Cancers attributable to infections among adults with HIV in the United States

APPENDIX

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APPENDIX: Attributable fractions by cancer site and infectious agent

For each infectious agent and its associated cancer site, we give below a short literature review of the current state of knowledge in the HIV population, explain the assumptions we have made, and provide the data used for Attributable fraction (AF) calculations. Two cancer sites do not need a specific review: Kaposi sarcoma and cervical cancer are both known to be 100% attributable to Kaposi sarcoma-associated herpes virus (KSHV), and human papillomavirus (HPV), respectively [1].
In most cancer sites except gastric cancer we used the proportion of cancer cases positive for the infectious agent as the AF estimate [2]. AF were derived from case series conducted in the HIV population for lymphomas and liver cancers, or in the general population when robust data from HIV-infected people were not available or when the literature shows little or no difference in AF in HIV-infected people compared to the general population. A summary of the methods and AF estimates by cancer sites and histological types is given in **Appendix Table 1**.

Lymphomas and Epstein Barr virus (EBV)

EBV causes different histological types of lymphoma [1]. Since the vast majority of the world population is infected by EBV, serological detection of EBV antibodies is not sufficient to attribute a lymphoma case to EBV. The most widely-accepted way to measure the causal involvement of EBV in tumor development is the detection of EBV-encoded small RNAs (EBERs) or EBV DNA by *in situ* hybridization (ISH) techniques in tumor cells derived from lymphoma cases [3, 4]. EBERs are transcribed in large quantities in all forms of EBV latencies, and therefore they can be detected in all types of EBV-associated lymphomas [5].

Two histological types of non-Hodgkin lymphoma, i.e., diffuse large B-cell lymphomas (DLBCL), and Burkitt lymphomas, are strongly associated with HIV infection and were among the earliest identified AIDS-defining illnesses [6]. DLBCL is especially frequent in the central nervous system (CNS) in severely immunosuppressed people. HIV-infected people also show an excess risk of Hodgkin lymphoma [1]. DLBCL includes three main morphologic variants: centroblastic, immunoblastic and anaplastic [7]. Centroblastic DLBCL predominates in the general population whereas the immunoblastic variant is the most frequent variant in severely immunosuppressed HIV-infected patients. Other very rare DLBCL that are associated with HIV/AIDS such as primary effusion lymphomas (caused by KSHV) and plasmablastic lymphomas were not considered in our analyses.

The vast majority of immunoblastic DLBCL in HIV-infected people with CD4 <100 are EBER-positive. Similarly, nearly all lymphomas of the CNS in HIV-infected people are immunoblastic DLBCL and EBER-positive. We reviewed studies of EBV in CNS lymphomas in HIV-infected people in North America and Europe (**appendix Table 2a**). In 7 studies, 107 of 111 CNS lymphoma cases were EBER-positive (prevalence 96%; 95%CI: 92-99).

For non-CNS DLBCL, the introduction of combined antiretroviral treatment (cART) has been associated with a decrease in the proportion of EBV-associated tumors [8]. Data from a Californian cancer registry show that the proportions of DLBCL types changed from the pre- to the post-cART period, decreasing from 38% to 19% for the high grade types (i.e. mostly immunoblastic), and increasing from 33% to 49% for the intermediate types (i.e. mostly centroblastic). Other or unclassified DLBCL types remained stable [9]. Only two cases series have been published on DLBCL in the late cART period [10, 11]. In these studies, 28 out of 105 DLBCL cases were EBER-positive. We calculated the AF for EBV in non-CNS DLBCL from the prevalence of 27%, (95%CI: 19-36) in these two studies. For comparison, approximately 80% of all DLBCL were associated with EBV

infection in the pre cART era in the HIV population, and around 10% are currently estimated to be EBV-associated in the general population [7].

We reviewed studies of EBV in Burkitt and Burkitt-like lymphomas among HIV-infected people in North America and Europe (**appendix Table 2b**). In 12 studies, 99 of 219 cases were EBER-positive (prevalence 45%; 95%CI: 36-49). There has been no significant change in prevalence after the introduction of cART (prevalence of 42% before 1996 *versus* 48% after, **appendix Table 2b**). For comparison, the percentage of EBER-positivity in sporadic Burkitt lymphoma occurring in the general population in the United States and Europe is approximately 20%.

Hodgkin lymphomas occurring in HIV-infected people are nearly always EBER-positive. We reviewed studies of EBV in Hodkgin lymphoma in North America and Europe (**appendix Table 2c**). In 6 studies, 209 of 229 cases were EBER-positive (prevalence 91%, 95%CI: 87-96) with no reduction after the introduction of cART. By comparison, the EBV-attributable fraction in Hodkgin lymphoma in the general population in the more developed countries is around 40% [2].

Lymphomas and Hepatitis C Virus (HCV)

The association of HCV with non-Hodgkin lymphomas is weaker [12-14] in HIV-infected people than the corresponding association in the general population. Given the scarcity of available data allowing more precise estimates, we attribute no non-Hodgkin lymphomas in HIV-infected people to HCV.

Ano-genital cancers and human papillomavirus (HPV)

For ano-genital cancer sites associated with HPV other than cervical cancer (i.e. anal, vulvar, vaginal, and penile sites), no data from HIV-infected people were available, and we therefore derived AFs from HPV DNA prevalence by PCR in case series conducted in the North American general population, as presented in two meta-analyses [15, 16]. For penile cancer, HPV was found in 135 out of 295 cases (prevalence 46%; 95%CI: 40-51) from 9 studies in the United States (appendix A in Backes et al [16]). For vaginal cancer, HPV was found in 45 out of 64 cases (prevalence 70%; 95%CI: 59-81) from 3 studies in the United States (De Vuyst et al [15] table A.IV). For anal cancer, HPV was found in 155 out of 171 cases (prevalence 91%; 95%CI: 86-95) from 3 studies in the United States (De Vuyst et al table [15] A.VI). Although prevalence data on anal cancers were available for 3 other studies in the United States, these were not included as they did not use the most accurate PCR-based assays [15]. For vulvar cancer, HPV prevalence decreases with age [15]. Hence, we took the prevalence in women under 60 years of age to match the young age of the HIV-infected population. In this age group, HPV was found in 80% of 113 women (95%CI: 72-87) in studies conducted in the United States and Canada (De Vuyst et al Table II) [15].

Oropharyngeal cancers (OPC) and HPV

In the upper aero-digestive tract, the gold standard for attribution of cancer to HPV is detection of HPV DNA in tumor cells by ISH, or detection of HPV E6/E7 mRNA [17]. Studies using these gold standard methods show that HPV is found in oropharyngeal cancer (OPC) which includes cancer in the base of the tongue (ICD-10 code C01), lingual tonsil (C02.4), soft palate (C05.1), uvula (C05.2), tonsil (C09.0-C09.9), oropharynx (C10.0-C10.9), and Waldeyer's ring (C14.2). Conversely, HPV is rarely found in other sites in head and neck cancer. A meta-analysis of head and neck cancer case series using ISH has shown that HPV-positivity was 71% for OPC (n=561), 2.6% for oral cavity cancer (n=350), 7.2% for laryngeal cancer (n=265), and 0% for hypopharyngeal cancer (n=20) [17]. Data from HPV E6/E7 mRNA are consistent with ISH data but much more limited than for ISH [17]. HPV16 was the type detected in nearly all HPV-positive OPC. HPV involvement in the oesophagus is unlikely.

Information on HPV-positivity in the upper aero-digestive tract in HIV-infected people is available from two studies, although these studies used PCR rather than one of the gold-standard methods. D'Souza et al [18] reported HPV16-positivity by PCR in 6/11 (55%) OPC, 0/22 (0%) oral cavity cancers, 1/9 (11%) laryngeal cancers, and 1/10 (10%) multiple-site cancers. D'Souza et al [18] also showed that HPV16-positivity in OPC in the HIV population and in the general United States population was similar [19]. A smaller case-series provided information on 19 cancers of the upper aero-digestive tract in HIV-infected people from the United States and Spain [20]. HPV16 was detected by PCR in 5/9 OPC.

An approximately 2-3-fold increased risk of OPC has been consistently reported among HIV-infected people compared to the general population but this increase is similar to that shown for other cancer sites heavily associated with tobacco smoking, e.g., oral cavity, oesophagus, larynx, and lung [21]. HIV-infected people have higher prevalence of both oral HPV infection and smoking than the general population. It is, therefore, unclear whether HPV is causing a larger or smaller fraction of OPC in people with HIV/AIDS than in the general population. We applied, therefore, to HIV-infected people the fraction of HPV-positivity found in OPC in the general United States population. A meta-analysis of 8 studies showed HPV in 397 of 561 OPC cases (71%; 95%CI: 67-75). We did not attribute to HPV any other cancer of the upper aero-digestive tract, although that may neglect a small proportion of truly HPV-attributable tumors.

Liver cancers and hepatitis viruses

Liver cancer incidence in HIV-infected people has increased in the United States in the late cART era [22]. This trend likely reflects the heavy burden of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in HIV-infected people and the improvement of survival. Three case-series of liver cancers in the HIV-infected United States population have been published in the late cART period [23-25]. Overall, serological markers of HCV (anti-HCV) or chronic HBV (HBsAg) were detected in 198 of 211 cases (prevalence 94%; 95%CI: 90-97). HBV was found alone in 42 cases and HCV alone in 151 cases with 6 coinfections and 13 cases with no evidence of HBV or HCV. We divided the attribution of liver cancer between HBV and HCV in proportion to their prevalence in single infections (i.e. 42 vs 151 cases), leading to an AF of 73% (95%CI: 67-79) for HCV and 20% (95%CI: 15-26) for HBV.

Nasopharyngeal cancer (NPC) and EBV

Based on a previous review, we applied the same AF of 85% to NPC as in our previous estimate of the global burden of cancers attributable to infection [2]. This estimate is based on extremely sparse data. To account for the substantial uncertainty in this estimate we calibrated the plausible range of values for the AF to have a lower limit of 50% and an upper limit of 100%.

Non-cardia stomach cancers and *Helicobacter pylori (H. pylori)*

No studies on *H. pylori* prevalence in HIV-infected people in the United States are available. Furthermore, for non-cardia stomach cancer, *H. pylori* is often undetectable in cancer patients and we therefore used an alternative method to calculate the AF, based on the prevalence and relative risk in prospective studies where cases and controls were tested with the gold-standard serologic test, i.e. immunoblot. We applied an AF of 89% (95%CI: 79-95), which was derived from a pooled analysis of prospective studies in the general population using *H. pylori* detection by immunoblot [26]. *H. pylori* is also responsible for gastric mucosa-associated lymphoid tissue (MALT) NHL [1]. On account of the rarity of the disease and the lack of studies in HIV-infected people, gastric MALT NHL was not included in AF estimates.

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Infection related Cancer site/type	AF (95% CI)	Causal agent	Case series used for AF estimations		
			Geographical location	Population studied	Laboratory method
Kaposi sarcoma	100%	KSHV	worldwide	HIV	PCR
Non-Hodgkin lymphoma					
CNS NHL	96% (92-99)	EBV	Western countries	HIV	ISH
Non-CNS DLBCL	27% (19-36)	EBV	United States	HIV (in cART era)	ISH
Non-CNS Burkitt	45% (36-49)	EBV	Western countries	HIV	ISH
Hodgkin lymphoma	91% (87-96)	EBV	Western countries	HIV	ISH
Ano-genital carcinomas					
Cervix uteri carcinoma	100%	HPV	worldwide	general population	
Anal carcinoma	91% (86-95)	HPV	North America	general population	PCR
Vulva cancer	80% (72-87)	HPV	North America	general population (<60y)	PCR
Vaginal cancer	70% (59-81)	HPV	North America	general population	PCR
Penile cancer	46% (40-51)	HPV	North America	general population	PCR
Head and Neck cancers					
Oropharyngeal cancer	71% (67-75)	HPV	United States	general population	ISH
Nasopharyngeal cancer	85% (50-100)	EBV	worldwide	general population	ISH
Liver cancer	20% (15-26)	HBV	North America	HIV	HBsAg in serum
	73% (67-79)	HCV	North America	HIV	$2^{nd}/3^{rd}$ generation ELISA in serum
	94% (90-97)	HBV + HCV	North America	HIV	*either test above*
Non-cardia gastric cancer	89% (79-95)	*H. pylori*	worldwide	general population	immunoblot in serum

Appendix Table 1: Attributable fraction (AF) estimates for infectious agents in the HIV population by cancer site and histological type

Abbreviations: CNS central nervous system; NHL non-Hodgkin lymphoma; DLBC Diffuse large B-cells lymphomas; KSHV Kaposi sarcoma herpes virus; EBV Epstein-Barr virus; HPV human papillomavirus; HBV hepatitis B virus; HCV hepatitis C virus; *H. pylori Helicobacter pylori*; HIV human immunodeficiency virus; cART combined antiretroviral treatment; PCR polymerase chain reaction; *ISH in situ* hybridization; HBsAg hepatitis B surface antigen; ELISA enzyme-linked immunosorbant assay.

Reference	Country	N cases	N positive	% positive
a. Central nervous system (CNS) lymphomas				
MacMahon et al., Lancet, 1991 [1]	United States (MD)	21	21	100%
Pedersen et al., Eur J Canc, 1991 [2]	Denmark	10	10	100%
Hamilton-Dutoit et al., Blood, 1993 [3]	France/Denmark	16	15	94%
Guterman et al., Clin Neuropathol, 1996 [4]	Germany	17	17	100%
Camilleri-Broet et al., Hum Pathol, 1997 [5]	France	34	31	91%
Davi et al., J Clin Oncol, 1998 [6]	France	9	9	100%
Vaghefi et al., AIDS, 2006 [7]	France	4	4	100%
Total		**111**	**107**	**96% (95%CI: 92-99)**
b. Burkitt and Burkitt-like lymphomas				
Pedersen et al. Eur J Canc, 1991 [2]	Denmark	7	2	29%
Hamilton-Dutoit et al., Blood, 1993 [3]	France/Denmark	35	12	34%
Delecluse et al., Blood, 1993 [8]	France	7	4	57%
Shibata et al., Blood, 1993 [9]	United States (CA)	28	16	57%
Ballerini et al., Blood, 1993 [10]	United States (MD)	16	5	31%
Ometto et al., Blood 1997 [11]	Italy	5	4	80%
Spina et al., Cancer, 1998 [12]	Italy	36	13	36%
Davi et al., J Clin Oncol, 1998 [6]	France	44	28	64%
Hansen et al., Eur J Haematol, 2000 [13]	Denmark	7	2	29%
Vaghefi et al., AIDS, 2006 [7]	France	8	1	13%
Lenze et al., Leukemia, 2011 [14]	Germany	15	5	33%
Mbulaiteye et al., APMIS, 2014 [15]	United States	11	7	64%
Total		**219**	**99**	**45% (95%CI: 36-49)**
c. Hodgkin Lymphomas				
Hamilton-Dutoit et al., Blood, 1993 [3]	France/Denmark	11	11	100%
Herndier et al., Am J Pathol, 1993 [16]	United States (CA)	11	11	100%
Tirelli et al., J Clin Oncol, 1995 [17]	Italy	18	14	78%
Carbone et al., Blood, 1999 [18]	Italy	27	25	93%
Glaser et al., Cancer, 2003 [19]	United States (CA)	59	53	90%
Hentrich et al., J Clin Oncol, 2012 [20]	Germany/Austria	103	95	92%
Total		**229**	**209**	**91% (95%CI: 87-96)**

Appendix Table 2. Studies of Epstein-Barr virus (EBV) in a) Central nervous system lymphomas; b) Burkitt and Burkitt-like lymphomas; and c) Hodgkin lymphomas, among HIV-infected people in North America and Europe, using the detection of EBV-encoded small RNAs (EBERs) or EBV DNA by *in situ hybridization* (ISH) techniques in tumor cells.

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Statistical methods for confidence interval calculations

Confidence intervals for the number of incident cases were calculated by simulation using a pseudo-Bayesian approach. The parameters of the Poisson regression model were randomly sampled from a multivariate normal distribution with mean given by the maximum likelihood estimate and variance defined by the variance-covariance matrix of the fitted model. The expected numbers of cases for the HIV population were calculated from these randomly sampled estimates and the case counts were randomly sampled from a Poisson distribution. The two levels of simulation represent different sources of error: estimation error for the incidence rates and prediction error for the number of cancers given the incidence rate. The simulations were replicated 1000 times and empirical 95% confidence intervals were obtained from the lower 2.5% and upper 97.5% quantiles of the replicated data sets.

Confidence intervals for the numbers of cases attributable to infection include the uncertainty in the estimated AF. This was again carried out by simulation since the calculations were based on the previously estimated numbers of cancer cases in the HIV-infected population. For each of the 1000 replicate data sets used to estimate uncertainty in the case counts, the AF was randomly sampled from a beta distribution with mean matching the estimated AF with 2.5% and 97.5% quantiles matching the limits of the 95% confidence interval. The number of cases attributed to infection was then sampled from the total cases using a binomial distribution.

A. All cancers

Infectious agent	General population	HIV-infected people
KSHV	0.14	12.66
EBV	0.34	12.33
HPV	1.63	10.14
HBV/HCV	0.81	4.57
H. pylori	1.14	0.63
Non-attributable to infection	95.95	59.69

B. Cancers attributed to infection

Infectious agent	General population	HIV-infected people
KSHV	3.43	31.41
EBV	8.29	30.57
HPV	40.17	25.16
HBV/HCV	20.02	11.35
H. pylori	28.10	1.55

Appendix Table 3: Cancer infection attributable fraction (%) in the general population and HIV-infected people in the USA in 2008

Data plotted in Figure 1.

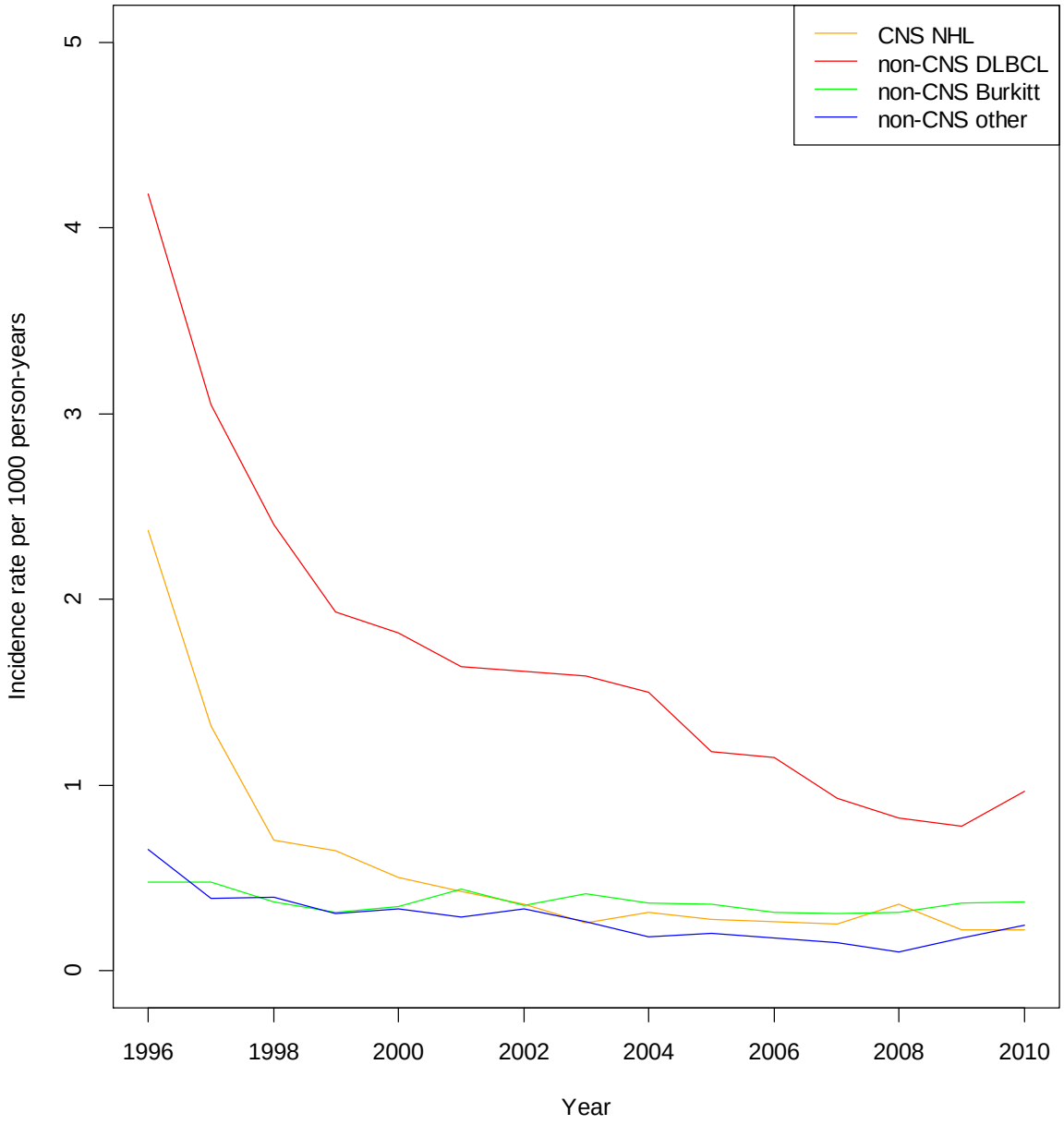
Abbreviations: KSHV Kaposi sarcoma herpes virus; EBV Epstein-Barr virus; HPV human papillomavirus; HBV hepatitis B virus; HCV hepatitis C virus; *H. pylori Helicobacter pylori*

Infectious agent / Age group (years)	15 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70+
KSHV	0.21	1.51	1.34	0.96	0.63	0.53	0.24
EBV	0.6	0.83	0.97	0.98	0.92	0.93	1
HPV	0.2	0.24	0.54	0.88	1	1	0.69
HBV/HCV	0.09	0.02	0.07	0.24	0.72	0.96	0.7
H. pylori	0.03	0.01	0.01	0.03	0.07	0.18	0.34
Non-attributable to infection	1.17	1.19	2.07	3.51	7.16	13.3	14.63

Appendix Table 4: Estimated cancer incidence per 1000 person-years among HIV-infected people in the USA in 2008 by age

Data plotted in Figure 2.

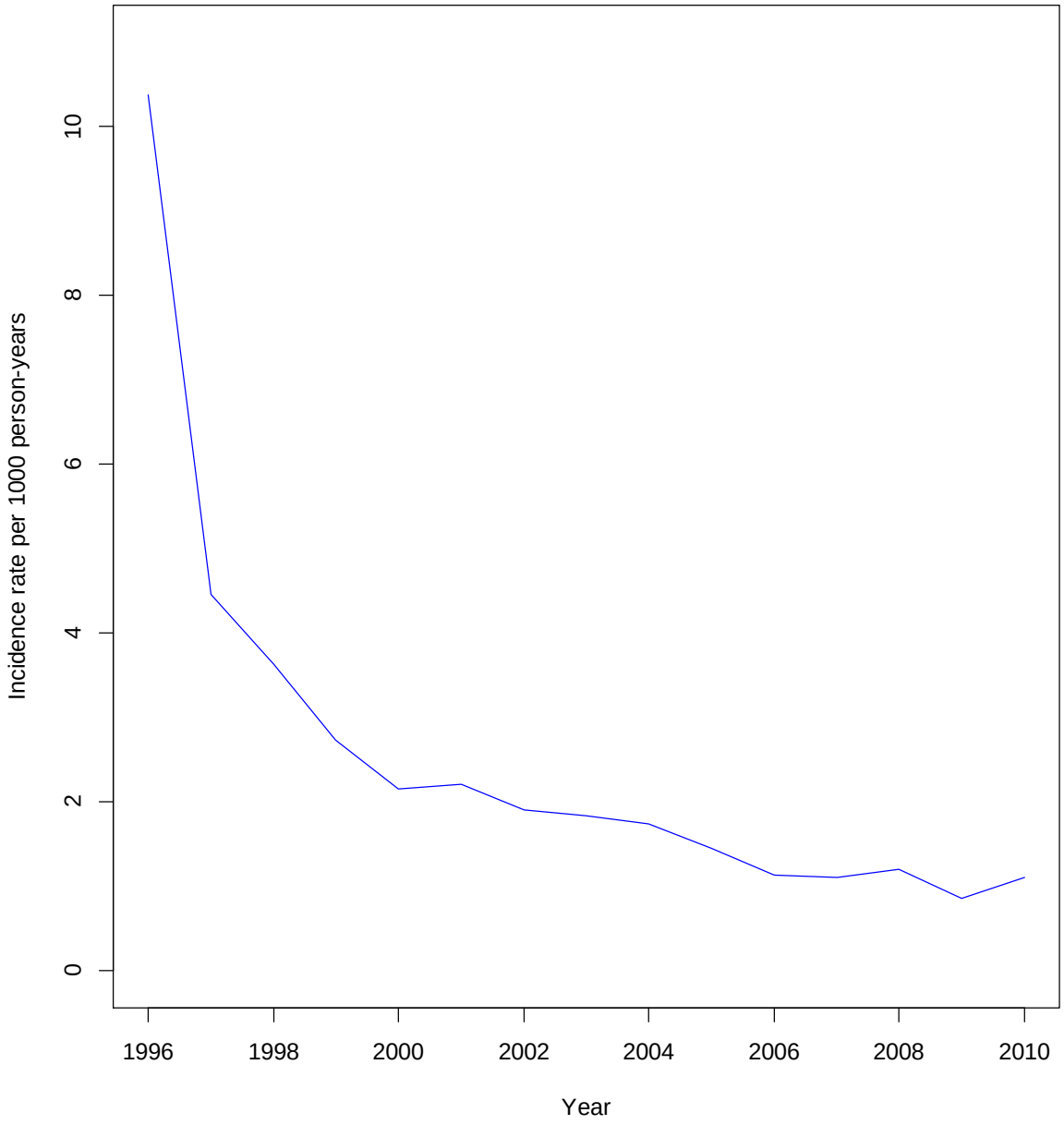
Abbreviations: KSHV Kaposi sarcoma herpes virus; EBV Epstein-Barr virus; HPV human papillomavirus; HBV hepatitis B virus; HCV hepatitis C virus; *H. pylori Helicobacter pylori*



Appendix Figure 1: Standardized incidence of non-Hodgkin lymphoma by year

Incidence rates estimated from the HIV AIDS Cancer Match Study standardized by age and sex to the 2008 US HIV population.

Abbreviations: CNS=Central Nervous System; NHL=Non-Hodgkin Lymphoma; DLBCL=Diffuse Large B-Cell Lymphoma



Appendix Figure 2: Standardized incidence of Kaposi sarcoma by year

Incidence rates estimated from the HIV AIDS Cancer Match Study standardized by age and sex to the 2008 US HIV population.