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# Survival among anal cancer patients with and without HIV in the United States, 2001–2019: A cohort study

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## Summary

**Background:** Anal cancer risk is elevated among people with HIV (PWH), particularly in men who have sex with men with HIV. Estimating survival by HIV status and sex and identifying high-risk groups is critical for documenting prognostic differences between populations.

**Methods:** We used data from linked HIV and cancer registries in the U.S. on anal cancer patients aged 20–79 diagnosed during 2001–2019. We assessed sex-specific adjusted hazard ratios (aHRs) of all-cause and anal cancer-specific mortality by HIV status using Cox proportional-hazard models, adjusting for year, age, race/ethnicity, histology, stage, region, and treatment. We identified predictors of mortality by HIV status. Models among PWH further adjusted for AIDS and HIV transmission group.

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Contributors

JZS, EAE, ERZ, and MSS contributed to the conceptualization of this study, for which JZS and MSS were responsible for the investigation. JZS and MSS directly accessed and verified the underlying data reported in the manuscript. JZS, RMP, and MSS contributed to the development of the methodology. JZS conducted the formal analysis and wrote the original draft of the manuscript. AA, JHH, AM, and KSP were responsible for data curation. MAC, ARK, and AJK contributed to the validation of the research. JZS and AJK created visualizations. MSS provided supervision. M-JH and QL provided project administration. All authors contributed to the reviewing and editing of the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

AM received funding support from the Centers for Disease Control and Prevention (PS12-1201, PS18-1802) and received travel and registration support to attend the Council of State and Territorial Epidemiologists annual conference (June 2022 in Louisville, KY, and June 2023 in Salt Lake City, UT). All other authors declare no competing interests.

Data sharing

The data used in this study cannot be shared publicly due to the terms of the U.S. National Cancer Institute's data use agreement with the cancer and HIV surveillance systems.

**Findings:** Between 2001–2019, 43·6% (1161) of 2662 PWH with anal cancer died versus 35·4% (7722) of 21824 patients without HIV. HIV was associated with a 1·35-fold [95% confidence interval (95%CI)=1·24-1·47] increase in all-cause mortality among male patients, and a 2·47-fold (95%CI=2·10-2·90) increase among female patients. Among PWH with anal cancer, all-cause mortality was greater among non-Hispanic Black individuals (aHR=1·19, 95%CI=1·04-1·38), people with AIDS (aHR=1·36, 95%CI=1·10-1·68), people who inject drugs (PWID) (aHR=1·49, 95%CI=1·17-1·90), those with adenocarcinoma (aHR=2·74, 95%CI=1·82-4·13), and those without surgery treatment (aHR=1·34, 95%CI=1·18-1·53). HIV was associated with anal cancer-specific mortality among female patients only (aHR=1·52, 95%CI=1·18-1·97). Among PWH, anal cancer-specific mortality was greater among those with adenocarcinoma (aHR=3·29, 95%CI=1·89-5·72), those with no/unknown treatment compared to any treatment with either surgery, radiation, and/or chemotherapy (aHR=1·59, 95%CI=1·17-2·17), and among PWID (aHR=1·60, 95%CI=1·05-2·44).

**Interpretation:** Among anal cancer patients, HIV was associated with all-cause mortality, with a much stronger association among female patients. Anal cancer-specific mortality was elevated among female patients with HIV. As anal cancer screening becomes more widespread, examining impacts of screening on survival by HIV status and sex is crucial.

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## Introduction

Human papillomavirus causes 90% of anal squamous cell carcinomas (SCCs) worldwide, most of which are diagnosed in high-resource settings.[1,2] In the United States (U.S.), anal cancer incidence is rare relative to other cancers, with a rate of 1·9 per 100000 during 2015–2019.[3] The risk of anal cancer is extremely elevated in immunosuppressed individuals, especially people with HIV (PWH).[4–6] Anal cancer incidence is 19-times higher among PWH compared with the general U.S. population, with rates 39-times higher in men who have sex with men (MSM) with HIV.[6] Anal cancer rates have increased for decades in many populations globally,[7] including the U.S., where the incidence of anal SCC, the most common histologic subtype, increased annually by 2·7% during 2001–2015.[8]

Because the proportion of older adults with HIV in the U.S. is increasing considerably due to improvements in antiretroviral therapy and increased longevity,[9,10] recent estimates of survival among PWH are needed to determine whether there have been improvements over time, particularly for high-risk individuals, such as PWH with anal cancer. Further, given the heterogeneity in anal cancer incidence between people with and without HIV and between female and male individuals, particularly MSM,[6] examining survival by HIV status, sex, and HIV transmission risk group is important for accurately documenting prognostic differences between populations.

According to a recent meta-analysis of survival among anal cancer patients by HIV status,[11] most survival analyses comparing anal cancer patients with and without HIV examined cancer treatment outcomes in specific cohorts (e.g., veterans, patients at a single hospital, etc.),[12,13] rather than comparing survival of anal cancer patients by HIV status in the general population. Additionally, the most recent survival analyses among anal cancer patients by HIV status in the general U.S. population only examined data through 2014 (all-cause)[14] and

2010 (anal cancer-specific),[15] and none stratified by sex. Using the largest linked database with HIV and cancer cases in the U.S., we 1) compared all-cause and anal cancer-specific survival between anal cancer patients with and without HIV during 2001–2019, stratified by sex; and 2) determined predictors of survival among anal cancer patients, stratified by HIV status.

## Methods

### Data sources and study population

We utilized 2001–2019 data from the HIV/AIDS Cancer Match Study, a data linkage study of 13 population-based HIV and cancer registries throughout the U.S. (https://hivmatch.cancer.gov/), including Colorado (2001–2015), Connecticut (2002–2016), Washington, D.C. (2007–2015), Georgia (2004–2012), Louisiana (2001–2015), Massachusetts (2007–2016), Maryland (2008–2018), Michigan (2001–2015), North Carolina (2001–2014), New Jersey (2001–2012), New York (2001–2019), Puerto Rico (2003–2017), and Texas (2001–2015). Institutional Review Boards at participating registries approved all research activity for the HIV/AIDS Cancer Match Study, as required.

We restricted the analyses to individuals aged 20–79 years who were diagnosed with invasive anal cancer (behavior code 3) between 2001–2019, identified through population-based cancer registries (appendix p2). We identified anal cancer patients using International Classification of Diseases (ICD) for Oncology, 3rd edition topography codes C210 (anus, not otherwise specified), C211 (anal canal), C212 (cloacogenic zone), and C218 (overlapping lesion of rectum, anus, and anal canal). We excluded transgender anal cancer patients (N=28) due to the under ascertainment of transgender identity in the cancer registry data.

We only included first anal cancers and excluded patients who had an anal cancer site code with one of the following ICD histology codes: 8000–8005 (poorly specified malignant neoplasms), 9050–9055 (mesothelioma), 9140 (Kaposi sarcoma), and 9590–9992 (malignant lymphoma and other hematologic conditions). HIV status was obtained through a linkage with the population-based HIV registries–we classified anal cancer patients as having HIV if their HIV report date preceded their anal cancer diagnosis date. We followed patients starting on the anal cancer diagnosis date and ending on the earlier of either death date, end of registry coverage, or the month before the individual's 85th birthday. Death certificates, obtained from cancer registries, included cause of death information.

### Outcomes

Due to possible miscoding of anal cancer deaths among anal cancer patients on death certificates, we considered deaths caused by cancers of the anus (ICD codes C210, C211, C212, C218), colon (C187, C189), rectum (C20, C209), or rectosigmoid junction (C19, C199) as "anal cancer-specific" to minimize the misclassification of site of origin and maximize the capture of anal cancer-specific deaths (N=4603). To ensure that we only counted the most likely misclassified causes of death, we identified all anal cancer patients with colon, rectal, or rectosigmoid junction cancer listed as their cause of death who were also previously diagnosed with a corresponding incident colon, rectal, or rectosigmoid

cancer (N=105); we reclassified these patients' cause of death as non-anal cancer-specific, resulting in 4498 total anal cancer-specific deaths in the analysis (appendix p3).

## Predictors of interest

We selected characteristics of interest *a priori* from the literature: year of anal cancer diagnosis (2001–2004, 2005–2009, 2010–2014, 2015–2019), sex (male, female), age at diagnosis (20–39 years, 40–59 years, 60–79 years), race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White), histology (SCC, adenocarcinoma, other/unspecified), anal cancer stage (localized, regional, distant, unknown), and anal cancer treatment [any (yes, no/unknown), surgery (yes, no/unknown), chemotherapy (yes, no/unknown), radiation (yes, no/unknown)]. We did not include 'non-Hispanic other' race/ethnicity (n=19) and unknown race/ethnicity (n=101) in the models due to small sample sizes. For anal cancer histology, we identified SCC using ICD codes 8050–8076, 8083–8084, 8123–8124; we identified adenocarcinoma using codes 8140–8145, 8190–8231, 8260–8263, 8310, 8401, 8480–8490, 8570–8574. Among PWH, we further examined AIDS status at the time of anal cancer diagnosis (yes, no) and HIV transmission risk group [MSM only—not including people who inject drugs (PWID), PWID including MSM, heterosexual, other/unknown].

## Statistical analysis

We described characteristics anal cancer patients overall and by HIV status. For crude examinations of survival, we calculated Kaplan-Meier curves with log-rank p-values, 5-year survival, and median survival by HIV status and sex. We only calculated 5-year survival patients who were diagnosed with anal cancer during 2001–2014 to allow enough follow-up through 2019. We also identified the five leading causes of death by HIV status.
To estimate adjusted associations of HIV on all-cause mortality and anal cancer-specific mortality overall, we used Cox proportional hazard models, adjusting for year of anal cancer diagnosis, sex, age, race/ethnicity, histology, stage at diagnosis, registry region/state, and treatment. We also calculated sex-specific adjusted hazard ratios and tested an interaction term for HIV status and sex. We calculated p-heterogeneity using a likelihood ratio test.

To identify predictors of all-cause mortality and anal cancer-specific mortality, we estimated adjusted hazard ratios for year of anal cancer diagnosis, sex, age at anal cancer diagnosis, race/ethnicity, histology, stage at diagnosis, and treatment in models stratified by HIV status. For models among PWH, we additionally adjusted for AIDS and HIV transmission risk group and assessed these characteristics as potential predictors. To examine associations between year of anal cancer diagnosis and mortality by HIV status, we calculated p-trends, modeled using continuous year of diagnosis. Because anal cancer stage at diagnosis is a key determinant of survival, we further investigated the association of anal cancer stage on mortality by sex and HIV status.

For all analyses of all-cause mortality, we modeled initial treatment using three variables: surgery (yes, no/unknown), chemotherapy (yes, no/unknown), and radiation (yes, no/unknown). Because only 434 deaths among PWH and 4064 deaths among people without HIV were anal cancer-specific (appendix p4), for analyses of anal cancer-specific mortality, we modeled treatment as one binary variable (any treatment) to improve statistical power.

For anal cancer-specific mortality analyses, we excluded patients from Connecticut due to missing cause of death information. We determined statistical significance using two-sided p-values<0·050 and performed all analyses using Stata 17·0 (StataCorp LLC, College Station, TX, USA) and R Statistical Software (v4.2.1; R Core Team, Vienna, Austria).

## Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report, but did review a final version of the manuscript before submission.

## Results

In the HIV/AIDS Cancer Match Study, 24486 people (2662 PWH; 21824 people without HIV) were diagnosed with anal cancer between January 1, 2001, and December 31, 2019 (Table 1). Compared with anal cancer patients without HIV, a greater proportion of PWH were male, younger, non-Hispanic Black or Hispanic, diagnosed with SCC, and received surgery for anal cancer treatment. Most anal cancer patients with HIV had a prior AIDS diagnosis and were MSM only (not including PWID). 7·8% (n=209) of anal cancer patients with HIV were MSM and PWID, while 12·6% (n=335) were PWID only.

Male patients had a higher proportion of anal adenocarcinomas compared with female patients (appendix p5). Among male patients, the distribution of anal cancer stage significantly differed by HIV status (p<0·0001). Specifically, a higher proportion of localized anal cancers were observed among male patients with HIV and among MSM with HIV compared with male patients without HIV. Among female patients, anal cancer stage did not significantly differ by HIV status (p=0·44). Receiving treatment with surgery or chemotherapy did not significantly differ by HIV status among male patients but significantly differed by HIV status among female patients (p=0.0018 for surgery, p=0.0074 for chemotherapy).

Between 2001 and 2019, 43·6% (1161 of 2662) of anal cancer patients with HIV died from any cause, compared to 35·4% (7722 of 21824) of anal cancer patients without HIV (appendix p4). The leading causes of death among anal cancer patients with HIV were anal cancer, HIV, ischemic heath disease, lung and bronchus cancer, and miscellaneous neoplasms. Among anal cancer patients without HIV, the leading causes of death were anal cancer, miscellaneous neoplasms, ischemic heart disease, lung and bronchus cancer, and chronic obstructive pulmonary disease and allied conditions.

Crude Kaplan-Meier curves demonstrated similar overall survival between male patients with HIV and without HIV (log-rank p=0·88), but poorer overall survival in female patients with HIV compared with without HIV (log-rank p<0·0001) (Figure 1). 5-year overall survival and median survival were lower among anal cancer patients with HIV compared with those without HIV (Figure 2). In adjusted analyses, the association between HIV status and all-cause mortality significantly differed by sex (p-heterogeneity<0·0001); HIV was associated with a 1·35-fold (95%CI=1·24-1·47) increase in all-cause mortality among

male patients after adjusting for confounders, and a 2·47-fold (95%CI=2·10-2·90) increase in all-cause mortality among female patients.

Among both anal cancer patients with and without HIV, all-cause mortality was significantly higher among those aged 60–79 years at diagnosis versus 40–59, and among-Hispanic Black versus non-Hispanic White individuals (Figure 3). Additionally, adenocarcinoma versus SCC, more advanced or unknown anal cancer stage versus localized, and no/unknown surgery receipt were associated with increased mortality. Stratified by sex, more advanced anal cancer stage (regional or distant compared to localized) remained significantly associated with mortality among both male and female patients, irrespective of HIV status, and did not substantially differ between sexes (appendix p6-7).

Among anal cancer patients with HIV, all-cause mortality was also significantly higher for people with AIDS and PWID versus those with heterosexual transmission, though mortality did not differ between MSM and those with heterosexual transmission (Figure 3). All-cause mortality among anal cancer patients without HIV was significantly elevated among male patients and among those who had no/unknown chemotherapy receipt or no/unknown radiation receipt. All-cause mortality declined over time among anal cancer patients with and without HIV (p-trend<0·0001 for both groups) (appendix p8). Compared with PWH who were diagnosed with anal cancer in 2001–2004, PWH who were diagnosed in 2015–2019 had 38% (95%CI=19%−52%) lower (Figure 3) all-cause mortality. Compared with individuals without HIV who were diagnosed with anal cancer in 2001–2004, individuals without HIV diagnosed during 2015–2019 had 19% (95%CI=10%−27%) lower all-cause mortality.

Between 2001 and 2019, 16·8% (434 of 2582) of anal cancer patients with HIV who had cause of death information died from anal cancer, compared to 19·3% (4064 of 21051) of anal cancer patients without HIV (appendix p4). Notably, only a small proportion of patients had missing cause of death information: 3·0% (80 of 2662) among PWH and 3·5% (773 of 21824) among patients without HIV. Crude Kaplan-Meier curves demonstrated better anal cancer-specific survival among male patients with HIV compared with those without HIV (log-rank p<0·0001), but better anal cancer-specific survival among female patients without HIV compared with those with HIV (log-rank p=0·036) (Figure 1). Among male anal cancer patients, 5-year anal cancer-specific survival was higher among PWH compared with those without HIV but, lower among female anal cancer patients with HIV compared with female patients without HIV (Figure 2). After adjusting for confounders, HIV was not associated with anal cancer-specific mortality overall however, the association between HIV status and anal cancer-specific mortality significantly differed by sex (p-heterogeneity=0·0027). Among female patients, anal cancer-specific mortality was 1·52-fold (95%CI=1·18-1·97) higher for PWH compared with patients without HIV; however, among male patients, HIV was not associated with anal cancer-specific mortality.

Among both anal cancer patients with and without HIV, anal cancer-specific mortality was significantly higher for those with adenocarcinoma versus SCC, more advanced or unknown anal cancer stage versus localized, and no/unknown treatment receipt (Figure 4). Additionally, among anal cancer patients with HIV, anal cancer-specific mortality

was significantly higher for PWID versus heterosexual transmission. Anal cancer-specific mortality was not significantly different between MSM with HIV compared with PWH with heterosexual transmission. Exclusively among PWH, anal cancer-specific mortality was significantly higher among male individuals, people aged 60–79 years at anal cancer diagnosis versus 40–59 years, and non-Hispanic Black versus non-Hispanic White individuals. Anal cancer-specific mortality significantly declined over time among anal cancer patients without HIV (p-trend=0·0019) (Figure 4 and appendix p8). A declining trend in anal cancer-specific mortality was also observed for PWH but was not significant (p-trend=0·13).

## Discussion

In this large, population-based study using HIV and cancer registry data from 13 diverse U.S. areas, all-cause mortality was 53% higher among anal cancer patients with HIV compared with those without HIV during 2001–2019, with large heterogeneity by sex. Among female anal cancer patients, HIV was associated with 2·5-times the risk of dying. Among male anal cancer patients, HIV was associated with 1·4-times the risk of dying. Anal cancer was the leading cause of death among anal cancer patients, regardless of HIV status; however, anal cancer-specific mortality was 52% higher in female patients with HIV compared with female patients without HIV but did not differ by HIV status among male patients.

When examining predictors of mortality among anal cancer patients with HIV, sex was not associated with mortality. However, among patients without HIV, male patients had significantly elevated all-cause and anal cancer-specific mortality compared with female patients. These observations may partially explain the heterogeneity in the role of HIV on mortality by sex due to a higher baseline for male patients without HIV compared with the baseline for female patients without HIV. It is also possible that the poorer survival in male versus female anal cancer patients without HIV is partially due to misclassification of HIV status. Roughly one-third of U.S. anal cancer cases in male patients occur in those with HIV.[16] Undiagnosed HIV infection or imperfect sensitivity of the linkage between HIV and cancer registries could result in some anal cancer patients with HIV being classified as not living with HIV, which could lead to poorer survival.

The elevated all-cause mortality in anal cancer patients with HIV may be due to generally increased comorbidities and poorer prognoses among PWH compared with people without HIV, regardless of cancer diagnosis. Additionally, among PWH, HIV is a competing cause of death, which we observed as the second leading cause of death among anal cancer patients with HIV (16%), with a proportion nearly as high as anal cancer-related deaths (17%). Further, among anal cancer patients, a much higher proportion of PWH were of a minoritized racial/ethnic group (non-Hispanic Black or Hispanic) compared with patients without HIV, highlighting the importance of considering the intersectionality of racial/ethnic disparities and HIV status on mortality among anal cancer patients.

Among PWH, non-Hispanic Black individuals, and those with adenocarcinoma, more advanced cancer stage, and lack of treatment, were all associated with poorer all-cause

survival. These same variables were also significant among those without HIV, emphasizing the underlying disparities that contribute to the overall elevated mortality irrespective of HIV status. For instance, non-Hispanic Black individuals in the U.S. are diagnosed with higher rates of anal adenocarcinoma,[17] and are less likely to receive standard anal cancer treatment,[18] which may contribute to the increased mortality in this population. Our results also showed that among anal cancer patients with HIV, PWID were significantly more likely to die. A possible explanation is because PWID often experience more difficulty receiving care due to social barriers, lack of insurance, and lack of access.[19]

Our findings differ from a recent meta-analysis, which concluded no significant differences in all-cause mortality among anal cancer patients by HIV status during the current antiretroviral therapy era (after 1996).[11] However, many of these studies were conducted specifically to compare treatment outcomes between anal cancer patients with and without HIV, and therefore, eliminated potential treatment receipt disparities between anal cancer patients with and without HIV that would occur in the general population.[26–28] These findings of similar survival among anal cancer patients who received comparable treatment modalities by HIV status emphasizes the critical role of equitable cancer treatment in curtailing disparities in mortality between anal cancer patients with and without HIV.

Prior studies also indicate no significant differences in anal cancer-specific mortality by HIV status however, they did not stratify by sex.[11,15] To our knowledge, our study is the first to report profoundly elevated anal cancer-specific mortality specifically among female patients with HIV compared with without HIV, but no differences for male patients by HIV status. This could be a result of targeted anal cancer screening for MSM, who contribute to a large proportion of PWH. For example, MSM with HIV are more likely to be screened for anal cancer and down staged, which attenuates the survival deficit compared with male individuals without HIV. Specifically, increased screening awareness for MSM may aid in the identification of earlier stage anal cancers among PWH compared with without HIV, as shown by other studies, reporting that PWH are more likely to be diagnosed with less advanced anal cancers compared with individuals without HIV.[14,21] Our data corroborate these observations, showing that MSM with HIV had a higher proportion of localized anal cancer diagnoses compared with male patients without HIV, and even compared with female patients.

Our study was limited by the imperfect capture of HIV status among all anal cancer patients during the linkage of the HIV/AIDS and cancer registries; however, we previously estimated that the sensitivity of our linkages is 84%,[22] emphasizing that most cases are adequately ascertained. Additionally, we did not have data for all registries through 2019. For example, only one registry had data for 2019, two registries for 2018, and three for 2017. We conducted two sensitivity analyses comparing different period restrictions and observed nearly unchanged results, confirming the validity of our findings (appendix p9-10). Further, our study only represents anal cancer patients from the HIV/AIDS Cancer Match Study catchment areas, which could limit generalizability to the entire U.S. population. Another limitation is the potential misclassification of cause of death; however, we attempted to methodologically reduce misclassification by including commonly miscoded causes of death among anal cancer patients (colon, rectum, and rectosigmoid junction) and also reclassifying

anal cancer patients with incident colon, rectum, or rectosigmoid junction cancers who also had a matching colon, rectum, or rectosigmoid cancer cause of death code. We did not have individual-level information on insurance status and other medical comorbidities, which are important contributors to the receipt of cancer treatment, type of treatment modality, and cancer-specific survival. [23] Therefore, these unmeasured variables may have contributed to some residual confounding. Lastly, although transgender individuals are disproportionately affected by HIV and human papillomavirus-associated cancers,[24,25] we could not examine transgender individuals separately due to the under ascertainment of gender identity in cancer registries.[26,27] Despite the North American Association for Central Cancer Registries data dictionary providing the opportunity to report gender identity (including transgender), most hospitals do not systematically collect this information, resulting in underreporting of transgender individuals in registries.[27]

A major strength of this study is the use of a large, population-based data linkage study from 13 regions across the U.S. with long-term follow-up. The HIV/AIDS Cancer Match Study is currently the largest database of linked cancer cases among PWH in the U.S., allowing us to examine mortality among anal cancer patients with HIV overall and in subgroups with greater statistical power than prior studies.[11]

Despite the rarity of anal cancer in the U.S., several high-risk groups experience elevated anal cancer incidence and mortality, irrespective of HIV status. The first step for reducing anal cancer mortality is through primary and secondary prevention of anal cancer, including increasing human papillomavirus vaccination and improving screening to detect anal cancer precursors. A recent randomized clinical trial found significantly reduced anal cancer risk among PWH following treatment of anal high-grade squamous intraepithelial lesions compared to active monitoring without treatment.[28] Future analyses examining the impact of anal cancer screening on survival in PWH and other high-risk groups by sex will be invaluable as anal cancer screening becomes more widespread.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Research in context

### Evidence before this study

We searched PubMed for peer-reviewed articles published between Jan 1, 2000, and Dec 31, 2022, using the search terms: (“anal cancer” AND “HIV”) AND (“survival” OR “mortality”). As a result of this search, we found and reviewed the most recent meta-analysis of survival among anal cancer patients with and without HIV, which was published in February 2022. The meta-analysis reported no significant association between HIV and survival among anal cancer patients, with a pooled hazard ratio of 1.11 (95% CI=0.85–1.44) for overall survival and 1.15 (95% CI=0.69–1.93) for anal cancer-specific survival among anal cancer patients with HIV compared with those without HIV. Studies of overall survival had low heterogeneity and studies of anal cancer-specific survival had medium heterogeneity. Most studies were extremely limited in sample size, with fewer than 50 anal cancer patients with HIV. Additionally, analyses of overall and anal cancer-specific survival among anal cancer patients by HIV status in the general U.S. population have not been updated for a decade and we are unaware of any recent, if any, studies that stratify by sex.

### Added value of this study

To our knowledge, our study is the largest and most recent evaluation of survival among anal cancer patients with HIV in the general U.S. population, and importantly, it presents results stratified by sex, which prior studies did not consider. We observed that the association of HIV on survival was highly heterogenous between male and female anal cancer patients during 2001 to 2019. After adjusting for year of cancer diagnosis, age, race and ethnicity, histology, stage, region, and treatment, we found that in female anal cancer patients, HIV was associated with a 2·5-fold increased risk of dying, while in male anal cancer patients, HIV was associated with a 1·4-fold increased risk of dying. Further, a novel finding is that anal cancer-specific mortality is significantly elevated in female patients with HIV compared with female patients without HIV. This association was masked in prior studies of anal cancer-specific mortality that combined male and female individuals. Among anal cancer patients with HIV, elevated all-cause and anal cancer-specific mortality were observed for individuals with later stage anal cancer, anal adenocarcinoma, people who inject drugs, and those with who were not treated for their cancer with surgery or at all. Our findings differ from the recent meta-analysis because many previous survival analyses among anal cancer patients in the context of HIV were specifically aimed at comparing cancer treatment outcomes between people with and without HIV in specific cohorts (e.g., veterans, patients at a single hospital, etc.), rather than comparing survival of anal cancer patients with and without HIV in the general population, as done in our study.

### Implications of all the available evidence

Anal cancer patients with HIV in the general U.S. population have significantly elevated mortality compared with anal cancer patients without HIV, especially among female

patients. Early detection, anal screening, and cancer treatment should be prioritized to improve prognosis for anal cancer patients, particularly those with HIV.

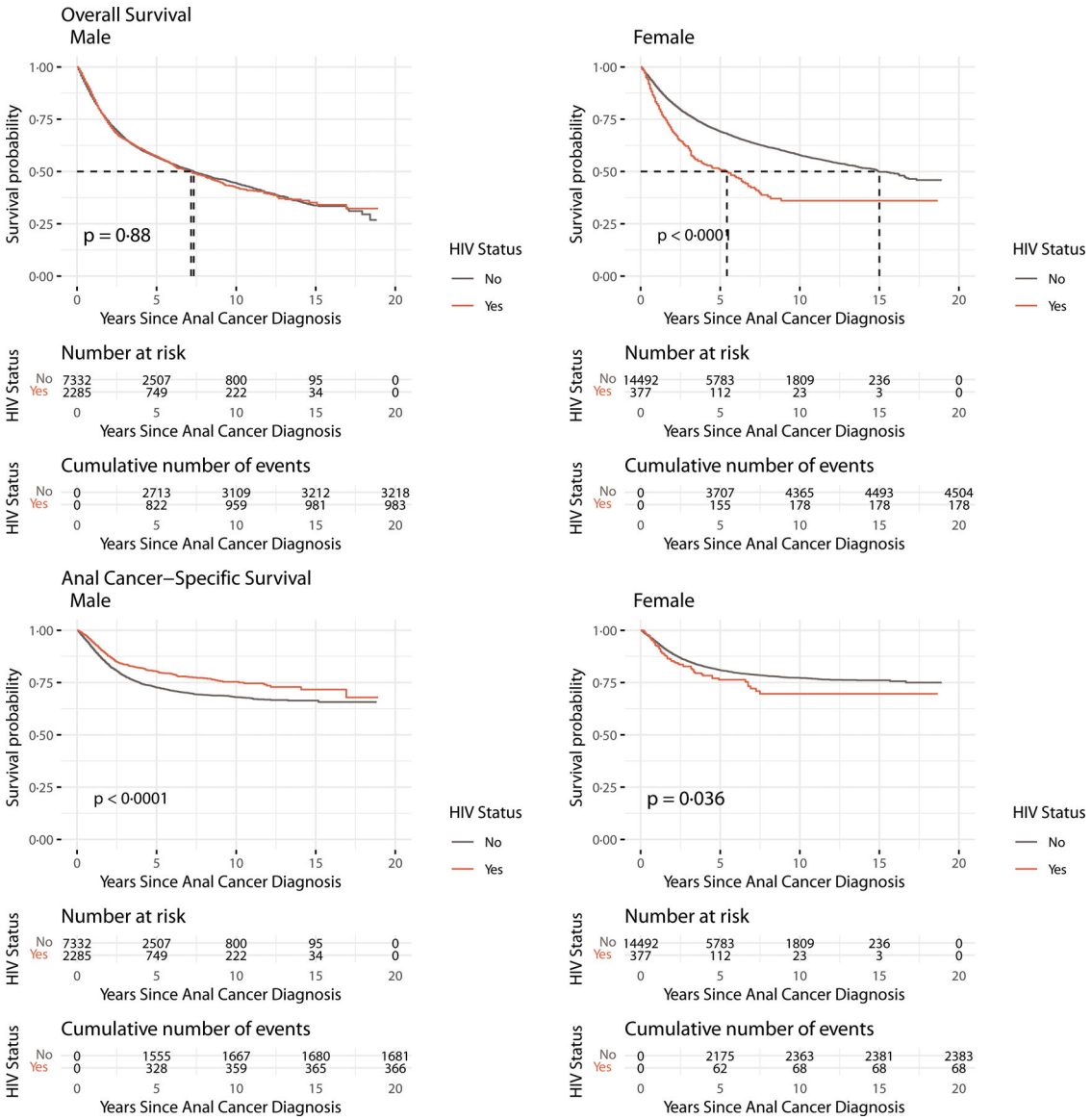


**Figure 1.**

Kaplan-Meier curves of overall survival and anal cancer-specific survival by HIV status and sex among anal cancer patients in the HIV/AIDS Cancer Match Study, 2001–2019.

The dashed lines indicate median survival.

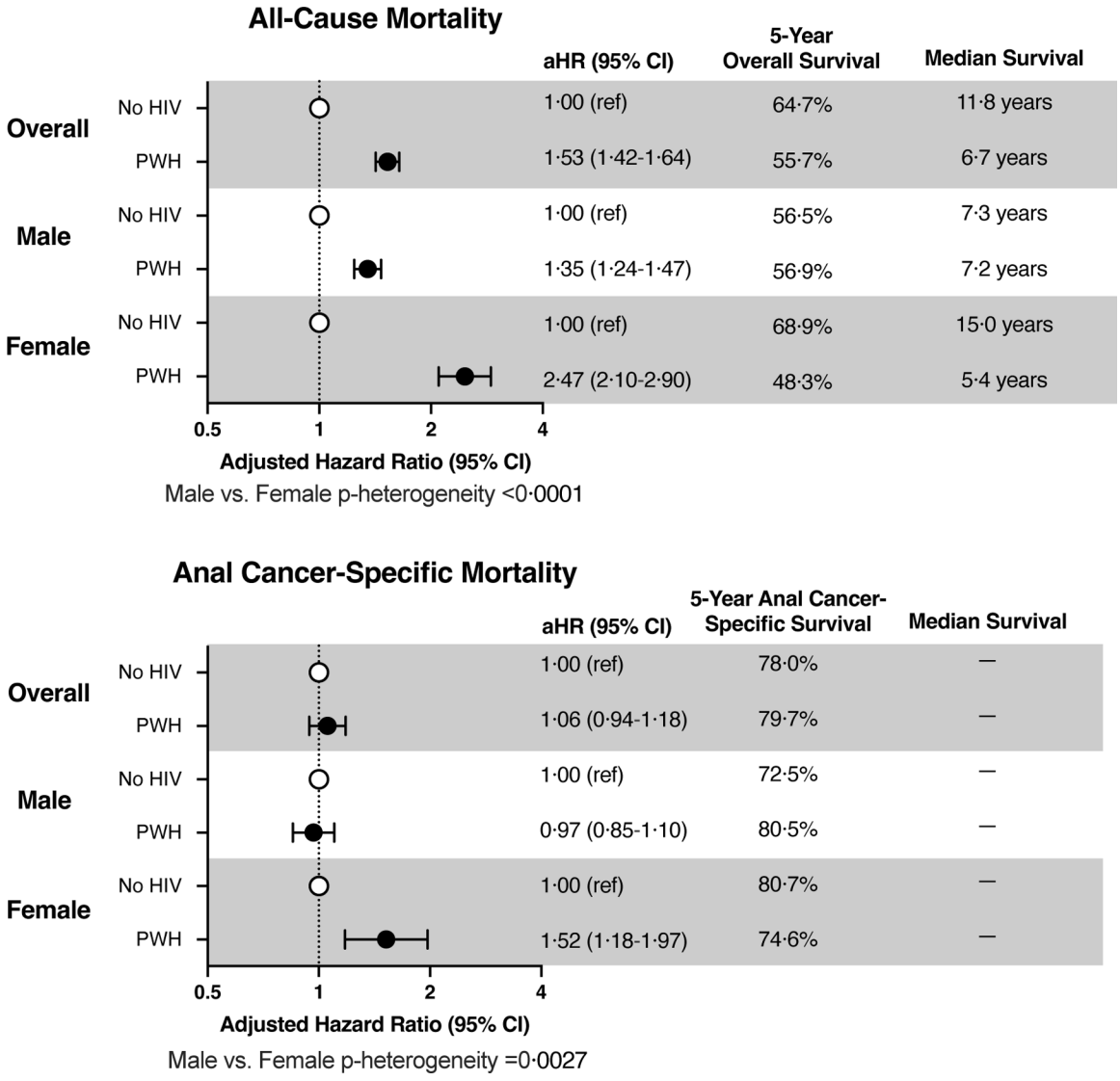


**Figure 2.**

Adjusted hazard ratios, 5-year survival[a], and median survival[b] for all-cause mortality[c] and anal cancer-specific mortality[d] overall and by sex among anal cancer patients in the HIV/AIDS Cancer Match Study, 2001–2019.

aHR = adjusted hazard ratio; CI = confidence interval; PWH= people with HIV.

[a] 5-year survival was only calculated among anal cancer patients who were diagnosed during 2001–2014 to allow enough follow-up through 2019.

[b] Median survival was only reported for all-cause mortality because median survival for anal cancer-specific mortality was not reached.

[c] The Cox proportional hazard model for all-cause mortality was adjusted for year of anal cancer diagnosis, sex, age at anal cancer diagnosis, race and ethnicity, histology, anal cancer stage, registry region, surgery, chemotherapy, and radiation (in the sex-stratified models, all covariates were adjusted for except for sex).

[d] The Cox proportional hazard model for anal cancer-specific mortality was adjusted for year of anal cancer diagnosis, sex, age at anal cancer diagnosis, race and ethnicity, histology,

anal cancer stage, registry region, and any treatment (in the sex-stratified models, all covariates were adjusted for except for sex); Analyses for anal cancer-specific mortality excluded Connecticut due to missing cause of death information.

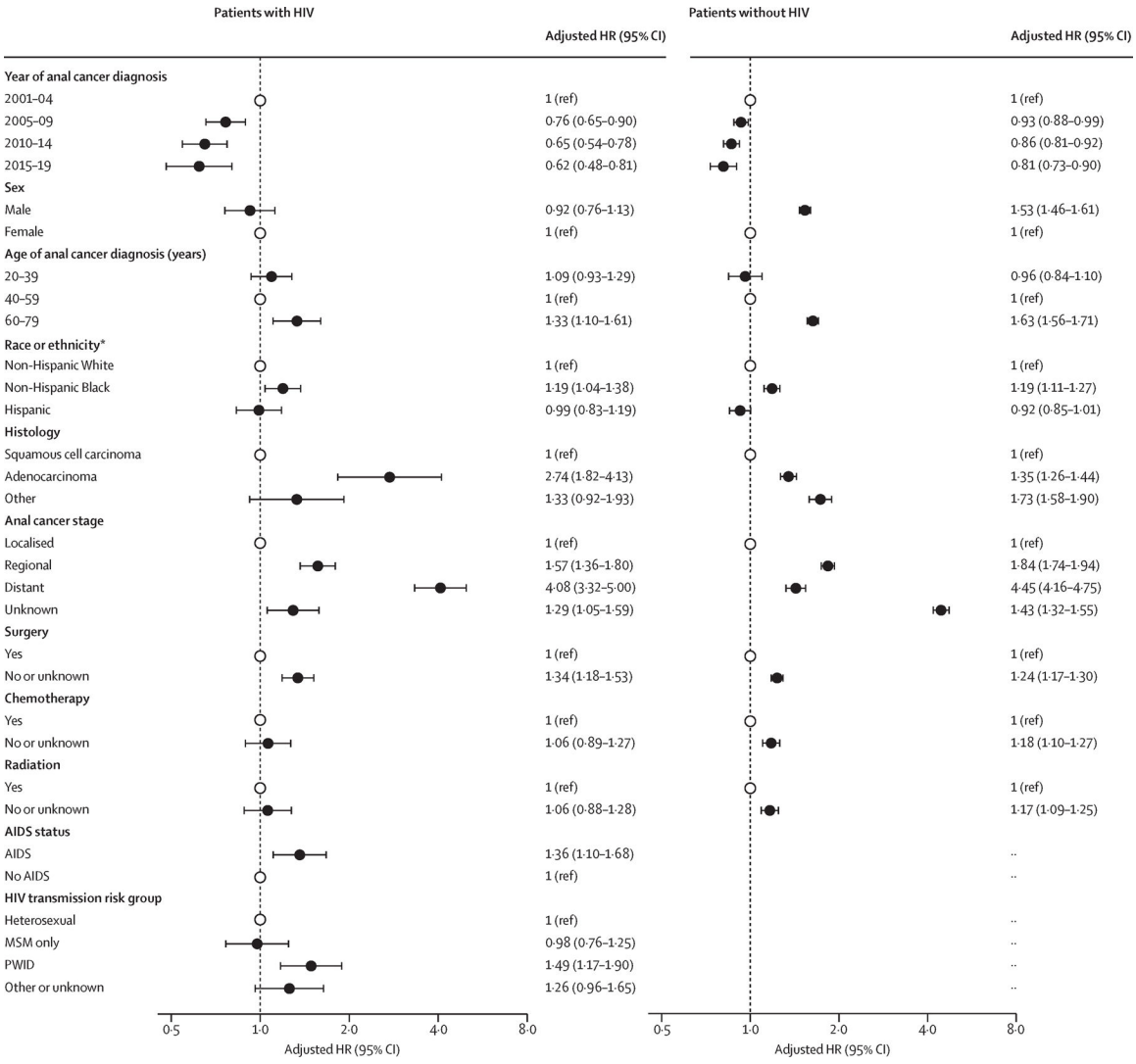


**Figure 3.**

Characteristics of all-cause mortality [a] by HIV status among anal cancer patients in the HIV/AIDS Cancer Match Study, 2001–2019.

aHR = adjusted hazard ratio; CI = confidence interval; MSM = men who have sex with men; NH = non-Hispanic; PWID = people who inject drugs; SCC = squamous cell carcinoma.

[a] The Cox proportional hazard model for all-cause mortality was adjusted for year of anal cancer diagnosis, sex, age at anal cancer diagnosis, race and ethnicity, histology, anal cancer stage, registry region, surgery, chemotherapy, and radiation; Models among people with HIV additionally adjusted for AIDS and HIV transmission risk group; ‘Other’ or ‘unknown’ race and ethnicity was not included in the Cox proportional hazard model due to low sample size.

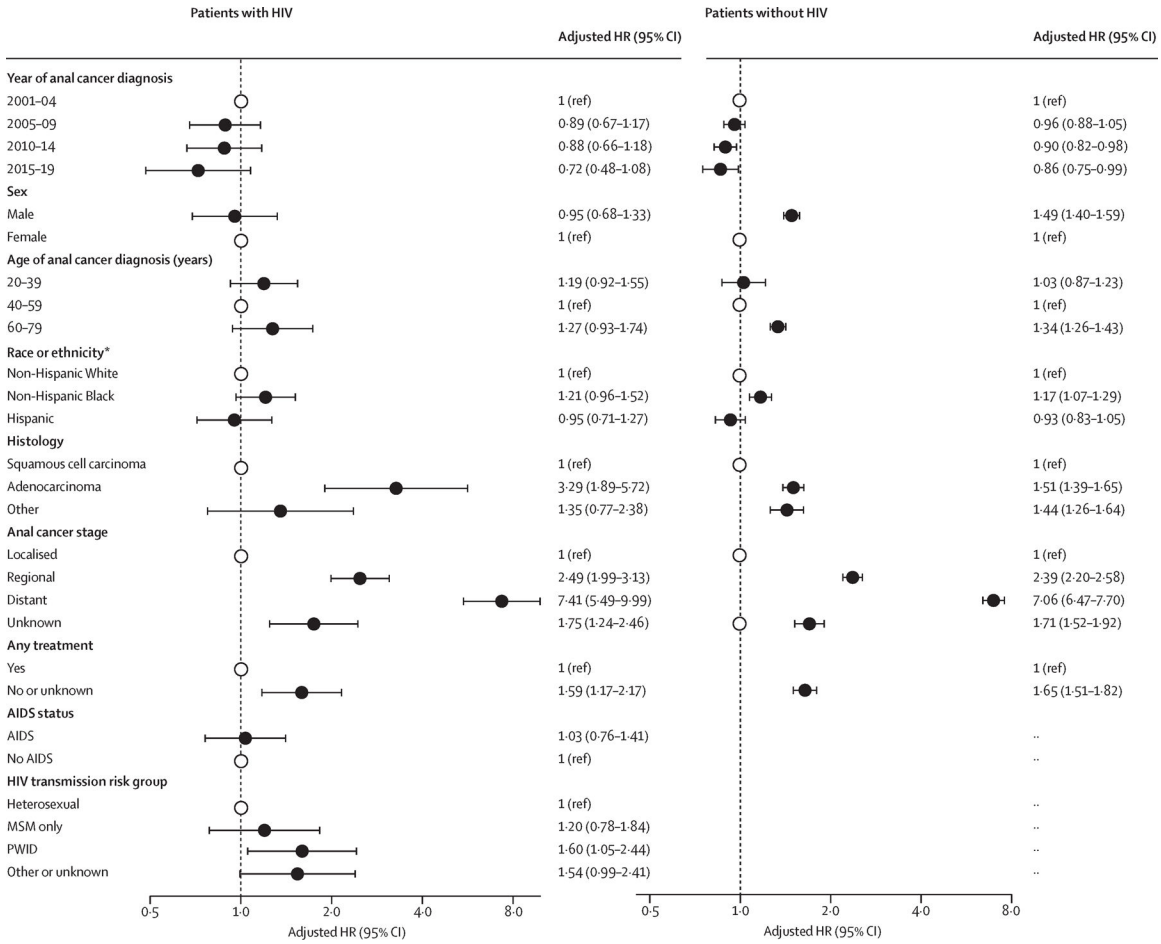


**Figure 4.**

Characteristics of anal cancer-specific mortality [a] by HIV status among anal cancer patients in the HIV/AIDS Cancer Match Study 2001–2019. aHR= adjusted hazard ratio; CI = confidence interval; MSM = men who have sex with men; NH = non-Hispanic; PWID = people who inject drugs; SCC = squamous cell carcinoma. [a] The Cox proportional hazard model for anal cancer-specific mortality was adjusted for year of anal cancer diagnosis, sex, age at anal cancer diagnosis, race and ethnicity, histology, anal cancer stage, registry region, and any treatment; Models among people with HIV additionally adjusted for AIDS and HIV transmission risk group; Analyses for anal cancer-specific mortality excluded Connecticut due to missing cause of death information; ‘Other’ or ‘unknown’ race and ethnicity was not included in the Cox proportional hazard model due to low sample size.

**Table.**

Patient characteristics overall and by HIV status

| Empty Cell | Empty Cell | Overall (n=24 486) | Patients with HIV (n=2662) | Patients without HIV (n=21 824) |
|---|---|---|---|---|
| **Year of anal cancer diagnosis** | | | | |
| 2001–04 | | 4110 (16·8%) | 376 (14·1%) | 3734 (17·1%) |
| 2005–09 | | 7588 (31·0%) | 837 (31·4%) | 6751 (30·9%) |
| 2010–14 | | 8845 (36·1%) | 946 (35·5%) | 7899 (36·2%) |
| 2015–19 | | 3943 (16·1%) | 503 (18·9%) | 3440 (15·8%) |
| Median (IQR) | | 2010 (2006–2013) | 2010 (2007–2014) | 2010 (2006–2013) |
| **Sex** | | | | |
| Male | | 9617 (39·3%) | 2285 (85·8%) | 7332 (33·6%) |
| Female | | 14 869 (60·7%) | 377 (14·2%) | 14 492 (66·4%) |
| **Age at anal cancer diagnosis, years** | | | | |
| 20–39 | | 1070 (4·4%) | 379 (14·2%) | 691 (3·2%) |
| 40–59 | | 12 024 (49·1%) | 1954 (73·4%) | 10 070 (46·1%) |
| 60–79 | | 11 392 (46·5%) | 329 (12·4%) | 11 063 (50·7%) |
| Median (IQR) | | 58·9 (51·0–67·4) | 49·1 (43·3–55·3) | 60·2 (52·5–68·3) |
| **Race and ethnicity** | | | | |
| Non-Hispanic White | | 17 221 (70·3%) | 984 (37·0%) | 16 237 (74·4%) |
| Non-Hispanic Black | | 3656 (14·9%) | 998 (37·5%) | 2658 (12·2%) |
| Hispanic | | 2874 (11·7%) | 560 (21·0%) | 2314 (10·6%) |
| Other | | 271 (1·1%) | 19 (0·7%) | 252 (1·2%) |
| Unknown | | 464 (1·9%) | 101 (3·8%) | 363 (1·7%) |
| **Histology** | | | | |
| Squamous cell carcinoma | | 20 975 (85·7%) | 2560 (96·2%) | 18 415 (84·4%) |
| Adenocarcinoma | | 2412 (9·9%) | 40 (1·5%) | 2372 (10·9%) |
| Other or unspecified | | 1099 (4·5%) | 62 (2·3%) | 1037 (4·8%) |
| **Anal cancer stage** | | | | |
| Localised | | 11 692 (47·7%) | 1399 (52·6%) | 10 293 (47·2%) |
| Regional | | 7607 (31·1%) | 805 (30·2%) | 6802 (31·2%) |
| Distant | | 2714 (11·1%) | 194 (7·3%) | 2520 (11·5%) |
| Unknown | | 2473 (10·1%) | 264 (9·9%) | 2209 (10·1%) |
| **Anal cancer treatment** | | | | |
| Any | | | | |
| | Yes | 22 057 (90·1%) | 2409 (90·5%) | 19 648 (90·0%) |
| | No or unknown | 2429 (9·9%) | 253 (9·5%) | 2176 (10·0%) |
| Surgery | | | | |
| | Yes | 10 047 (41·0%) | 1273 (47·8%) | 8774 (40·2%) |
| | No or unknown | 14 439 (59·0%) | 1389 (52·2%) | 13 050 (59·8%) |
| Chemotherapy | | | | |
| | Yes | 17 056 (69·7%) | 1698 (63·8%) | 15 358 (70·4%) |
| | No or unknown | 7430 (30·3%) | 964 (36·2%) | 6466 (29·6%) |

| Empty Cell | Empty Cell | Overall (n=24 486) | Patients with HIV (n=2662) | Patients without HIV (n=21 824) |
|---|---|---|---|---|
| Radiation | | | | |
| | Yes | 17 403 (71·1%) | 1821 (68·4%) | 15 582 (71·4%) |
| | No or unknown | 7083 (28·9%) | 841 (31·6%) | 6242 (28·6%) |
| **AIDS status** | | | | |
| Yes | | .. | 2279 (85·6%) | .. |
| No | | .. | 383 (14·4%) | .. |
| **HIV transmission risk group** | | | | |
| MSM only | | .. | 1562 (58·7%) | .. |
| MSM and PWID | | .. | 209 (7·9%) | .. |
| PWID only | | .. | 335 (12·6%) | .. |
| Heterosexual | | .. | 263 (9·9%) | .. |
| Other or unknown | | .. | 293 (11·0%) | .. |

Data are n (%), unless otherwise specified. MSM=men who have sex with men. PWID=people who inject drugs.