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Spectrum of cancers among HIV-infected persons in Africa: The Uganda AIDS-Cancer Registry Match Study

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Although more than 25 million people in sub-Saharan Africa have human immunodeficiency virus (HIV) infection, little is known regarding their cancer risk. We investigated cancer risk among persons with HIV/AIDS in Uganda using record-linkage. We linked records of 12,607 HIV-infected persons attending The AIDS Support Organization (TASO) in Kyadondo County from October 1988 through December 2002 to the Kampala Cancer Registry. We calculated standardized incidence ratios (SIRs) to identify increased cancer risks in the early (4–27 months after TASO registration), late (28–60 months), or combined (4–60 months) incidence periods. We identified 378 cancers (181 prevalent, 197 incident) among TASO participants. Of incident cancers, 137 (70%) were AIDS-defining cancers. Risk was increased in the early-incident period, compared to the general population, for the AIDS-defining cancers: Kaposi sarcoma (SIR 6.4, 95%CI 4.8–8.4), non-Hodgkin lymphoma (6.7, 1.8–17), and cervical carcinoma (2.4, 1.1–4.4). These three cancers were also increased in the combined periods. Risks of five non-AIDS-defining cancers were increased in the combined periods: Hodgkin lymphoma (5.7, 1.2–17) and cancers of the conjunctiva (SIR 4.0; 1.5–8.7), kidney (16, 1.8–58), thyroid (5.7, 1.1–16), and uterus (5.5, 1.5–14). Cancers of the breast, nasopharynx, and lung were increased either in the early or late incident periods only. Among 407 children, seven cancers were observed, of which five were Kaposi sarcoma. The application of a record-linkage design in Africa broadens the repertoire of epidemiological tools for studying HIV-infected populations. We confirm the increased risks of AIDS-defining cancers and report increased risks of a few non-AIDS-defining cancers.

Key words: HIV; AIDS; Kaposi sarcoma; lymphoma; record-linkage; TASO; Uganda

The United Nations Joint Program on AIDS estimates that 25 million people were living with human immunodeficiency virus (HIV) infection in sub-Saharan Africa in 2004,[1] making this region the worst affected by the epidemic. Despite pioneering efforts to control the epidemic,[2] Uganda has an estimated 1 million people living with HIV infection.[1] That number will quite likely increase as access to life-extending antiretroviral therapies increases.[3]

The HIV epidemic provides an unprecedented opportunity to study the risks of cancers in immunosuppressed populations. In the West, where most epidemiological research has been done, risk is greatly increased for Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL)[4–6] and, to a lesser extent, cervical cancer. Diagnosis of these cancers in HIV-infected persons is considered AIDS-defining. Moderately increased risks of Hodgkin lymphoma, and cancers of the lung, lip, testis, and anogenital region have been reported.[7–11] The introduction of antiretroviral therapies has dramatically reduced the risk of KS and some NHL types, but the impact on risk of other cancers is still being evaluated.

In sub-Saharan Africa, relatively few studies have been done on the patterns of cancer among HIV-infected persons.[12–16] In Uganda, cancer-registry studies observed a sharp increase in KS incidence with the advent of the AIDS epidemic, but the incidence of NHL and cervical cancer has increased only slightly.[17] Because cancer registry studies do not capture individuals' HIV status, it is not possible to determine whether the reported trends in overall cancer incidence are due to the HIV epidemic or to other factors. Case-control studies have demonstrated association between KS and HIV infection, but associations with NHL have been inconsistent, and they have failed to demonstrate increased risks of other virally-associated cancers (e.g., cancers of liver, nasopharynx, and penis).[13,18] However, these studies have observed a novel association of HIV infection with conjunctival cancer.[19] Cohort studies have not been used to study risk of cancer among persons with HIV/AIDS in Africa.

Data on cancer incidence may be obtained by linking databases identifying persons with HIV/AIDS to cancer registries. Here, we report results of the first HIV record-linkage study implemented in Africa, which we conducted to evaluate cancer incidence among persons with HIV/AIDS in Uganda.

Material and methods

Study design

Study subjects were persons with HIV/AIDS who were registered with The AIDS Support Organization (TASO) from October 1988 through December 2002. TASO was established in 1987 as the first AIDS care organization in Uganda to provide medical care and social support to people with HIV/AIDS and their relatives.[20] Because TASO adopted an open-access policy, individuals diagnosed with HIV/AIDS were eligible for TASO registration regardless of tribe, religion, or socioeconomic status. Initially, most referrals came from local hospitals; however, that pattern has changed to more referrals coming from voluntary counseling and testing centers as these are established. Detailed demographic data, including sex, birthdates, residence, and physical address were obtained at registration. Clients received medical treatment at biweekly clinics. As previously described,[21] we used data on medical conditions present at registration to derive the WHO AIDS stage, which ranges from stage 1 (asymptomatic) to stage 4 (AIDS). Clients were counseled and received other support at the triweekly clinics. TASO also monitored the vital status of clients, but these data were incompletely updated. Up to 2002, TASO medical services did not include HIV-specific antiretroviral therapies.

By December 2002, TASO had centers in seven districts and had registered approximately 80,000 HIV/AIDS clients, of whom

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about 15,000 resided in Kyadondo County (~20% of people with HIV infection in the county). Only clients residing in Kyadondo County, which includes Kampala, the Ugandan capital, and its environs, were studied (1991 population: 1,038,941). Most of the county population is of the Ganda tribe, but the majority of the 52 other Ugandan tribes are also represented.[22]

Cancer records were obtained from the Kampala Cancer Registry (KCR), established in 1951 to cover Kyadondo County.[17] KCR maintained continuous cancer registration until 1971 when registration was interrupted by civil disturbance. Registration resumed in 1989 and has been continuous since.[17] For the record-linkage, we used cases registered from January 1989 to December 2002. Briefly, cancer registrars actively identified cases through monthly hospital visits. Transcribed demographic and clinical data of cases were computerized using the CanReg-4 program.[23] The program also eliminated incorrectly specified or duplicate entries. A recent study estimated that KCR ascertains about 90% of cancer cases in Kyadondo County.[24]

As in similar linkage studies in developed countries, TASO and KCR both provided text files (match-compatible files) with family and other names, sex, sub-district (urban or rural), and birthyear or age at registration. In contrast to registries in developed countries, TASO and KCR records did not have unique personal identification numbers and birthdates. We edited the names by deleting title prefixes and correcting common variations in spelling to improve match sensitivity. Furthermore, because we lacked birthdates, we created a new variable (birthyear5), which spanned a range of 5 years centered on the reported or calculated birthyear. These match-compatible files were linked to each other using a probabilistic matching algorithm in three passes that each employed different matching strategies.[25] The first pass blocked (i.e., considered records with exact matching values) on family name and first initial. The second pass blocked on family name and birthyear5, while the third pass blocked on sex, first four characters of family name, first initial, and sub-district. In each pass, the similarity of records within blocks was determined by calculating scores based on the remaining variables. Coordinators from TASO and KCR reviewed potential matches, while blinded to the type of cancer linked, and selected those deemed valid. When potential matches were questionable, coordinators reviewed the original TASO and KCR files. The Uganda National Council for Science and Technology gave ethical approval to conduct the study.

Statistical analysis

For the linkage, we analyzed cancers arising in the period from 60 months before to 60 months after TASO registration. As in U.S record-linkage studies,[7] cancers were categorized as prevalent at TASO registration (arising 60 months before to 3 months after TASO registration); early-incident (4–27 months postregistration), and late-incident (28–60 months postregistration). We evaluated the association of various cancers with HIV infection by estimating standardized incidence ratios (SIRs) in the early-, late-, or combined (i.e., 4–60 months postregistration) incident periods. SIRs were calculated as the number of cancers observed among subjects divided by the number expected. The number of expected cases for each cancer type was calculated as a sum of the products of person-time of TASO clients and the corresponding sex-, age- (in 5-year groups), and period- (1989–1993, 1994–1998, and 1999–2002) specific cancer rates from KCR. Exact confidence intervals for SIRs were calculated. No adjustment was done for multiple comparisons. We present data on prevalent cancers for descriptive purposes, but SIRs were not estimated.

Because dates of death of TASO clients were not consistently recorded, subjects were assumed to be under followup until 60 months after TASO registration or until censoring (December 31, 2002). Since HIV-associated mortality would be expected to deplete the cohort over time, the early-incident period yielded less biased estimates of cancer incidence than the late-incident period. However, the data from the late-incident period provided some information on cancer risk, especially when the SIR was increased. Together, the combined incident periods provided the largest number of available cases and, assuming the late-incident SIRs were not biased downward too much by unreported deaths or loss to followup, the most precise estimates of overall association. We therefore considered cancers to be associated with HIV infection if SIRs were significantly increased both in the early- and the late-incident periods (and thus also in the combined periods). We considered cancers to be possibly associated if their SIRs were elevated in one of the two incident periods or only in the combined periods.

HIV prevalence is high in Kyadondo County (10–15%[26]) and thus the expected counts for cancers for which the HIV-associated relative risk is very high, such as KS, will be inflated, and the SIR, as an estimate of HIV-associated relative risk, will be biased downward.[27] We therefore recalculated SIRs for KS using expected rates derived from KCR data prior to the AIDS epidemic (1960–1971). We also compared the incidence of KS and cervical cancer (the two most common cancers in TASO clients) across demographic and WHO AIDS stage categories using Poisson regression.

Results

Table I shows characteristics of the 12,607 TASO clients, including 407 children (ages 0–14 years). Approximately two-thirds were female. The median age was 30 years (interquartile range [IQR] 25–35) and was significantly lower among females than males (29 vs. 32 years, $p<0.001$). Subjects were predominantly urban, tended to have early HIV disease (WHO AIDS stages 1 or 2), and made a median of 3 (IQR 1–7) medical visits to

TABLE I – BASELINE CHARACTERISTICS OF HIV-INFECTED PERSONS REGISTERED WITH THE AIDS SUPPORT ORGANIZATION (TASO), UGANDA (OCT 1989 TO DEC 2002, N=12,607)

Characteristic	Value
Sex, n (%)	
Male	4184 (33)
Female	8423 (67)
Age in years, n (%)	
0–14	407 (3)
15–24	2360 (19)
25–34	6299 (50)
35–44	2714 (21)
45–54	645 (5)
55+	182 (1)
Median age, years (IQR)	30 (25–35)
Calendar year of registration, n (%)	
1989–1993[1]	4806 (38)
1994–1998	3569 (28)
1999–2002	4232 (34)
Median calendar year of registration (IQR)	1995 (1992–2000)
Location of residence, n (%)	
Urban	11045 (88)
Rural	1562 (12)
WHO AIDS stage, n (%)	
Stage 1	3542 (28)
Stage 2	2272 (18)
Stage 3	4217 (33)
Stage 4	134 (1)
Unknown[2]	2442 (19)
Number of medical visits, n (%)	
0	2442 (19)
1–5	6094 (48)
6–10	1859 (15)
11 or more	2219 (18)
Median number of medical visits (IQR)	3 (1–7)

IQR: interquartile range.–[1]Includes 11 subjects registered in between October and December 1988.–[2]Individuals who did not have a medical form completed at registration were not assigned WHO AIDS stage.

TASO. Subjects were considered at risk of cancer for 21,250 person-years in the early-incident period and for 23,040 person-years in the late-incident period.

Overall, 378 cancers were linked to the period from 60 months before to 60 months after TASO registration, representing 3.5% of the 10,782 KCR cancer records. Eighty percent of the matches were exact matches. Of the linked cancers, 181 were prevalent and 197 were incident (Table II). Forty one additional cancers diagnosed earlier than 60 months before TASO registration were identified. We excluded the 222 persons whose cancer was diagnosed in the prevalent period or earlier and 312 persons who were censored within first 3 months after registration. Thus, among the 12,073 remaining persons considered at risk we identified 96 cancers in the early-incident period and 101 cancers in the late-incident period. Overall, 137 (70%) of the cancers in the combined incidence periods were AIDS-defining cancers, i.e., 105 (53%) KS, 5 (3%) NHL, and 27 (14%) cervical cancer, while 60 (30%) were non-AIDS-defining cancers (Table II).

AIDS-defining cancers

The AIDS-defining cancers comprised most early-incident cancers. These occurred in significant excess compared to the general population: KS (54% of all cancers; SIR 6.4, 95%CI 4.8–8.4), NHL (4%; 6.7, 1.8–17), and cervical carcinoma (10%; 2.4, 1.1–4.4). KS and cervical cancer risks were also increased in the late-incident period. NHL incidence was not significantly increased in the late-incident period, but its SIR was imprecisely estimated (SIR 1.3, 95%CI 0–7.1). In the combined periods, risks of all three AIDS-defining cancers were significantly increased compared to the general population (Table II). For KS, SIRs in the early-incident period were similar among males (5.3, 95% CI 3.2–8.3) and females (7.2, 5–10). Using pre-AIDS KS rates strongly amplified the KS SIRs, both for males (70, 95% CI 40–110) and females (1,200, 800–1,650).

Overall, KS incidence among HIV-infected persons was 240 per 100,000 person-years in the early-incident period. As shown in Table III, KS incidence was similar among males and females ($p = 0.69$). By age, KS incidence peaked at 380 per 100,000 person-years among persons aged 15–24 years and decreased thereafter. KS incidence was similar among rural and urban residents ($p = 0.89$) and increased slightly but nonsignificantly with calendar time ($p = 0.10$). KS incidence was unrelated to WHO AIDS stage at TASO registration ($p = 0.45$). These findings were unchanged when we used data from the combined incidence periods (not shown).

NHL incidence in the early-incident period was 19 per 100,000 person-years. Including the three prevalent cases, NHLs were classified histologically as diffuse (n = 2), Burkitt (1), follicular (n = 1), and unspecified (n = 4) subtypes.

Among females, cervical cancer incidence in the early-incident period was 70 per 100,000 person-years. By age, incidence peaked at 200 per 100,000 among women aged 35–44 before decreasing. Incidence was similar among rural and urban women ($p = 0.32$) and was unrelated to calendar year ($p = 0.87$) or WHO AIDS stage at TASO registration ($p = 0.84$). These results were unchanged when we used data from the combined incidence periods (not shown).

Non-AIDS-defining cancers

None of the non-AIDS-defining cancers met our criteria for association with HIV infection; however, eight were considered possibly associated (Table II). Five cancers were increased in at least one of the incident periods and in the combined periods: Hodgkin lymphoma (SIR in combined incidence periods, 5.7, 95% CI 1.2–17), and cancers of the eye and orbit (3.7, 1.3–8.0), kidney (16, 1.8–58), thyroid (5.7, 1.1–16), and uterus (5.5, 1.5–14). The Hodgkin lymphomas cases were not further classified histologically. The six incident cancers of the eye and orbit were exclusively squamous cell carcinomas of the conjunctiva (SIR 4.0; 1.5–8.7), as were the 8 prevalent cases. The two kidney cancers were not histologically verified, while 2 of 3 thyroid cancers were confirmed by histology. Of four uterine cancers, one was in a 30-year-old (perhaps representing a misclassified cervical carcinoma); other cases included a leiomyosarcoma, an endometrial adenocarcinoma, and an unspecified uterine cancer.

Female breast cancer was significantly increased in the early-incident period, based on six cases (SIR 3.3, 95%CI 1.2–7.2). The incidence was not increased in the late-incident period and the SIR in the combined period was not statistically significant. Two other non-AIDS-defining cancers were significantly elevated only in the late-incident period but not in the combined period: cancers of the nasopharynx (SIR 7.1, 95% CI 1.4–21) and lung and bronchus (8.5, 1.7–25).

Cancers in children

Seven cancers were identified among 407 children. Five were KS, including three prevalent cancers (in children aged 4, 9, and 10 years at registration) and two late-incident (in children aged 4 and 10 years at registration). KS incidence was 160 per 100,000 person-years for the combined period, corresponding to an SIR of 100 (95% CI 20–350). Using the pre-AIDS era KS incidence to derive expected rates gave a KS SIR of 640 (95% CI 77–2,300). The other two cancers prevalent were Burkitt lymphoma in a 13-year-old and kidney cancer in a 1-year-old.

Discussion

Our study is the first to use a record-linkage design to derive comprehensive estimates of cancer incidence among persons with HIV/AIDS in Africa. We observed, as expected, a significant excess of AIDS-defining cancers, namely, KS, NHL, and cervical cancer. Although failing to meet our strict criteria for association, several non-AIDS-defining cancers, including conjunctival cancer and Hodgkin lymphoma, appeared to have increased incidence among persons with HIV/AIDS.

KS incidence was clearly elevated in our cohort; however, the relative risk was lower than in developed countries.[7,28,29] The low KS SIRs may be artifactual, reflecting, in part, the high prevalence of HIV infection in Kyadondo County and thus a high incidence of AIDS-related KS in non-TASO participants. The high background incidence would bias the SIR downwards.[27] KS SIRs increased substantially (i.e., SIRs were 70 for males, 1,200 for females) when the expected KS cases were estimated using pre-AIDS KS rates, confirming the strong effect of HIV on KS risk previously demonstrated in case-control studies in Africa.[13,16,30]

Infection with human herpesvirus 8 (HHV-8) is a prerequisite for the development of KS. HHV-8 infection is common among adult Africans (estimated 20–80% prevalence[31,32]) and the prevalence is of a comparable magnitude to that seen among men who have sex with men (MSM) in the U.S. (~30%).[33] Thus, one might expect KS incidence in our cohort to be similar to incidence among HIV-infected MSM. However, KS incidence in our cohort was much lower (240 vs. 5,700 per 100,000 person-years in HIV-infected MSM with AIDS in the U.S.).[34] Another discrepancy was that KS incidence in our cohort was unrelated to WHO AIDS stage at the time of TASO registration (Table III), even though KS risk increases with declining CD4 counts among persons with AIDS in the U.S.[35]

The lower KS incidence we observed could be due to under-ascertainment of KS by KCR. However, this explanation is not supported by a prior study that showed high cancer ascertainment by KCR.[24] Our record-linkage could have missed some cases, especially if persons used different names at TASO and at the hospital. However, we consider this unlikely, as the practice was rare. Because we lacked followup data, we could have overestimated survival and thus time at risk for KS, which would result in low KS incidence. However, at registration about half of subjects were in WHO stages 1 or 2, which are associated with longer median

TABLE II – OBSERVED CANCERS AND STANDARDIZED INCIDENCE RATIOS FOR HIV-INFECTED PERSONS REGISTERED WITH THE AIDS SUPPORT ORGANIZATION (TASO), UGANDA

Cancer type	ICD10 code	Observed cancers by time of onset, n (%)			Standardized incidence ratio by onset time (95% CI)					
		Prevalent	4–27 mo	28–60 mo	4–27 mo		28–60 mo		4–60 mo	
AIDS-defining cancers										
Kaposi sarcoma	C46	107 (59)	52 (54)	53 (53)	6.4	(4.8–8.4)	5.1	(3.8–6.7)	5.7	(4.6–6.8)
Non-Hodgkin lymphoma	C82–85,C96	3 (2)	4 (4)	1 (1)	6.7	(1.8–17)	1.3	(0–7.1)	3.6	(1.2–8.4)
Cervix uteri	C53	24 (13)	10 (10)	17 (17)	2.4	(1.1–4.4)	3.0	(1.8–4.9)	2.7	(1.8–4.0)
All AIDS-defining cancers		134 (74)	66 (69)	71 (70)	5.1	(3.9–6.5)	4.2	(3.3–5.3)	4.6	(3.8–5.4)
Non-AIDS-defining cancers										
All mouth	C00–06	0	0	0	0	(0–31)	0	(0–21)	0	(0–13)
Salivary gland	C07–08	1 (0.5)	0	0	0	(0–55)	0	(0–41)	0	(0–23)
Nasopharynx	C11	4 (2)	0	3 (3)	0	(0–13)	7.1	(1.4–21)	4.2	(0.8–12)
Other pharynx	C09–10,C12–14	0	0	0	0	(0–44)	0	(0–33)	0	(0–19)
Esophagus	C15	3 (2)	1 (1)	1 (1)	2.0	(0–11)	1.3	(0–7.2)	1.6	(0.2–5.6)
Stomach	C16	0	1 (1)	0	3.5	(0.1–20)	0	(0–9.3)	1.5	(0 -8.2)
Colon, rectum, and anus	C18–21	1 (0.5)	0	0	0	(0–8.1)	0	(0–6.1)	0	(0–3.5)
Liver	C22	6 (3)	2 (2)	1 (1)	3.1	(0.4–11)	1.3	(0–7.0)	2.1	(0.4–6.0)
Gall bladder and other biliary	C23–24	0	0	0	0	(0–310)	0	(0–230)	0	(0–130)
Pancreas	C25	0	0	0	0	(0–46)	0	(0–37.8)	0	(0–21)
Lung and bronchus	C34	1 (0.5)	0	3 (3)	0	(0–15)	8.5	(1.7–25)	5.0	(1.0–15)
Pleura/mesothelioma	C38.4, C45.0	1 (0.5)	0	0	0	(0–230)	0	(0–280)	0	(0–130)
Bones and joints	C40–41	1 (0.5)	1 (1)	1 (1)	9.1	(0.2–51)	8.6	(0.1–48)	8.8	(1.0–32)
Melanoma of the skin	C43	0	0	0	0	(0–67)	0	(0–52)	0	(0–29)
Other nonepithelial skin	C44	2 (1)	2 (2)	1 (1)	7.9	(0.9–29)	2.8	(0–16)	4.9	(1.0–14)
Peripheral nerves	C47	0	0	0	0	(0–690)	0	(0–3800)	0	(0–590)
Connective and soft tissue	C49	0	2 (2)	0	6.6	(0.7–24)	0	(0–8.54)	2.7	(0.3–9.8)
Breast	C50	7 (4)	6 (6)	2 (2)	3.3	(1.2–7.2)	0.8	(0.1–3.0)	1.9	(0.8–3.7)
Vulva	C51	1 (0.5)	0	0	0	(0–100)	0	(0–8.2)	0	(0–45)
Vagina	C52	1 (0.5)	0	1 (1)	0	(0–88)	18	(0.2–100)	10	(0.1–57)
Uterus	C54–55	2 (1)	2 (2)	2 (2)	6.1	(0.7–22)	5.1	(0.6–18)	5.5	(1.5–14)
Ovary	C56	1 (0.5)	2 (2)	2 (2)	4.0	(0.4–14)	2.9	(0.3–10)	3.3	(0.9–8.5)
Placenta	C58	1 (0.5)	0	0		(0–34)	0	(0–31)	0	(0–16)
Penis	C60	0	0	0	0	(0–59)	0	(0–42)	0	(0–24)
Prostate	C61	0	1 (1)	1 (1)	3.5	(0.1–20)	2.5	(0–14)	2.9	(0.3–11)
Testis	C62	0	1 (1)	0	52	(0.7–290)	0	(0–180)	25	(0.3–140)
Kidney	C64	1 (0.5)	0	2 (2)	0	(0–56)	34	(3.8–120)	16	(1.8–58)
Renal pelvis and ureter	C65–66, C68	0	0	0	0	(0–160)	0	(0–140)	0	(0–75)
Urinary bladder	C67	0	0	0	0	(0–51)	0	(0–39)	0	(0–22)
Eye and orbit[1]	C69	8 (4)	3 (3)	3 (3)	4.5	(0.9–13)	3.1	(0.6–9.1)	3.7	(1.3–8.0)
Brain and nervous system	C70–72	0	0	1 (1)	0	(0–43)	7.1	(0.1–39)	4.4	(0.1–24)
Thyroid	C73	1 (0.5)	1 (1)	2 (2)	4.7	(0.1–26)	6.4	(0.7–23)	5.7	(1.1–16)
Hodgkin lymphoma	C81	0	2 (2)	1 (1)	8.8	(1.0–32)	3.4	(0–19)	5.7	(1.2–17)
Multiple myeloma	C90	1 (0.5)	1 (1)	0	21	(0.3–120)	0	(0–52)	8.5	(0.1–47)
Lymphocytic leukemia	C91		0	1 (1)	0	(0–110)	29	(0.4–160)	15	(0.2–80)
Unspecified leukemia	C92–5	1 (0.5)	0	0	0	(0–33)			0	(0–13
Other or unspecified cancer	Other, assorted	2 (1)	2 (2)	2 (2)	3.0	(0.3–11)	2.3	(0–5.5)	2.6	(0.7–6.6)
All non-AIDS defining cancers		47 (26)	30 (31)	30 (30)	3.3	(2.2–4.7)	2.4	(1.6–3.5)	2.8	(2.1–3.6)
All Sites		181 (100)	96 (100)	101 (100)	4.4	(3.5–5.3)	3.5	(2.8–4.2)	3.8	(3.3–4.4)

ICD10: International Classification of Diseases, 10th edition; CI: Confidence interval [1]All eye and orbit cases identified were squamous cell carcinoma of the conjunctiva. However, computation of the expected cases included other eye and orbital cancers (see text).

survival (7.2 and 5.4 years, respectively[21]) than the period we considered them at risk of cancer.

The lower incidence of KS in TASO participants compared to homosexual men in the West therefore requires an explanation. We hypothesize that age at HHV-8 infection or, as suggested by others,[36] the timing of HHV-8 infection relative to the acquisition of HIV, modulates KS risk. In the U.S., HHV-8 infection usually occurs during adulthood, probably through sexual contact.[33] Possibly, adult HHV-8 infection, particularly if it occurs simultaneous with or after HIV infection, is associated with high risk of KS because of poor immunologic control of HHV-8 infection.[36,37] By contrast, HHV-8 infection usually occurs during childhood in Africa[38] prior to HIV infection, which might be associated with more effective immunologic control and lower subsequent risk of KS.

Our study indicates that persons with HIV/AIDS in Africa have an increased risk of NHL. Three case-control studies conducted in Africa have previously reported significant associations between HIV infection and NHL (odds ratios 5–13).[13,16,30] A fourth study observed an odds ratio of 2, which was not statistically significant.[18] Intriguingly, similar to KS, the NHL incidence in our cohort was much lower than that seen in the U.S. and Europe (i.e. 20 vs. 8,000–9,000 per 100,000 person-years).[39,40] The low NHL incidence among TASO participants may partly be due to under-ascertainment. Still, the enormous difference in NHL incidence between our cohort and Western populations again suggests that other factors are important. Epstein Barr virus (EBV) might play a role in African AIDS-related NHL, and if it does, age at EBV infection could modify risk of AIDS-related NHL, as we suggest for HHV-8 and KS.

We observed a modest, albeit significant, excess of cervical cancer among HIV-infected women in our cohort. Despite this excess, we are not convinced that cervical cancer is HIV-related.

TABLE III – INCIDENCE OF KAPOSI SARCOMA AMONG HIV-INFECTED PERSONS REGISTERED WITH THE AIDS SUPPORT ORGANIZATION (TASO), UGANDA, 4–27 MONTHS AFTER TASO REGISTRATION

Characteristic	Cases, n (%)	Incidence, per 100,000 person-years	Relative risk	95% CI	*p*-value*
All subjects	52 (100)	240	–	–	–
Age group, (years)[1]					0.06
0–14	0	0	0	–	
15–24	10 (19)	380	1.0	Reference	
25–34	35 (67)	310	1.7	0.8–3.4	
35–44	6 (12)	110	0.7	0.3–1.9	
45–54	1 (2)	80	0.4	0.1–3.1	
55 +	0	0			
Sex					0.69
Male	19 (36)	260	1.0	Reference	
Female	33 (64)	230	0.9	0.5–1.6	
Location of residence					0.89
Urban	47 (90)	240	1.0	Reference	
Rural	5 (10)	230	0.9	0.4–2.4	
Calendar year of registration					0.10
1989–1993	19 (33)	200	1.0	Reference	
1994–1998	16 (28)	230	1.2	0.6–2.2	
1999–2002	17 (33)	350	1.8	0.9–3.4	
WHO AIDS stage					0.45
Stage 1	16 (31)	260	1.0	Reference	
Stage 2	11 (21)	300	1.1	0.5–2.5	
Stage 3	14 (27)	200	0.8	0.4–1.6	
Stage 4	0	–	0	–	
Unknown[2]	11 (21)	240	0.9	0.4–1.9	

*p values are tests of heterogeneity.–[1]Age at onset at start of early incident period (4 months after TASO registration).–[2]Individuals who did not have a medical form at registration were not assigned WHO AIDS stage.

Previous studies have not shown a clear association between risk of cervical cancer and immune suppression.[15] The modest excess risk observed in our study and case-control studies conducted in Africa[15,13] could be due to a higher prevalence of human papillomavirus infection among HIV-infected women compared to uninfected women, since both infections are sexually transmitted.[41] Although the SIR of cervical cancer among HIV-infected women was not large, cervical cancer was the second most frequent tumor after KS in infected women.

Only 8 of 37 non-AIDS-defining cancers fulfilled our criterion for possible association with HIV infection. Conjunctival cancer and Hodgkin lymphoma showed significant excesses in either the early or late periods and in the combined periods. Thus, our study corroborates the novel association of conjunctival cancer with HIV infection initially reported from Uganda[14] and elsewhere in Africa.[15] Because conjunctival cancer incidence is highest in tropical countries, investigators have proposed solar ultraviolet radiation as an etiologic factor.[42] The novel association of conjunctival cancer with HIV infection has now prompted researchers to look for infectious cofactors.[14,15] Our finding of a significant excess of Hodgkin lymphoma among HIV-infected persons in Africa is new. Two relatively small case-control studies did not find a significant association with HIV infection.[13,16] Although based on small numbers, our finding agrees with results from studies conducted in the U.S.,[7] Italy,[29] and Australia,[43] which indicate a role for HIV infection in Hodgkin lymphoma.

Six other non-AIDS-defining cancers were possibly associated with HIV infection. Some of these associations may be spurious (for example, some uterine cancers may have been miscoded cervical cancers), but others might warrant further inquiry. Interestingly, we did not observe significant excesses of several virus-associated cancers, such as cancers of the liver or penis (related to infections with hepatitis B virus and human papillomavirus, respectively), although these cancers are relatively common in Uganda.

Among children, only KS occurred in significant excess, as previously reported.[17,44] KS was known to occur in children before the advent of the AIDS epidemic. Our results highlight the enormous increase in risk conveyed by childhood HIV infection (SIR 640). By contrast, we did not observe an excess of Burkitt lymphoma, a common childhood cancer in sub-Saharan Africa. This result is consistent with findings of a case-control study conducted in Kampala, Uganda, in which Burkitt lymphoma in children was not associated with HIV infection.[18]

Our study demonstrates the feasibility of using record-linkage design in Africa and its value in obtaining cancer incidence data. This design minimizes selection and response biases that often limit hospital-based case-control studies. Our study sample was likely representative of HIV-infected persons in Uganda and elsewhere in eastern Africa, because TASO uses an open-access policy. Nonetheless, we acknowledge some limitations. Despite its large size, our study identified somewhat few cancers, thereby limiting some analyses. Furthermore, because we lacked detailed clinical data, only limited risk factor analyses could be undertaken. Because we lacked precise dates of birth on cancer records, we used a record-linkage algorithm (i.e., largely relying on exact matches on surname, first initial, and birthyear5) less stringent than that used in linkage studies in developed countries. Our algorithm maximized sensitivity of the matches, but it probably decreased their specificity, which could account for some of the elevated SIRs for non-AIDS-associated cancers. We performed multiple statistical comparisons, which should be considered when interpreting our results. Finally, our results are susceptible to bias arising from differential cancer ascertainment among TASO versus non-TASO participants. However, because Kyadondo County is well served with health services and a good transport network, we believe that such bias would have been minimal.

To conclude, we observed significant excess of AIDS-defining cancers and a few non-AIDS-defining cancers among persons with HIV/AIDS in Uganda. Novel associations may become apparent as persons with HIV/AIDS in Africa begin to access life-extending therapies. We demonstrate that record-linkage studies are feasible in Africa. Such studies will provide a valuable tool for future investigations.

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