Increased Risk of Stomach and Esophageal Malignancies in People With AIDS

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See Covering the Cover synopsis on page 875.

BACKGROUND & AIMS: People infected with human immunodeficiency virus (HIV) have an increased risk of some malignancies, but little is known about the effects of infection on risk of cancers of the upper gastrointestinal tract. We evaluated the risks of different histologic and anatomic subtypes of carcinomas and non-Hodgkin lymphomas (NHLs) of the stomach and esophagus in people with acquired immunodeficiency syndrome (AIDS). **METHODS:** We analyzed data from the HIV/AIDS Cancer Match Study, which links data collected from 1980 to 2007 for 16 US population-based HIV and AIDS and cancer registries. We compared risks of stomach and esophageal malignancies in people with AIDS (N = 596,955) with those of the general population using standardized incidence ratios (SIRs). We assessed calendar trends using Poisson regression. **RESULTS:** People with AIDS had increased risks of carcinomas of the esophagus (SIR, 1.69; 95% confidence interval [CI], 1.37–2.07; n = 95) and stomach (SIR, 1.44; 95% CI, 1.17–1.76; n = 96). Risk was increased for esophageal adenocarcinoma (SIR, 1.91; 95% CI, 1.31–2.70) and squamous cell carcinoma (SIR, 1.47; 95% CI, 1.10–1.92). People with AIDS had greater risks of carcinomas of the gastric cardia (SIR, 1.36; 95% CI, 0.83–2.11) and noncardia (SIR, 1.53; 95% CI, 1.12–2.05) than the general population. Although most stomach and esophageal NHLs that developed in people with AIDS were diffuse large B-cell lymphomas, these individuals also had an increased risk of stomach mucosa–associated lymphoid tissue lymphoma (SIR, 5.99; 95% CI, 3.19–10.2; n = 13). The incidence of carcinomas remained fairly constant over time, but rates of NHL decreased from 1980 to 2007 ($P_{trend} < .0001$). **CONCLUSIONS: People with AIDS are at increased risk for developing esophageal and stomach carcinomas and NHLs. Although the incidence of NHL decreased from 1980 to 2007 as treatments for HIV infection improved, HIV-infected individuals face continued risks of esophageal and stomach carcinomas.**

Keywords: MALT Lymphoma; Epidemiology; Virus-Associated Cancers; Immunosuppression.

Immunosuppressed people, such as people with human immunodeficiency virus (HIV) infection and transplant recipients, have an increased risk of developing cancer compared with the general population. In people with HIV, some of these cancers are associated with immunosuppression, the high prevalence of coinfections, and increased prevalence of other risk factors such as tobacco smoking.[1–4] The risks of 3 virus-related cancers (Kaposi sarcoma, non-Hodgkin lymphoma [NHL], and cervical cancer) are strongly elevated in HIV-infected individuals and are considered among the events that define progression to acquired immunodeficiency syndrome (AIDS).[5] With the introduction of highly active antiretroviral therapy (HAART) in 1996, survival among HIV-infected people has improved markedly, and the proportion of older individuals living with HIV infection has grown. As a result, the number of non–AIDS-defining cancers occurring in HIV-infected individuals is increasing.[6]

In the context of aging of the HIV population, it is important to investigate rates of stomach and esophageal malignancies in HIV-infected individuals. Most esophageal and stomach cancers in the United States are diagnosed in older adults (age 65 years or older).[7,8] The infectious etiology of a subset of gastric cancers caused by *Helicobacter pylori*[9] suggests that the risk of gastric cancer might be elevated in people with HIV infection. Other risk factors common in the HIV-infected population, such as smoking and obesity, might also increase the risk of these cancers. Finally, whereas some studies have reported increased risks of esophageal and stomach cancers in HIV-infected people, other studies have reported no associations.[1–3,10–14] Although there is substantial etiologic heterogeneity for subcategories of these cancers, prior studies have not assessed whether the risks of specific histologic or anatomic subtypes of stomach and esophageal cancers are elevated in HIV-infected people.

Abbreviations used in this paper: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; IDU, injecting drug user; HAART, highly active antiretroviral therapy; HACM, HIV/AIDS Cancer Match; HIV, human immunodeficiency virus; MALT, mucosa-associated lymphoid tissue; MSM, men who have sex with men; NHL, non-Hodgkin lymphoma; RR, rate ratio; SIR, standardized incidence ratio.

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The availability of data for approximately 600,000 people with AIDS obtained from population-based US HIV/AIDS registries and cancer registries allowed us to evaluate the risk of stomach and esophageal cancers in people with AIDS, stratified by histology and anatomic subsite, compared with the risk of these cancers in the general population. In addition, trends over time were evaluated to assess the possible impact of HAART-related immune reconstitution on the incidence of these cancers among people with AIDS.

Patients and Methods

Study Population and Definition of Cancer Outcomes

The HIV/AIDS Cancer Match (HACM) Study links 16 US population-based state and metropolitan area HIV/AIDS registries to corresponding cancer registries (http://hivmatch.cancer.gov/). Records were linked using a probabilistic approach, and only de-identified data were retained by investigators. The HACM Study was approved by institutional review boards at the participating registries.

The main analysis examining cancer risk in people with AIDS (1980–2007) included the registries of Los Angeles, San Diego, and San Francisco, California; Colorado; Connecticut; Washington, DC; Florida; Georgia; Illinois; Maryland; Massachusetts; Michigan; New Jersey; New York City, New York; Texas; and Seattle, Washington. In a subanalysis, we restricted our evaluation to 12 HIV/AIDS registries that also provided information on HIV-infected people without AIDS (ie, HIV only; 1982–2007): Los Angeles; Colorado; Connecticut; Washington, DC; Florida; Georgia; Illinois; Maryland; Michigan; New Jersey; Texas; and Seattle.

We ascertained cancers through linkage with the cancer registries. All analyses were restricted to first esophageal or stomach malignancies and included only invasive carcinomas or NHLs, because other diagnoses were either too rare (eg, Kaposi sarcoma) or of uncertain validity. Individuals diagnosed with first malignancies other than esophageal and stomach cancers were censored at the date of diagnosis, and any subsequent malignancy was excluded. Tumors were classified by histology and anatomy based on codes of the International Classification of Diseases for Oncology, 3rd Edition,[15] as described in Supplementary Tables 1 and 2. Briefly, esophageal malignancies were classified into the following main histology groups: carcinomas (further divided into adenocarcinoma, squamous cell carcinoma, and type not specified) and NHLs (further divided into diffuse large B-cell lymphoma [DLBCL], Burkitt lymphoma, mucosa-associated lymphoid tissue [MALT] lymphoma, and other/unspecified NHLs). Esophageal carcinomas were also separately divided by anatomic site: cervical/upper third, thoracic/middle third, abdominal/lower third, and unspecified site. Stomach malignancies were also classified histologically as carcinomas (adenocarcinoma or other/unspecified carcinoma) or NHLs (with the same subdivisions as esophageal NHLs), and the adenocarcinomas were further subclassified as diffuse, intestinal, or unspecified. The anatomic sites of stomach cancer were separated into cardia or noncardia (which was further classified as fundus/body, antrum/pylorus, or unspecified).

Statistical Analysis

In the main analysis, people with AIDS contributed follow-up during 1980–2007, from 4 months after diagnosis of AIDS or the start of cancer registry coverage (whichever came last) until the earliest of cancer diagnosis, death, last date of cancer registry coverage, or 120 months after diagnosis of AIDS. The period 0–3 months after diagnosis of AIDS was excluded from analysis, because NHL is an AIDS-defining condition and cancer risk in this period can appear artificially high due to intensive medical evaluations. Data collection was restricted to 120 months after diagnosis of AIDS to minimize the impact of outmigration from the cancer registry catchment area over time.

The use of cancer registries allowed us to compare cancer incidence in people with AIDS with that in the general population of the corresponding registry areas using standardized incidence ratios (SIRs). SIRs of esophageal and stomach malignancies by histologic type and anatomic subsite were calculated by dividing the observed counts in people with AIDS by expected counts. Expected counts were estimated by applying general population incidence rates to the AIDS population, in strata defined by age, race, sex, calendar year, and cancer registry. We also estimated cancer incidence rates among people with AIDS and the excess absolute risk compared with the general population (ie, observed incidence minus expected incidence).

Poisson regression was used to estimate rate ratios (RRs) comparing cancer incidence among subgroups of people with AIDS. RRs were estimated across categories of attained age (0–29, 30–49, 50–69, and 70+ years old), and age-adjusted RRs were estimated by sex, race/ethnicity (non-Hispanic white, non-Hispanic black, and Hispanic), HIV transmission category (men who have sex with men [MSM], injecting drug users [IDUs], MSM/IDUs, heterosexuals, and other or unknown transmission), attained calendar year as a surrogate for HIV therapy (1980–1989 [largely no antiretroviral therapy], 1990–1995 [monotherapy and combination therapy], 1996–2000 [early HAART], and 2001–2007 [recent HAART]), and CD4 count at diagnosis of AIDS (0–49, 50–99, 100–199, and 200+ cells/mm^3).

A subanalysis was restricted to registries with data on people who were initially reported to registries with HIV only (without AIDS). In these registries, we calculated SIRs for people with HIV only (during the full follow-up time in those who never developed AIDS and during the follow-up time before a diagnosis of AIDS in those who eventually developed AIDS) and for people with AIDS (during the follow-up time after a diagnosis of AIDS in those who eventually developed AIDS). We also used Poisson regression in these registries to compare cancer risk in people who had HIV only (during the time they had HIV only) with cancer risk in people with AIDS (during the time they had AIDS in the subset who eventually developed AIDS).

Results

Characteristics of AIDS and HIV-Only Populations

Our main cohort included 596,955 people with AIDS, who contributed a total of 1,920,274 person-years between 1980 and 2007 (Table 1). The main study cohort included predominantly men (79% of follow-up time). Further, non-Hispanic black was the largest race/ethnicity group (42%). Most of the follow-up time was for subjects between 30 and 49 years of age (75%) and in the MSM HIV

Table 1. Characteristics of People Diagnosed With HIV or AIDS in the United States[a]

Characteristics	Registries with data on people with AIDS	Registries with data on people initially registered with HIV only	
	AIDS, 1980–2007	Follow-up while HIV only, 1982–2007	Follow-up after diagnosis of AIDS, 1983–2007
Total	1,920,274 (100)	531,007 (100)	118,743 (100)
Sex			
Male	1,522,706 (79.3)	369,908 (69.7)	81,228 (68.4)
Female	397,567 (20.7)	161,100 (30.3)	37,516 (31.6)
Race/ethnicity			
Non-Hispanic white	736,361 (38.3)	180,473 (34.0)	33,356 (28.1)
Non-Hispanic black	806,812 (42.0)	259,838 (48.9)	63,703 (53.6)
Hispanic	377,101 (19.6)	90,696 (17.1)	21,685 (18.3)
Attained age (*y*)			
0–29	178,988 (9.3)	95,266 (17.9)	11,980 (10.1)
30–49	1,433,190 (74.6)	361,692 (68.1)	87,247 (73.5)
50–69	297,482 (15.5)	71,452 (13.5)	18,963 (16.0)
70+	10,613 (0.6)	2598 (0.5)	553 (0.5)
HIV risk group			
MSM	831,634 (43.3)	184,751 (34.8)	35,384 (29.8)
IDU	476,310 (24.8)	107,640 (20.3)	35,779 (30.1)
MSM and IDU	125,462 (6.5)	29,021 (5.5)	8694 (7.3)
Heterosexuals	262,863 (13.7)	99,963 (18.8)	23,694 (20.0)
Other	224,005 (11.7)	109,634 (20.6)	15,193 (12.8)
Attained calendar year			
1980–1989	53,338 (2.8)	167 (0.03)	70 (0.06)
1990–1995	394,465 (20.5)	46,067 (8.7)	5109 (4.3)
1996–2000	791,163 (41.2)	135,793 (25.6)	34,157 (28.8)
2001–2007	681,308 (35.5)	348,980 (65.7)	79,407 (66.9)

[a]All values are expressed as person-years (percent of total follow-up).

transmission category (43%). Also, the majority of follow-up (77%) was in the early HAART (1996–2000) and recent HAART (2001–2007) eras. Overall, 65% of the follow-up in the main cohort was in people with reported CD4 counts at diagnosis of AIDS, of which 14%, 9%, 28%, and 13% of the follow-up corresponded to CD4 counts in the range of 0–49, 50–99, 100–199, and 200 or more cells/mm^3, respectively.

Table 1 also presents the distribution of person-years across characteristics of 143,370 people initially reported to registries with HIV only (without AIDS) between 1982 and 2007, including 531,007 person-years before diagnosis of AIDS and 118,743 person-years after diagnosis of AIDS (in the subset of individuals who later developed AIDS). The personal characteristics of these 2 subgroups were similar (Table 1). A larger proportion of the follow-up in these individuals was in the early HAART (1996–2000) and recent HAART (2001–2007) eras compared with the analyses of the main cohort, reflecting later adoption of HIV reporting in the United States.

Incidence of Esophageal and Stomach Malignancies Among People With AIDS

Overall, the incidence of esophageal carcinoma was increased in people with AIDS relative to the general population (SIR, 1.69; 95% confidence interval [CI], 1.37–2.07) (Table 2). Risk was elevated for both esophageal adenocarcinoma (SIR, 1.91; 95% CI, 1.31–2.70) and squamous cell carcinoma (SIR, 1.47; 95% CI, 1.10–1.92). SIRs for esophageal carcinomas were elevated in all anatomic sites of the esophagus, although the elevated risk of carcinoma of the middle esophagus was of borderline statistical significance.

The incidence of stomach carcinoma was also higher in people with AIDS than in the general population (SIR, 1.44; 95% CI, 1.17–1.76) (Table 3). All types of adenocarcinoma were elevated, including diffuse adenocarcinoma (SIR, 1.65; 95% CI, 1.08–2.41) and intestinal adenocarcinoma (SIR,

Table 2. Risk of Esophageal Malignancies in People With AIDS in the United States Compared With the General Population

Tumor histology/anatomy	Σ observed	SIR (95% CI)
Carcinomas by histology		
Total carcinoma	95	1.69 (1.37–2.07)
Adenocarcinoma	32	1.91 (1.31–2.70)
Squamous cell carcinoma	54	1.47 (1.10–1.92)
Other/unspecified carcinomas	9	3.45 (1.58–6.54)
Carcinomas by anatomic site		
Cervical/upper	13	2.57 (1.37–4.39)
Thoracic/middle	23	1.54 (0.98–2.31)
Abdominal/lower	43	1.92 (1.39–2.59)
Unspecified site	16	1.16 (0.66–1.88)
NHLs by histology		
Total NHL	45	261 (190–349)
Diffuse large B-cell	28	270 (180–391)
Burkitt	1	2000 (50.6–11,100)
Other/unspecified NHLs	16	255 (146–414)

Table 3. Risk of Stomach Malignancies in People With AIDS in the United States Compared With the General Population

Tumor histology/anatomy	Σ observed	SIR (95% CI)
Carcinomas by histology		
Total carcinoma	96	1.44 (1.17–1.76)
Adenocarcinoma total	89	1.40 (1.12–1.72)
Adenocarcinoma, diffuse	26	1.65 (1.08–2.41)
Adenocarcinoma, intestinal	10	1.96 (0.94–3.61)
Unspecified adenocarcinomas	53	1.24 (0.93–1.62)
Other/unspecified carcinomas	7	2.33 (0.94–4.80)
Carcinomas by anatomic site		
Cardia	20	1.36 (0.83–2.11)
Total noncardia	46	1.53 (1.12–2.05)
Fundus/body noncardia	7	0.96 (0.39–1.98)
Antrum/pylorus noncardia	32	2.30 (1.57–3.25)
Unspecified noncardia site	7	0.80 (0.32–1.64)
Unspecified site	30	1.37 (0.92–1.95)
NHLs by histology		
Total NHL	348	35.5 (31.9–39.5)
Diffuse large B-cell	228	48.8 (42.7–55.6)
Burkitt	16	54.5 (31.1–88.4)
MALT	13	5.99 (3.19–10.2)
Other/unspecified NHLs	91	34.2 (27.5–42.0)

1.96; 95% CI, 0.94–3.61). The risk of stomach carcinoma also appeared elevated in both cardia and noncardia anatomic sites, although only the SIR for noncardia stomach carcinoma was significant (SIR, 1.53; 95% CI, 1.12–2.05).

As shown in Tables 2 and 3, risks of NHLs of the esophagus and stomach were strongly elevated in people with AIDS, with SIRs of 261 (95% CI, 190–349) and 35.5 (95% CI, 31.9–39.5), respectively. This elevated risk was largely related to the occurrence of DLBCL at both sites. Burkitt lymphoma was much less common but also occurred at higher rates than in the general population. MALT lymphoma was not reported in the esophagus, but risk of gastric MALT lymphoma was elevated in people with AIDS compared with the general population (SIR, 5.99; 95% CI, 3.19–10.2), although the number of cases was small (n = 13).

In Table 4, we present estimates of the incidence of selected cancers in people with AIDS, and the excess absolute risk compared with the general population, for a subset of these cancers. The incidence of esophageal and stomach carcinomas overall was similar (4.95 vs 5.00 per 100,000 person-years, respectively), corresponding to excess absolute risks of 2.02 and 1.53 per 100,000 person-years, respectively, above the general population. In comparison, stomach NHL was much more common (incidence, 18.1 per 100,000 person-years) and represented a substantial excess absolute risk (17.6 per 100,000 person-years). MALT lymphoma of the stomach occurred at a low incidence in people with AIDS (0.68 per 100,000 person-years).

Table 4. Incidence of Selected Cancers Among People With AIDS

Cancer outcome	Incidence per 100,000 person-years	Excess absolute risk per 100,000 person-years
Esophageal carcinomas	4.95	2.02
Adenocarcinoma	1.67	0.79
Squamous cell carcinoma	2.81	0.90
Stomach carcinomas	5.00	1.53
Cardia	1.04	0.28
Noncardia	2.40	0.83
Stomach NHLs	18.1	17.6
MALT	0.68	0.56

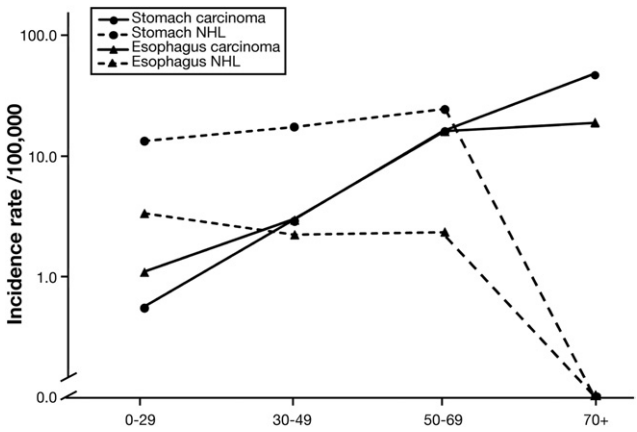

Figure 1. Incidence of stomach and esophageal carcinoma and NHL in people with AIDS by age. Incidence rates of stomach (*circles*) and esophageal (*triangles*) malignancies in subjects 0–29, 30–49, 50–69, and 70+ years old. *Solid lines* show carcinomas, and *dashed lines* show NHLs. There were no cases of NHL among 70+ year olds. The *vertical axis* is broken to allow depiction of this incidence rate of zero on the logarithmic scale.

Risk of Carcinomas by Demographic Characteristics, Calendar Year, and AIDS Status

The incidence of both esophageal and stomach carcinomas increased with age ($P_{trend} < .0001$; Figure 1). The incidence of stomach NHL also increased with age ($P_{trend} = .003$), although this was only through 50–69 years; no trend was apparent for NHL of the esophagus ($P_{trend} = .51$). We estimated the age-adjusted associations of a number of demographic characteristics, HIV risk group, and calendar year with the risk of stomach and esophageal carcinomas. Compared with non-Hispanic white subjects, Hispanic subjects had a lower risk of esophageal carcinoma (RR, 0.43; 95% CI, 0.19–0.97), and non-Hispanic black and Hispanic subjects had a higher risk of stomach carcinoma with an RR of 1.75 (95% CI, 1.09–2.82) and 1.82 (95% CI, 1.02–3.24), respectively. Further, compared with MSM, people in the heterosexual HIV risk group had a higher risk of esophageal carcinoma (RR, 2.08; 95% CI, 1.20–3.63). No associations were observed between sex and risk of esophageal or stomach carcinoma (data not shown).

CD4 count at onset of AIDS was not associated with risk of esophageal ($P_{trend} = .16$) or stomach carcinoma ($P_{trend} = .45$). This analysis included 10 years of follow-up

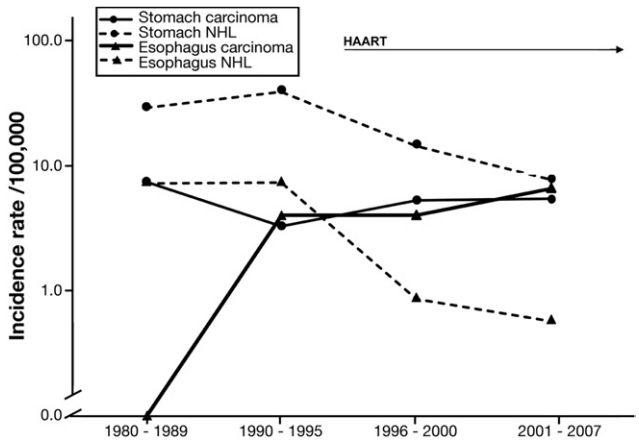

Figure 2. Incidence of stomach and esophageal carcinoma and NHL in people with AIDS by year. Age-adjusted incidence rates of stomach (*circles*) and esophageal (*triangles*) malignancies between 1980 and 2007. *Solid lines* show carcinomas, and *dashed lines* show NHLs. For esophageal carcinoma, there were no cases during 1980–1989. The *vertical axis* is broken to allow depiction of this incidence rate of zero on the logarithmic scale.

after diagnosis of AIDS. Because we did not have information on CD4 cell counts at diagnosis of cancer, we conducted a further analysis restricted to the 4–27 months after diagnosis of AIDS to represent the period with CD4 counts measured closest to diagnosis of cancer. In that analysis, we also did not observe any association between CD4 cell count and esophageal carcinoma (P_{trend} = .45) or stomach carcinoma (P_{trend} = .08).

The crude incidence rates of esophageal and stomach carcinomas were somewhat flat across calendar periods (Figure 2), and these trends remained nonsignificant after adjustment for age (age-adjusted P_{trend} = .30 for esophageal carcinoma, age-adjusted P_{trend} = .58 for stomach carcinoma). In contrast, the incidence of NHLs declined significantly in people with AIDS after the introduction of HAART in 1996 in both the esophagus and the stomach (age-adjusted P_{trend} < .0001 for both; Figure 2).

Compared with the general population, the risks of carcinomas of the esophagus or stomach were not elevated in people with HIV only (esophagus: SIR, 0.95; 95% CI, 0.53–1.56; stomach: SIR, 0.89; 95% CI, 0.56–1.33; Table 5). Furthermore, compared with people with HIV only, individuals with AIDS had a higher risk of carcinomas of the esophagus (age-adjusted RR, 2.49; 95% CI, 1.09–5.68) and the stomach (age-adjusted RR, 4.79; 95% CI, 2.73–8.40).

Discussion

In this study, we report higher risks of carcinomas in the esophagus and the stomach among people diagnosed with AIDS compared with the general population, irrespective of anatomic or histologic subtypes. Our examination of subtypes of stomach and esophageal malignancies expands on results of prior studies, some of which have documented elevated overall risks of stomach and esophageal cancers in HIV-infected populations.[1,2,11,12,16] Previous studies of immune-suppressed organ transplant recipients have reported similar findings with SIRs ranging from 1.56 to 3.05 for esophageal cancer and from 1.67 to 2.04 for stomach cancer, although analyses of transplant populations have not been stratified by subtypes of carcinomas.[1,17] Further, we also observed increased risks of NHLs arising in the esophagus and stomach, including, for the first time, documentation of an elevated risk of gastric MALT lymphoma.

Our analysis showed a significant 53% increased risk of noncardia stomach cancer in people with AIDS. *H pylori* infection causes noncardia stomach cancer,[9,18–21] so one explanation for an increased risk of this cancer in patients with AIDS might be an increased prevalence of *H pylori* infection in people with AIDS. Most previous studies, however, have shown a lower prevalence of *H pylori* (as measured by serology, endoscopic biopsy histology, endoscopic biopsy culture, or the rapid urease test) in patients with HIV or AIDS compared with the general population and an even greater reduction in the prevalence of *H pylori* among patients with AIDS with lower CD4 counts.[22–30] Possible reasons for these inverse associations include the possibility that CD4 cells are necessary to sustain *H pylori* infection or its accompanying inflammation,[31] extensive use of antibiotics in patients with AIDS, the progressive hypochlorhydria observed in patients with advanced AIDS (resulting in a pH not conducive to *H pylori* infection), and reduced antigenic recognition of *H pylori* in patients with advanced AIDS (important only for serologic results).[28] Alternatively, the prevalence of *H pylori* infection could appear artifactually low in patients with AIDS evaluated for upper gastrointestinal symptoms (eg, dyspepsia, epigastric pain, loss of appetite), because AIDS-related opportunistic infections can also lead to these symptoms.

Table 5. Risk of Stomach and Esophageal Carcinomas in People With HIV or AIDS

Tumor anatomy	Σ observed	SIR (95% CI)	RR (95% CI)	*P* value	Age-adjusted RR (95% CI)	*P* value
Esophageal carcinoma						
HIV only	15	0.95 (0.53–1.56)	1.0		1.0	
AIDS	9	2.17 (0.99–4.12)	2.68 (1.17–6.13)	.02	2.49 (1.09–5.68)	.03
Stomach carcinoma						
HIV only	23	0.89 (0.56–1.33)	1.0		1.0	
AIDS	26	3.81 (2.49–5.58)	5.06 (2.88–8.86)	<.0001	4.79 (2.73–8.40)	<.0001

NOTE. Limited to follow-up time among people who were first registered with HIV only.

H pylori is inversely associated with the risk of esophageal and gastric cardia adenocarcinomas,[32,33] so it is possible that the reduced prevalence of *H pylori* in patients with AIDS may exacerbate the risk of these cancers.

Other coinfections in the setting of immunosuppression could also contribute to the elevated risk of these carcinomas in people with AIDS. Although the etiologic relevance is uncertain, approximately 10% of gastric adenocarcinomas (mostly cancers of the cardia and corpus) are associated with Epstein–Barr virus (EBV).[34] There are also mixed data regarding the presence of EBV in some esophageal squamous cell carcinomas.[35,36] Although we are not aware of any study describing the prevalence of EBV infection in stomach or esophageal cancers from HIV-infected people, a recent report describes a case of EBV-associated lymphoepithelioma-like carcinoma of the stomach.[37] Human papillomavirus also causes several cancers that are elevated in people with HIV. Although human papillomavirus has been detected in the mucosa of the esophagus, there is little evidence of a connection with esophageal or stomach carcinogenesis, with the exception of esophageal squamous cell carcinoma, for which the data remain inconclusive.[38–40]

The remarkably elevated risk that we observed for NHLs of the esophagus and stomach is not surprising. DLBCL and Burkitt lymphoma both occur much more commonly among HIV-infected people than in the general population due to immunosuppression and can localize to extranodal sites such as the gastrointestinal tract.[41] EBV is responsible for the majority of DLBCLs and may be etiologically relevant in some cases of Burkitt lymphoma.[42,43] The decline in the incidence of esophageal and stomach NHLs that we observed beginning in 1996 is likely due to the introduction of HAART.

Our finding of an elevated risk of gastric MALT lymphoma among people with AIDS is novel. *H pylori* is also the cause of gastric MALT lymphoma,[44] and the excess risk of gastric MALT lymphoma in people with AIDS could relate to a dysregulated localized immune response to *H pylori* infection. However, because the association was based on a small number of cases of lymphoma, we could not further characterize risk factors.

A further possible explanation for the elevated risk of esophageal carcinomas and gastric cardia carcinoma in people with AIDS could be their more frequent use of tobacco and alcohol. For instance, the prevalence of smoking is at least twice as common in HIV-infected people[4,45–47] compared with the general population in the United States.[48] Tobacco use has been correlated with esophageal and gastric cardia carcinomas, with stronger associations at higher exposures.[49,50] Further, alcohol-related disorders are 4-fold more common in HIV-infected people than in the general population.[51] Although risk of esophageal squamous cell carcinoma increases with alcohol consumption, alcohol is not associated with adenocarcinomas of the esophagus or stomach.[49,52] Based on the described differences in the prevalence of smoking and alcohol use among HIV-infected people and the relative risks of these cancers conveyed by smoking and alcohol use, one can make a rough estimation of the SIRs that would have been observed without an HIV effect.[53] For example, if one estimates that the prevalence of current smoking is approximately 20% in the general population[48] and 45% in people with AIDS,[46] then the relative risk of noncardia stomach cancer of 2.04 associated with smoking[49] would by itself translate into an SIR of 1.22 for people with AIDS. Therefore, we believe that the SIR of 1.53 for noncardia stomach cancer among people with AIDS that we report here could partly be explained by smoking. Arguing against tobacco and alcohol as the sole explanation of the elevated risks, however, are the higher risks for these carcinomas that we found among people with AIDS than among people with HIV only. Also, if the risk of esophageal carcinoma among people with AIDS were mainly attributed to smoking, one would expect the SIR for esophageal squamous cell carcinoma to be higher than for esophageal adenocarcinomas, which we did not observe. Nonetheless, given uncertainties in the contribution of tobacco and alcohol, further investigations are needed to assess their impact among HIV-infected people.

As noted, the risk of stomach and esophageal carcinomas was higher among people with AIDS than HIV-infected people without AIDS (ie, HIV only). In addition, the risk of these cancers among people with AIDS did not decline across calendar years, even with the introduction of HAART in 1996. This stable trend could be explained by an increase in *H pylori* infection or reflux disease since HAART was introduced.[54] Alternatively, these findings suggest that extended immunosuppression plays a role in the development of these cancers but that use of HAART after the development of AIDS may not be effective in halting this process. Paralleling well-described patterns in the general population,[7,8,55] we also found strong increases among people with AIDS in the incidence of esophageal and stomach cancer with older age. Therefore, it will be important to monitor trends in the incidence of these cancers as HIV-infected people survive longer to older ages.

As suggested by the results presented in Table 4, the risks of these cancers, while elevated, are likely not high enough to justify cost-effective screening of the overall HIV population. Stomach and esophageal carcinomas occur at rates of approximately 5 cases per 100,000 person-years, representing modest increases of approximately 1.5–2 cases per 100,000 person-years above the incidence in the general population. Obviously, screening may be indicated for HIV-infected people who are at especially high risk (eg, with Barrett's esophagus), and targeted evaluation should be performed for symptomatic patients. NHL is much more common, but there is no established role for screening for this malignancy.

Another limitation of our study is that we had no individual information on use of HAART; instead, we used calendar year as a proxy for availability of HAART. Additionally, we focused most of our analyses on people with AIDS, because the HACM study has more limited

data on people with HIV only. The main strength of this study is its large, population-based design (incorporating data on almost 600,000 people with AIDS), which allowed us to estimate the risk of esophageal and stomach malignancies stratified by histologic subtype and anatomic site.

In conclusion, we found that people with AIDS have 69% and 44% increased risks of esophageal and stomach carcinomas, respectively, compared with the general population. The risks of NHLs in the stomach and esophagus were also strongly elevated. Further, the incidence of esophageal and stomach carcinomas has not declined with the introduction of HAART. In the clinical setting, additional efforts to implement tobacco cessation and moderation of alcohol use may have an effect in reducing the occurrence of esophageal and stomach carcinomas. Further research on the epidemiology of *H pylori* infection in HIV-infected people, and its relation to HAART use, would also be of value.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.07.013.

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Conflicts of interest

The authors disclose no conflicts.

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Supplementary Table 1. Tumor Histology and Anatomy Definitions of Esophageal Malignancies

Tumor histology/anatomy	International Classification of Diseases for Oncology, 3rd edition code included in type or site
Carcinomas by histology	
Total carcinoma	8010, 8140–8145, 8051, 8052, 8070–8076, 8083, 8084, 8094, 8200, 8201, 8210, 8211, 8230, 8255, 8260–8263, 8310, 8323, 8330, 8480, 8481, 8490, 8500, 8503, 8550, 8570, 8572, 8574, 8576
Adenocarcinoma	8140–8145, 8200, 8201, 8210, 8211, 8230, 8255, 8260–8263, 8310, 8323, 8330, 8480, 8481, 8490, 8500, 8503, 8550, 8570, 8572, 8574, 8576
Squamous cell	8051, 8052, 8070–8076, 8083, 8084, 8094
Other/unspecified carcinomas	8010
Carcinomas by anatomic site	
Cervical/upper	C150, C153
Thoracic/middle	C151, C154
Abdominal/lower	C152, C155
Unspecified site	C158, C159
NHLs by histology	
Total NHL	9590–9596, 9670–9671, 9673, 9675, 9678–9680, 9684, 9687, 9689–9691, 9695, 9698–9702, 9705, 9708–9709, 9714–9719, 9727–9729, 9823, 9827
Diffuse large B-cell	9678–9680, 9684
Burkitt	9687
MALT	9699
Other/unspecified NHLs	9590–9596, 9670–9671, 9673, 9675, 9689–9691, 9695, 9698, 9700–9702, 9705, 9708, 9709, 9714–9719, 9727–9729, 9823, 9827

Supplementary Table 2. Tumor Histology and Anatomy Definitions of Stomach Malignancies

Tumor histology/anatomy	International Classification of Diseases for Oncology, 3rd edition code included in type or site
Carcinomas by histology type	
Total carcinoma	8010, 8140–8145, 8190, 8200, 8201, 8210, 8211, 8214, 8220, 8221, 8230, 8255, 8260–8263, 8310, 8320, 8323, 8331, 8401, 8440, 8441, 8450, 8460, 8470, 8480, 8481, 8490, 8500, 8503, 8550, 8570, 8572, 8574, 8576
Adenocarcinoma total	8140–8145, 8190, 8200, 8201, 8210, 8211, 8214, 8220, 8221, 8230, 8255, 8260–8263, 8310, 8320, 8323, 8331, 8401, 8440, 8441, 8450, 8460, 8470, 8480, 8481, 8490, 8500, 8503, 8550, 8570, 8572, 8574, 8576
Adenocarcinoma, diffuse	8142, 8145, 8490
Adenocarcinoma, intestinal	8144, 8200, 8201, 8211, 8480, 8481
Unspecified adenocarcinomas	8140, 8141, 8143, 8190, 8210, 8214, 8220, 8221, 8230, 8255, 8260–8263, 8310, 8320, 8323, 8331, 8401, 8440, 8441, 8450, 8460, 8470, 8500, 8503, 8570, 8572, 8574, 8576
Other/unspecified carcinomas	8010
Carcinomas by anatomic site	
Cardia	C160
Total noncardia	C161–C166
Fundus/body noncardia	C161, C162
Antrum/pylorus noncardia	C163, C164
Unspecified noncardia site	C165, C166
Unspecified site	C168, C169
NHLs by histology	
Total NHL	9590–9596, 9670, 9671, 9673, 9675, 9678–9680, 9684, 9687, 9689–9691, 9695, 9698–9702, 9705, 9708, 9709, 9714–9719, 9727–9729, 9823, 9827
Diffuse large B-cell	9678–9680, 9684
Burkitt	9687
MALT	9699
Other/unspecified NHLs	9590–9596, 9670, 9671, 9673, 9675, 9689–9691, 9695, 9698, 9700–9702, 9705, 9708, 9709, 9714–9719, 9727–9729, 9823, 9827