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Invasive cervical cancer risk among HIV-infected women: A North American multi-cohort collaboration prospective study

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Abstract

Objective—HIV infection and low CD4+ T-cell count are associated with an increased risk of persistent oncogenic HPV infection – the major risk factor for cervical cancer. Few reported prospective cohort studies have characterized the incidence of invasive cervical cancer (ICC) in HIV-infected women.

Methods—Data were obtained from HIV-infected and -uninfected female participants in the NA-ACCORD with no history of ICC at enrollment. Participants were followed from study entry or January, 1996 through ICC, loss-to follow-up or December, 2010. The relationship of HIV infection and CD4+ T-cell count with risk of ICC was assessed using age-adjusted Poisson regression models and standardized incidence ratios (SIR). All cases were confirmed by cancer registry records and/or pathology reports. Cervical cytology screening history was assessed through medical record abstraction.

Results—A total of 13,690 HIV-infected and 12,021 HIV-uninfected women contributed 66,249 and 70,815 person-years (pys) of observation, respectively. Incident ICC was diagnosed in 17 HIV-infected and 4 HIV-uninfected women (incidence rate of 26 and 6 per 100,000 pys, respectively). HIV-infected women with baseline CD4+ T-cells of ≥ 350, 200–349 and <200 cells/uL had a 2.3-times, 3.0-times and 7.7-times increase in ICC incidence, respectively, compared with HIV-uninfected women (P_{trend} =0.001). Of the 17 HIV-infected cases, medical records for the 5 years prior to diagnosis showed that 6 had no documented screening, 5 had screening with low grade or normal results, and 6 had high-grade results.

Conclusions—This study found elevated incidence of ICC in HIV-infected compared to -uninfected women, and these rates increased with immunosuppression.

Keywords

Human papilloma virus; HIV-infection; Invasive Cervical Cancer; Immunosuppression

INTRODUCTION

Human papillomavirus (HPV), a common sexually transmitted virus, is a necessary cause of invasive cervical cancer (ICC). While the vast majority of cervical HPV infections clear or become undetectable, these infections persist in a subset of women. HIV-infected women are significantly more likely than HIV-uninfected women to have incident and persistent HPV cervical infections, [1] and to develop incident pre-cancers such as squamous intraepithelial lesions (SIL) [1–4] , including high-grade SIL (HSIL) [5;6]. Among HIV-infected women the incidence of HPV infection and SIL increases with lower CD4+ T-cell count (CD4) [7;8] . These collective findings strongly support a dose-response relationship between host immune status and the risk of early and intermediate stages of HPV-related tumorigenesis[1;9;10].

There are few data, however, regarding the influence of immunodeficiency on the risk of incident ICC [11]. Few prospective studies of HIV-infected women have had sufficient size to evaluate ICC as an outcome. Though ICC was included as an AIDS defining event in the 1993 case definition, the evidence for inclusion came from studies of cervical dysplasia rates among HIV-infected women [11;12]. Inferences regarding the risk of ICC in HIV-infected women have been based primarily on evidence from studies linking HIV/AIDS diagnosis with cancer registries. These studies have reported several-fold greater incidence of ICC among women with HIV/AIDS compared with the general population [13–16]. Linkage studies, however, lack detailed prospective data to assess the temporality between host

immunity and cancer risk. To our knowledge, only one prospective cohort study examined the association between time-updated current CD4 and ICC [17]. In this study, based in the French Hospital Database on HIV cohort, Guiguet *et al.* reported a significant association of CD4 with risk of ICC.

The current study is the first multi-cohort prospective investigation of the relationship between HIV infection, immunosuppression, and incident ICC in North America. Using data from 18 collaborating cohorts of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), we examined rates of incident ICC based on cases ascertained through a rigorous standardized validation procedure. The association between CD4 and ICC risk was assessed prospectively to characterize the relevant periods of immunosuppression in relation to ICC risk.

METHODS

Study Population and Design

Cases of ICC were identified from 18 prospective cohorts collaborating in the NA-ACCORD [18]. The NA-ACCORD represents more than 60 clinical sites and uses standardized methods of data collection with approval by local institutional review boards. Briefly, each contributing cohort has developed standardized cohort-specific methods of data collection. At scheduled intervals, these cohorts submit data regarding enrolled participants' demographic characteristics, dates of prescribed antiretrovirals, dates and results of laboratory tests including HIV-1 RNA viral load and CD4, dates of clinical diagnoses and vital status. These data are transferred securely to the NA-ACCORD's central Data Management Core, where they undergo quality control for completeness and accuracy before they are combined into harmonized data files. Quality control included instituting measures to reduce the probability that an individual was participating in more than one clinical cohort. The human subject activities of the NA-ACCORD and of each of the participating cohort studies have been reviewed and approved by their respective local institutional review boards. HIV-infected women from these cohorts contributed follow-up time to the analysis from January 1, 1996 or study entry until the earliest of ICC diagnosis, loss-to-follow-up, death or cohort-specific end of follow-up (December 31, 2010 for most cohorts). Three cohorts (Kaiser Permanente Northern California [KPNC], Women's Interagency Health Study [WIHS] and AIDS Linked to the IntraVenous Experience [ALIVE] Study) also contributed data from HIV-uninfected women.

Case Validation

Cases of ICC were initially identified by each cohort through chart review, linkage to a formal cancer registry or diagnostic codes. For this study, each case was individually reviewed using a standardized abstraction survey which included histologic confirmation of cancer, date of diagnosis, and source of cancer confirmation (medical records, pathology reports and/or cancer registry records); only cases that had clear documentation of a histologic diagnosis of invasive cervical cancer were included. This approach emphasized specificity over sensitivity since it is well established that estimates of association between exposure (e.g. host immune status) and disease are more influenced by specificity when the outcome is rare (as is the case for ICC)[19]. This is a particular concern for ICC since precancerous cervical lesions, including carcinoma-in-situ, are much more common than invasive cancer, and record misclassification can readily occur. For incident case analyses, we limited cases to those women diagnosed 6 or more months after cohort enrollment to reduce the likelihood of including prevalent but undiagnosed cases; i.e., the starting time at risk for these analyses began 6 months after study enrollment. A sensitivity analysis was done that limited cases to those women diagnosed 18 or more months after cohort

enrollment to assess the impact on estimates of the possible inclusion of a prevalent ICC case.

Screening History

A supplementary survey collected information from each cohort on the completeness of Papanicolaou (Pap) test history records and likelihood of women receiving screening or treatment outside of the study care facility. The survey also collected abstracted Pap screening history and colposcopy results for each case.

Using Pap screening, colposcopy, biopsy and surgery records, we classified each incident case of ICC as associated with one of the following screening histories: 1) no known prior Pap screening within the past 5 years, 2) Pap screening within the past 5 years without detection of disease, or 3) a high grade abnormal cytology detected within the past 5 years with no/insufficient treatment of disease.

Statistical Methods

Using all validated ICC cases (prevalent and incident), trends in ICC risk were assessed graphically by plotting the cumulative incidence of ICC as a function of age, stratified by HIV serostatus, baseline CD4 (categorized as <200, 200–349, and ≥ 350 cells/uL) and baseline HIV-1 RNA viral load (categorized as <4000, 4000–99,999, ≥ 100,000 copies/ml). Crude ICC incidence rates were calculated by age strata (<40, 40–49, ≥ 50 years; time-updated) and compared to general population data from SEER[20] with a χ^2 test. Standardized incidence ratios (SIR) by age strata were estimated to assess risk in HIV-infected women relative to the general population. To test whether HIV-infected women were diagnosed with ICC at younger ages compared to the general population, the observed distribution of age-at-diagnosis among the HIV-infected cases was compared to the expected age-at-diagnosis distribution of age-at-diagnosis in the general population following the method of Sheils *et al*[21].

Linear mixed-effects Poisson regression was used to model the incidence of ICC. The model included time-updated age and CD4 count with HIV-infected women treated as the reference category. We separately assessed CD4 measured at the time of outcome ascertainment or diagnosis (± 6 months), at 18 months prior to the time of outcome ascertainment or diagnosis (± 6 months), and at entry into the study (which approximates nadir CD4 in many of the clinical cohorts). Differences in the incidence of ICC by cohort were accounted for using a random intercept in the model. . Separate models assessed the effects of HIV RNA level (categorized as previously specified with HIV-uninfected as a reference) and calendar period (1996–2001, 2002–2010) adjusted for age..

In addition to the incidence analysis using the full prospective data, we conducted two nested case-control studies to characterize and contrast the changes in CD4 prior to diagnosis in those who did and did not develop incident ICC. In the first study, which looked prospectively at CD4 patterns following effective antiretroviral therapy (ART) initiation, we included only incident cases of ICC among women who initiated ART - defined as a regimen containing at least three drugs, including a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), an entry inhibitor or an integrase inhibitor (new agents); or three nucleoside reverse-transcriptase inhibitors (NRTI), including abacavir or tenofovir -during observation and prior to the ICC diagnosis date. Controls were individually matched to cases on the following factors: the date of ART initiation (± 6 months); duration of follow-up after ART initiation (± 6 months); CD4 category (≤ 200, 200–350, 350–500, and >500 cells/uL); age within ± 2 years; and study cohort. All controls who met the matching criteria were included and each case had at least one matched control.

Using these data, the post-ART (pre-diagnosis) CD4 patterns were compared between cases and controls using piecewise-linear mixed effects models with spline terms (broken lines) at one year and three years following initiation and random intercepts for case-control clusters and individual repeated measurements. Cases and controls contributed CD4 measurements from ART initiation to the time of diagnosis (or equivalent follow-up for controls). Models were only fit to the first five years of data following ART initiation due to sparse data beyond five years post-ART.

In the second nested case-control study, which looked retrospectively at CD4 patterns leading up to ICC diagnosis, all incident ICC cases regardless of ART history were matched individually to controls at the time of cancer diagnosis using the following variables: age (± 3 months), cohort, current ART use (yes/no) and exact calendar year. Specifically, CD4 changes over time were compared between cases and controls over the five years prior to diagnosis using piecewise-linear mixed effects models with random intercepts for case-control clusters and individual repeated measurements.

RESULTS

A total of 13,690 HIV-infected women without a prior diagnosis of ICC contributed 66,249 person-years (pys) to this analysis. In addition, there were 12,021 HIV-uninfected women from three cohorts who contributed 70,815 pys. A cohort-level description of the cases and pys contributed is provided in the Appendix. The median follow-up time was 4.5 years (interquartile range [IQR] = 1.5 – 8.3 years) for HIV-infected women and 5.0 years (IQR=2.3 – 10.0) for HIV-uninfected women. At enrollment, HIV-infected and -uninfected women both had a median age of 37 years, though HIV-infected women were more likely to have enrolled later (P<0.001) and be of Black race (P<0.001). The median baseline CD4 in HIV-infected women was 342 cells/uL, and the prevalence of current or prior ART use was low (29%), although 71% initiated therapy during follow-up (Table 1).

Case Validation

There were 119 initially identified HIV-infected ICC cases and after review, a total of 67 ICC cases were validated. Most importantly, of the 30 that were considered potential incident cases, 17 were validated, whereas nine were found to be cancer-in-situ, three were HSIL (cervical pre-cancer), and one case had insufficient records for an ICC diagnosis to be validated; results that emphasize the importance of case validation given the known risk of record misclassification of cervical precancerous lesions as ICC (see Methods). Among the 17 confirmed HIV-infected ICC cases, the median time to diagnosis was 3.0 years (IQR: 2.2 – 5.9). Among the HIV-uninfected women, 4 ICC cases were confirmed (with diagnoses at 3.1 years, 4.0 years, 4.9 years and 8.2 years).

Comparison of HIV-infected Women with the General Population

SEER data were used as reference to estimate expected numbers of ICC cases and estimate SIRs by age strata. Overall, the SIR contrasting ICC incidence rates in HIV-infected NA-ACCORD women to expected rates based on SEER was 4.1 (95% confidence interval [95%CI]: 2.3 – 6.6). When stratified by age group, the SIR was 4.0 (95%CI: 1.3 – 9.3) for women <40 years and 5.0 (95% CI: 2.3 – 9.6) for women 40–49 years whereas it was 2.3 (95%CI: 0.3 – 8.3) for women 50 and older. A comparison of the distributions of age-at-diagnosis between the observed cases in HIV-infected women and expected cases in the general population was not significant (P=0.098).

Screening Data

Six of the 17 incident ICC cases (35%) in our study, each from a separate cohort, had no known Pap tests within the five years before diagnosis. However two of these cases came from cohorts that reported women may seek screening outside the cohort and that information may not be captured. Five (29%) of the women who developed ICC had a history of recent Pap screening without detection of disease. This included one case with a normal Pap test seven months before diagnosis, one case whose last Pap test was insufficient/uninterpretable, two with atypical squamous cells of undetermined significance (ASC-US) and one with low grade squamous intraepithelial lesions (LSIL), all within a year of diagnosis. Six cases (35%) had high grade SIL detected through Pap screening an average of three years before their ICC diagnosis (range 2–4 years) without subsequent treatment. Four of these six women with prior HSIL Pap had colposcopy, but none of the six received treatment. For two of these cases, notes were made in the medical files indicating that the patient had been referred for surgical excision but had missed scheduled appointments.

Cumulative ICC Risk Trends Among all Cases

The differences in lifetime ICC risk by HIV serostatus are shown in Figure 1a. There was an increasing disparity with increasing age in the cumulative incidence of ICC experienced by HIV-infected women compared to HIV-uninfected women or the general US population, represented by SEER. The trends in ICC risk by CD4 in Figure 1B show that the risk groups differentiate by approximately age 45 and indicate the highest risk is among HIV-infected women with a CD4<200 cells/uL while the lowest risk is among HIV-uninfected women in the participating cohorts. No clear differences in ICC risk could be readily discerned between HIV RNA strata; HIV-uninfected women continued to show the lowest risk of ICC.

Prospective Analysis

The crude ICC incidence rate (IR) among HIV-infected women was 26 per 100,000 pys (95% CI: 16 – 41). When stratified by age, the IR was lower among HIV-infected women <40 years of age than those aged 40 to 49 years (18 versus 39 per 100,000 pys, P=0.005), but similar to the rate among women ≥ 50 years and over (16 per 100,000 pys). The overall age-standardized incidence of ICC was higher among HIV-infected compared with -uninfected women in the study (16 vs 5 per 100,000, P=0.03), although this difference was primarily in those younger than 50 years.

When stratified by CD4, women with lower CD4 had significantly higher ICC incidence (P_{trend}=0.003) regardless of whether CD4 was assessed at baseline, 18 months prior to the outcome assessment or at the time of outcome assessment (Table 2). Although ICC incidence decreased with higher CD4, the rate among HIV-infected women with CD4 ≥ 350 cells/uL was more than twice the rate of HIV-uninfected women, (14 vs 6 per 100,000, Table 2). Figure 1B shows the increased cumulative ICC incidence among immunosuppressed women. ICC risk was associated with higher HIV viral load, although the association was weaker than that observed for CD4 cell count; no trend over calendar period was noted (results not shown).

In age-adjusted Poisson regression models with HIV-uninfected women as the referent, the incidence rate ratio (IRR) of ICC was increased by 2.3-times. 3.0-times and 7.7-times among HIV-infected women with baseline CD4 ≥ 350, 200–349, and <200 cells/uL, respectively (Table 3). Results were similar whether CD4 at the time of ICC diagnosis or 18 months before diagnosis were considered.

Nested Case-Control Analyses

Among the 17 incident cases of ICC, nine cases occurred in women who initiated ART during follow-up. Cases were diagnosed up to six years following ART initiation and the median time between ART initiation and diagnosis was 1.3 years. These nine cases were individually matched to 103 controls from among the 7,463 HIV-infected women without an ICC diagnosis who initiated ART therapy during follow-up. The non-parametric smoothed fit of the mean CD4 trajectories after ART initiation and associated 95% CIs are shown in Figure 2A. The estimates from the linear mixed model indicate non-significant differences in the slope of the CD4 trajectory in the first year following ART initiation (8 cells/uL per month gain for controls versus 6 cells/uL per month gain for cases) and from one to three years following ART initiation (6 cells/uL per month gain for controls versus 3 cells/uL per month gain for cases). However, by three years following ART initiation, a deviation in the case and control trajectories is noted from the non-parametric fit to the data, with cases exhibiting falling CD4 on average, compared with controls (Figure 2A); albeit, the observed smoothed trajectory shown in Figure 2A could not be modeled due to sparse data, as most cases were diagnosed prior to three years following ART initiation. Furthermore, the suggested decline is consistent with the second matched analysis using all 17 cases, which indicated falling CD4 levels in cases prior to diagnosis (Figure 2B). From the linear mixed model the slope in the controls was estimated to be flat (~0 cells/uL per month) compared to a −2 cells/uL per month estimated slope in the cases, resulting in a substantial CD4 discrepancy at the time of diagnosis of −185 cells/uL (P=0.01).

Sensitivity Analyses

In the main analyses, we limited cases to those women diagnosed 6 or more months after cohort enrollment to reduce the likelihood of including prevalent but undiagnosed cases. However, there is still the possibility that prevalent cases were included in the analysis. Therefore we reran the analysis using the 14 women diagnosed18 months or more after cohort enrollment. Results were consistent in terms of the magnitude and direction of effect estimates compared to the main analysis. The estimated relative rates for the CD4 strata <200, 200–350 and >350 using CD4 lagged 18 months and excluding cases during the first 18 months were 9.5, 5.3, and 2.0, respectively, compared to 9.2, 5.1, and 1.9, respectively from the primary analysis that excluded cases during the first 6 months (Table 3).

DISCUSSION

In this multi-cohort analysis of incident ICC, HIV-infected women had significantly higher risk of incident ICC than HIV-uninfected women, and the risk of ICC increased significantly with diminishing immune status as measured by CD4 count. Further, women who developed ICC after initiation of antiretroviral therapy were characterized by declining CD4 counts prior to diagnosis, which was not observed in non-cases. The increased burden of ICC may persist in HIV-infected women even at higher CD4 counts, as HIV-infected women with CD4 counts ≥ 350 cells/uL still experienced significantly higher rates of ICC than the general population or HIV-uninfected women in these cohorts. Nevertheless, these results suggest that the use of ART to maintain CD4 above 350 cells/uL may reduce ICC risk.

As in the general population where ICC risk increases with age, we noted a doubling of the incidence of ICC in HIV-infected women comparing those 40 to 49 years old to those younger than 40 years. However, the rate of ICC decreased in HIV-infected women 50 years and older. After accounting for the different age structure in the HIV-infected and general populations, the SIRs suggest an elevated ICC incidence among HIV-infected women in the younger age groups relative to the general population, though the difference in median age-at-diagnosis was not significant, likely due to the small sample size. Competing risks that

preferentially remove HIV-infected women at highest risk of ICC from the risk set -which are not accounted for in the present analysis - may explain the noted differences in SIRs between age strata. Alternatively, cervical screening at earlier stages of ICC may result in diagnosis of ICC at earlier ages. Cancer staging information was not available for this study and thus we could not access whether HIV-infected women tend to be diagnosed at earlier disease stages. No other studies that we are aware of have examined the question of age-at-ICC diagnosis among HIV-infected women and further research is warranted to determine whether HIV-infected ICC cases are more likely to occur at younger ages relative to the general population. Addressing this question could also shed light on the etiologic underpinnings of the increased risk of ICC among HIV-infected women by implicating a more rapid progression of cervical disease as a result of immunosuppression.

Given that regular screening and treatment for precancerous lesions is thought to prevent most ICC cases [22–24], it is notable that 6 incident cases had no evidence of Pap screening within the 5 years prior to diagnosis. Some of these women may not have been engaged in regular care, or some may have been receiving HIV specialty care only, with gynecologic screening provided elsewhere. HIV-uninfected women in our study had a relatively low rate of ICC - lower than that observed in the general (SEER) population. Most of the HIV-uninfected women in our study were women in a primary care setting, and their low cancer rate may speak to the effectiveness of regular cervical cancer screening for preventing ICC.

While Pap smear results are specific, they have only moderate sensitivity and false-negative results occur – a concern that is partially alleviated through repeated testing [25]. Only one case was identified that had a Pap test within two years of diagnosis indicating normal cytology. The majority of cases (9 of 17) had recent Paps indicating ASC-US (n=2), LSIL (n=1), or HSIL (n=6), representing potentially preventable disease if colposcopy and appropriate therapy had occurred. Barriers to colposcopy and treatment following abnormal Pap have been extensively studied [26–33] although only a few studies have focused on HIV-infected women [34;35].

This study benefited from extensive follow-up of a large population of HIV-infected women enrolled in formal cohort studies with longitudinal information on CD4, screening and treatment. The results were strengthened, however, by a rigorous validation process for the cases assuring high specificity of the case definition. While our study had fewer cases than the study by Guiguet *et al.* [17], the difference between the final validated cases and those initially identified in the current study is consistent with other reports of the high degree of misclassification that can result from relying on less rigorous case definitions such as diagnostic codes like ICD10. The reported ICC incidence in the HIV-infected women in Guiguet *et al.* [17] was notably higher than that observed in our study (6900 vs 26 per 100,000) despite a higher median current CD4 cell count than cases in our study (287 vs 178 cells/ul). However, their estimate included cases diagnosed within the first six months of follow-up.

Overall, the data from this large prospective study of ICC in HIV-infected women suggest that maintaining CD4 at higher counts could lower ICC risk. While prevention of ICC may not alone provide an adequate indication for the early initiation of ART [36], our data provide important information regarding the impact of host immunity on ICC in HIV-infected women as they continue to live longer through ART. Cervical cancer screening is important for preventing progression to ICC [37] and further research is warranted on the barriers among HIV-infected women to seeking treatment following abnormal Paps.

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*Kaiser Permanente Northern California (Michael Horberg, Michael Silverberg)

*Multicenter Hemophilia Cohort Study – II (MHCS-II; James Goedert) Multicenter AIDS Cohort Study (MACS; Lisa Jacobson)

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*Ontario HIV Treatment Network Cohort Study (OHTN; Sean Rourke, Anita Rachlis)

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APPENDIX

Table

ICC incidence among the HIV-infected and – uninfected women by contributing cohort

Cohorts	Events	Person-years	Incidence Rate per 100,000	95% CI[a] LL	95% CI[a] UL
HIV-infected					
AIDS Link to the IntraVenous Experience	1	1173	85	12	605
Adult AIDS Clinical Trials Group Longitudinal Linked Randomized Trials	1	1585	63	9	449
HIV Research Network	2	7794	26	6	103
HAART Observational Medical Evaluation and Research	1	4783	21	3	148
HIV Outpatient Study	2	5816	34	9	138
Johns Hopkins HIV Clinical Cohort	1	6759	15	2	105
John T. Carey Special Immunology Unit Patient Care and Research Database	0	1572	0	0	235
Kaiser Permanente Northern California	1	3303	30	4	215
Multicenter Hemophilia Cohort Study – II	0	6	0	0	58554
Montreal Chest Institute Immunodeficiency Service Cohort	2	2570	78	20	311
Ontario HIV Treatment Network Cohort Study	0	1301	0	0	284
Southern Alberta Clinic Cohort	0	1667	0	0	221
University of Alabama at Birmingham Clinic Cohort	1	2451	41	6	290

Cohorts	Events	Person-years	Incidence Rate per 100,000	95% CI[a] LL	95% CI[a] UL
University of North Carolina, Chapel Hill HIV Clinic Cohort	0	2108	0	0	175
University of Washington HIV Cohort	1	2377	42	6	299
Veterans Aging Cohort Study	0	539	0	0	685
Vanderbilt-Meharry CFAR Cohort	0	2371	0	0	156
Women's Interagency HIV Study	4	18074	22	8	59
HIV-uninfected					
AIDS Link to the IntraVenous Experience	0	2468	0	0	150
Kaiser Permanente Northern California	4	62098	6	2	17
Women's Interagency HIV Study	0	6249	0	0	59

[a]The lower limit (LL) and upper limit (UL) of the 95th percentile confidence interval (95% CI)

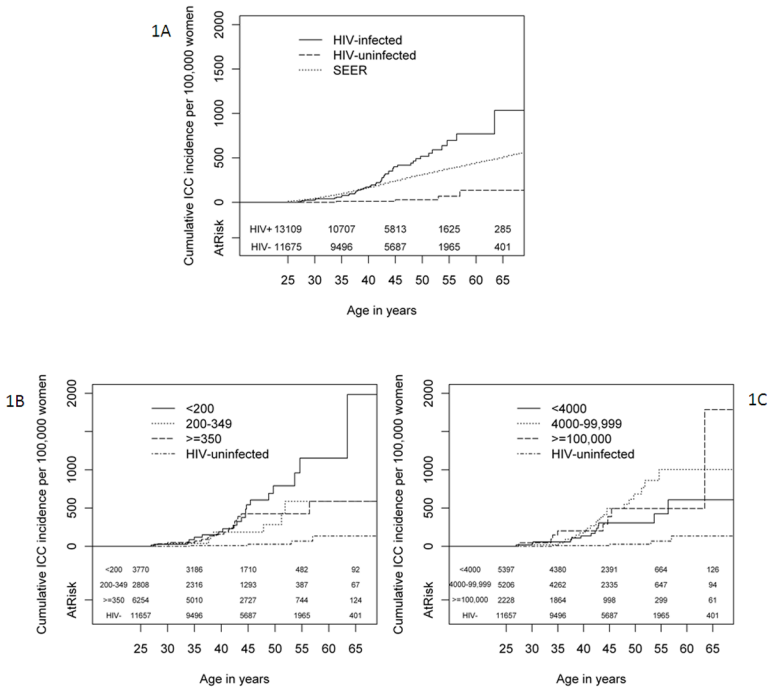

Figure 1.

Non-parametric estimation of the cumulative incidence of cervical cancer among all validated cases (prevalent and incident). 1A) Cumulative incidence of cervical cancer (ICC) per 100,000 person-years, by time-updated age, in HIV-infected compared with HIV-uninfected women in NA-ACCORD and compared with the general U.S. population sampled by SEER. 1B) Cumulative ICC per 100,000 person-years by time-updated age, by baseline HIV status and CD4 cell count. 1C) Cumulative incidence of ICC per 100,000 person-years by time-updated age, by baseline HIV status and HIV viral load.

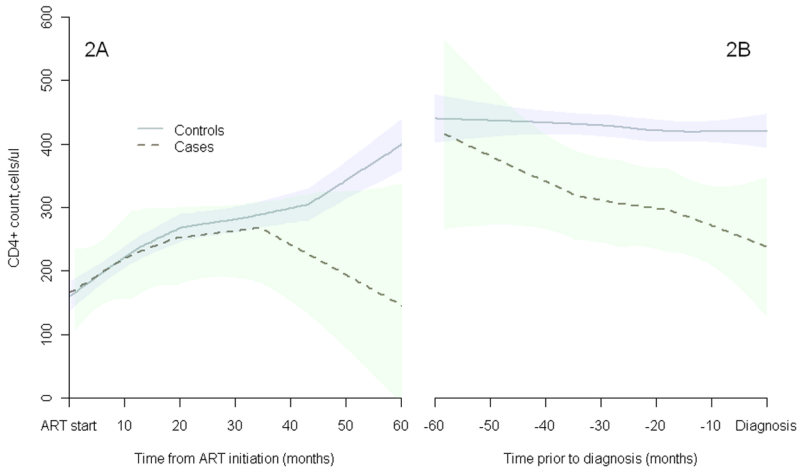

Figure 2.

CD4 T-cell count mean trajectories and 95% CIs over time among incident invasive cervical cancer cases (dashed) and matched controls (solid) from NA-ACCORD cohorts. 2A) trajectories of cases and controls matched at antiretroviral therapy (ART) initiation on CD4 T-cell count, age, cohort, year of ART initiation, and time subject followed after ART initiation. 2B) trajectories of cases and controls matched at ICC diagnosis on ART use, age and calendar year.

Table 1

Baseline characteristics of HIV-infected women diagnosed with invasive cervical cancer in NA-ACCORD 1996–2010, stratified into incident cases (detected >6 months after enrollment) and prevalent (detected before enrollment or within first 6 months of enrollment). Characteristics of all HIV-infected women in the study, HIV-uninfected women from a three cohorts and women diagnosed with invasive cervical cancer in the general population (SEER) are shown for comparison.

Demographic Characteristics[1]	**HIV-infected**			**HIV- uninfected**	**SEER**[2]
	All women in cohort N=13,690	**Incident Cases N=17**	**Prevalent Cases N=50**	**All women in cohort N=12,021**	**Cases N=67,684**
Age; years	37 (31 – 44)	39 (35 – 42)	41 (35 – 47)	37 (31 – 44)	48 (38 – 62)
<40	59%	59%	46%	60%	28%
40–49	30%	35%	38%	29%	24%
>=50	11%	6%	16%	11%	48%
Race					
White	22%	18%	36%	36%	76%
Black	50%	65%	48%	17%	14%
Other/unknown	28%	18%	16%	47%	10%
Year of entry					
1996–2001	56%	71%	44%	68%	
2002–2010	44%	29%	56%	32%	
ART use at baseline					
Never users	71%	82%	64%		
Former users	2%		2%		
Current users	26%	18%	34%		
CD4 cells/uL	342 (173 – 546)	178 (67 – 411)	308 (109 – 437)		
<200	29%	53%	34%		
200–349	22%	18%	21%		
350–499	19%	6%	27%		
>=500	30%	24%	18%		
Nadir CD4; cells/uL	187 (60 – 327)	25 (10 – 127)	112 (27 – 253)		
HIV RNA; $\log_{10}$(copies/ml)	3.96 (2.67 – 4.81)	4.07 (3.69– 4.67)	4.11 (2.6 – 4.9)		

[1] Median (interquartile range) unless otherwise indicated

[2]Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2010 Sub (1973–2008 varying) - Linked To County Attributes - Total U.S., 1969–2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011 (updated 10/28/2011), based on the November 2010 submission.

Table 2

Crude incidence of invasive cervical cancer (ICC) among HIV-infected women in NA-ACCORD by CD4 cell count at entry into study cohorts (baseline), at 18 months prior to outcome ascertainment or ICC diagnosis, and at the time of outcome ascertainment or ICC diagnosis.

	ICC Incidence Rate per 100,000 person-years (95% CI)		
	Baseline CD4[1]	**CD4 18 months prior to diagnosis**[1]	**CD4 at diagnosis**[1]
HIV-infected women			
< 200 CD4 cells/uL	47 (25 – 91)	70 (29 – 168)	59 (28 – 124)
200 – 350 CD4 cells/uL	18 (6 – 57)	32 (10 – 98)	42 (19 – 94)
≥ 350 CD4 cells/uL	14 (6 – 33)	12 (4 – 37)	10 (4 – 27)
HIV-uninfected women		6 (2 – 16)	

[1] Significant trend (P=0.003) across CD4 category as evaluated using a linear CD4 term in Poisson model

Table 3

Results from the Poisson regression model assessing the association of CD4 T-cell count (CD4) with the rate of incident cervical cancer adjusting for age. The effect of CD4 was evaluated separately using measurements obtained at three time points: baseline CD4, CD4 at 18 months prior to outcome ascertainment or ICC diagnosis and CD4 at the time of outcome ascertainment or ICC diagnosis.

Risk Factor	Incidence Rate Ratio (95% Confidence Interval)		
	Baseline CD4	**CD4 18 months prior to diagnosis**	**CD4 at diagnosis**
Age; years			
20 – 39	1	1	1
40 – 49	1.9 (0.8 – 5.0)	2.2 (0.9 – 5.7)	2.1 (0.8 – 5.4)
50 and older	1.4 (0.4 – 5.4)	2.3 (0.7 – 7.7)	1.7 (0.5 – 6.5)
HIV status & CD4 cell count			
HIV-uninfected	1	1	1
HIV-infected			
CD4 ≥ 350	2.3 (1.3 – 4.1)	1.9 (1.0 – 3.8)	1.7 (0.9 – 3.2)
CD4 200–349	3.0 (1.1 – 8.6)	5.1 (2.0 – 12.5)	5.8 (2.3 – 14.6)
CD4 <200	7.7 (4.7 – 12.6)	9.2 (4.3 – 19.8)	8.4 (4.6 – 15.3)