



# A case-control study of HIV infection and cancer in the era of antiretroviral therapy in Rwanda

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The aim of this study was to assess the association between HIV infection and cancer risk in Rwanda approximately a decade after the introduction of antiretroviral therapy (cART). All persons seeking cancer care at Butaro Cancer Center of Excellence (BCCOE) in Rwanda from 2012 to 2016 were routinely screened for HIV, prior to being confirmed with or without cancer (cases and controls, respectively). Cases were coded according to ICD-O-3 and converted to ICD10. Associations between individual cancer types and HIV were estimated using adjusted unconditional logistic regression. 2,656 cases and 1,196 controls differed by gender (80.3% vs. 70.8% female), age (mean 45.5 vs. 37.7 years), place of residence and proportion of diagnoses made by histopathology (87.5% vs. 67.4%). After adjustment for these variables, HIV was significantly associated with Kaposi Sarcoma ( $n = 60$ ; OR = 110.3, 95%CI 46.8–259.6), non-Hodgkin lymphoma (NHL) ( $n = 265$ ; OR = 2.5, 1.4–4.6), Hodgkin lymphoma (HL) ( $n = 76$ ; OR = 5.2, 2.3–11.6) and cancers of the cervix ( $n = 560$ ; OR = 5.9, 3.8–9.2), vulva ( $n = 23$ ; OR = 17.8, 6.3–50.1), penis ( $n = 29$ ; OR = 8.3, 2.5–27.4) and eye ( $n = 17$ ; OR = 4.7, 1.0–25.0). Associations varied by NHL/HL subtype, with that for NHL being limited to DLBCL ( $n = 56$ ; OR = 6.6, 3.1–14.1), particularly plasmablastic lymphoma ( $n = 6$ , OR = 106, 12.1–921). No significant associations were seen with other commonly diagnosed cancers, including female breast cancer ( $n = 559$ ), head and neck ( $n = 116$ ) and colorectal cancer ( $n = 106$ ). In conclusion, in the era of cART in Rwanda, HIV is associated with increased risk of a range of infection-related cancers, and accounts for an important fraction of cancers presenting to a referral hospital.

HIV-related immunosuppression worsens the outcome of oncogenic viral infections, so that people infected with HIV (PHIV) are at increased risk of developing a wide range of infection-related cancers.<sup>1</sup> In 2012, an International Agency for Research on Cancer (IARC) working group judged that there was sufficient evidence of a causal role of HIV infection

for Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), as well for cancers of the cervix, anus and conjunctiva.<sup>2</sup> Associations were also observed with cancers of the vulva, vagina, penis, liver and skin, but data—which came almost entirely from high-income countries—were too scarce to be sure of a causal association at that time.<sup>2</sup>

**Key words:** HIV, cancer, epidemiology

**Abbreviations:** ALL: acute lymphoblastic lymphoma; BCCOE: Butaro Cancer Center of Excellence; BL: Burkitt lymphoma; cART: anti-retroviral therapy; CHL: classical type Hodgkin lymphoma; CI: confidence intervals; CLL: chronic lymphocytic leukaemia; DLBCL: diffuse large B-cell lymphoma; HL: Hodgkin lymphoma; IARC: International Agency for Research on Cancer; ICD-O-3: International Classification of Diseases for Oncology; KS: Kaposi Sarcoma; LDCHL: lymphocyte-depleted CHL; LRCHL: lymphocyte-rich CHL; MCCHL: mixed cellularity CHL; NHL: non-Hodgkin lymphoma; NSCHL: nodular sclerosis CHL; OR: odds ratios; PBL: plasmablastic lymphoma; PHIV: people infected with HIV; SLL: small cell lymphocytic lymphoma; WHO: World Health Organization

**Conflict of Interest:** The authors declare that they have no conflicts of interest.

**Grant sponsor:** Fondation de France; **Grant number:** 00039621

**DOI:** 10.1002/ijc.31537

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**History:** Received 2 Feb 2018; Accepted 9 Apr 2018; Online 16 Apr 2018

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**What's new?**

Human immunodeficiency virus (HIV) infection is linked to the development of certain cancers of infectious origin. The incidence and character of these malignancies have likely been impacted by widespread access to antiretroviral therapy. This study, involving patients in Rwanda, confirms associations between HIV and Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma (HL) and cervical, anal and conjunctival cancers and further describes associations with lymphoma subtypes. In particular, HIV infection was associated with plasmablastic lymphoma and with certain HL subtypes. The findings show that despite access to antiretroviral therapy, there is ongoing need for monitoring and control of HIV-associated cancers.

Despite suffering the largest part of the worldwide HIV epidemic, data on the link between HIV and cancer in sub-Saharan Africa remain limited. Valuable data have been published from Uganda,<sup>3</sup> South Africa,<sup>4</sup> Ivory Coast/Benin<sup>5</sup> and a previous small study from Rwanda.<sup>6</sup> However, most of these studies describe periods in which the majority of PHIV had no access to antiretroviral therapy (cART) and hence suffered severe competitive mortality from opportunistic infections. In the era of cART, prolonged survival of PHIV in conditions of partial immune reconstitution is expected to give more time for the long-term sequelae of carcinogenic viruses to manifest themselves as infection-related cancers. Rwanda has implemented comprehensive nationwide access to cART since 2005,<sup>7</sup> with the proportion of people living with HIV receiving cART estimated at 68% in 2014, rising to 80% in 2016, (<http://aidsinfo.unaids.org>).<sup>8</sup> HIV prevalence in Rwanda is estimated to have been stable from 2005 to 2015 at about 3% among adults age 15–49.<sup>9</sup>

Previous studies in sub-Saharan Africa predominantly assessed the association of HIV with cancer by comparing a set of *a priori* chosen infection-related cancers with a set of *a priori* non-infection-related cancers, using a “case:referent” approach. In this study, however, following routine HIV testing in everyone seeking cancer care at Butaro Cancer Centre of Excellence (BCCOE), a national cancer referral hospital in Rwanda, our objective was to compare HIV infection across the full spectrum of cancer types with that among a comparable set of controls from the same hospital in whom the presence of cancer was confidently excluded.

**Methods****Study design**

Our study is a hospital-based case-control study set in BCCOE, Burera district, Northern Rwanda. The hospital opened in July 2012 to serve as a cancer referral center for the whole country. Medical records were computerized for this project (in part by data entry from paper records, in part extracted from an existing electronic medical record system) for all 5,701 persons seeking cancer care between July 2012 and December 2016. Of these patients, 3,220 were confirmed as cancer cases, while cancer was excluded in 1,532 patients hereafter referred to as controls (Fig. 1). The assignment to cancer and noncancer status was based principally upon histopathology. In 2012, histopathological diagnoses were made predominantly by pathologists at Brigham and Women's

Hospital (BWH), Boston, MA, where tissue blocks were sent. From 2013 onward, they were increasingly made by local pathologists at BCCOE, with ongoing support from BWH.

For 917 patients, no definitive diagnosis was available, main reasons being poor documentation in medical records ( $n = 578$ ), lack of possibility for confirmation in BCCOE and/or referral elsewhere ( $n = 309$ ) and death before confirmation ( $n = 28$ ). These patients were excluded, along with 34 patients diagnosed with precancerous conditions (including 15 breast ductal carcinoma *in situ*, 13 anogenital intraepithelial neoplasia and 5 lymphoproliferative disorders) (Fig. 1).

**HIV testing**

According to BCCOE protocol, every patient seeking cancer care is assessed for HIV serological status (unless the patient is known to be HIV positive, in which case the test is not reconfirmed). Patients are tested first with a high sensitivity rapid test and HIV-positive cases subsequently confirmed by a second rapid test with higher specificity. If the two rapid tests are inconsistent, an ELISA test is performed as a tie-breaker. Of note, these tests do not distinguish HIV-1 and HIV-2 infection. For 564 (18%) of 3,220 cancer cases and 336 (22%) of 1,532 noncancer controls, HIV status was unavailable, leaving 2,656 cancer cases and 1,196 noncancer controls with known HIV status in the following analyses of associations between cancer sites and HIV status (Fig. 1).

**Classification by cancer site**

All cancer diagnoses were coded according to World Health Organization (WHO) International Classification of Diseases for Oncology (ICD-O-3) guidelines,<sup>10</sup> and subsequently converted to WHO International Classification of Diseases version 10 (ICD-10) codes using the IARCcrgTools check and conversion program for cancer registries ([www.iacr.com.fr/iacr\\_iarcrgtools.htm](http://www.iacr.com.fr/iacr_iarcrgtools.htm)),<sup>11</sup> the gold-standard practice in cancer registries worldwide. For certain cancers, two-digit ICD-10 codes were combined into larger categories, most notably head and neck cancer (ICD-10 codes C00–14, C31, C32). In addition, lymphomas were classified into subtypes according to the 2010 update of the InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research.<sup>12</sup> Last (except for lymphoma subtype analyses), rare cancer types (<4 cases) were grouped into a miscellaneous category ( $n = 55$ ) and combined with confirmed cancers of unspecified primary site ( $n = 84$ ).

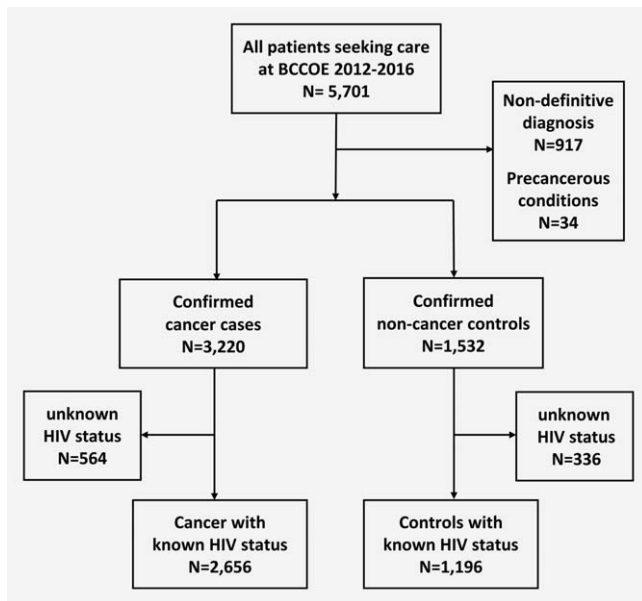


Figure 1. Selection of case-control study population.

### Statistical analysis

A case-control approach was used to assess the relationship between specific cancer sites and HIV infection. Characteristics of cancer cases and noncancer controls were compared by *p* values of chi-squared test for heterogeneity. Unconditional logistic regression was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for HIV seropositivity by specific cancer sites. Unless otherwise specified, ORs were adjusted for gender, age group (<15, 15–24, 25–34, 35–44, 45–54, 55–64, 65+) and place of residence (Kigali City vs. North/South/West/East/Outside Rwanda, chosen based on province-specific HIV patterns in 2015<sup>9</sup>). For sex-specific cancers, models were restricted to include controls of the appropriate gender only. Analyses were undertaken in STATA, version 13.0.

### Results

Major characteristics of 2,656 cases and 1,196 controls seeking care at BCCOE are compared in Table 1. Both cases and controls were predominantly female, but the proportion of females was significantly higher in controls (80.3%) than cases (70.8%). Median age was 45.5 years in cases versus 37.7 years in controls ( $p < 0.001$ ). Cases and controls came from all over Rwanda, and a small proportion from outside Rwanda, with controls being significantly over-represented by patients from Northern Province, where BCCOE is situated. For the majority of cases and controls, diagnosis was confirmed or excluded by histopathology, but this proportion was significantly higher in cases (87.5%) than in controls (67.4%) (Table 1). All cancers and controls were of African ethnicity.

The distribution of major cancer types is shown by gender and HIV status in Figure 2. Among the 1,881 cancers in females, cervical ( $n = 560$ ) and breast ( $n = 559$ ) cancer each accounted

Table 1. Characteristics of cancer cases and noncancer controls diagnosed in Butaro Cancer Centre of Excellence, Rwanda, 2012–2016

	Cancer cases		Non-cancer controls		<i>P</i> value
	<i>N</i>	%	<i>N</i>	%	
<b>Total</b>	2,656	100	1,196	100	
<i>Gender</i>					
Female	1,881	70.8	960	80.3	<0.001
Male	775	29.2	236	19.7	
<i>Age</i>					
<15	261	9.8	61	5.1	<0.001
15–24	136	5.1	191	15.9	
25–34	265	10.0	326	27.3	
35–44	469	17.6	231	19.3	
45–54	579	21.8	196	16.4	
55–64	585	22.0	113	9.5	
65+	361	13.6	78	6.5	
<i>Place of residence</i> <sup>1</sup>					
Northern Province	607	22.8	608	50.8	<0.001
Western Province	589	22.2	292	24.4	
Southern Province	497	18.7	71	5.9	
Eastern Province	454	17.1	109	9.1	
Kigali City	367	13.8	96	8.0	
Outside Rwanda	139	5.2	19	1.6	
<i>Year of diagnosis</i>					
2012	245	9.2	49	4.1	<0.001
2013	477	18.0	186	15.6	
2014	670	25.2	342	28.6	
2015	641	24.1	322	26.9	
2016	623	23.5	297	24.8	
<i>Diagnostic method</i>					
Histopathology	2,324	87.5	806	67.4	<0.001
Clinical only	332	12.5	390	32.6	

<sup>1</sup>Three missing values not shown.

for 30% of cases, and were the two most common cancers in both HIV-negative and HIV-positive females. However, whereas breast cancer was the most common type diagnosed in HIV-negative females, cervix was the most common cancer in HIV-positive females. Among 775 cancers in males, the most commonly diagnosed types were NHL ( $n = 162$ , 21%), head and neck ( $n = 83$ , 11%) and colorectal cancer ( $n = 53$ , 7%) (Fig. 1). In HIV-positive men, however, the most commonly diagnosed cancer was KS, followed by NHL and penis.

Associations between HIV infection and specific cancer types are described in Table 2. Following adjustment for gender (as appropriate), age and place of residence, HIV infection was significantly associated with KS (OR: 110.3, 95%CI 46.8–259.6), vulva (17.8, 6.3–50.1), penile (8.3, 2.5–27.4) and

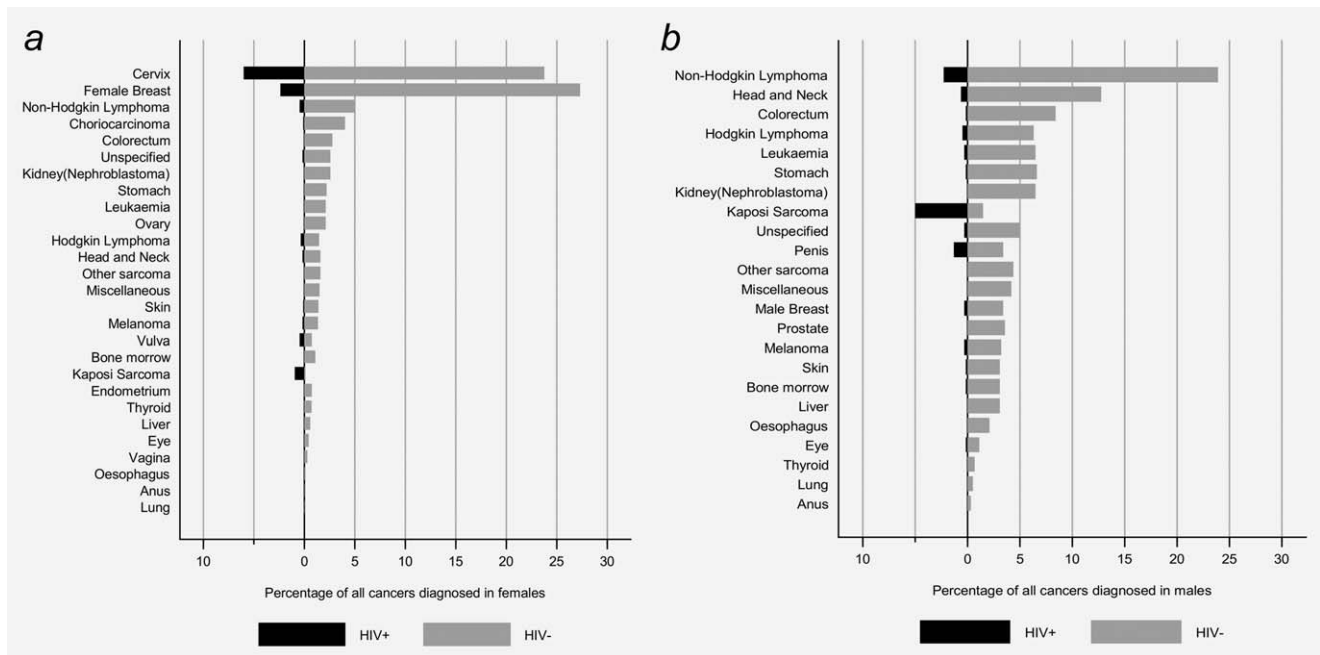


Figure 2. Proportion of individual cancer types among all cancers diagnosed at Butaro Cancer Centre of Excellence, Rwanda, 2012–2016, by HIV status (a, females; b, males) (see Table 2 for corresponding numbers).

cervical cancer (5.9, 3.8–9.2), HL (5.2, 2.8–11.6) and NHL (2.5, 1.4–4.6). An association of borderline significance was observed for eye cancer (4.7, 1.0–25.0), and one of four patients with anal cancers were HIV positive (OR: 7.7, 0.6–93.0) (Table 2). ORs for breast cancer in females and head and neck cancers in both genders were 1.5 (95%CI 0.9–2.3) and 1.4 (0.5–3.5), respectively. Although HIV prevalence was low or zero in many cancer sites, for none was HIV prevalence significantly lower than among controls, for example, ORs for relatively common colorectal cancer and gastric cancer were 0.3 (95% CI 0.8–1.4) and 0.4 (95%CI 0.1–1.7), respectively.

Table 3 shows the distribution of lymphomas by subtype, and their association with HIV. Among NHL, B-Cell NHL ( $n = 159$ ) predominated over T-cell NHL ( $n = 33$ ). The most commonly diagnosed B-cell NHL type was diffuse large B-cell lymphoma (DLBCL) ( $n = 56$ ), followed by acute lymphoblastic lymphoma (B-cell ALL) ( $n = 33$ ), chronic lymphoblastic/small-cell lymphocytic lymphoma (CLL/SLL) ( $n = 21$ ) and Burkitt lymphoma (BL) ( $n = 20$ ). Of note, with exception of one T-cell NHL, all HIV-positive NHLs were DLBCL. HIV was significantly associated with DLBCL (OR = 6.6, 95%CI 3.1–14.1) and particularly strongly with plasmablastic lymphoma (PBL) (OR = 106, 12.1–921). There was no association with HIV for T-cell NHL (Table 3).

All HL were of classical type (CHL), among which the most common were nodular sclerosis (NSCHL) ( $n = 24$ ) and mixed cellularity (MCCHL) ( $n = 17$ ) subtypes (Table 3). No HIV infection was seen in NSCHL, but HIV was significantly associated with lymphocyte-depleted (LDCHL) (OR = 20.3, 95%CI 2.3–17.5) and MCCHL (OR = 12.0 CI 2.7–53.2) and

was detected in one out of three cases of lymphocyte-rich (LRCHL) (OR = 10.6, 0.9–118) (Table 3).

Given the large number of cases, the positive association of HIV with cervical cancer was further investigated by age group. HIV positivity was 40% in 20 cervical cancers diagnosed in women 25–34 years, and decreased steadily with age to reach 7.9% in cervical cancer among 239 women aged  $\geq 55$ . The corresponding OR versus controls varied similarly, from 37.3 (95%CI 10.4–133) in women aged 25–34 years down to 2.4 (95%CI 0.9–6.7) in women aged  $\geq 55$  (Table 4).

**Discussion**

This study is the first, to our knowledge, to compare HIV infection in the full spectrum of cancer types with patients seeking cancer care at the same hospital in whom cancer was subsequently excluded. Using this approach, we were able to confirm strong associations between HIV and AIDS-defining cancers,<sup>1,4,6</sup> and to show that, in the era of access to cART in Rwanda, HIV is significantly associated with a wide range of infection-related cancer (sub)types.

KS showed the strongest link with HIV, as observed already in the pre-cART era in Rwanda.<sup>6</sup> Relative risk for HIV (OR~100) was nevertheless lower than that in high-income settings (>1,000)<sup>1</sup> where KS is otherwise very rare. Indeed, KS was relatively frequent in Rwanda even before the spread of HIV.<sup>13</sup>

Association of HIV with NHL in Rwanda<sup>6</sup> was also confirmed. Benefitting from detailed histopathological assessment, we were able to describe the heterogeneity of HIV associations by individual NHL subtypes, for which little prior data exist in sub-Saharan Africa. We found a significant association with

**Table 2.** Association of HIV infection with specific cancers diagnosed in Butaro Cancer Centre of Excellence, Rwanda, 2012–2016

Cancer type/site <sup>1</sup>	Cases		Controls		OR <sup>3</sup>	95%CI
	N	% HIV+	N	% HIV+		
Kaposi sarcoma	60	81.7	1,196	4.5	<b>110.3</b>	<b>46.8, 259.6</b>
Vulva	23	39.1	960 <sup>4</sup>	4.4	<b>17.8</b>	<b>6.3, 50.1</b>
Penis	29	27.6	236 <sup>5</sup>	5.1	<b>8.3</b>	<b>2.5, 27.4</b>
Anus	4	25.0	1,196	4.5	7.7	0.6, 93.0
Cervix	560	20.2	960 <sup>4</sup>	4.4	<b>5.9</b>	<b>3.8, 9.2</b>
Hodgkin lymphoma	76	13.2	1,196	4.5	<b>5.2</b>	<b>2.3, 11.6</b>
Eye	17	11.8	1,196	4.5	<b>4.7</b>	<b>1.0, 25.0</b>
Melanoma	50	10.0	1,196	4.5	2.4	0.9, 6.7
Non-Hodgkin lymphoma	265	8.7	1,196	4.5	<b>2.5</b>	<b>1.4, 4.6</b>
Male breast	23	8.7	236 <sup>5</sup>	5.1	1.9 <sup>6</sup>	1.0, 3.0
Female breast	559	8.1	960 <sup>4</sup>	4.4	1.5	0.9, 2.3
Skin	48	6.3	1,196	4.5	1.4	0.4, 4.8
Esophagus	16	6.3	1,196	4.5	1.3	0.1, 13.2
Head and neck	116	6.0	1,196	4.5	1.4	0.6, 3.5
Bone marrow	41	4.9	1,196	4.5	1.6	0.4, 8.0
Leukemia	83	3.6	1,196	4.5	0.6	0.1, 2.1
Liver	31	3.2	1,196	4.5	0.6	0.8, 4.6
Choriocarcinoma	78	2.6	960 <sup>4</sup>	4.4	0.5	0.1, 2.0
Stomach	84	2.4	1,196	4.5	0.4	0.1, 1.7
Ovary	41	2.4	960 <sup>4</sup>	4.4	0.3	0.0, 2.7
Colorectum	106	1.9	1,196	4.5	0.3	0.8, 1.3
Kidney (nephroblastoma) <sup>2</sup>	88	0.0	61	0.0	-	-
Other sarcoma	57	0.0	1,196	4.5	0.0 <sup>6</sup>	0.0, 1.4
Prostate	22	0.0	236 <sup>5</sup>	5.1	0.0 <sup>6</sup>	0.0, 3.7
Thyroid	17	0.0	1,196	4.5	0.0 <sup>6</sup>	0.0, 5.4
Endometrium	14	0.0	960 <sup>4</sup>	4.4	0.0 <sup>6</sup>	0.0, 5.5
Vagina	5	0.0	960 <sup>4</sup>	4.4	0.0 <sup>6</sup>	0.0, 15.5
Lung	4	0.0	1,196	4.5	0.0 <sup>6</sup>	0.0, 20.6
Miscellaneous/unspecified	139	4.3	1,196	4.5	0.8	0.3, 2.0

<sup>1</sup>Shown in descending order of HIV prevalence.

<sup>2</sup>As 98% of all kidney cancers are nephroblastoma/Wilms tumor in children, cases and controls are restricted to those <15 years only.

<sup>3</sup>Adjusted for gender [as appropriate], age and province of residence.

<sup>4</sup>Females only.

<sup>5</sup>Males only.

<sup>6</sup>Crude ORs and 95% CIs are shown, as adjusted model does not converge.

HIV for B-cell NHL, an association explained entirely by the association with DLBCL, most notably with PBL, a rare and aggressive DLBCL subtype which occurs almost uniquely in the presence of HIV and frequently arises in the oral cavity. Indeed, DLBCL has been recognized to be strongly increased in PHIV since the beginning onset of the AIDS epidemic.<sup>2,14</sup> HIV infection was not present in other B-cell NHL subtypes (including BL, see below), but numbers were often small. We saw no cases of primary effusion lymphoma, also considered to be strongly associated with HIV.<sup>15</sup> Nor did we find any

associations with T-cell NHL subtypes, consistent with large studies in high-income settings.<sup>16,17</sup>

We observed no HIV in BL, which is somewhat inconsistent with associations seen in other sub-Saharan African populations,<sup>3,4,18,19</sup> and the fact that BL is a recognized AIDS-defining subtype of NHL in adults.<sup>17</sup> Of note, the endemic variant of BL in sub-Saharan Africa mainly affects children and all cases occurred in persons <18 years old in Rwanda. Early adoption of measures to prevent maternal to child HIV transmission, and the consequently very low HIV prevalence



**Table 3.** Association of HIV infection with subtypes<sup>1</sup> of lymphoma diagnosed in Rwanda 2012–2016

	N	HIV+		OR <sup>2</sup>	95%CI
		n	%		
Controls	1,196	54	4.5	1.0	
<i>Non-Hodgkin lymphoma</i>					
B-cell	159	16	10.1	2.5	1.3, 4.9
Diffuse large B-cell lymphoma	56	16	28.6	6.6	3.1, 14.1
Plasmablastic lymphoma	6	5	83.0	106 <sup>3</sup>	12.1, 921
Acute lymphoblastic lymphoma (B-cell ALL)	33	0	0.0		
CLL/SLL	21	0	0.0		
Burkitt lymphoma	20	0	0.0		
Multiple myeloma	11	0	0.0		
Follicular lymphoma	5	0	0.0		
MALT lymphoma	4	0	0.0		
Mantle cell lymphoma	3	0	0.0		
T-cell	33	1	3.0	1.1	0.1, 9.4
Acute lymphoblastic lymphoma (T-cell ALL)	20	0	0.0		
Anaplastic large cell lymphoma	5	0	0.0		
<i>Hodgkin lymphoma</i>					
Classical	76	10	13.2	5.2	2.3, 11.6
Lymphocyte-depleted	4	2	50.0	20.3	2.3, 175
Nodular sclerosis	24	0	0.0		
Mixed cellularity	17	3	17.6	12.0	2.7, 53.2
Lymphocyte-rich	3	1	33.3	10.6 <sup>3</sup>	0.9, 118
Nodular lymphocyte predominant	0	0	-	-	-

<sup>1</sup>According to InterLymph hierarchy of WHO classification.<sup>12</sup>

<sup>2</sup>Adjusted for gender [as appropriate], age and province.

<sup>3</sup>Crude ORs and 95% CIs are shown, as adjusted model does not converge.

**Table 4.** Association of HIV infection with cervical cancer, by age group in Rwanda, 2012–2016

Age (years)	Cervical cancers		Controls <sup>1</sup>		OR <sup>2</sup>	95%CI
	N	% HIV+	N	% HIV+		
25–34	20	40.0	274	1.8	33.8	9.3, 122.6
35–44	106	37.8	198	8.1	6.8	3.6, 13.1
45–54	195	23.6	163	6.7	4.2	2.1, 8.3
55+	239	7.9	143	3.5	2.4	0.9, 6.5

<sup>1</sup>Females only.

<sup>2</sup>Adjusted for province of residence.

in children (0% among 61 controls aged <15 years, consistent with 0.2% HIV prevalence estimated in this age group in a national survey in 2015),<sup>9</sup> probably explains the absence of HIV involvement in BL during 2012–2016 in Rwanda. Of note, BL accounted for only 8% of all NHL diagnosed in Rwanda, which is much lower than the proportion reported in studies from neighbouring Uganda,<sup>20</sup> and was not the most commonly diagnosed cancer in children.

Of note, we did not present cancers in children ( $n = 261$ , 0–15 years) and adults separately, but patterns of HIV

association were consistent (data not shown), and none of the most commonly diagnosed childhood cancers (86 kidney cancers [nephroblastoma], 25 B-cell ALL, 15 BL, 12 T-cell ALL, 11 bone cancer and 10 other sarcomas) were HIV positive. Absence of HIV involvement in childhood kidney cancer and leukemia is consistent with previous sub-Saharan African studies.<sup>18</sup>

CHL was associated with HIV, but there was heterogeneity in the relationship by CHL subtype. Whereas MCCHL and LDCHL were strongly associated with HIV infection, all

NSCHL, the most commonly diagnosed HL type in Rwanda, were HIV negative. This is consistent with studies in high-income settings,<sup>21–23</sup> but is the first formal report from sub-Saharan Africa.

HIV is an established risk factor for cervical cancer,<sup>2</sup> but relative risks have been relatively weak in pre-cART era studies in sub-Saharan Africa.<sup>3,4,24–26</sup> Risk for cervical cancer in Rwanda was the highest reported in sub-Saharan Africa to date (OR = 5.9), likely related to early roll out of cART in Rwanda and increasing avoidance of competing HIV-related mortality. Indeed, cervical cancer accounted for one-fifth of all cancers diagnosed at BCCOE, of whom a majority were diagnosed above 45 years old. The fraction attributable to HIV was much higher for cervical cancer diagnosed in younger women.

With respect to other HPV-related cancers, previous studies in sub-Saharan Africa have reported significant associations for all noncervical anogenital sites combined.<sup>4,5</sup> In our cancer site-specific approach, HIV was significantly associated with both vulva and penis cancer in Rwanda and, although they were much rarer than cervical cancer, their link with HIV was considerably stronger. Indeed, the strength of the vulva and penis cancer associations lends support to a causal effect of HIV-related immunosuppression, for which a IARC working group deemed data were too scarce to be sure of a causal association with HIV in 2012.<sup>2</sup> Of note, HIV positivity was 39% in 29 vulva cancers in Rwanda, and 76% in a series of 54 cases from Botswana.<sup>27</sup> Findings for anal cancer were consistent with the established causal link with HIV,<sup>2</sup> but cases were too few to see a statistically significant association. Of note, low frequency of anal cancer in comparison to high-income settings is not expected to be due to misclassification with colorectal cancer (which were almost entirely adenocarcinoma), but may reflect differences due to younger average age and different homosexual/heterosexual transmission of HIV/HPV in sub-Saharan Africa. Although we could not control for sexual behaviors that favor acquisition of both HIV and HPV, we expect associations to reflect an independent effect of HIV-related immunosuppression on cancer risk, beyond that of increased HPV exposure, as has been clearly proven for both cervical,<sup>28,29</sup> and anal cancer,<sup>30</sup> as measured by CD4 counts.

A strong association of HIV was observed for eye cancer, confirming a nonsignificant excess (8.4; 0.8–96.9) seen in Rwanda pre-cART.<sup>6</sup> HIV is an established cause of conjunctiva cancer, based on the results of a number of case-control and cohort studies.<sup>2,31–33</sup> Of note, although conjunctiva was rarely specified in BCCOE medical records, our observed association was mainly due to squamous cell carcinoma (2 HIV-positive out of 4) compared to other histologies (0 out of 13) of eye cancer.

For other cancers with known infectious etiology, we saw no associations between HIV and head and neck cancer,<sup>4,5</sup> not even when restricting to sites considered more strongly HPV-related (ICD codes C01, C02.4, C09, C10 and C14,<sup>34</sup> 0

of 6 HIV-positive), or EBV-related ( $n = 0$  of 19 nasopharynx cancers were HIV-positive). Neither was an association found with skin cancer, which has been reported in high-income,<sup>1</sup> and certain sub-Saharan settings.<sup>4,5</sup> Nor did we see associations with stomach or liver cancer, corroborating previous negative associations in African studies.<sup>3,4,24,35</sup>

This study is associated with a number of limitations. First of all, the distribution of cancer types diagnosed at BCCOE should not be considered representative of incident cancers arising in Rwanda. This is because cancers unamenable to treatment by surgery and chemotherapy are under-represented in our study, either because they are not referred to BCCOE, or because diagnostic work-up was not pursued. However, this is not expected to greatly influence the association of individual cancer types with HIV. Furthermore, although a minority of cancers included in this study were diagnosed only clinically, they were clearly differentiated from those cancers for which local physicians could not make a definitive diagnosis (who were excluded), and relative risks for HIV remained statistically significant in a sensitivity analysis restricted to histopathologically confirmed cases and controls only (e.g., ORs for KS = 73.5, vulva = 21.6, penis = 9.4, cervix = 5.8, HL = 4.3, eye = 6.4 and NHL = 2.6).

The paramount requirement of hospital-based case-control studies is making sure that controls derive from the same population source as from which cases are drawn. This is particularly the case for studying cancer in low-income settings, where cancer patients, but not diseases of lesser severity, can be referred from large distances. A major strength of this study is, therefore, that both cancer cases and noncancer controls presented to BCCOE, a national referral center, with suspicion of cancer. Hence, although cases were older and less likely to be resident in the Northern Province where BCCOE is situated than controls, adjustment for these characteristics should have avoided major bias in relative risks. ORs were also unchanged upon additional adjustment for calendar year (e.g., ORs for KS = 111, vulva = 17.9, penis = 7.6, cervix = 6.1, HL = 5.2, eye = 5.1 and NHL = 2.6; data not shown), which is not unexpected given that our calendar period was only 5 years and that HIV prevalence has been estimated to be stable at 3% from 2005 to 2015 in Rwanda.<sup>9</sup> Furthermore, no *a priori* assumptions were made about the link between individual cancer sites and their potential link to oncogenic infections and HIV, and the absence of significant associations with common cancers at BCCOE which are not deemed to be infection-related (e.g., breast cancer, colorectal cancer, etc.), lends support to the appropriateness of the control group. In the end, we did not identify any associations with cancers without a known infectious cause, and the same significant associations would have been seen if we had used a set of *a priori* defined non-infection-related cancers as controls (ORs for KS = 103, vulva = 12.6, penis = 11.1, cervix = 4.0, HL = 6.4, eye = 5.1 and NHL = 2.6), lending support also to the validity of the case:referent design.<sup>3–6</sup> Last, age-, gender- and province-specific HIV

prevalence in controls were broadly consistent with patterns estimated in a national Rwandan survey in 2015.<sup>9</sup>

In conclusion, our study provides a description of cancer types diagnosed in a large referral hospital in Rwanda in the era of full access to cART, and their individual associations with HIV infection. To varying degrees, HIV was significantly associated with KS, DLBCL (most notably PBL), mixed cellularity and lymphocyte-depleted CHL sub-types, cervix, anus, penis, vulva and eye cancer. Using a crude calculation of attributable fractions for these cancers based on the difference in HIV prevalence between cases and controls, we estimate that ~170 (6%) of all 2,656 cancers diagnosed at BCCOE between 2012 and 2016 can be attributed to HIV, of

which approximately half are cervical cancers and one quarter KS. Our findings may be generalizable to other sub-Saharan African settings with reasonably good access to cART and highlight the need for continued investment in HIV and cancer control in Rwanda as well as the merits of establishing a population-based cancer registry to monitor the changing cancer burden in the cART era.

### Acknowledgement

The work reported in this article was undertaken by Tharcisse Mpunga during the tenure of PhD studentship granted by the International Agency for Research on Cancer, under joint supervision with the University of Rwanda, School of Public health.

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