Despite being an upper-middle-income economy,[27] treatment completion is similarly a challenge—in a recent study, only 48% of women in Botswana treated with curative intent completed the recommended radiation therapy.[18]

In this same Botswana study, investigators found that HIV infection nearly doubled the adjusted hazard ratio of death after a cervical cancer diagnosis. Three-year cervical cancer survival was 35% for HIV-positive women and 48% for HIV-negative women. While they did not adjust for CD4 cell count, in a subgroup analysis, they found the adverse effect of HIV was attenuated among women with higher CD4 cell counts. Investigators in Brazil found HIV's adverse effects on cervical cancer survival increased over time; HIV infection was not associated with mortality

within the first year. However, after one year of follow-up, HIV infection was associated with a statistically significant increase in hazard of death.[17] Similar to in our study, the survival curves from the Brazilian cohort showed similar survival until approximately one year, after which a noticeable divergence in survival was observed.

In addition to cancer treatment, mediators of poorer survival could include anemia at cancer diagnosis and immune status (Figure 1). HIV infection can often lead to anemia,[36,37] which may explain the differences in median hemoglobin in our study cohort. Furthermore, anemia at presentation and during treatment have been correlated with shorter survival in cervical cancer, perhaps due to inferior responses to radiation therapy and chemotherapy.[38–41] It has been hypothesized that anemia results in a larger hypoxic cell fraction in the tumor, which confers on these cells greater resistance to radiotherapy, however the impact anemia has on tumor biology and correlation with tumor oxygenation is not well understood.[41] It is unclear whether anemia is a driver of poorer outcomes or simply a marker of disease severity.

Regarding immune status, while the median CD4 count at enrollment (373 cells/mm^3) among HIV-positive individuals in our study was above the threshold at which opportunistic infections are considered a risk, this is still far below the median CD4 count among HIV-negative individuals (926 cells/mm^3). The divergence in survival after one year could therefore be due to subtle differences in immune factors, even though most HIV-positive individuals in both our cohort and the Brazilian cohort were on ART and had higher CD4 counts. Increasing evidence supports the adaptive immune system's role in ongoing clinical benefits from cancer therapy such as radiation and chemotherapy.[42] Furthermore, T-cell responses in the peripheral blood are not necessarily reflective of mucosal immune responses, such as in the cervix,[21] and mucosal CD4 cell populations in HIV-positive women may not recover after initiation of ART.[20] A potential clinical consequence of this could be earlier recurrence after treatment, which was seen in the Brazilian cohort, and can therefore impact overall survival. In the Brazilian cohort, HIV-positive and HIV-negative patients had similar treatment response rates, but HIV infection was associated with a higher risk of cancer relapse.[17] Because post-treatment follow-up is less structured in Uganda than in Brazil, recurrence data were not available for our study population. Similarly, late toxicities were not available in our study, nor similar studies,[17,18] but could also explain differences in later survival if late toxicities occur at a higher rate or result in greater morbidity among HIV-positive individuals.

This study is limited by small sample size, which may have resulted in limited power to detect differences in prognostic factors for survival. Cause of death information was not available. However the majority of deaths were attributable to cervical cancer in recent studies from Botswana and Brazil—and the same is likely true in Uganda. While our results may be applicable to patients who present to the UCI for care, they may not reflect the general population in Uganda where ART coverage is 57%, compared to 77% in our study.[28] HIV-positive individuals who have established care for their infection have more frequent interactions with the healthcare system and may therefore be more likely to follow-up on other health problems. Nevertheless, our study population represents the group of Ugandan cervical cancer patients among whom it may make the most sense to focus initial efforts to improve survival. It is one of the few studies on cervical cancer survival in more resource-limited settings where the majority of the global cervical cancer burden exists, and where it will be important to define optimal intervention strategies for those settings.

In conclusion, we found that despite similar stage distribution between HIV-positive and HIV-negative cervical cancer patients in this prospective cohort study, there was a difference in survival distribution between the two groups with a divergence in survival curves at one year.

The impact that HIV infection has on cervical cancer presentation and survival is likely complex and warrants continued exploration. Potential pathways to explore include differences in cellular immunity, treatment initiation, treatment completion, and long-term toxicities. With the majority of new cervical cancer cases occurring in low- and middle-income economies, there is an imperative to continue detailed studies of the natural history of cervical cancer and explore novel treatment and retention strategies in these populations.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D BF. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed August 25, 2015.
2. Maiman M, Fruchter RG, Clark M, Arrastia CD, Matthews R, Gates EJ. Cervical cancer as an AIDS-defining illness. *Obstet Gynecol*. 1997;89(1):76-80.
3. Chen C-H, Chung C-Y, Wang L-H, Lin C, Lin H-LH-C, Lin H-LH-C. Risk of cancer among HIV-infected patients from a population-based nested case-control study: implications for cancer prevention. *BMC Cancer*. 2015;15(1):133. doi:10.1186/s12885-015-1099-y.
4. Abraham AG, D'Souza G, Jing Y, et al. Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. *J Acquir Immune Defic Syndr*. 2013;62(4):405-413. doi:10.1097/QAI.0b013e31828177d7.
5. Calabresi A, Ferraresi A, Festa A, et al. Incidence of AIDS-defining cancers and virus-related and non-virus-related non-AIDS-defining cancers among HIV-infected patients compared with the general population in a large health district of Northern Italy, 1999-2009. *HIV Med*. 2013;14(8):481-490. doi:10.1111/hiv.12034.
6. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. 2007;370(9581):59-67. doi:10.1016/S0140-6736(07)61050-2.
7. Walboomers JM, Jacobs M V, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12-19. doi:10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F.
8. Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sex Transm Dis*. 2014;41(11):660-664. doi:10.1097/OLQ.0000000000000193.
9. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890-907. doi:10.1016/S0140-6736(07)61416-0.
10. Ahdieh L, Klein RS, Burk R, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis*. 2001;184(6):682-690. doi:10.1086/323081.
11. Brickman C, Palefsky JM. Human Papillomavirus in the HIV - Infected Host : Epidemiology and Pathogenesis in the Antiretroviral Era . PubMed Commons. *Curr HIV/AIDS Rep*. 2015;12(1):25644977. doi:10.1007/s11904.
12. Lomalisa P, Smith T, Guidozzi F. Human immunodeficiency virus infection and invasive cervical cancer in South Africa. *Gynecol Oncol*. 2000;77(3):460-463. doi:10.1006/gyno.2000.5775.
13. Maiman M, Fruchter RG, Serur E, Remy JC, Feuer G, Boyce J. Human immunodeficiency virus infection and cervical neoplasia. *Gynecol Oncol*. 1990;38(3):377-

382.
14. Fruchter RG, Maiman M, Arrastia CD, Matthews R, Gates EJ, Holcomb K. Is HIV infection a risk factor for advanced cervical cancer? *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18(3):241-245.
15. Moodley M, Mould S. Invasive cervical cancer and human immunodeficiency virus (HIV) infection in KwaZulu-Natal, South Africa. *J Obstet Gynaecol*. 2005;25(7):706-710. doi:10.1080/01443610500294599.
16. Gichangi P, Bwayo J, Estambale B, et al. HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. *Gynecol Oncol*. 2006;100(2):405-411. doi:10.1016/j.ygyno.2005.10.006.
17. Ferreira MP, Coghill AE, Chaves CB, et al. Outcomes of cervical cancer among HIV-infected and uninfected women treated at the Brazilian National Institute of Cancer (2001-2013). *AIDS*. 2017;31(4):523-531. doi:10.1097/QAD.0000000000001367.
18. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, et al. HIV Infection and Survival Among Women With Cervical Cancer. *J Clin Oncol*. August 2016. doi:10.1200/JCO.2016.67.9613.
19. Okoye AA, Picker LJ. CD4(+) T-Cell Depletion In Hiv Infection: Mechanisms Of Immunological Failure. *Immunol Rev*. 2013;254(1):54-64. doi:10.1111/imr.12066.
20. Nkwanyana NN, Gumbi PP, Roberts L, et al. Impact of human immunodeficiency virus 1 infection and inflammation on the composition and yield of cervical mononuclear cells in the female genital tract. *Immunology*. 2009;128(1 PART 2):e746-57. doi:10.1111/j.1365-2567.2009.03077.x.
21. Trimble CL, Peng S, Thoburn C, Kos F, Wu TC. Naturally occurring systemic immune responses to HPV antigens do not predict regression of CIN2/3. *Cancer Immunol Immunother*. 2010;59(5):799-803. doi:10.1007/s00262-009-0806-4.
22. Eifel PJ, Winter K, Morris M, et al. RTOG 99-01: Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. *J Clin Oncol*. 2004;22(5):872-880. doi:10.1200/JCO.2004.07.197.
23. ClinicalTrials.gov. Radical Versus Simple Hysterectomy and Pelvic Node Dissection in Patients With Low-risk Early Stage Cervical Cancer (SHAPE). https://clinicaltrials.gov/ct2/show/NCT01658930. Accessed September 2, 2015.
24. Deeken JF, Pantanowitz L, Dezube BJ. Targeted therapies to treat non-AIDS-defining cancers in patients with HIV on HAART therapy: treatment considerations and research outlook. *Curr Opin Oncol*. 2009;21(5):445-454. doi:10.1097/CCO.0b013e32832f3e04.
25. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet (London, England)*. 2014;384(9939):241-248. doi:10.1016/S0140-6736(14)60604-8.
26. Casper C. The increasing burden of HIV-associated malignancies in resource-limited regions. *Annu Rev Med*. 2011;62(1):157-170. doi:10.1146/annurev-med-050409-103711.
27. World Bank Data Help Desk. World Bank Country and Lending Groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed March 8, 2017.
28. UNAIDS AIDSinfo. HIV Prevalence. http://aidsinfo.unaids.org/. Accessed April 3, 2017.
29. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. *Int J Gynaecol Obstet*. 2014;125(2):97-98. doi:10.1016/j.ijgo.2014.02.003.
30. *Common Terminology Criteria for Adverse Events (CTCAE), v4.0*. Bethesda, MD; 2011. doi:10.1080/00140139.2010.489653.
31. Kapp DS, Fischer D, Gutierrez E, Kohorn EI, Schwartz PE. Pretreatment prognostic factors in carcinoma of the uterine cervix: A multivariable analysis of the effect of age,

stage, histology and blood counts on survival. *Int J Radiat Oncol Biol Phys*. 1983;9(4):445-455. doi:10.1016/0360-3016(83)90060-3.
32. American Cancer Society. *Cancer Facts & Figures 2016*. Atlanta; 2016.
33. Carlson JA, Rusthoven C, DeWitt PE, Davidson SA, Schefter TE, Fisher CM. Are we appropriately selecting therapy for patients with cervical cancer? Longitudinal patterns-of-care analysis for stage IB-IIB cervical cancer. *Int J Radiat Oncol Biol Phys*. 2014;90(4):786-793. doi:10.1016/j.ijrobp.2014.07.034.
34. Trimble EL, Harlan LC, Gius D, Stevens J, Schwartz SM. Patterns of care for women with cervical cancer in the United States. *Cancer*. 2008;113(4):743-749. doi:10.1002/cncr.23682.
35. Vale C, Tierney JF, Stewart LA, Brady M, Dinshaw K, Jakobsen A, Parmar MK, Thomas G, Trimble T, Alberts DS, Chen H, Cikaric S, Eifel PJ, Garipagaoglu M, Keys H, Kantardzic N, Lal P, Lanciano R, Leborgne F, Lorvidhaya V, Onishi H, Pearcey RG, Pras E, Rober WC. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol*. 2008;26(35):5802-5812. doi:10.1200/JCO.2008.16.4368.
36. Berhane K, Karim R, Cohen MH, et al. Impact of highly active antiretroviral therapy on anemia and relationship between anemia and survival in a large cohort of HIV-infected women: Women's Interagency HIV Study. *J Acquir Immune Defic Syndr*. 2004;37(2):1245-1252. doi:10.1097/01.qai.0000134759.01684.27.
37. Sullivan PS, Hanson DL, Chu SY, Jones JL, Ward JW. Epidemiology of anemia in human immunodeficiency virus (HIV)-infected persons: results from the multistate adult and adolescent spectrum of HIV disease surveillance project. *Blood*. 1998;91(1):301-308.
38. Evans JC, Bergsjo P. The influence of anemia on the results of radiotherapy in carcinoma of the cervix. *Radiology*. 1965;84(4):709-717. doi:10.1148/84.4.709.
39. Ferrandina G, Distefano M, Smaniotto D, et al. Anemia in patients with locally advanced cervical carcinoma administered preoperative radiochemotherapy: Association with pathological response to treatment and clinical outcome. *Gynecol Oncol*. 2006;103(2):500-505. doi:10.1016/j.ygyno.2006.03.039.
40. Fuso L, Mazzola S, Marocco F, et al. Pretreatment serum hemoglobin level as a predictive factor of response to neoadjuvant chemotherapy in patients with locally advanced squamous cervical carcinoma: A preliminary report. In: *Gynecologic Oncology*. Vol 99. ; 2005:S187-91. doi:10.1016/j.ygyno.2005.07.079.
41. De Los Santos JF, Thomas GM. Anemia correction in malignancy management: Threat or opportunity? *Gynecol Oncol*. 2007;105(2):517-529. doi:10.1016/j.ygyno.2006.12.037.
42. Coulie PG, Van den Eynde BJ, van der Bruggen P, Boon T. Tumour antigens recognized by T lymphocytes: at the core of cancer immunotherapy. *Nat Rev Cancer*. 2014;14(2):135-146. doi:10.1038/nrc3670.

Tables and Figures

Figure 1: Directed Acyclic Graph illustrating causal assumptions applied to potential confounding and mediating variables in a cohort of patients with cervical cancer where the exposure of interest is HIV serostatus and the outcome of interest is overall survival. Arrows represent direction of causal effects between two variables. The black pathway represents the hypothesized association between HIV and survival; the red pathway represents a potential confounding relationship; green pathways represent potential mediating relationships.

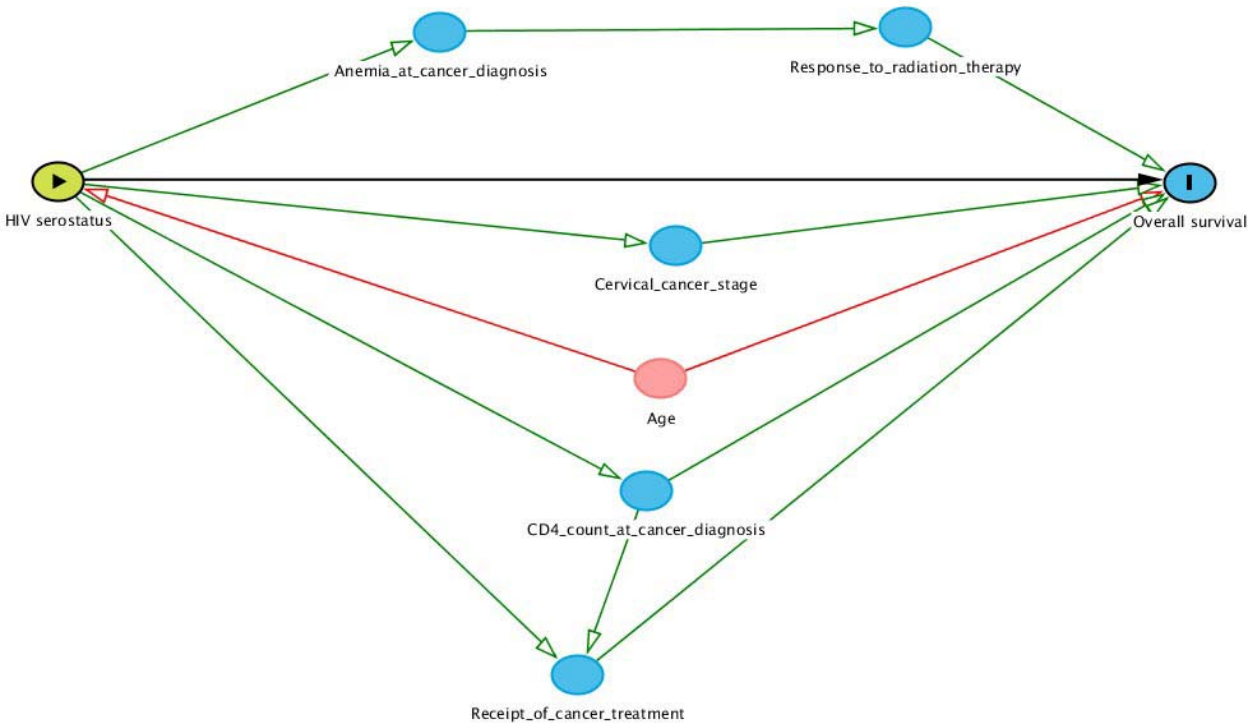

Table 1: Selected cervical cancer patient demographic, clinical and treatment characteristics, cervical cancer prognosis study, Kampala, Uganda, 2013-2015*

Characteristic	HIV-negative, % (#) (n=96)	HIV-positive, % (#) (n=53)
Median age (IQR), years	54 (47-62)	44 (39-48)
Highest education completed		
- None	34 (25)	19 (8)
- Primary	57 (42)	52 (22)
- Secondary or greater	9 (7)	29 (12)
- Unknown	(22)	(11)
Tobacco use		
- Lifelong non-smoker	94 (90)	98 (51)
- Current smoker	1 (1)	0 (0)
- Former smoker	5 (5)	2 (1)
- Unknown	(0)	(1)
Live births		
- 0	1 (1)	0 (0)
- 1-3	13 (12)	38 (20)
- 4-7	34 (33)	45 (24)
- 8+	52 (50)	17 (9)
Median BMI (IQR)	23 (20-27)	23 (19-25)
ECOG performance status		
- 0	2 (2)	0 (0)
- 1	84 (80)	91 (48)
- 2	8 (8)	7 (4)
- 3	6 (6)	2 (1)
Transport cost to UCI (USh)		
- 20,000	52 (50)	79 (42)
- 21,000-40,000	27 (26)	15 (8)
- 41,000-60,000	17 (16)	6 (3)
- >60,000	4 (4)	0 (0)
FIGO stage		
- I	12 (12)	19 (10)
- II	49 (47)	49 (26)
- III	35 (33)	28 (15)
- IV	4 (4)	4 (2)
Tumor histology		
- Squamous	95 (91)	90 (48)
- Adenocarcinoma	4 (4)	8 (4)
- Other	1 (1)	2 (1)
Tumor grade		
- Well differentiated	1 (1)	10 (5)
- Moderately differentiated	23 (22)	25 (13)
- Poorly/undifferentiated	76 (71)	65 (33)
- Unknown	(2)	(2)
Type of initial treatment		
- Chemoradiation	25 (21)	21 (10)
- Chemotherapy only	1 (1)	2 (1)
- Radiation therapy only	49 (40)	56 (27)
- Surgery only	0 (0)	2 (1)

- Surgery + adjuvant treatment[a] - No treatment - Unknown	0 (0) 25 (21) (13)	4 (2) 15 (7) (5)
Total radiation therapy received - <73.75 Gy - >=73.75 Gy - Unknown - Did not receive upfront radiotherapy	 42 (25) 58 (34) (2) (35)	 43 (15) 57 (20) (2) (16)
Median baseline hemoglobin[b] (IQR), g/dL	12.0 (9.9-12.9)	10.5 (8.6-12.5)
Median CD4 at enrollment, (IQR), cells/mm^3	926 (639-1045)	373 (300-502)
Enrolled in HIV care services at enrollment - Yes - No - Unknown	 -- -- --	 88 (45) 12 (6) (2)
Duration of HIV infection - <1 year - 1-5 years - >5 years - Unknown	 -- -- -- --	 16 (8) 33 (17) 51 (26) (2)
HIV plasma RNA level at enrollment - <500 copies/mL - >=500 copies/mL	 -- --	 77 (41) 23 (12)
HAART use at enrollment - No - Yes	 -- --	 77 (41) 23 (12)

Abbreviations: IQR = interquartile range; UCI = Uganda Cancer Institute; USh = Ugandan shillings; ECOG = Eastern Cooperative Oncology Group

*Missing data are shown as separate category for categorical variables, but percentages were calculated among non-missing data only.

[a]1 patient received radiation therapy; 1 patient received concurrent chemoradiation

[b]Baseline hemoglobin was not available for 34 (35%) of HIV-negative and 16 (30%) of HIV-positive patients

Table 2: Univariable and multivariable associations of selected characteristics with late stage at cervical cancer diagnosis, Kampala, Uganda, 2013-2015

Characteristic	**Univariable analysis PR (95%CI)** (n=143)	**Multivariable analysis*** **PR (95%CI)** (n=143)
HIV serostatus		
- HIV-negative	REF	REF
- HIV-positive	0.83 (0.52-1.33)	1.03 (0.60-1.78)
Age		
(Per 10-year age increase)	1.15 (0.98-1.36)	1.07 (0.85-1.34)
Live births		
(Per each additional 1 live birth)	1.05 (0.98-1.12)	1.04 (0.95-1.13)
Transport cost to UCI (USh)		
- 20,000	REF	REF
- 21,000-40,000	0.66 (0.34-1.28)	0.66 (0.33-1.33)
- 41,000-60,000	1.47 (0.88-2.44)	1.40 (0.83-2.35)
- >60,000	2.09 (1.11-3.93)	1.92 (0.93-3.99)

Abbreviations: PR = prevalence ratio; USh = Ugandan Shillings

* Multivariable analysis adjusted for HIV serostatus, age, number of live births, transport cost

Table 3: HIV-specific treatment characteristics by cervical cancer stage at diagnosis among HIV-positive patients*, Kampala, Uganda, 2013-2015

	Early stage, % (#) (n=36)	Late stage, % (#) (n=17)
Duration of HIV infection		
- <1 year	17 (6)	12 (2)
- 1-5 years	29 (10)	44 (7)
- >5 years	54 (19)	44 (7)
- Unknown	(1)	(1)
CD4 T-cell count at enrollment		
- >500	25 (9)	29 (5)
- 201-500	67 (24)	47 (8)
- 0-200	8 (3)	24 (4)
HIV plasma RNA level at enrollment		
- <500 copies/mL	75 (27)	82 (14)
- >=500 copies/mL	25 (9)	18 (3)
HAART use at enrollment		
- No	22 (8)	24 (4)
- Yes	78 (28)	76 (13)
Enrolled in HIV care services at enrollment		
- No	9 (3)	18 (3)
- Yes	91 (31)	82 (14)
- Unknown	(2)	(0)

*Missing data are shown as separate category for categorical variables, but percentages were calculated among non-missing data only.

Figure 2: Kaplan-Meier plot of overall cervical cancer survival stratified by HIV serostatus, Kampala, Uganda, 2013-2015

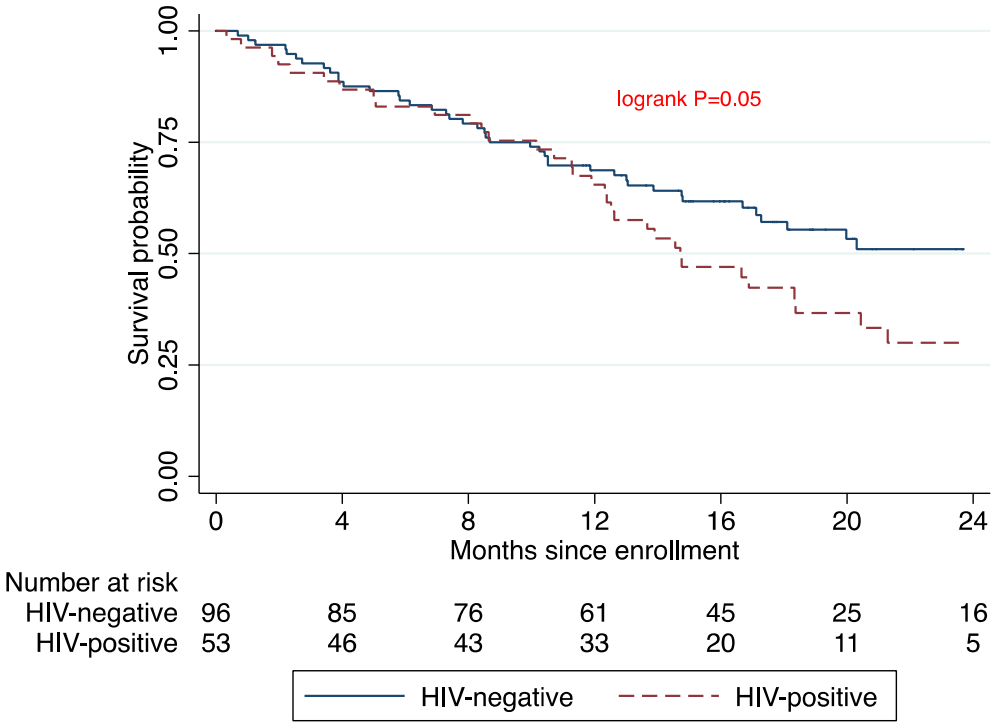

Table 4: Univariable and multivariable associations of selected characteristics with overall survival among cervical cancer patients, Kampala, Uganda, 2013-2015

	Univariable analysis HR (95%CI)	**Multivariate analysis* HR (95%CI)**
HIVSeroStatus - HIV-negative - HIV-positive	 REF 1.55 (1.01-2.39)	 REF 1.35 (0.83-2.17)
Age *(per 1-year age increase)*	0.98 (0.97-1.00)	0.98 (0.96-1.00)
FIGO stage - Early (stage I-II) - Late (stage III-IV)	 REF 2.27 (1.45-3.57)	 REF 2.77 (1.73-4.44)

Abbreviations: HR = hazard ratio; CI = confidence interval

* Adjusted for HIV serostatus, age, and FIGO stage